

STRESS

IN HEALTH AND DISEASE

HANS SELYE

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*Like its predecessor (Stress)
written 25 years ago
this book is dedicated to those
who suffer from stress.*

TO those who—in their efforts for good or evil, for peace or war—have sustained wounds, loss of blood or exposure to extremes of temperature, hunger, fatigue, want of air, infections, poisons or deadly rays.

To those who are under the exhausting nervous strain of pursuing their ideal—whatever it may be. To the martyrs who sacrifice themselves for others, as well as to those hounded by selfish ambition, fear, jealousy,—and worst of all by hate.

FOR my stress stems from the urge to help and not to judge.

But most personally, this book is dedicated to her who helped so much to write it, for she understood that I cannot, and should not, be cured of my stress but merely taught to enjoy it.

FOREWORD

PURPOSE AND SCOPE

In our time, characterized by a rapid increase in the rate of medical and social developments, research on stress and adaptation to change assumes particular importance in health and disease. We can no longer count on "having finished our training" for our work or on "having arrived at our goal" in society; nowadays, the skills and knowledge demanded by any job, as indeed the goals of society itself, are developing (or at least changing) at such an unprecedented rate that our first objective must be to learn how to cope with the stress of adaptation to change as such, both in our work and in our social goals. Only thus can we hope to succeed in overcoming the distressing loss of stability and perhaps even to enjoy the challenge of adjustment to ever-changing tasks, aspirations and possibilities.

Of course, the need to adjust to constant change arises from the fact that the more we know and the larger the number of people who acquire knowledge, the faster the pace of development, or at least of exploratory change, in all fields. This situation is primarily created by recent progress in mathematics, physics, chemistry and engineering with its resulting industrial implications: computers, automation and extraordinary acceleration in the rate at which people and information travel and alter the world.

All this is durable, and sometimes even enjoyable, but only within the limits of human adaptability. In the final analysis, the mastery we gain over our inanimate surroundings and the psychosocial consequences thereof are essentially physiologic and medical problems.

For the reasons just mentioned, interest in stress as it influences the lives of individuals, and even entire societies, has grown enormously during the past few decades. There has been a phenomenal increase in the number of laboratories, technical articles, books, journals and congresses dealing with the far-reaching implications of stress in virtually all fields of human endeavor, including medicine, physiology, psychology, psychiatry, sociology and philosophy. Nowadays, even the lay press, television and radio are constantly discussing stress, although frequently without real awareness of the objective scientific proofs upon which certain conclusions are based.

The magnitude and danger of the resulting confusion stem mainly from the fact that, unlike all other research subjects, stress (as defined in medicine) affects every aspect of life in health and disease; indeed, it exerts an ever-increasing influence upon even the most sophisticated activities of the mind. A real understanding of stress is therefore essentially dependent upon a holistic and integrative approach; no special

aspect of it can be analyzed in depth without a full realization of where and how it fits into the whole picture.

These are the considerations that encouraged us to attempt the somewhat Herculean task of providing a guide to the seemingly limitless number of publications concerned with stress in all its aspects. This effort has been inspired by the daring (and perhaps somewhat overoptimistic) hope that stress research, at the present critical period in its history, could best be promoted by providing an easily available source of at least key references to all of its implications. Only thus could we facilitate ready access to relevant data for highly specialized scientists lacking the bibliographic resources for an overview of the entire concept, which data would allow a proper evaluation of their own findings relative to the whole.

Since the publication in 1936 of a letter to the editor of *Nature* on "A syndrome produced by diverse noxious agents," about ninety-five thousand articles, reviews and books have dealt with what has become known as the *Stress Syndrome* or *General Adaptation Syndrome* (*G.A.S.*). The documentation service and library attached to our Institute have made every effort to collect and fully index all relevant published data.

I cannot claim to have studied thoroughly every one of these works, but I have at least glanced through all of them to maintain an overview of the subject, while scrutinizing more closely those that struck me as particularly important. I was best aided in this effort by my long-standing involvement in the field since its birth almost forty years ago, when biologic stress as we now understand it was first described. During this time I have studied and lectured throughout the world at most of the centers where important stress research was being done. It was of considerable help to me on these trips, as well as in the evaluation of the literature, that my own varied personal background had forced me to acquire at least a working knowledge of most languages in which pertinent data are described; hence, I could read and speak to foreign scientists in their own tongues without excessive linguistic handicaps.

These are the credentials that emboldened me to undertake the task of selecting and evaluating what I consider key references. The resulting work is meant to include most of the important publications on the mechanism of stress reactions without limiting itself to these. Many data are mentioned merely because of the difficulty in finding publications on highly specialized topics (for example: stress in plants and uncommon animals and the applicability of the stress concept to problems of forensic medicine, executive life, diabetes, emigration, concentration camps, captivity, air-traffic control, urbanism and noise). On some of these subjects reliable data are scarce, and here even relatively unimportant papers are mentioned to give at least one or two key references. On the other hand, subjects that occupy the attention of a great many contemporary scientists—such as the mechanism of the stress reaction, its biochemical and morphologic indices, and its applications to psychology, psychiatry and sociology—are generously documented, even if available space permits only the briefest summary of the contents or merely the listing of a descriptive original title.

It is hardly possible to draw a sharp line between stress research as such and work on organs involved in the mechanism of stress reactions. In this treatise I give considerable attention to the types of agents that can act as stressors or modifiers ("conditioners") of the stress response, the role of nervous and hormonal mediators, and the diseases primarily dependent upon inappropriate reactions to stress, called "de-

railments of the G.A.S." On the other hand, only cursory mention is made of the embryology, anatomy, histology and physiology of nerve centers and endocrine glands, the biosynthesis and degradation of hormones and metabolic changes, except insofar as they are directly related to the stress concept. Thus, I do not deal with the embryology of the hypothalamo-pituitary system, the enzymatic mechanisms leading to the synthesis or secretion of corticoids, or the electron microscopic (EM) structure of the median eminence (ME) unless such topics are of particular interest for the interpretation of stress reactions. Even the effects of catecholamines, ACTH or corticoids are considered only in this limited sense.

A glance at the table of contents and the subject index will suffice to show the wide variety of topics that are thus included. They will readily guide the reader to any particular field (as does an encyclopedia or dictionary), without the need to wade through the rest of the text.

PREFATORY REMARKS ON THE STYLE OF THIS BOOK

General Structure. In five previous monographs, *The Mast Cells* (Butterworths, Washington, D.C., 1965), *Thrombohemorrhagic Phenomena* (Thomas, Springfield, Ill., 1966), *Anaphylactoid Edema* (Green, St. Louis, Mo., 1968), *Experimental Cardiovascular Diseases* (Springer-Verlag, Berlin, Heidelberg and New York, 1970), and *Hormones and Resistance* (Springer-Verlag, Berlin, Heidelberg and New York, 1971), I have tested the practicality of what might be called the *analytico-synthetic style*. In essence, it attempts to facilitate fact-finding by strictly separating: (1) the *analysis* of previous publications in search of facts, which must be objective, and (2) the author's evaluation and *synthesis* which, being guided by his personal experience, are largely subjective.

The lessons learned in compiling these earlier monographs are incorporated in the present treatise, and since no major changes in method have been made, the rationale of the analytico-synthetic style may be described here in essentially the same terms.

Conventionally, the preparation of a monograph progresses through two stages:

- (1) The author surveys the literature and makes brief abstracts of each publication pertinent to his subject.
- (2) In writing the successive chapters of his book, he transforms these abstracts into a current narrative.

In theory, this seems to be a perfectly logical procedure, and it can be successfully applied in some cases. However, the second phase of the work usually meets with virtually insurmountable difficulties. Whenever numerous data are accumulated by many investigators who have used different techniques, the interpretations may be consonant, contradictory or unrelated, so that a unified, concise report of all relevant facts and views is hardly possible without confusing distortions or oversimplifications.

Take a sentence such as "Allegedly, it is possible to augment corticosterone secretion by a single intravenous injection of substance X in the rabbit (Smith and Johnson, 1943; Jones, 1944; Jackson, 1952) but not in the mouse (Simpson, 1961; Walker, 1964); however, the latter claim has been challenged by several investigators (McKay, 1963; Dow, 1963; Fisher, 1964), who have obtained positive results in both these species." Did all these investigators use exactly the same technique? Did all of them use the same criteria for a "positive result?" Were the animals used of the same age and weight? Were the animals invariably killed after the same length of time following the injection, so as to give them an equal chance to develop the response? Only in the rarest instances would the answers to all these questions be affirmative. In other words, the sentence designed to combine the three reports has made them quite meaningless.

But why yield to the customary practice of verbal acrobatics to give the un-unifiable the appearance of unity? To make sense, the incongruous monster sentences painfully synthesized by the author must be broken down mentally into their constituent parts by the reader. What the author has coded, the reader must decode. Statements must be very diplomatically worked to fit several papers because the different authors bracketed after one remark have rarely, if ever, said exactly the same thing. Hence, such texts are difficult to read, and in the final analysis, they do little more than act as indices to the literature, which still must be procured and read in the original before it can serve as a reliable guide to further work. The essential weakness of this conventional style is that the author must formulate his remarks very vaguely whenever he wants to cite several related, but of course never identical, papers in support of a statement. This procedure is necessary for unification, but the result is uninformative or misleading; usually both.

I learned these facts by bitter experience while writing sixteen earlier medical texts in the conventional style. Could the usual drawbacks of monographs be avoided by a totally different approach? In compiling a scientific treatise, it is undoubtedly necessary first to peruse all pertinent publications and to prepare concise abstracts of them. (Indeed, I never minded this part of the work, for it was instructive and pleasant and gave me a panoramic view of the observations and reflections of others, the very basis for any correlative scientific study.) Then, however, came the deadly and uninstructive task of modifying and paraphrasing portions of my summaries so that they could be squeezed into more or less cohesive, current prose. Why bother? All that was accomplished in this second stage was to conform with the style sanctified by common usage, but in the process the practical value of my abstract collection was largely lost. I must admit that even after the book appeared in print, I usually still preferred to look up my original résumés. After all, the volume contained only portions of these, and even they were not expressed as clearly as in the abstracts, mainly for three reasons:

- (1) Whenever several references were cited to document a statement, certain details had to be eliminated or diluted to make the text fit all the supporting publications.
- (2) Transitional sentences were needed to connect one idea with another, and these were only confusing ballast that served no real purpose.
- (3) Many circumlocutions were necessary to distinguish tactfully between data that were fully, partly, or not at all, acceptable.

In other words, the first part of the work, the reading and abstracting, was pleasant, instructive and comparatively easy, while the second part, the paraphrasing into current narrative, was tedious and largely spoiled the earlier accomplishments.

Of course, a collection of abstracts is not a monograph; it does not possess any overall structure or continuity, and even with the aid of an extensive index, it cannot act as a handy guide to a new field. Such a compendium is also necessarily uncritical and devoid of originality. It gives none of the interpretations or personal findings of the reviewer.

How could I devise a style that would combine concise, objective reporting with original interpretations without creating any confusion between the two? How could the writing of scientific monographs be simplified sufficiently so that even a large field might be covered by a single author who could give it unity? This is what I have tried to accomplish, and the technique has been described in detail in *Experimental Cardiovascular Diseases* and in *Hormones and Resistance*.

References. In this treatise there is only one major deviation from the style used in my earlier analytico-synthetic works. Previously, the full references (title, journal, volume, inclusive page numbers and year) were listed at the end of the book, in alphabetic order (according to the senior author's name), with the accession number assigned by our library, whereas in the text each abstract was preceded only by the name of the author(s), followed by the same accession number. Hence the reader had to consult the bibliography for the details necessary to locate the publication in a library other than our own. In this treatise, each abstract is preceded by the complete reference. Often, the title itself yields enough information on the material discussed or even on the principal observations, making it possible for me to shorten, and sometimes even eliminate, abstracts. Each abstract provides data on the journal, number of pages and the original language in which the publication appeared. To facilitate orientation, there are section titles indicating the topic under discussion; in addition, the key words in abstracts or even in titles (when no abstracts were necessary) are *italicized*, especially in sections where many subjects are summarized under such titles as "Varia," "Metabolites," or "Other Hormones." Having made this statement here, we shall not have to repeat "italics mine" in quoted abstract texts or in abstract titles. In addition, all authors are now listed with the abstract; this is very useful because the senior author may not be the one whose work is best known to the reader.

Finally, an alphabetic Author Index is added at the end of the book. This includes even coworkers not mentioned in the first position of the publication itself, and gives each page number in the text where their work is cited. Thus, the complete reference is cited with each abstract and all text references to the work of any author or coauthor can be located by the page numbers after his name in the alphabetic Author Index.

Critique and Personal Observations. This classified collection of concise abstracts served as a convenient guide to the literature on the physiology and pathology of stress. However, precisely because of its strict objectivity and the absence of any connecting sentences between the abstracts, this text lacked both originality and continuity. It was useful for the experienced specialist who wanted only to consult the literature on a particular point, but it gave no guidance to the beginner and contributed no new unpublished thoughts or observations.

My published data are handled in the usual manner, in objective abstracts prepared for the small-print sections. However, my own interpretation of the literature and hitherto unpublished observations are reported in an entirely different, current narrative form; this text is clearly separated from the rest by being printed in large type. Here there are no references, it being tacitly understood that the conclusions are my own, based on a critical interpretation of the literature and on my personal experience. Only when a remark is to be attributed to one of the abstracts in the immediately following small-print section do I refer to its author(s) and serial number.

For the sake of clarity, the titles of groups and subgroups are printed in fonts of decreasing prominence. Italics are used to indicate the lowest groups or subdivisions in the original texts, abstracts and even in titles (where no abstracts are required) or quotations. They should not be interpreted as words emphasized by the original authors by means of italics or boldface print. In this treatise, the origin of foreign words or their importance is rarely emphasized by special fonts, except in a few cases where this is done by the use of italics.

Thus, we end up having a book within a book: the *small-print* sections representing concise and impersonal abstracts of published and unpublished data, formulated in telegraphic style, to be looked up but not to be read through from cover to cover; the *large-print* text being both a critical summary of the most noteworthy highlights in the literature and a description of unpublished observations. The reader who wishes only to get an overall view of the present status of knowledge on stress can do so without becoming lost in details and confusing contradictory statements if he reads only the large-type sections. The investigator who wants to verify a special point quickly will find it merely by consulting the classified abstracts in the corresponding section.

This analytico-synthetic style would not lend itself to the writing of textbooks for students, nor would it be suitable for monographs on entirely new subjects on which there is little if any earlier literature. However, I think it can be (and sometimes already has been) profitably employed in the compilation of doctoral theses, reviews or monographs that are to combine an extensive literature survey with personal observations and critical interpretations.

In our era, when interest in research has reached unprecedented proportions, one of the greatest handicaps to the further development of science is the growing difficulty in keeping track of the ever-expanding mass of literature. Hence, a generally acceptable, simplified style of reporting could be of immeasurable value. Of course, many laboratory men will say that they lack the time, money, library facilities, or the knowledge of foreign languages necessary for a thorough personal search of the original literature in an extensive field. Yet any competent scientist must master his own subject. The breadth of his investigations may be limited by lack of documentation, but in his restricted field he will eventually gather valuable expertise that should be made available to others as well. It is hoped that the extreme simplicity of reporting in the style recommended here will encourage the writing of surveys by authors who would not have ventured to do so in the more time-consuming conventional form. Should this be the case, correlative investigations would certainly receive a welcome stimulus at a time when mass production threatens to discourage the integration of knowledge.

Reviews

OUR EARLIER STRESS MONOGRAPHS

Selye, H.: *Stress*, p. 822. Montreal: Acta Inc., 1950.
B40,000/50

Selye, H.: *First Annual Report on Stress*, p. 644. Montreal: Acta Inc., 1951.
B58,650/51

Selye, H., Horava, A.: *Second Annual Report on Stress*, p. 526. Montreal: Acta Inc., 1952.
B87,000/52

Selye, H., Horava, A.: *Third Annual Report on Stress*, p. 637. Montreal: Acta Inc., 1953.
B90,100/53

Selye, H., Heuser, G.: *Fourth Annual Report on Stress*, p. 749. Montreal: Acta Inc., 1954.
C1,001/54

Selye, H., Heuser, G.: *Fifth Annual Report on Stress 1955-56*, p. 815. Montreal: Acta Inc., 1956.
C9,000/56

Each of the above monographs discusses 5,000-6,000 references directly connected with our subject. They are cited separately here because, to save space, we shall often refer to them conjointly as our earlier stress monographs. The large collection of find-

ings to which they refer will not be repeated in the present work, except where it is indispensable for the evaluation of new data.

The following references are subdivided into three sections:

1. *General*, which lists technical, English language reviews and books concerned with the entire G.A.S. concept,

2. *Popular*, which enumerates reviews and books on stress irrespective of language,

3. *Foreign*, which discusses technical data in languages other than English.

GENERAL

(See also our earlier stress monographs, p. xiii)

Selye, H.: "The alarm reaction." In: Piersol, G. M. and Bortz, E. L., *The Cyclo-pedia of Medicine, Surgery and Specialities*, Vol. 15, pp. 15-38. Philadelphia: F A Davis, 1940 (341 refs.). A8,048/40

Selye, H.: "The general adaptation syndrome and the diseases of adaptation." *J. Clin. Endocrinol.* 6: 117-230 (1946).

B1,204/46

First detailed review on the G.A.S. and the diseases of adaptation, presented in a special number of the *Journal of Clinical Endocrinology* (over 700 refs.).

Pincus, G.: "Studies of the role of the adrenal cortex in the stress of human subjects." *Rec. Prog. Horm. Res.* 1: 123-145 (1947). 98,426/47

Excellent review on the biochemical changes characteristic of the G.A.S. in man, with special reference to 17-KS excretion and blood count under the influence of circadian variations, the stresses of daily life, operating a Hoagland-Werthessen pursuit meter, flying and exposure to heat. The response of schizophrenics is abnormal in many respects, and the question is raised whether adrenal malfunction may play a pathogenic role in mental disease (20 refs.).

Selye, H.: *Textbook of Endocrinology*, p. 914. Montreal: Acta Endocrinologica, 2nd ed., 1949. 94,572/49

Textbook of endocrinology with an extensive section on the concept of the G.A.S. as it appeared before the discovery of cortisone.

Yacorzyński, G. K.: "The alarm and the general homeostatic syndrome (the adaptation syndrome of Selye) in psychopathological and psychosomatic relationships" (abstracted). *Am. Psychol.* 7: 347 (1952).

J13,183/52

Jensen, J.: *Modern Concepts in Medicine*, p. 636. St. Louis, Mo.: C V Mosby, 1953. B84,030/53

Voluminous treatise which attempts to reinterpret virtually the whole of physiology, biochemistry and medicine using the G.A.S. as a unifying concept. Very painstaking compilation of data interpreted in a rather daringly speculative manner.

Symposium on Stress, p. 332. Washington, D.C.: Army Medical Service Graduate School, 1953.

B87,548/53

Conference on stress sponsored by the Division of Medical Sciences, National Research Council and the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C. Numerous papers on the hormonal and nervous regulation of stress responses, with special reference to combat situations, interpersonal relationships, nutrition and adaptation to catastrophic events.

Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Reddy, W.: "Response of the adrenal cortex to stress in man." *Trans. Assoc. Am. Physicians* 66: 48-64 (1953).

B91,232/53

Noble, R. L.: "Physiology of the adrenal cortex." In: Pincus, G. and Thimann, K. V., *The Hormones. Physiology, Chemistry and Applications*, Vol. 3, pp. 685-819. New York and London: Academic Press, 1955.

C22,214/55

An extensive chapter on the adrenal cortex in an encyclopedia on hormones, with numerous discussions on the relation of corticoids to stress reactions (1,263 refs.).

Liebman, S. (ed.): *Stress Situations*, p. 144. Philadelphia and Montreal: J B Lippincott, 1955.

C4,030/55

Anthology of publications on emotional reactions to the stress of frustration, illness, catastrophes, marriage, fertility and sterility, divorce, death and suicide, presented in highly simplified lay language.

Hinkle, L. E. Jr.: "Physiological aspects of life stress." *J. Dent. Med.* 11: 69-77 (1956).

J13,193/56

Brief review on the role of the G.A.S. in "life stress."

Fox, H. M., Gifford, S., Murawski, B. J., Rizzo, N. D., Kudarauskas, E. N.: "Some methods of observing humans under stress." *Psychiatr. Res. Rep. APA* 7: 14-26 (1957).
J11,149/57

Review on the G.A.S. with special reference to behavioral changes in man.

Applezweig, M. H. (ed.): *Psychological Stress and Related Concepts: A Bibliography*, p. 185. Technical Report No. 7. New London, Conn.: Dept. of Psychology, Connecticut College, 1957.
J13,040/57

An extensive bibliographic list on stress, with special reference to the psychologic and psychosomatic implications of the G.A.S., but without annotations or comments (2,611 refs.).

Hambling, J. (ed.): *The Nature of Stress Disorder*, p. 298. Springfield, Ill.: Charles C Thomas, 1959.
E4,674/59

Proceedings of the Conference of the Society for Psychosomatic Research (Royal College of Physicians, London). Several experts discuss the G.A.S. on the basis of animal experiments and observations in man. Special sections deal with stress in aviation, skin disorders, gastrointestinal disease, industry and the family setting, as well as genetic predisposition.

Engel, G. L.: "A unified concept of health and disease." *Perspect. Biol. Med.* 3: 459-485 (1960).
J12,716/60

Singer, H. A.: "The management of stress." *Advanc. Management* 25: 11-13 (1960).
J14,314/60

Popular review on stress, especially as it affects the manager, with recommendations concerning the avoidance of distress.

Ganong, W. F., Forsham, P. H.: "Adenohypophysis and adrenal cortex." *Ann. Rev. Physiol.* 22: 579-614 (1960) (317 refs.).
C83,368/60

Messner, J.: "Über die Einheitlichkeit der Krankheitsabwehr im lebenden Organismus" (The uniform nature of disease defense in the living organism). *Z. Gesamt. Inn. Med.* 16: 111-117 (1961).
D5,855/61

Highly theoretical but extensive review on the uniformity of defensive phenomena in various diseases which suggest a participation of the stress mechanism (70 refs.).

Hamburg, D. A.: "The relevance of recent

evolutionary changes to human stress biology." In: Washburn, S., *Social Life of Early Man*, pp. 278-288. Chicago: Aldine, 1961.

J16,062/61

Farber, S. M., Mustacchi, P., Wilson, R. H. L. (eds.): *Man Under Stress*, p. 173. Berkeley and Los Angeles: University of California Press, 1964.
E4,227/64

Proceedings of a symposium organized by the University of California. A group of physicians, surgeons and basic research men (among them Brock Chisholm, René Dubos, Seymour Farber, Stanley Sarnoff, Hans Selye, Paul Dudley White) discussed various aspects of stress in relation to the philosophy of life, the social environment, cardiovascular disease and space medicine. Most of the speakers refrained from highly technical discussions, but key references to scientific papers are given.

Dubos, R.: *Man Adapting*, p. 527. New Haven and London: Yale University Press, 1965.
E10,710/65

Scientifically well-founded monograph on adaptation, with many sections referring to Cannon's "emergency reaction" and the G.A.S. The volume formed the subject of the Silliman Lectures at Yale University.

Edholm, O. G., Bacharach, A. L. (eds.): *The Physiology of Human Survival*, p. 581. New York and London: Academic Press, 1965.
E6,283/65

Monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal and muscular exercise. Each chapter is written by a specialist in the corresponding field, and numerous references indicate the difference between specific defense mechanisms and the stressor effect of the agents used.

Howard, A., Scott, R. A.: "A proposed framework for the analysis of stress in the human organism." *Behav. Sci.* 10: 141-160 (1965).
G40,977/65

An encompassing theoretical scheme which "proposes to reduce the conceptual barriers between various biochemical, physical, psychological, and sociocultural models of stress." Numerous references to the technical literature.

Weitz, J.: *Stress*. Research paper IDA/HQ 66-4672, pp. 251-294. Washington, D.C.: Inst. Defense Analyses, Research and Engi-

neering Support Div., 1966. J13,888/66

Review on stress research, particularly in relation to military medicine, with a section criticizing various currently used definitions of the term "stress" (16 refs.).

Levi, L.: *Stress, Sources, Management, and Prevention* (Foreword by Hans Selye), p. 192. New York: Liveright, 1967. E250/67

Very readable volume on the sources, management and prevention of stress, emphasizing both the purely medical and the psychologic aspects of everyday experiences.

Bajusz, E. (ed.): *Physiology and Pathology of Adaptation Mechanisms*, p. 583. Oxford, London and Edinburgh: Pergamon Press, 1969. E8,161/69

Technical monograph with independent articles by numerous specialists in adaptation. One large section deals with "the pituitary adrenocortical system, its regulation and adaptive functions," and another with "regulation of 'adaptive hormones' other than ACTH." Additional presentations are concerned with neuroendocrine regulatory adaptation mechanisms and adaptation to changes in environmental temperature.

Smelik, P. G.: "Integrated hypothalamic responses to stress." In: Martini, L., Motta, M. et al., *The Hypothalamus*, pp. 491-497. New York and London: Academic Press, 1970. J12,268/70

Dodge, D. L., Martin, W. T.: *Social Stress and Chronic Illness: Mortality Patterns in Industrial Society*, p. 331. Notre Dame, Ind., and London: University of Notre Dame Press, 1970. E10,654/70

Monograph attempting to evaluate modern concepts of systemic stress within the body in relation to social stressors.

* Harris, R.: "Stress." *Aust. Dent. J.* **16**: 255-256 (1971). J19,854/71

Levi, L. (ed.): *Society, Stress and Disease*, p. 485. New York, Toronto and London: Oxford University Press, 1971. E9,300/71

International Interdisciplinary Symposium sponsored by the University of Uppsala and the WHO. The principal subjects for discussion were: definition of problems and objectives of stress research, relationships between the G.A.S. and social adjustment, neuroendocrine function, potentially pathogenic psychosocial stressors in today's society, epidemiologic evidence for diseases produced by stressors, and possible ways of modifying or

preventing psychosomatic diseases through social action. First formulation of the definition: "biologic stress is the nonspecific response of the body to any demand made upon it." An excellent overview of contemporary ideas on the different somatic and psychic manifestations of stress. A rich source of useful references.

Selye, H.: *Hormones and Resistance*, 2 vols., p. 1140. New York, Heidelberg and Berlin: Springer-Verlag, 1971. G79,100/71

Very extensive encyclopedic treatise on the role of various hormones in resistance to specific and stressor agents. First detailed description of the difference between syntoxic and catatoxic hormones and the results of extensive screenings of steroids for these actions. Among all compounds tested, pregnenolone-16 α -carbonitrile (PCN) proved to be the most active catatoxic substance.

Grant, J. K., Hall, P. E.: "Laboratory investigation of the human hypothalamic-pituitary-adrenocortical system." *Scott. Med. J.* **16**: 157-167 (1971). G83,953/71

Review on the results of laboratory investigations on human hypothalamic-pituitary-adrenocortical reactions, especially to stress (about 50 refs.).

Levi, L.: "Definition and evaluation of stress." *Rep. Lab. Clin. Stress Res.* (Stockholm) No. 25: 1-11 (1971). G87,068/71

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H31,407/70

How to Use This Book

In surveying the literature, I was keenly aware that my lack of expertise in many fields prevented me from making useful critical comments concerning certain sections. Hence, I have restricted my personal evaluation to those fields with which I am particularly familiar. In other areas, relevant data have merely been listed, especially when I felt that even consultation with colleagues would not help much, because the volume of known facts greatly exceeds the possibility of coordinating them all in an instructive manner. This is true, for example, of most sections concerning the "Nervous Mechanisms" involved in stress reactions, the innumerable "Stress Tests," and some of the poorly-understood "Diseases of Adaptation" in which the role of stress is not yet clearly established. In such instances, this treatise can only serve as a collection of data carefully arranged according to subjects, objectively described, and in the case of foreign publications, translated into English. With these facts in mind, I hope that the text will be of considerable heuristic value for those who want to do further research in a particular field without having to waste too much time accumulating, translating and abstracting pertinent publications. Texts of special interest should be consulted in the original, since our abstracts are intended only as a guide to selection. Full coverage of a topic will require consultation of related entries. Only some related entries could be pointed out by cross-references, and each reader will have his own view as to which material may be worth scanning for additional information.

Certain observations are listed somewhat arbitrarily either under Functional or under Morphologic Manifestations of Stress, for the two areas are often interdependent, and to repeat the same references under both headings would have added uselessly to the length and expense of the text. For example, connective tissue changes (wound healing, inflammation and so on) are discussed only under Morphologic Changes, and alterations in muscle contractility only under Functional Changes.

In many fields, the literature is seemingly quite contradictory, such as that concerning typical stress-induced changes in the secretion of thyroid hormones, STH or insulin, the variations in blood cholesterol and many other areas. It is characteristic of the difficulty investigators experience in finding pertinent data that these evident contradictions are often left without comment, frequently because the authors reporting one type of change are quite unaware of the multitude of data indicating opposite results to be "typical of stress." From the published evidence, it is often impossible to arrive at a suitable explanation. It must be kept in mind, however, that some determinations are made with inadequate techniques whose flaws are not obvious from the printed texts. Sometimes diurnal variations have not been considered in describing

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In many fields, the literature is seemingly quite contradictory, such as that concerning typical stress-induced changes in the secretion of thyroid hormones, STH or insulin, the variations in blood cholesterol and many other areas. It is characteristic of the difficulty investigators experience in finding pertinent data that these evident contradictions are often left without comment, frequently because the authors reporting one type of change are quite unaware of the multitude of data indicating opposite results to be "typical of stress." From the published evidence, it is often impossible to arrive at a suitable explanation. It must be kept in mind, however, that some determinations are made with inadequate techniques whose flaws are not obvious from the printed texts. Sometimes diurnal variations have not been considered in describing

the findings, or even in planning the studies. Furthermore, we must remember that there exist mutual antagonisms between various stress-induced changes. The effect of a stressor upon one parameter may depend largely upon inherited, dietary and other conditioning factors that influence another—a fact which is not always taken into consideration. For example, STH, corticoids, insulin and glucagon may interact among themselves and with other parameters; hence the determination of one hormone at one particular time in individuals of a certain species and of a certain age can virtually never be indicative of stress as such, even if it occurs under the influence of several stressors. Finally, many determinations of stress-dependent metabolites fail to consider blood levels in relation to rates of secretion, resynthesis and distribution, which may be influenced by many factors.

Such interactions among the effects of various stressors and conditioning agents are especially likely to confuse interpretations if, as is often the case, the investigators are not sufficiently aware of one of the most fundamental concepts in stress research, namely, that no agent is only a stressor, without specific effects of its own, and that no specific agent is completely devoid of all nonspecific (that is, stressor) effects. The best way to avoid errors in this vein is to accept as true stress-manifestations only those changes associated with exposure to all kinds of demands as long as these do not specifically nullify the nonspecific change under study. Thus, the hyperglycemic response to stress could not be expected if insulin is used as a stressor, any more than an increase in blood corticoid levels could occur if hypophysectomy or adrenalectomy were employed to cause increased demands for adaptation. Furthermore, the EP secretion classically elicited by fighting causes a decrease in the size of the spleen that is undoubtedly typical of the alarm reaction, although after repeated fights among animals, the spleen is often enlarged because of the associated wound infections. The same is true if an alarm reaction is produced by overloading the circulation with particulate substances that are stored in the RES cells of the spleen.

Perhaps the most useful advice I can give, especially to those not particularly familiar with stress research, is to consult the carefully-prepared Subject Index. There, virtually every topic discussed in the text is identified as such along with cross-references under diverse synonymous designations.

Although this encyclopedia attempts to cover the subject of stress as completely as possible from every point of view, it should be kept in mind that it is no longer possible to quote in a single monograph all papers dealing with the G.A.S. Moreover, unlike our earlier stress monographs, this treatise could not elaborate on subjects only indirectly related to stress, such as the structure or function of stress hormones (for example, catecholamines, corticoids, ACTH, CRF) or specific (not stress-dependent) problems related to common stressors, such as anxiety, trauma, infection and so on.

Those who wish to have more complete literature surveys on any particular subject may obtain them at cost from our documentation service by writing to the Chief Documentalist, Institute of Experimental Medicine and Surgery, University of Montreal, C.P. 6128, Montreal 101, Quebec, Canada.

Glossary*

This glossary furnishes succinct descriptions of some of the technical terms and abbreviations most commonly used in this treatise. For additional definitions, see the section on terminology (p. 14), as well as the corresponding entries in the Subject Index.

- ACTH** Adrenocorticotrophic hormone of the pituitary.
- ADH** Antidiuretic hormone. See **Vasopressin**.
- ADP** Adenosine diphosphate.
- AMP** Adenosine monophosphate.
- androgen** See **Testoid**.
- ANS** Autonomic nervous system.
- ARH** Adrenal regeneration hypertension.
- ATCs** Air-traffic controllers.
- ATP** Adenosine triphosphate.
- ATPase** An enzyme metabolizing ATP.
- BMR** Basal metabolic rate.
- BTS** Blue-tetrazolium-reducing steroids.
- cAMP** Cyclic adenosine monophosphate.
- catatoxic actions** Increased metabolic degradation and/or excretion of potentially toxic substances.
- catecholamines** Any of a group of biologic amines containing a catechol moiety (e.g., epinephrine, norepinephrine, dopamine).
- cGMP** Cyclic guanosine monophosphate.
- CHD** Coronary heart disease.
- CNS** Central nervous system.
- compound 48/80** A histamine liberator.
- conditioning actions** Actions that prepare an organism for a special type of response. These may be positive, sensitizing through the induction of receptivity (also known as permissive actions), or inhibitory, desensitizing (blocking actions).
- corticoids** Hormones of the adrenal cortex. It is customary to subdivide them into the anti-inflammatory glucocor-
- ticoids and proinflammatory mineralocorticoids.
- CRF** Corticotropin-releasing factor.
- CSF** Cerebrospinal fluid.
- DA** Dopamine.
- DCA** Desoxycorticosterone acetate.
- DMSO** Dimethyl sulfoxide.
- DOC** Desoxycorticosterone. Also known as **DOCA**.
- DOPA** Dihydroxyphenylalanine, an epinephrine derivative.
- dopamine** Aminoethylpyrocatechol, an antihypotensive agent.
- E** See **EP**.
- ECG** Electrocardiogram.
- ECT** Electroconvulsive therapy.
- ectohormone**. See **pheromone**.
- EEG** Electroencephalogram.
- EM** Electron microscopy.
- EMG** Electromyogram.
- EOG** Electrooculogram.
- EP** Epinephrine.
- ESCN** Electrolyte steroid cardiopathy with necrosis.
- FFA** Free fatty acids.
- FLA-63** Bis(4-methyl-1-homopiperazinyl-thiocarbonyl) disulphide (an inhibitor of dopamine- β -hydroxylase).
- folliculoid** Follicle hormone-like, gynecogenic, estrogenic, or estromimetic (e.g., estradiol, estrone).
- FSH** Follicle-stimulating hormone. A gonadotropic hormone of the pituitary.
- GABA** γ -aminobutyric acid.
- galvanic skin resistance** See **CSR**.

* Although linguistically the suffix “-trophic” (nourishing, nurturing) is more correct, the ending “-tropic” is likewise employed in the literature, and hence, throughout the text, the two are used interchangeably in such expressions as “gonadotrophic” (gonadotropic), “thyrotrophic” (thyrotropic), and “somatotrophic” (somatotropic).

- galvanic skin response** See **GSR**.
- G.A.S.** General adaptation syndrome.
- GDP** Guanosine diphosphate.
- GH** Growth hormone. See **STH**.
- glucocorticoid** Possessing the effects of the carbohydrate-active hormones of the adrenal cortex (e.g., cortisol, corticosterone, dexamethasone).
- GMP** Guanosine monophosphate.
- GPT** Glutamic pyruvic transaminase.
- CSR** Galvanic skin response. A change in electric resistance of the skin which serves as a dependent variable in conditioning and is used in lie detection tests.
- CTP** Guanosine triphosphate.
- 5-HIAA** See **5-hydroxyindoleacetic acid**.
- 5-HT** 5-Hydroxytryptamine or serotonin.
- 5-HTP** 5-Hydroxytryptophan.
- 5-hydroxyindoleacetic acid** Principal metabolite of 5-HT.
- 4-hydroxy-3-methoxy-mandelic acid** See **Vanillylmandelic acid**.
- Ig** Immunoglobulin.
- 17-KGS** 17-Ketogenic steroids.
- 17-KS** 17-Ketosteroids. Principally, metabolites of corticoids and testoids (androgens).
- lactotropic hormone** See **LTH** or **prolactin**.
- L.A.S.** Local adaptation syndrome.
- LDH** Lactic dehydrogenase.
- L-dopa** Levadopa.
- LH** Luteinizing hormone. A gonadotropic hormone of the anterior pituitary.
- LH-RF** LH-releasing factor. See **LH**.
- LPL** Lipoprotein lipase.
- LRF** Luteinizing releasing factor.
- LTH** Luteotropic or lactotropic hormone, synonym of prolactin.
- luteoid** Corpus luteum hormone-like, progestational, gestagenic, progestagenic (e.g., progesterone).
- MAD** Methylandrostenediol. A testoid hormone capable of being transformed into a mineralocorticoid within the adrenal.
- MAO** Monoamine oxidase.
- MBH** Medial basal hypothalamus.
- ME** median eminence.
- ME-CRF** CRF produced by the median eminence.
- α -methyl-p-tyrosine** See **α -MT**.
- α -methyltyrosine** See **α -MT**.
- MHPG** 3-Methoxy-4-hydroxyphenylglycol.
- mineralocorticoid** Possessing the effects of the salt metabolism regulating hormones of the adrenal cortex (e.g., aldosterone, DOC).
- MSH** See **MTH**.
- α -MT** α -methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase.
- MTH** Melanophorotropic hormone. Also known as MSH (Melanophore-stimulating hormone of the middle lobe of the pituitary, which increases deposition of melanin in the melanocytes).
- NAHD** The NAHD reaction of Camber (1949), a histochemical demonstration of ketosteroids in tissue.
- NADPH** Reduced nicotinamide-adenine dinucleotide phosphate.
- NDV** Newcastle disease virus.
- NE** See **NEP**.
- NEP** Norepinephrine.
- NPN** Nonprotein nitrogen.
- 11- or 17-OHCS** 11- or 17-Hydroxycorticosteroids. Commonly-used indicators of corticoids.
- 18-OH-DOC** 18-Hydroxy-desoxycortosterone.
- PAS** Periodic acid Schiff.
- PBI** Protein-bound iodine.
- PCN** pregnenolone- 16α -carbonitrile.
- PCPA** p-Chlorophenylalanine. An agent blocking 5-HT synthesis.
- PGR** Psychogalvanic reflex.
- pH** Hydrogen-ion concentration.
- pheromones** Substances secreted externally by one individual and received by a second individual of the same species whose behavior or develop-

- ment they modify. Also known as ectohormones.
- PK** Pyruvate kinase.
- PPLO** Pleuropneumonia-like organisms or "micoplasma."
- prolactin** See LTH.
- RER** Rough endoplasmic reticulum.
- RES** Reticuloendothelial system.
- RF** Reticular formation; term also used for releasing factors of pituitary hormones.
- SER** Smooth endoplasmic reticulum.
- SGOT** Serum glutamic oxalacetic transaminase.
- SH** Sulfhydryl groups.
- STH** Somatotropic or growth hormone.
- STH-RF** STH-releasing factor. See STH.
- syntoxic actions** Stimulation of biologic responses that permit coexistence with potential pathogens by increasing the resistance of the host's tissues, without attacking the pathogens.
- T3** Triiodothyronine, or thyroid hormone.
- T4** Tetraiodothyronine, thyroxine.
- testoid** Male hormone-like, androgenic, andromimetic (e.g., androsterone, testosterone).
- THC** Tetrahydrocannabinol.
- TM** Transcendental Meditation.
- TPNH** Reduced triphosphopyridine nucleotide, the former name for the reduced form of nicotinamide-adenine dinucleotide phosphate.
- TSH** See TTH.
- TRH** Thyrotropin-releasing hormone.
- TTH** Thyrotropic hormone of the anterior pituitary.
- TTH-RF** TTH-releasing factor. See TTH.
- UMP** Uridine monophosphate.
- vanillinemandelic acid** See vanillylmandelic acid.
- vanillylmandelic acid** A major metabolite of catecholamines excreted in the urine. (Also designated vanillinemandelic acid or VMA.)
- vasopressin** A pressor and antidiuretic hormone of the posterior pituitary. (Also designated ADH.)
- VDM** Vasodepressor material.
- VEM** Vasooexcitatory material.
- VMA** See vanillylmandelic acid.
- Indicates action on (e.g., A→B means: effect of A on B).
- + Refers to two agents given simultaneously (e.g., A+B means: A given conjointly with B).

Stress Tests

The most commonly used stress tests are listed here with their abbreviations.

- AAR** Adjusted Averaged Evoked Response Questionnaire.
- APQ** Autonomic Perception Questionnaire.
- BPI** Berkeley Psychological Inventory.
- BUPI** Boston University Personality Inventory.
- CFF** Critical Flicker Fusion.
- CMACL** Composite Mood Adjective Check List.
- CMI** Cornell Medical Index.
- CST** Controlled Stress Test.
- EPI** Eysenck Personality Inventory.
- FPJP** Frequency of Perceived Job Pressure.
- GSR** Galvanic skin resistance (or response, or reflex).
- HOS** Health Opinion Survey.
- HSTT** Harrower Stress Tolerance Test.
- IES** Impulse Expression Scale.
- IPAT Anxiety Scale** Institute for Personality and Ability Testing Anxiety Scale.
- JAS** Jenkins Activity Survey.
- LCI** Life Change Inventory.
- LCU** Life Change Unit.

- LEI** Life Events Inventory.
- MARS** Manifest Affect Rating Scale.
- MAS** See **TMAS**.
- MMPI** Minnesota Multiphasic Personality Inventory.
- MPI** Maudsley Personality Inventory.
- RLCQ** Recent Life Change Questionnaire.
- RMM** Running Matching Memory Test.
- SEI** Subjective Experience Inventory.
- SHG** Sustained handgrip.
- SIRS** Seriousness of Illness Rating Scale.
- SPL** Skin potential level. See **GSR**.
- SPQ** Somatic Perception Questionnaire.
- SPRS** Suicide Potential Rating Scale.
- S-R Inventory** Stimulus-Response Inventory.
- SRE** Schedule of Recent Experience.
- SRRQ** Social Readjustment Rating Questionnaire.
- SRRS** Social Readjustment Rating Scale.
- SSFIPD** Social Stress and Functionability Inventory for Psychotic Disorders.
- SSS** Subjective Stress Scale.
- STAI** State-Trait Anxiety Inventory.
- SVS** Stress Value Scale.
- TAQ** Test Anxiety Questionnaire.
- TMAS** Taylor Manifest Anxiety Scale.
- TPT** Halstead Tactual Performance Test.
- TRI** Total Response Index.
- WCST** Wisconsin Card Sorting Test.
- WSSA** Worcester Scale of Social Attainment.

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It is only fair to add that I must take responsibility for any errors that may have occurred in the selection, abstraction or interpretation of the papers quoted.

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I. HISTORY AND GENERAL OUTLINE OF THE STRESS CONCEPT

HISTORY

(See also under headings of various agents, changes, and mechanisms known to be characteristic of stress.)

Prescientific Intuitive Feelings Foreshadowing the Existence of Stress

The concept of stress is very old. It must have occurred even to prehistoric man that there was something common in the loss of vigor and the feeling of exhaustion that overcame him after hard labor, prolonged exposure to cold or heat, loss of blood, agonizing fear or any kind of disease. He may not have been conscious of the uniformity of his response to anything that was just too much for him, but when the feeling came he must have realized that he had exceeded the limits of what he could reasonably handle; in other words, that "he had had it."

Man soon must have discovered also that whenever faced with a prolonged and unaccustomed strenuous task—be it swimming in cold water, lifting rocks or going without food—he passes through three stages: at first the experience is a hardship; then he gets used to it; but finally he cannot stand it any longer. He did not think of this three-phase response as a general law regulating the behavior of living beings faced with an exacting task. The immediate necessities of finding food and shelter kept him too busy to meditate about such concepts as homeostasis, the maintenance of the *milieu intérieur*, or biologic stress. Yet the vague outlines of all this were there, ready to be analyzed and translated from intuitive feelings into the precise terms of science, a language that can be appraised by intellect and tested by the critique of reason.

How could different agents produce the same result? Is there a nonspecific adaptive reaction to change as such? In 1926, as a second-year medical student, I first came across this problem of a stereotyped response to any exacting task. The story of its elucidation has been told many times, although it is still unfinished, but here are the salient points:

I began to wonder why patients suffering from the most diverse diseases have so many signs and symptoms in common. Whether a man suffers from a severe loss of blood, an infectious disease or advanced cancer, he loses his appetite, his muscular strength and his ambition to accomplish anything; usually the patient also loses

weight, and even his facial expression betrays that he is ill. What is the scientific basis of what I thought of at the time as the "syndrome of just being sick"? Could the mechanism of this syndrome be analyzed by modern scientific techniques? Could it be reduced to its elements and expressed in the precise terms of biochemistry, biophysics and morphology?

The concept that every specific disease must have its own particular cause gained acceptance mainly during the nineteenth century. Following the emergence of modern bacteriology, it became evident that the characteristic syndrome of any one infectious malady, such as tuberculosis or diphtheria, could be elicited only by its own specific germ. Research in the field of nutrition and endocrinology similarly showed that one kind of derangement can always be traced to the lack or the excess of a particular vitamin or hormone.

Very few diseases are moncausal in the sense that their development is the inevitable consequence of one particular cause (as is, for example, a skin burn, paralysis after spinal cord transection or sterility following ovariectomy). Many maladies are predominantly pluricausal in that the "soil factor" (individual variations of disease proneness) plays an important role: influenza does not befall all persons exposed to an influenza virus, but only the susceptible ones. The typical pluricausal diseases are not caused by any particular pathogen but are the consequence of "pathogenic constellations." To this group belong peptic ulcers, accidental thymus involution, many forms of collagen disease, nephrosclerosis, thrombohemorrhagic lesions, atopic dermatitis, various neuroses and many other diseases. In fact, the possibility of a pluricausal pathogenesis must be considered in the case of all "idiopathic" maladies.

The history of this field suggests that the key to real progress in stress research was the discovery of three objective indices of stress: adrenal enlargement, thymicolumphatic atrophy and acute gastrointestinal ulcers. Yet even these signs were known to some physicians long before we began to realize that there is such a thing as a nonspecific stress syndrome. In England, as early as 1823 Swan, and in 1842, Curling, described acute gastrointestinal ulcers in patients who suffered extensive skin burns. In 1867, the German surgeon Billroth reported similar findings after major surgical interventions complicated by infections. But there was no reason to connect these lesions with other changes that today would be regarded as part of the stress syndrome—for example, with those described at the Pasteur Institute in Paris by Roux and Yersin, who noted that the adrenals of guinea pigs infected with diphtheria are often enlarged, bloodshot and hemorrhagic. In fact, these people did not even know about each other's work.

The so-called accidental thymus atrophy and the loss of body weight of individuals affected by disease have been described so often that it would be difficult to trace their history; but who would have thought of them in relation to Cannon's "emergency adrenalin secretion" in response to fear or rage? One important link was missing—that connecting all these phenomena as merely individual manifestations of a single coordinated syndrome.

Beginnings of a Scientific Analysis

It was not until 1936 that the problem presented itself again, now under conditions more suited to scientific analysis. At that time I was working in the Biochemistry Department of McGill University, trying to find a new hormone in extracts of cattle

ovaries. I injected the preparations into rats to see if their organs would show unpredictable changes that could not be attributed to any known hormone. Much to my satisfaction, even the first and most impure extracts caused a characteristic triad: (1) The adrenal cortex became enlarged and discharged its lipid secretory granules. (2) The thymus, spleen, lymph nodes and all other lymphatic structures showed severe involution.

(3) Deep, bleeding ulcers appeared in the stomach and duodenum.

The close interdependence of the three types of change implied a definite syndrome. The alterations varied from slight to pronounced, depending only upon the amount of extract injected.

At first I ascribed all these changes to a new sex hormone in the extracts. But soon I found that all toxic substances—extracts of kidney, spleen, or even a toxicant not derived from living tissue—produced the same syndrome. Gradually, my classroom concept of the “syndrome of just being sick” came back to me. I realized that the reaction I had produced with my impure extracts and toxic drugs was an experimental replica of this syndrome. Adrenal enlargement, thymicolymphatic involution, and gastrointestinal ulcers were the omnipresent signs of damage to the body when under attack. The three changes thus became the objective indices of stress and the basis for the development of the entire stress concept.

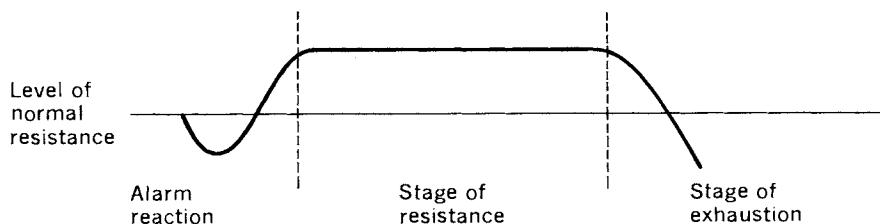
The reaction was first described in *Nature* (July 4, 1936) as “A syndrome produced by diverse noxious agents”; it subsequently became known as the *General Adaptation Syndrome* (*G.A.S.*) or biologic stress syndrome. In the same paper I suggested the name *alarm reaction* for the initial response, arguing that it probably represents the somatic expression of a generalized “call to arms” of the body’s defensive forces.

The General Adaptation Syndrome (G.A.S.)

The *alarm reaction*, however, was evidently not the entire response. Upon continued exposure of an organism to any noxious agent capable of eliciting this reaction, a stage of adaptation or resistance ensues. In other words, no organism can be maintained continuously in a state of alarm. If the agent is so damaging that continued exposure becomes incompatible with life, the animal dies during the alarm reaction within the first hours or days. If it can survive, this initial reaction is necessarily followed by the *stage of resistance*. The manifestations of this second phase are quite different from—indeed, often the exact opposite of—those characterizing the alarm reaction. For example, during the alarm reaction, the cells of the adrenal cortex discharge their secretory granules into the bloodstream and thus become depleted of corticoid-containing lipid storage material; but in the stage of resistance the cortex becomes particularly rich in secretory granules. Whereas in the alarm reaction there is hemoconcentration, hypochloremia and general tissue catabolism, during the stage of resistance there is hemodilution, hyperchloremia and anabolism, with a return towards normal body weight (Figure 1).

Curiously, after still more exposure to the noxious agent, the acquired adaptation is lost again. The animal enters a third phase, the *stage of exhaustion*, which follows inexorably if the stressor is severe enough and is applied for a sufficient length of time.

Because of its great practical importance, it should be pointed out that the triphasic



The body shows the changes characteristic of the first exposure to a stressor. At the same time, its resistance is diminished and, if the stressor is sufficiently strong (severe burns, extremes of temperature), death may result.

It ensues if continued exposure to the stressor is compatible with adaptation. The bodily signs characteristic of the alarm reaction have virtually disappeared and resistance rises above normal. Following long continued ex-

posure to the same stressor, to which the body has become adjusted, eventually adaptation energy is exhausted. The signs of the alarm reaction reappear, but now they are irreversible, and the individual dies.

Figure 1. The three stages of the G.A.S. (Reproduced from *Stress Without Distress*, Fig. 3, p. 39, 1974, by permission of the J B Lippincott Company).

nature of the G.A.S. gave us the first indication that the body's adaptability, or *adaptation energy*, is finite, since under constant stress, exhaustion eventually ensues. We still do not know precisely what is lost, except that it is not merely caloric energy, since food intake is normal during the stage of resistance. One would think that once adaptation has occurred and ample caloric energy is available, resistance should go on indefinitely. Not so. Just as any inanimate machine gradually wears out, so does the human machine sooner or later become the victim of constant wear and tear. These three stages are suggestive of childhood (with its characteristic low resistance and excessive responses to any kind of stimulus), adulthood (during which the body has adapted to most commonly encountered agents and resistance is increased), and senility (characterized by loss of adaptability and eventual exhaustion). Hence we suspected some relationship between stress and *aging*.

As is shown by the literature cited in this book, since 1936 numerous biochemical and structural changes of previously unknown origin have been traced to nonspecific stress. Among these, clinicians have given special attention to changes in the chemical constituents of the body and to nervous reactions. Much progress has also been made in the analysis of the hormonal mediation of stress reactions. It is now generally recognized that the emergency discharge of epinephrine (EP) during the "fight or flight" response of Cannon represents only one aspect of the acute phase of the alarm reaction to stressors. The hypothalamus-pituitary-adrenocortical axis is at least equally important for homeostasis, and it probably participates in the regulation of many disease phenomena as well.

History

(See also our earlier stress monographs, p. xiii)

Corvisart, J. N.: *An Essay on the Organic Diseases and Lesions of the Heart and Great*

Vessels. Boston: Bradford and Read, 1812.
E3,955/1812

All heart diseases stem "from the action of the organ and from the passions of man." The heart can be injured by crying in in-

fancy, wrestling, fencing, playing wind instruments, laughing, weeping, reading, declamation, anger, madness, fear, jealousy, terror, love, despair, joy, avarice, cupidity, ambition, revenge and "every kind of effort." However, "to conceive man without passions, is to conceive a being without his attributes."

Swan, J.: "Burns." *Mth. Gaz. Health* 8: 612-613 (1823). 6,901/1823

Swan, J.: "Practical observations." *Edinb. Med. J.* 19: 344-347 (1823). 11,389/1823

Probably the first descriptions of what is now known as a "stress ulcer," in a five-year-old child who died from severe burns. "At different times he vomited a blackish matter, and the day before he died, appeared so weak and cold, that a little wine and sago were given him. On opening the abdomen, every part appeared sound, except the stomach, in the villous coat of which were several black spots and stripes like sloughs, extending deep, and quite black... There can be no doubt that the diseased appearances of the head of the stomach were produced by the irritation of the skin."

Cooper, S.: "Pathology of burns and scalds." *Lond. Med. Gaz.* 23: 837-838 (1839). 72,145/1839

In an eight-year-old girl who died about five weeks after severe scalds of the chest, an ulcer "about the size of a shilling" was noted in the duodenum just beyond the pylorus. Duodenal ulcers were also found in other children after scalds and burns.

Long, J.: "On the post-mortem appearances found after burns." *Lond. Med. Gaz.* 25: 743-750 (1840). B4,643/1840

One of the first descriptions of perforating duodenal ulcers in eleven patients who died from extensive burns. "I have been induced to give the two cases of perforation of the duodenum in detail, as I believe they are unique; indeed I am not aware of any case being recorded, of perforation of the gastrointestinal tube occurring after a burn, except the one I have quoted from Liston, which approximates to my two cases by the perforation being near the pylorus, and by the change which had taken place in the duodenum."

Curling, T. B.: "On acute ulceration of the duodenum in cases of burns." *Tr. Med.-Chir. Soc. London* 25: 260 (1842).

B37,649/1842

One of the first descriptions of duodenal

ulcers in burned patients. Although the phenomenon had been discussed by several earlier investigators, these lesions are usually referred to as "Curling's ulcers."

Bernard, C.: *Introduction à l'étude de la médecine expérimentale* (Introduction to the study of experimental medicine), p. 302. Paris: Flammarion, 1945 (Original edition, 1865). B18,006/45

Recent annotated edition of Bernard's classic book combining the observations and interpretations published in various articles and books during the second half of the nineteenth century and culminating in the concept of the indispensability of the fixity of the *milieu intérieur*.

Billroth, T.: "Aus klinischen Vorträgen. I. Ueber Duodenalgeschwüre bei Septicämie" (From clinical lectures. I About duodenal ulcers in septicemia). *Wien. med. Wochenschr.* 17: 705-709 (1867). 23,917/1867

Description of patients with duodenal ulcers following septicemia as a consequence of operations on the thyroid and other causes. The so-called Curling's ulcer after extensive skin burns is also ascribed to the associated blood poisoning, that is, to sepsis.

Roux, E., Versin, A.: "Contribution à l'étude de la diphtérie" (Contribution to the study of diphtheria). *Ann. Inst. Pasteur* 3: 273-288 (1889). 7,004/1889

In guinea pigs treated with sublethal or lethal doses of diphtheria toxin, there are multiple hemorrhages in various organs, but the particularly constant feature is hyperemia of the adrenals.

Oppenheim, R.: "La fonction antitoxique des capsules surrénales. Etude expérimentale, anatomique et clinique de la glande surrénale dans les infections et les intoxications aiguës" (The antitoxic function of the adrenal glands. Experimental, anatomic and clinical study of the adrenal gland in acute infections and intoxications). Thesis, University of Paris, 1902. 6,966/02

Crude adrenal extracts, given intravenously, were found to be extremely toxic and imitated the actions of sympathetic stimulation. When such extracts were mixed with microbial poisons they tended to diminish the toxicity of the latter and to increase resistance. In severe intoxications, adrenal necroses and hemorrhages were virtually constant and could cause almost complete destruction of the glandular parenchyma. Such damage

could also be produced by intoxication with arsenic, phosphorus and mercury.

Cannon, W. B., Paz, D. de la: "Emotional stimulation of adrenal secretion." *Am. J. Physiol.* **28**: 64-70 (1911). 34,664/11

In cats frightened by the proximity of a barking dog, there was indirect physiologic evidence of EP secretion.

Cannon, W. B., Hoskins, R. G.: "The effects of asphyxia, hyperpnoea, and sensory stimulation on adrenal secretion." *Am. J. Physiol.* **29**: 274-279 (1911). 57,883/11

In cats, asphyxia or electric stimulation of the sciatic nerve, even when they were under anesthesia, caused increased EP secretion.

Cannon, W. B.: "The stimulation of adrenal secretion by emotional excitement." *Proc. Am. Phil. Soc.* **1**: 226-227 (1911).

35,529/11

Cannon, W. B.: "The emergency function of the adrenal medulla in pain and the major emotions." *Am. J. Physiol.* **33**: 356-372 (1914). 57,873/14

Reviews on the earliest animal experiments showing that fear, rage, asphyxia and pain cause a discharge of EP from the adrenal medulla and that this response is mediated through the splanchnic nerves. Direct stimulation of the latter exerts the same effect. The resulting glycogenolysis and increase in blood sugar furnish energy. At the same time blood circulation is improved. Stimulation of the splanchnics also hastens blood coagulation and thereby protects against bleeding in the event of injury. All these changes are "directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve."

Cannon, W. B., Shohl, A. T., Wright, W. S.: "Emotional glycosuria." *Am. J. Physiol.* **29**: 280-287 (1912). B26,719/12

Personal observations on emotional glycosuria in cats separately caged next to a barking dog, and review of earlier literature on "Fesselungsdiabetes" elicited by restraint in cats, and on the appearance of diabetes in patients following severe emotional upset. The emotional glycosuria in cats following restraint is abolished by adrenalectomy, presumably as a consequence of EP-induced hyperglycemia. "A mobilization of sugar in the blood under these circumstances might be of signal service to the laboring muscles."

Kolosko: "Ueber Befunde an den Nebennieren bei Verbrennungstod" (Adrenal changes after death in burned patients). *Viertel Jschr. Gerichtl. Med.* **47** Supp.: 217 (1914). 3,525/14

Folin, O., Denis, W., Smillie, W. G.: "Some observations on 'emotional glycosuria' in man." *J. Biol. Chem.* **17**: 519-520 (1914).

58,703/14

Among students undergoing academic examinations, 18 percent exhibited at least traces of sugar in the urine. Hence, "mental and emotional strain may produce temporary glycosuria in man."

Crile, G. W.: *The Origin and Nature of the Emotions. Miscellaneous Papers*, p. 240. Philadelphia and London: W B Saunders, 1915. A32,669/15

First systematic monograph attempting to demonstrate the biochemical and morphologic basis of emotions in man and other animal species. Histologic examination of virtually all tissues of the body showed characteristic changes in three organs only: the brain, the adrenal medulla and the liver. These were essentially similar after emotional arousal and surgical shock. "The excessive use of alcohol, anesthetics, excessive work, intense emotion, all produce lesions of the kidney and of the liver. The explanation is found in the fact that all these stimuli increase the acidity of the blood, and that, if long continued, the neutralizing mechanism must be broken down and so the end-products of metabolism are insufficiently prepared for elimination. In view of these considerations we may well conclude that the maintenance of the normal potential alkalinity of the blood is to be estimated as the keystone of the foundation of life itself." Sleep rapidly restores these functions to normal. [The importance of this monograph is not so much due to new factual data reported, but to the great influence it exerted upon medical thinking in its time. It was very often quoted and greatly helped to call attention to essentially nonspecific reactions, although many of the allegedly nonspecific histologic and biochemical changes reported would no longer be acceptable today (H.S.).]

Weiskotten, H. G.: "Fatal superficial burns and the suprarenals. Note on the occurrence of suprarenal lesions in uncomplicated fatal cases of extensive superficial burns." *J.A.M.A.* **69**: 776 (1917). 92,580/17

In patients with widespread fatal superficial burns, the adrenals are usually swollen and deep red, exhibiting hemorrhages, necroses and polymorphonuclear cell infiltrations. Similar changes had been described by Kolosko in several cases of extensive superficial burns and were interpreted by him as hemorrhagic infarction.

Hammar, J. A.: "Beiträge zur Konstitutions-anatomie, VI" (Studies of the constitutional anatomy, VI). *Z. Angew. Anat. Konstat. Lehre* 4: 1-107 (1918). 50,856/18

Meticulous histologic studies on the human thymus with special sections on the so-called accidental involution elicited by various dietary deficiencies, bacterial infections, snake venoms and other damaging agents. This is probably the first systematic monograph on the subject.

Hollingshead, L., Barton, J. W.: "The adrenal cortex and emotion." *Psychol. Rev.* 38: 538-541 (1931). 91,447/31

After analyzing seven earlier publications concerning metabolic changes in cases of adrenal insufficiency, the authors formulate "the hypothesis that the adrenal cortical hormone is responsible for the variations in the non-protein nitrogen of the blood, and that the cortical hormone acts as an excitatory agent in emotional states." [This is probably the first publication on the relationship between the adrenal cortex and emotion, although it is based on data and arguments incompatible with contemporary knowledge (H.S.).]

Cannon, W. B.: *The Wisdom of the Body*, p. 332. New York: W W Norton, 1932. B14,905/32

Monograph in semipopularized style, but with many detailed descriptions of experiments which led to the concept of homeostasis.

Selye, H.: "A syndrome produced by diverse noxious agents." *Nature* 138: 32 (1936). 36,031/36

Brief Letter to the Editor describing the most characteristic signs of what is now known as the stress syndrome, particularly the thymicolymphatic involution, gastroduodenal ulcers, lipid discharge from the adrenal cortex and loss of chromaffinity in the medulla. Delimitation of the three stages. "We consider the first stage to be the expression of a general alarm of the organism when suddenly confronted with a critical situation,

and therefore term it the 'general alarm reaction.' Since the syndrome as a whole seems to represent a generalized effort of the organism to adapt itself to new conditions, it might be termed the 'general adaptation syndrome.'" The reaction is regarded as a non-specific adaptive response to various kinds of agents, and in view of its stereotypical appearance is ascribed to the liberation of some common initiating substance, possibly histamine.

Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* 17: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction" characterized by adrenocortical enlargement with acute loss of lipids, thymicolymphatic atrophy and decrease in body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for 48 hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and to a lesser extent hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug" but will greatly shorten survival. Perhaps the adrenal enlargement as well as the loss of body weight and the other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Selye, H., Collip, J. B.: "Fundamental factors in the interpretation of stimuli influencing endocrine glands." *Endocrinology* 20: 667-672 (1936). 66,617/36

Stressors such as formaldehyde, which caused marked adrenal hypertrophy in normal but not in hypophysectomized rats, remained without effect even if the adrenal cortex was prevented from undergoing atrophy by the administration of a pituitary extract. "The effect of such a drug on the adrenal appears to be an indirect one, due to pituitary stimulation."

Selye, H.: "Studies on adaptation." *Endocrinology* 21: 169-188 (1937).

38,798/37

First detailed description of the three stages of the G.A.S. and the concept of "adaptation energy" with an extensive and illustrative characterization of the morphologic lesions produced by stress, especially in the

hypophysis, adrenals, thymicolumphatic apparatus, pancreas, gastrointestinal tract, and by inflammation (anaphylactoid edema).

Rogoff, J. M.: "A critique on the theory of emergency function of the adrenal glands: implications for psychology." *J. Gen. Psychol.* **32**: 249-268 (1945). B28,082/45

Summary of the literature, particularly the observations of the author and his coworker G. N. Stewart, in which Cannon's emergency theory is vehemently rejected. "The emergency theory concept of a direct relation of adrenal gland secretion to emotional excitation, or to painful stimulation, is untenable since it is based upon inadequate experimental investigations.... Endocrine implications for psychology that are based upon the premise of a direct and immediate endosecretory role in various bodily reactions are lacking in substantial experimental support."

Selye, H.: "The general adaptation syndrome and the diseases of adaptation." *J. Clin. Endocrinol.* **6**: 117-230 (1946).

B1,204/46

First detailed review on the G.A.S. and the diseases of adaptation, presented as a special number of the *Journal of Clinical Endocrinology* (over 700 refs.).

Green, J. D., Harris, G. W.: "The neurovascular link between the neurohypophysis and adenohypophysis." *J. Endocrinol.* **5**: 136-146 (1947). B1,426/47

In rabbits, monkeys and man, nervous connections between the neuro- and adenohypophysis are scanty. Vascular connections are prominent in rats, guinea pigs, rabbits, dogs and man, particularly between the capillary loops of the ME, infundibular stem and the hypophyseal portal vessels. These vessels are well supplied with nerve fibers. "It is suggested that the central nervous system regulates the activity of the adenohypophysis by means of a humoral relay through the hypophysial portal vessels."

Weiss, E., English, O. S.: *Psychosomatic Medicine*, p. 803. Philadelphia and London: W B Saunders, 1949. B48,177/49

Extensive although now somewhat outdated textbook of psychosomatic medicine with a rich collection of historically interesting references.

Selye, H.: *Stress*, p. 822. Montreal: Acta Inc., 1950. B40,000/50

First extensive monograph devoted exclusively to stress, discussing virtually the

entire relevant literature (including precursors of the stress concept).

Groot, J. de, Harris, G. W.: "Hypothalamic control of the anterior pituitary gland and blood lymphocytes." *J. Physiol. (Lond.)* **111**: 335-346 (1950). B54,598/50

"Electrical stimulation of the posterior region of the tuber cinereum or of the mammillary body, of unanaesthetized, unrestrained rabbits resulted in a lymphopenia, which was similar in time relations and magnitude to that following an emotional stress stimulus." This response was not abolished by cervical sympathectomy and could not be duplicated by stimulation of other hypothalamic areas. A similar psychogenic stress lymphopenia was abolished by lesions in the zona tuberalis, and by transverse lesions in the posterior tuber cinereum or mammillary body, but not by lesions in the pars distalis, pars intermedia, or by interruption of the infundibular stem. It is concluded that stress-induced ACTH secretion "is under neural control via the hypothalamus and the hypophysial portal vessels of the pituitary stalk." [This is the first clear-cut demonstration of the hypothalamic regulation of stress-induced ACTH secretion (H. S.).]

Selye, H.: *The Story of the Adaptation Syndrome*, p. 225. Montreal: Acta Inc., 1952. B71,000/52

Monograph outlining the historical development of the stress concept and the G.A.S.

Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear and Rage*, p. 404. Boston: Charles T Branford, 1953. A19,828/53

Excellent summary of the author's classic observations on the somatic manifestations of acute emotions, particularly with regard to the effect of fear, rage, hunger and thirst upon the sympathetic nervous system and EP secretion.

Selye, H.: *Einführung in die Lehre vom Adaptationssyndrom* (Introduction to the theory of the general adaptation syndrome), p. 164. Stuttgart: George Thieme Verlag, 1953. B87,796/53

Translation of *The Story of the Adaptation Syndrome*.

Selye, H.: *The Story of the Adaptation Syndrome*, p. 204. Tokyo: Ishiyaku, 1953 (Japanese). B87,797/53

Maze, J. R.: "On some corruptions of the doctrine of homeostasis." *Psychol. Rev.* **60**: 405-412 (1953). J13,185/53

Selye, H.: *L'histoire du syndrome général d'adaptation* (The story of the general adaptation syndrome), p. 274. Paris: Editions Gallimard, 1954.

B91,010/54

Margetts, E. L.: "Historical notes on psychosomatic medicine." In: Wittkower, E. D. and Cleghorn, R. A., *Recent Developments in Psychosomatic Medicine*, pp. 41-68. London: I Pitman & Sons, 1954.

E89,578/54

Quotes motto of C. H. Parry (1755-1822): "It is much more important to know what sort of a patient has a disease, than what sort of a disease a patient has." The history of ideas about correlations between man, body and cell is traced back to antiquity and followed through up to the publication of Selye's first detailed monograph on stress (1950).

Friedrich, R.: *Medizin von Morgen. Neue Theorien und Forschungsergebnisse* (Tomorrow's medicine. New theories and fields of investigation), p. 357. München: Süddeutscher Verlag, 1955.

C1,721/55

A major portion of the volume is devoted to a description of stress and the G.A.S. in generally understandable terms. Special attention is given to the historic development of the stress concept.

Pronko, N. H., Leith, W. R.: "Behavior under stress: a study of its disintegration." *Psychol. Rep.* **2**: 205-222 (1956).

B28,732/56

To show the rapid development of studies on stress in connection with psychology, the authors state "one searches in vain for 'stress' in issues of *Psychological Abstracts* of 20 years or so ago. Since then, the expansion of stress studies is impressively revealed in the following tabulation of stress items indexed in the *Abstracts* by 5-year intervals:

1936-1940	0
1941-1945	8
1946-1950	32
1951-1955	207."
[1969-1973	2,252]*

* [A survey by our own library staff (H.S.).] (Table reproduced from *Psychol. Rep.* **2**: 1956, with permission of the authors.)

Selye, H.: *La sindrome di adattamento* (The adaptation syndrome), p. 221. Pavia: Casa Editrice Renzo Cortina, 1956.

C15,870/56

Translation of *The Story of the Adaptation Syndrome*.

Selye, H.: *The Stress of Life*, p. 324. New York, Toronto and London: McGraw-Hill, 1956; 2nd ed., 1975.

C19,000/56

A monograph on the stress concept with an entire section devoted to its historical development and first applications.

Ramey, E. R., Goldstein, M. S.: "The adrenal cortex and the sympathetic nervous system." *Physiol. Rev.* **37**: 155-195 (1957).

C35,830/57

Review of the literature on the relationship between Cannon's emergency theory and the G.A.S. (455 refs.).

Hetzl, B. S.: "Cannon revisited; emotions and bodily changes: their relevance to disease." *Med. J. Aust.* **1**: 193-198 (1960).

J23,260/60

Seyffarth, H.: "The conception of 'stress' as submitted by Hans Selye. An appraisement." *Acta Allergol. (Kbh.)* **15**: 532-543 (1960).

D7,006/60

Selye, H.: *The Story of the Adaptation Syndrome*, p. 252. Moscow: MEDGIZ, 1960 (Russian).

C97,130/60

Corcoran, A. C.: *A Mirror Up to Medicine*, p. 506. Philadelphia, New York and Montreal: J B Lippincott, 1961.

D16,010/61

Essentially a philosophic analysis of the history of medicine, primarily based on excerpts or direct quotations from the most important contributions of a variety of philosophers and physicians including Hippocrates, Aristophanes, Aristotle, Maimonides, Paracelsus, Sir Francis Bacon, R. T. H. Laennec, E. Darwin, O. W. Holmes, Sir William Osler, H. Cushing, Sir C. Sherrington, O. Loewi, Hans Zinsser, Albert Schweitzer, W. B. Cannon, Hans Selye, H. Sigerist and several others. The book makes interesting and instructive reading, and offers a judicious selection of aphorisms and pithy sentences about medicine in general. Four pages are devoted to an analysis of Selye's *The Stress of Life*.

Gasparetto, A.: "Evoluzione storica, validità teorica ed attualità pratica del concetto di stress chirurgico" (Historical evolution, theoretical validity, and practical application of the surgical stress concept). *Acta Anaesthesiol (Padova)* **12**: 1-48 (1961).

D23,496/61

Scharrer, E., Scharrer, B.: *Neuroendocrinology*, p. 289. New York and London: Columbia University Press, 1963.

E4,032/63

Highly technical treatise on the relationships between endocrine glands and the ner-

vous system. A chapter is devoted to the stress concept based on the works of Cannon and Selye. An extensive bibliography (74 pp.) provides access to the relevant technical literature.

Selye, H.: *From Dream to Discovery*, p. 419. New York, Toronto and London: McGraw-Hill, 1964; 2nd ed., New York: Arno Press, 1975. E24,140/64

Monograph on the psychology of discovery with a special section on the history of the G.A.S. concept.

Selye, H.: *Vom Traum zur Entdeckung. Vademeum eines Wissenschaftlers* (From dream to discovery. Handbook of a scientist), p. 560. Wien and Düsseldorf: Econ Verlag, 1965. G32,015/65

Barry, H., Buckley, J. P.: "Drug effects on animal performance and the stress syndrome." *J. Pharm. Sci.* **55**: 1159-1183 (1966) (326 refs.). F72,129/66

Selye, H.: *Od Marzenia do Odkrycia Naukowego* (From dream to discovery), p. 456. Warszawa: Państwowy Zakład Wydawnictwa Lekarskich, 1967 (Polish). E6,506/67

Selye, H.: *Od Snov k Objavom* (From dream to discovery), p. 503. Bratislava: Obzor, 1967 (Slovak). G46,704/67

Selye, H.: *In Vivo. The Case for Supramolecular Biology*, p. 168. New York: Liverright, 1967. G46,717/67

The development of the stress concept is surveyed within the framework of lectures on the importance of the holistic approach to medicine.

Selye, H.: *Álomtól a Felfedezésig. (Egy Tudós Vallomásai)* (From dream to discovery. [On being a scientist]), p. 523. Budapest: Akadémiai Kiado, 1967 (Hungarian). G46,718/67

Selye, H.: *Anaphylactoid Edema*, p. 318. St. Louis, Mo.: Warren H Green, 1968.

G46,715/68

Extensive monograph on anaphylactoid edema with emphasis on the role of stress, corticoids and catecholamines in its development.

Selye, H.: *De la Vis la Descoperire. Despre Omul de Știință* (From dream to discovery. On being a scientist), p. 454. București: Editura Medicala, 1968 (Roumanian).

G46,786/68

Selye, H.: *In Vivo, za Nemolekulární Bio-*

lógia (In vivo. The case for supramolecular biology), p. 159. Bratislava: Slovenskej akadémie vied.. 1968 (Slovak).

G46,788/68

Selye, H.: "Evolution du concept du stress. Le stress et la maladie cardiovasculaire" (The evolution of the stress concept. Stress and cardiovascular disease). *Med. et Hyg. (Genève)* **27**: 669-675 (1969). G60,010/69

Review on the evolution of the stress concept with special reference to its role in the pathogenesis of cardiovascular diseases (64 refs.).

Selye, H.: "Die Entwicklung des Stresskonzeptes. Stress und Herzkrankheiten" (The evolution of the stress concept. Stress and cardiovascular disease). *Med. Welt* **20**: 915-919; 927-933 (1969) (64 refs.).

G60,015/69

Selye, H.: "La evolución del concepto de stress. Stress y enfermedad cardiovascular" (The evolution of the stress concept. Stress and cardiovascular disease). *Folia Clin. Int.* **19**: 471-489 (1969) (64 refs.). G60,033/69

Selye, H.: "A stress elmélet kialakulása. A stress- és a szívér-betegségek" (The evolution of the stress concept. Stress and cardiovascular disease). *Orv. Hetil.* **110**: 2257-2265 (1969) (64 refs., Hungarian). G60,034/69

Selye, H.: *From Dream to Discovery*, p. 511. Tokyo: Rateis, 1969 (Japanese).

J4,238/69

Guilbert, J., Bounous, G., Gurd, F. N.: "Role of intestinal chyme in the pathogenesis of gastric ulceration following experimental hemorrhagic shock." *J. Trauma* **9**: 723-743 (1969).

J10,786/69

Allegedly, gastric ulcers and intestinal hemorrhagic necrosis following extensive burns were observed by Dupuytren (1823), Swan (1823), Cooper (1839) and Long (1840) before Curling (1842) described the lesions that now bear his name. The literature on these and many subsequent observations on peptic ulcers following surgical interventions is reviewed up to recent times when they were recognized as part of the G.A.S. (98 refs.).

Selye, H.: *In Vivo. A Szupramolekuláris Biológia Védelmében* (In vivo. The case for supramolecular biology), p. 122. Budapest: Akadémiai Kiado, 1970 (Hungarian).

G60,022/70

Venzmer, G.: *Fünftausend Jahre Medizin* (Five thousand years of medicine), p. 346. Bremen: Carl Schünemann Verlag, 1968. (English edition: *Five Thousand Years of Medicine*, p. 369. New York: Taplinger, 1972). E10,279/72

A résumé of highlights in the history of medicine since its recorded origins, presenting the stress theory and the diseases of adaptation in the context of their conceptual development and practical applications.

Fox, F. W.: "Nature, nurture, and stress." *Lancet* July 22, 1972, p. 183. J19,659/72

Selye, H.: "Homeostasis and heterostasis." *Perspect. Biol. Med.* **16**: 441-445 (1973). G88,052/73

First description of the essential difference between homeostatic and heterostatic adaptive reactions.

Selye, H.: "The evolution of the stress concept: 1936-1973." *Am. Sci.* **61**: 692-699 (1973). G88,094/73

Review of the history of the stress concept from its first formulation until 1973.

Selye, H.: *Du Rêve à la Découverte. L'Esprit Scientifique* (From dream to discovery. The scientific spirit), p. 445. Montreal: Les Editions La Presse, 1973. J4,209/73

Langley, L. L. (ed.): *Homeostasis. Origins of the Concept*, p. 362. Stroudsburg, Pa.: Dowden, Hutchinson and Ross, 1973.

E10,626/73

Anthology of classic papers on the historical development of the homeostasis concept.

Mason, J. W.: "A historical view of the 'stress' field. Part I." *J. Hum. Stress* **1** No. 1: 6-12 (1975). H97,891/75

Mason, J. W.: "A historical view of the 'stress' field. Part II." *J. Hum. Stress* **1** No. 2: 22-36 (1975). H97,892/75

Review of the evolution of the stress concept from Cannon's work on the emergency discharge of EP during fight-or-flight reactions up to present day views on the importance of the hypothalamus-pituitary-adrenocortical system, the triphasic nature of the G.A.S., and the nonspecific stereotyped response pattern of the body to any demand. Eustress is not discussed, but the author emphasizes that "of all the known responses of higher organisms, emotional arousal is certainly one of the most ubiquitous or relatively 'nonspecific' reactions common to a

great diversity of situations." On the other hand, he clearly recognizes that "this is not to conclude that the pituitary-adrenal cortical system responds only to psychological stimuli." In accordance with earlier work on the effect of internal and external conditioning factors upon the resulting reaction form, it is agreed that the response could not be absolutely nonspecific, even if it occurred after any demand (48 refs.).

Selye, H.: "Confusion and controversy in the stress field." *J. Hum. Stress* **1** No. 2:37-44 (1975). J4,295/75

Answer to the preceding articles. "The continued use of the word stress as a nonspecific response to any demand is deemed most desirable. The once vague term can now be applied in a well-defined sense and is accepted in all foreign languages as well, including those in which no such word existed previously in any sense. Subdivision of the stress concept has become necessary as more recent work has led to such notions as 'eustress,' 'distress,' 'systemic stress' and 'local stress.' Confusion between stress as both an agent and a result can be avoided only by the distinction between 'stress' and 'stressor.' It is explained that the stress syndrome is—by definition—nonspecific in its causation. However, depending upon conditioning factors, which can selectively influence the reactivity of certain organs, the same stressor can elicit different manifestations in different individuals."

Brooks, Ch.McC., Koizumi, K., Pinkston, J. O. (eds.): *The Life and Contributions of Walter Bradford Cannon 1871-1945*, p. 264. Papers at a Centennial Symposium. Brooklyn, N.Y.: State University of New York Downstate Medical Center, 1975.

E10,898/75

Symposium in which all surviving students and associates of W. B. Cannon have summarized his major contributions, especially to the understanding of homeostasis in relation to catecholamine secretion and the manner in which their own work was stimulated by this great master of physiology. Contains articles by H. W. Davenport, J. Farman, Ch. McC. Brooks, Z. M. Bacq, H. Selye, K. Lissák, Ph. Bard and R. Gerard.

Brooks, Ch.McC.: "Homeostasis and adaptation." In: Brooks, Ch.McC., Koizumi, K. et al., *The Life and Contributions of Walter Bradford Cannon 1871-1945*, pp. 84-86.

14 HISTORY AND GENERAL OUTLINE

Brooklyn, N.Y.: State University of New York Downstate Medical Center, 1975.

E10,900/75

Comparison of Cannon's and Selye's approaches to the problems of homeostasis and adaptation.

Selye, H.: "Homeostasis and the reactions to stress: a discussion of Walter B. Cannon's contributions." In: Brooks, Ch. McC., Koizumi, K. et al., *The Life and Contributions of Walter Bradford Cannon 1871-1945*, pp. 89-107. Brooklyn, N.Y.: State University of New York Downstate Medical Center, 1975.

G88,048/75

The development of the stress concept in relation to homeostasis.

Selye, H.: "Homeostasis and heterostasis." In: Brooks, Ch. McC., Koizumi, K. et al., *The Life and Contributions of Walter Bradford Cannon 1871-1945*, pp. 108-112. Brooklyn, N.Y.: State University of New York Downstate Medical Center, 1975.

J4,297/75

Comparison of the concepts of homeostasis and heterostasis with special emphasis on W. B. Cannon's stimulating effect upon the author's work on adaptation.

GENERAL OUTLINE

Definition and Terminology of Biologic Stress

A great deal of confusion has arisen in lay and even in scientific literature because the term *stress* means different things to different people. Stress is part of our daily human experience, but it is associated with a great variety of essentially dissimilar problems, such as surgical trauma, burns, emotional arousal, mental or physical effort, fatigue, pain, fear, the need for concentration, the humiliation of frustration, the loss of blood, intoxication with drugs or environmental pollutants, or even with the kind of unexpected success that requires an individual to reformulate his lifestyle. Stress is present in the businessman under constant pressure; in the athlete straining to win a race; in the air-traffic controller who bears continuous responsibility for hundreds of lives; in the husband helplessly watching his wife's slow, painful death from cancer; in a race horse, its jockey and the spectator who bets on them. Medical research has shown that, while all these subjects face quite different problems, they respond with a stereotyped pattern of biochemical, functional and structural changes essentially involved in coping with any type of increased demand upon vital activity, particularly adaptation to new situations.

All endogenous or exogenous agents that make such demands are called *stressors*. Distinguishing between their widely differing specific effects and the common biologic response that they elicit is the key to a proper understanding of biologic stress.

From the point of view of its stressor activity, it is even immaterial whether the agent or situation being faced is pleasant or unpleasant; all that counts is the intensity of the demand for readjustment or adaptation that it creates. The mother who is suddenly told that her only son died in battle suffers a terrible mental shock; if years later, it turns out that the news was false and the son unexpectedly walks into her room alive and well, she experiences extreme joy. The specific results of the two events, sorrow and joy, are completely different, in fact they are opposite to each other, yet their stressor effect—the nonspecific demand for readjustment to a new situation—is the same.

It is difficult to see at first how such essentially different things as cold, heat, drugs, hormones, sorrow and joy could provoke an identical biologic reaction. Nevertheless

this is the case; it can now be demonstrated by highly objective, quantitative biochemical and morphologic parameters that certain reactions are totally nonspecific and common to all types of agents, whatever their superimposed specific effects may be.

The conceptual distinction between the specific and the nonspecific consequences of any demand made on the body was the most important step in the scientific analysis of stress phenomena.

Contrary to previously widely held opinion, stress is not identical to emotional arousal or nervous tension. It occurs in experimental animals even after total surgical deafferentation of the hypothalamus, which eliminates all neurogenic input. It can occur during anesthesia in man as well as in lower animals. It can occur even in plants, which have no nervous system. On the basis of these considerations. I recommend the following definition:

Stress is the nonspecific response of the body to any demand.

With regard to nonspecificity, the concept of stress is not without precedent. All machines, whether animate or inanimate, require energy for any of their activities, be these constructive or destructive. In fact, we shall see that biologic stress is closely linked to, though not identical with, energy utilization. This explains its apparently paradoxical, yet inseparable combination with the specific effects of the particular agent that creates a need for adaptive work. Any demand made on the body must be for some particular, that is, specific activity and yet is inseparably associated with non-specific phenomena (that is, energy utilization), just as in the inanimate world specific demands made upon machines to increase or decrease room temperature, to produce light or sound, to accelerate or decrease motion are invariably dependent upon energy utilization.

Therefore, stress is not something to be avoided. Indeed, it cannot be avoided, since just staying alive creates some demand for life-maintaining energy. Even while man is asleep, his heart, respiratory apparatus, digestive tract, nervous system and other organs must continue to function. Complete freedom from stress can be expected only after death.

However, in everyday life we must distinguish between two types of stress effects, namely, *eustress* (from the Greek *eu* or good—as in euphony, euphoria, eulogy) and *distress* (from the Latin *dis* or bad—as in dissonance, disease, dissatisfaction). Depending upon conditions, stress is associated with desirable or undesirable effects.

In view of these considerations it is also quite obvious that there cannot be *different types of stress*, although the effects of stressors are almost invariably different. There is no “specific stress”; this expression is a contradiction in terms. Such terms as emotional stress, surgical stress, flying stress, failure stress, cold stress, sleep deprivation stress, gravitational stress, swimming stress, social stress, and so on are acceptable only if we clearly understand that they are mere abbreviations for the stress produced by this or that factor.

In order to avoid confusion with various misuses of the term “stress” for specific disturbances caused by overexertion of specific organs or biochemical systems, it has been suggested by Lennart Levi and accepted by others to speak of “stress (Selye)” when using the term in my sense. However, since in biology and medicine stress was defined as “the nonspecific response of the body to any demand,” the parenthetical explanatory remark would be necessary only for those who do not accept this generally used definition. Instead of this flattering, but somewhat undeserved eponymous designation for a concept in whose elaboration hundreds of investigators participated,

I would suggest that they might refer to "nonspecific stress." This, I believe, is what everybody means by "stress (Selye)," since nonspecific was the key word in my original definition of the phenomenon. Yet to me it seems redundant to add nonspecific since this is implied in my definition; whenever the word stress is used in this treatise it refers to nonspecific responses only. In fact, unless otherwise stated, it is used for systemic nonspecific reactions (systemic stress), others being clearly characterized as topical or local stress. Of course, in this sense topical does not necessarily mean any particular region of the body but instead refers to specific demands primarily affecting one system of an organism (such as emotional arousal, intellectual effort, muscular work or response to hemorrhage).

Definition of Biologic Stress in General

(See also our earlier stress monographs, p. xiii)

Selye, H.: "The alarm reaction." In: Piersol, G. M. and Bortz, E. L., *The Cyclo-pedia of Medicine, Surgery and Specialities*, Vol. 15, pp. 15-38. Philadelphia: F A Davis, 1940. A8,048/40

The alarm reaction is defined as "the sum of all biological phenomena elicited by sudden exposure to stimuli to which the organism is, quantitatively or qualitatively, not adapted."

Freeman, G. L.: "Suggestions for a standardized 'stress' test." *J. Gen. Psychol.* 32: 3-11 (1945). 35,101/45

The author is "careful to define stress in terms of bodily arousal in a social situation, where the individual is placed on the defensive and deliberately confused as to his progress toward a desired success."

Beier, E. G.: "The effect of induced anxiety on flexibility of intellectual functioning." *Psychol. Monogr.* 65: 1-26 (1951). D92,619/51

"For the purpose of this study 'stress' is defined as the perception of threat, with resulting anxiety."

Janis, I. L.: *Air War and Emotional Stress. Psychological Studies of Bombing and Civilian Defense*, p. 280. New York, Toronto and London: McGraw-Hill, 1951. E4,323/51

Monograph on the psychologic consequences of bombing in Hiroshima and Nagasaki, and of air war in general and civil defense. [No reference is made to the stress concept in medicine, and such terms as adrenal, adrenaline, corticoids, hypothalamus or adaptation syndrome are not even mentioned in the index. The word stress appears to be used as a synonym for mental

upset but it is nowhere defined, although it is in the title of the book (H.S.).]

Pronko, N. H., Leith, W. R.: "Behavior under stress: a study of its disintegration." *Psychol. Rep.* 2: 205-222 (1956).

B28,732/56

The term stress is "considered as synonymous with such setting factors as are related to the disintegration of the behavioral response configuration of the organism."

Selye, H.: *The Stress of Life*, p. 324. New York, Toronto and London: McGraw-Hill, 1956; 2nd ed., 1975. C19,000/56

Stress is defined as "the state manifested by the specific syndrome which consists of all the nonspecifically induced changes within a biologic system. Thus stress has its own characteristic form, but no particular specific cause." Other simpler but less precise definitions suggested are: "the sum of all non-specific changes caused by function or damage," or "the rate of wear and tear in the body."

Lazarus, R. S., Baker, R. W., Broverman, D. M., Mayer, J.: "Personality and psychological stress." *J. Pers.* 25: 559-577 (1957). B29,451/57

"By stressor conditions... we mean those experimental conditions which are designed by an experimenter to be stressful, but which are not necessarily responded to or perceived as such by the subject. We reserve the term stress to refer to a state of the organism rather than the circumstances to which the individual is exposed."

Selye, H.: "Perspectives in stress research." *Perspect. Biol. Med.* 2: 403-416 (1959). C60,261/59

"For working purposes we may say that stress is a state manifested by a specific syndrome which consists of all the non-

specifically induced changes in a biologic system."

Richter, D.: "Some current usages of the word 'stress' in different fields." In: Tanner, J. M., *Stress and Psychiatric Disorder*, pp. 31-33. Oxford: Blackwell, 1960.

J13,501/60

Engel, G. L.: "A unified concept of health and disease." *Perspect. Biol. Med.* **3**: 459-485 (1960). J12,716/60

Because "by definition we specify that psychological stress involves, first, the mental apparatus, we can also say that the first response to a psychological stress, whether it be primary or secondary, will be psychological and/or behavioral."

Wolff, H. G.: "Stressors as a cause of disease in man." In: Tanner, J. M., *Stress and Psychiatric Disorder*, pp. 17-31. Oxford: Blackwell, 1960. C90,493/60

Stress is defined as "that state within a living creature which results from the interaction of the organism with noxious stimuli or circumstances."

Haward, L. R. C.: "The subjective meaning of stress." *Br. J. Psychol.* **33**: 185-194 (1960). C99,584/60

Theoretical considerations concerning "the subjective meaning of stress" as defined by various authors.

Wolf, S.: "Stress and heart disease." *Mod. Concepts Cardiovasc. Dis.* **29**: 599-604 (1960). G62,498/60

"Stress, for the purpose of this discussion, is present when the adaptive mechanisms of the living organism, in this instance man, are taxed or strained. The results are by no means specific. In fact, the variability of response of the human being may be immense, varying from invention or artistic creation, on the one hand, to surrender or death on the other."

Winokur, G., Stern, J. A., Graham, D. T.: "Stress as an inhibitor of pathological processes." *Psychiatr. Res. Rep. APA* **12**: 73-80 (1960). J11,150/60

Definition of stress as "an occasionally beneficial and a sometimes deleterious force working on the organism."

Pickering, G.: "Language: the lost tool of learning in medicine and science." *Lancet* July 15, 1961, pp. 115-119. D10,655/61

A very formal and scholarly discourse on correct language in science which, curiously,

comes to the conclusion that "the modern use of the word stress we owe to Selye, who used it to express the first stage in the common reaction of the mammal to a variety of harmful environmental changes." [Did I? (H.S.)]

Dohrenwend, B. P.: "The social psychological nature of stress: a framework for causal inquiry." *J. Abnorm. Soc. Psychol.* **62**: 294-302 (1961). D15,127/61

"Stress is a state intervening between antecedent constraint and consequent efforts to reduce constraint." Admittedly, this definition refers only to "stressors that are primarily social in nature and do not involve direct and immediate physical harm to the individual."

Mechanic, D., Volkart, E. H.: "Stress, illness behavior, and the sick role." *Am. Sociol. Rev.* **26**: 51-58 (1961). J10,611/61

At least in the behavioral sciences the term stress "seems to signify a state of affairs characterized by anxiety, discomfort, emotional tension, and difficulty in adjustment.... In the present study, stress was operationally defined as the subject's report of the frequency with which he was bothered by 'loneliness' and 'nervousness.'"

Torrance, E. P.: "A theory of leadership and interpersonal behavior under stress." In: Petrullo, L. and Bass, B. M., *Leadership and Interpersonal Behavior*, pp. 100-117. New York: Holt, Rinehart and Winston, 1961.

J10,652/61

"The distinctive element in stress is to be found in the lack of structure or loss of anchor in reality experienced by the individual or group as a result of the condition labeled 'stressful.' In the group situation, this lack of structure or loss of anchor in reality makes it difficult or impossible for the group to cope with the requirements of the situation, and the problem of leadership and interpersonal behavior becomes one of evolving or supplying a structure or anchor and of supplying the expertise for coping with the demands of the situation."

Daure, M.: "Thérapeutique rhino-stressante (rhino-stress)" (Rhino-stress therapeutics). *Bull. Acad. Nat. Méd. (Paris)* **145**: 28-34 (1961). D1,159/61

Rhino-stress is defined as stress produced by stimulating the nasal membranes, a technique which allegedly has considerable therapeutic value.

Mechanic, D.: *Students Under Stress. A Study in the Social Psychology of Adaptation*, p. 231. Glencoe, Ill.: Free Press, 1962.

E10,421/62

"We will define stress as the discomforting responses of persons in particular situations."

Fessel, W. J.: "Mental stress, blood proteins, and the hypothalamus." *Arch. Gen. Psychiatry* 7: 427-435 (1962). D69,380/62

"The word stress is used according to Selye's definition: Stress is a non-specific deviation from the normal resting state; it is caused by function or damage and it stimulates repair."

Lazarus, R. S., Speisman, J. C., Mordkoff, A. M., Davison, L. A.: "A laboratory study of psychological stress produced by a motion picture film." *Psychol. Monogr.* 76: 1-35 (1962).

J11,289/62

"In spite of persistent confusion about the precise meaning of the term, stress is widely recognized as a central problem in human life. Scientists of many disciplines have conceptualized stress but each field appears to have something different in mind concerning its meaning. For the sociologist, it is social disequilibrium, that is, disturbances in the social structure within which people live. Engineers conceive of stress as some external force which produces strain in the physical materials exposed to it. Physiologists deal with physical stressors that include a wide range of stimulus conditions which are noxious to the tissue systems of the body.... In the history of psychological stress research, there has been no clear separation between physical stressors which attack biological tissue systems and psychological stressors which produce their effects purely because of their psychological significance."

Pearson, H. E. S., Joseph, J.: "Stress and occlusive coronary-artery disease." *Lancet* February 23, 1963, pp. 415-418.

D57,816/63

Confusion about usage of the word stress is due to the fact that it has a double derivation: "on the one hand it is derived from the Latin *stringere*, to draw tight, with its implication of a constraining force; and, on the other, as an aphetic form of 'distress,' which in its descent from the old French *destrece* and late Latin *districtus* has come to mean hardship or affliction, as of one who is 'pulled asunder.'"

Burns, N. M., Chambers, R. M., Hendler,

E. (eds.): *Unusual Environments and Human Behavior. Physiological and Psychological Problems of Man in Space*, p. 438. Glencoe, Ill.: Free Press, 1963.

E10,423/63

In the preface it is stated, "stress represents a special aspect of the relationships man establishes between himself and his environment."

Ruff, G. E.: "Psychological and psychophysiological indices of stress." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 33-59. Glencoe, Ill.: Free Press, 1963. E10,425/63

"The term stress usually implies a change in the conditions affecting an organism but requires an expenditure of effort so that the essential functions are maintained at the desired level."

Weybrew, B. B.: "Psychological problems of prolonged marine submergence." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 87-125. Glencoe, Ill.: Free Press, 1963.

E10,427/63

"Borrowed from physics, 'stress,' as applied to submarine psychology, has the connotation of 2 or more forces in opposition. One of these forces is motivational, resulting in goal-directed activity, and the other an immediately perceived or anticipated barrier to this activity."

Kelman, H.: "Tension is not stress." *Adv. Psychosom. Med.* 3: 21-27 (1963).

J22,955/63

Scotch, N. A.: "Sociocultural factors in the epidemiology of Zulu hypertension." *Am. J. Public Health* 53: 1205-1213 (1963).

J10,864/63

"For this paper stress is broadly defined as any stimulus or stimuli, experienced consciously or unconsciously, which is potentially harmful or threatening to the individual."

Weitz, J.: *Stress*. Research paper IDA/HQ 66-4672, pp. 251-294. Washington, D.C.: Inst. Defense Analyses, Research and Engineering Support Div., 1966.

J13,888/66

Review of stress research, particularly in relation to military medicine, with a section criticizing various currently used definitions of the term stress (16 refs.).

Back, K. W., Bogdonoff, M. D.: "Buffer conditions in experimental stress." *Behav. Sci.* 12: 384-390 (1967).

J9,369/67

"The organism experiences stress when it

faces problems which may constitute a threat."

Dohrenwend, B. P.: "Toward the development of theoretical models: I." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 155-162 (1967). J10,926/67

The word stress is derived from constraint. "Stress is viewed as a state of the individual intervening between strong antecedent constraint (of whatever type) and consequent efforts to reduce the constraint. In this social psychological view, as in Selye's formulation of the stress response in physical and chemical terms that influenced it, stress is seen as underlying both adaptive and maladaptive behavior."

Yates, F. E.: "Physiological control of adrenal cortical hormone secretion." In: Eisenstein, A. B., *The Adrenal Cortex*, pp. 133-183. Boston: Little, Brown, 1967.

E6,888/67

"The term stress itself is here defined as any stimulus that will provoke simultaneous increases in plasma glucocorticoid concentration and in glucocorticoid secretion rates. This definition specifically excludes increases in ACTH release (and glucocorticoid secretion rates) that may follow decreases in plasma glucocorticoid concentrations from consideration as stress responses."

Levine, S., Scotch, N. A.: "Toward the development of theoretical models: II." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 163-174 (1967). J10,927/67

"Life stress has been defined in terms of the degree to which the individual has experienced the following: blockage of occupational goals, job dissatisfaction, marital dissatisfaction, medical problems including hospitalizations and operations of family members, financial difficulties, service in the armed forces, including combat, and undesirable living accommodations."

Fraser, T. M.: "Men under stress." *Sci. Technol.* No. 73: 38-44; 82 (1968).

F98,050/68

Semipopular review on men under stress with special reference to environmental factors.

Klausner, S. Z.: *Why Man Takes Chances. Studies in Stress-seeking*, p. 267. Garden City, N.Y.: Doubleday, 1968. E10,636/68

Study of people who deliberately seek stress in the form of adventure, excitement, challenge and opportunity worthy of their

steel and who enjoy it. The author uses the term eustress.

Rasmussen, A. F. Jr.: "Emotions and immunity." *Ann. N.Y. Acad. Sci.* **164**: 458-462 (1969). H19,304/69

"'Stress' and 'stressor' are used interchangeably, as defined by Dr. Friedman and his associates elsewhere in this monograph." [This statement is cited only to show that even in 1969 the importance of distinguishing cause and effect in this field had not been generally recognized (H.S.).]

Holst, D. von: "Sozialer Stress bei Tupajas (*Tupaia belangeri*). Die Aktivierung des sympathischen Nervensystems und ihre Beziehung zu hormonal ausgelösten ethologischen und physiologischen Veränderungen" (Social stress in the tree shrew [*Tupaia belangeri*]. The activation of the sympathetic nervous system and its correlation with hormonally produced ethologic and physiologic phenomena). *Z. Vergl. Physiol.* **63**: 1-58 (1969). G90,282/69

"The term stress always refers to the state of the organism under the influence of a damaging agent (stressor)."

McGrath, J. E.: "A conceptual formulation for research on stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 10-21. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970.

E10,314/70

General discussion of various definitions of stress based on the provocative situation, the organism's response, the organism-environment transaction or engineering analogies. No preferred definition is formulated.

Kahn, R. L.: "Some propositions toward a researchable conceptualization of stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 97-103. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970.

E10,318/70

In this short address on how research on stress could be logically organized and clearly defined, the author states that "my preference is to call the demand in the external environment 'stress,' and the received demand 'strain' or 'not strain.'"

Weick, K. E.: "The 'ess' in stress: some conceptual and methodological problems." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 287-347. New York,

Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,328/70

Extensive lecture on the semantics of the term stress and its relation to the methodology of studying the phenomenon.

Bailit, H. L., Workman, P. L., Niswander, J. D., MacLean, C. J.: "Dental assymmetry as an indicator of genetic and environmental conditions in human populations." *Hum. Biol.* **42**: 626-638 (1970). J20,565/70

Dental assymmetry may occur in various human populations as a consequence of genetic or environmental stress factors. "Genetic stress may result from inbreeding due to the finite size of the population or to a mating pattern involving consanguinity. This can lead to a reduction in population fitness because of the exposure of deleterious recessive genes in a homozygous state or, more importantly, because of a breakdown in the coadaptation of the genetic system. Indications of inbreeding stress are provided by estimates of the inbreeding coefficient, the effective population size, the amount of gene flow into the population, or by a comparison of the genetic variance of different quantitative characters with that observed in large random mating populations. Another genetic stress may result from a drastic diminution in population size, leaving too little genetic variation to adapt to a changing or extremely heterogeneous environment."

Sells, S. B.: "On the nature of stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 134-139. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,321/70

The author proposes to define stress as follows: "The individual is called upon in a situation to respond to circumstances for which he has no adequate response available. The unavailability of an adequate response may be due to physical inadequacy; absence of the response in the individual's response repertoire; lack of training, equipment, or opportunity to prepare. The consequences of failure to respond effectively are important to the individual. Personal involvement in situations can be defined in terms of importance of consequences to the individual."

Parrot, J.: "The measurement of stress and strain." In: Singleton, W. T., Fox, J. G. et al., *Measurement of Man at Work. An Appraisal of Physiological and Psychological Criteria in Man-Machine Systems*, pp. 27-33. London: Taylor and Francis, 1971. J18,094/71

"A stimulus constitutes a stress for a particular system if a strain ensues within that system. In other words, under some threshold, a given factor may be a stress only for those individuals in whom it results in strain."

Levi, L. (ed.): *Society, Stress and Disease*, p. 485. New York, Toronto and London: Oxford University Press, 1971. E9,300/71

International Interdisciplinary Symposium, sponsored by the University of Uppsala and the WHO, at which specialists in many disciplines discussed the definition: "biologic stress is the nonspecific response of the body to any demand made upon it."

"Society, stress and disease." *WHO Chron.* **25**: 168-178 (1971). G85,103/71

Stress is defined as "the pattern of physiological reactions that prepares an organism for action." [The author of this definition is not identified, nor is it stated why the characteristic nonspecificity of the response and the teleonomically useless manifestations of shock due to overwhelming injury are not included (H.S.).]

Mason, J. W.: "A re-evaluation of the concept of 'nonspecificity' in stress theory." *J. Psychiatr. Res.* **8**: 323-333 (1971).

G86,484/71

Brief but excellent analysis of the evidence contradicting Selye's definition of stress. Mason states that stress "may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole."

Levi, L.: "Definition and evaluation of stress." *Rep. Lab. Clin. Stress Res.* (Stockholm) No. 25: 1-11 (1971). G87,068/71

Review of the hormonal, nervous and cardiovascular indices of stress which is defined as "the nonspecific response of the body to any demand made upon it."

McLean, A.: "Occupational 'stress.' A misnomer." *Occup. Ment. Health* **2** No. 4: 12-15 (1972). J15,754/72

The author concludes that "if we were to use the word stress to refer, say, only to Selye's adaptation syndrome, then its meaning would be restricted entirely to physiological stress reaction to stressor and in fact to an even narrower concept: namely the non-specific responsive tissues." [This shows a complete misunderstanding of the concept of "local stress" (which may selectively af-

fect, say, the nervous system). Hence it eliminates the key characteristic, nonspecificity, from the definition of stress (H.S.).]

Wardwell, W. I.: "A study of stress and coronary heart disease in an urban population." *Bull. N.Y. Acad. Med.* **49**: 521-531 (1973). J3,167/73

Discussion of seven definitions of stress, illustrating how meaningless the term is unless we restrict it to an internationally acceptable, clearly formulated concept.

Dohrenwend, B. S.: "Life events as stressors: a methodological inquiry." *J. Health Soc. Behav.* **14**: 167-175 (1973).

J16,337/73

On the basis of extensive statistical studies using questionnaires, the author concludes that "stressfulness is better conceived as life change than as undesirability of life events."

Ewbank, R.: "Use and abuse of the term 'stress' in husbandry and welfare." *Vet. Rec.* **92**: 709-710 (1973). J5,520/73

"A strong case can be made to revert (with modifications) to Selye's original terminology and to restrict the use of the term stress to the mechanisms by which an animal resists the effects of adverse stimuli. The mechanism will include all the means by which an animal attempts to adapt, and not just the C.N.S. pituitary adrenal pathway." Both excessive and insufficient degrees of stress are harmful.

Bugard, P.: *Stress, Fatigue et Dépression. L'Homme et les Agressions de la Vie Quotidienne* (Stress, fatigue and depression. Man and the aggression of everyday life), Vol. 1, p. 294; Vol. 2, p. 302. Paris: Doin Edit., 1974. E10,487/74

Stress simultaneously reflects both the pressure of a given environment and man's reaction to this pressure.

Aakster, C. W.: "Psycho-social stress and health disturbances." *Soc. Sci. Med.* **8**: 77-90 (1974). J10,857/74

"Stress is any environmental force which leads (or is expected to lead) to disequilibrium upon one or more of the essential variables of the system. Stress, therefore, always points to a relationship between system and environment. Well-known types of stress are conflicting expectations, goal-means conflict, overload, underload, deprivation, incapacity, trauma, perceived threats, etc."

Mason, J. W.: "A historical view of the

'stress' field. Part I." *J. Hum. Stress* **1** No. 1: 6-12 (1975). H97,891/75

Mason, J. W.: "A historical view of the 'stress' field Part II." *J. Hum. Stress* **1** No. 2: 22-36 (1975). H97,892/75

Review of the evolution of the stress concept from Cannon's work on the emergency discharge of EP during fight-or-flight reactions up to present day views on the importance of the hypothalamus-pituitary-adrenocortical system, the triphasic nature of the G.A.S., and the nonspecific stereotyped response pattern of the body to any demand. Eustress is not discussed, but the author emphasizes that, "of all the known responses of higher organisms, emotional arousal is certainly one of the most ubiquitous or relatively 'nonspecific' reactions common to a great diversity of situations." On the other hand, he clearly recognizes that "this is not to conclude that the pituitary-adrenal cortical system responds only to psychological stimuli." In accordance with earlier work on the effect of internal and external conditioning factors upon the resulting reaction form, it is agreed that the reaction could not be absolutely nonspecific, even if it occurred after any demand (48 refs.).

Selye, H.: "Confusion and controversy in the stress field." *J. Hum. Stress* **1** No. 2: 37-44 (1975). J4,295/75

Answer to the preceding articles. "The continued use of the word stress as a non-specific response to any demand is deemed most desirable. The once vague term can now be applied in a well-defined sense and is accepted in all foreign languages as well, including those in which no such word existed previously in any sense. Subdivision of the stress concept has become necessary as more recent work has led to such notions as 'eustress,' 'distress,' 'systemic stress' and 'local stress.' Confusion between stress as both an agent and a result can be avoided only by the distinction between 'stress' and 'stressor.' It is explained that the stress syndrome is—by definition—nonspecific in its causation. However, depending upon conditioning factors, which can selectively influence the reactivity of certain organs, the same stressor can elicit different manifestations in different individuals."

Selye, H.: "Homeostasis and heterostasis." In: Brooks, Ch.McC., Koizumi, K. et al., *The Life and Contributions of Walter Bradford Cannon 1871-1945*, pp. 108-112. Brook-

lyn, N.Y.: State University of New York Downstate Medical Center, 1975.

J4,297/75

Comparison of the concepts of homeostasis and heterostasis with special emphasis on W. B. Cannon's stimulating effect upon the author's work on adaptation.

greater degrees of specificity and sensitivity. Its successive nonadapted, adapted, and non-adapted stages, associated with increasing sensitization, probably involve similar endocrine and electrolyte mechanisms." Here, the alarm reaction is followed by addiction with high degrees of specific sensitivity. [The concept is not clearly defined (H.S.).]

Fox, H. M., Gifford, S., Murawski, B. J., Rizzo, N. D., Kudarauskas, E. N.: "Some methods of observing humans under stress." *Psychiatr. Res. Rep. APA*. 7: 14-26 (1957).

J11,149/57

"Psychological stress results from any external threat, from any intensification of the biological drives, or from any increased demand from the conscience which challenges the capacity of the individual to maintain a balance between his needs and his satisfactions."

Caron, A. J., Wallach, M. A.: "Personality determinants of repressive and obsessive reactions to failure-stress." *J. Abnorm. Soc. Psychol.* 59: 236-245 (1959). G82,249/59

The psychologic results of failure are ascribed to "failure-stress."

Randolph, T. G.: "Human ecology and susceptibility to the chemical environment." *Ann. Allergy* 19: 518-540; 657-677; 779-799; 908-929 (1961). D5,214/61

Extensive review on the chemical environment's influence upon resistance, with a section on stress. The author creates the concept of the specific adaptation syndrome, defined as "a clinical counterpart of Selye's general adaptation syndrome." [It is not clear how specific adaptation to each agent can result in a single, stereotyped syndrome (H.S.).]

Cambrelin, G.: "Reflexions sur le 'stress'" (Reflections on stress). *Acta Otolaryngol. (Stockh.)* 53: 259-260 (1961). D21,485/61

Semantic considerations lead the author to state that the English word stress should not be translated into French as *agression* but as *alerte, alarme, choc* or *tension*.

Ball, W. A.: "Anti-stress." *Practitioner* 190: 781-785 (1963). E20,610/63

According to the author, "Selye in his stress syndrome has given us a description of the part that stress or strain plays in the causation of ill health, and a new point of attack." For the opposite of this, the term anti-stress is suggested. [Apparently, the au-

Are There Different Types of Stress?

(See also our earlier stress monographs, p. xiii)

Symonds, C. P.: "The human response to flying stress. Lecture I: Neurosis in flying personnel." *Br. Med. J.* December 4, 1943, pp. 703-706; "Lecture II: The foundations of confidence." *Br. Med. J.* December 11, 1943, pp. 740-744. B26,422/43

The objection to the use of flying stress as a clinical diagnosis is the same one that applies to the terms aeroneurosis or aviator's neurasthenia. The term flying stress "should be used only to denote the load which aircrews have to carry."

Symonds, C. P.: "Use and abuse of the term flying stress." In: Air Ministry, *Psychological Disorders in Flying Personnel of the Royal Air Force, Investigated during the War, 1939-1945*, pp. 18-21. London: H M SO, 1947. B76,340/47

"It should be understood once and for all that flying stress is that which happens to the man, not that which happens in him: it is a set of causes, not a set of symptoms."

Smock, C. D.: "The influence of psychological stress on the 'intolerance of ambiguity,'" *J. Abnorm. Soc. Psychol.* 50: 177-182 (1955). B29,284/55

"The term 'psychological stress' is used in this study to refer to the psychological effects of a series of experimental operations designed to induce a feeling of failure."

Hinkle, L. E. Jr.: "Physiological aspects of life stress." *J. Dent. Med.* 11: 69-77 (1956). J13,193/56

"Life stress" is a general term which refers to the physiological and psychological effects of man's reaction to his life situation."

Randolph, T. G.: "The specific adaptation syndrome." *J. Lab. Clin. Med.* 48: 934 (1956). C26,899/56

"The specific adaptation syndrome resembles Selye's general adaptation except for

thor is unaware that as originally defined stress can be either harmful or useful depending upon the circumstances (H.S.).]

Junge-Hülsing, G.: (No Title) *Therapiewoche* **19**: 297 (1969). J11,885/69

Social stress is defined as "the discrepancy between required and actual accomplishments."

Dung, H. C., Swigart, R. H.: "Experimental studies of 'lethargic' mutant mice." *Tex. Rep. Biol. Med.* **30**: 273-288 (1971).

J10,269/71

The term swimming stress is used to describe fatigue caused by swimming.

Mason, J. W.: "A re-evaluation of the concept of 'nonspecificity' in stress theory." *J. Psychiatr. Res.* **8**: 323-333 (1971).

G86,484/71

Brief but excellent analysis of evidence contradicting Selye's definition of stress. Mason states that stress "may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole."

Holmes, D. J.: *Psychotherapy: Experience, Behavior, Mentation, Communication, Culture, Sexuality, and Clinical Practice*, p. 1077, sect. 1-6. Boston: Little, Brown, 1972.

E10,304/72

A voluminous yet very readable treatise on psychotherapy in which we counted fourteen pages that refer specifically to stress without defining the sense in which the author uses the term. We were unable to locate in the subject index any reference to the hypophysis, the hypothalamus, the limbic system or the role played by corticoids or catecholamines.

Tsukiyama, H., Otsuka, K., Kyuno, S., Fujishima, S., Kijima, F.: "Influence of immobilization stress on blood pressure, plasma renin activity and biosynthesis of adrenocorticoid." *Jap. Circ. J.* **37**: 1265-1270 (1973). H81,677/73

In rabbits, "shortly after the beginning of immobilization stress a remarkable elevation in the arterial pressure, a significant increase in plasma renin levels and plasma corticosterone concentrations were observed." However, the changes in plasma renin and corticosterone did not run parallel; hence, there appear to be different mechanisms activating the renin-angiotensin and pituitary-adrenocortical systems. EEG studies suggest that

the homeostatic mechanisms mediated by the mesencephalic reticular formation and grey matter regulate blood pressure and renin release while the hippocampus, amygdala and anterior hypothalamic area are less effective in this respect. Findings derived from selective electric stimulation of various brain areas are in accordance with this interpretation.

Lát, J.: "Methodological problems of hormone-behaviour relations during stress." In: Németh, Š.; *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 245-254. Bratislava: Slovak Academy of Sciences, 1973. E10,472/73

Theoretical considerations concerning the relative nonspecificity of stress reactions owing to superimposed specific effects of stressors. "A drug or hormone may have a nonspecific effect upon behaviour and at the same time a very specific effect upon some CNS structures which in turn exert a non-specific effect upon behaviour."

Forgács, P.: "Gravitational stress in lung disease." *Br. J. Dis. Chest* **68**: 1-10 (1974).

J10,403/74

The effects of acceleration are described and termed gravitational stress.

Wilkins, W. L.: "Social stress and illness in industrial society." In: Gunderson, E.K.E. and Rahe, R. H., *Life Stress and Illness*, pp. 242-254. Springfield, Ill.: Charles C Thomas, 1974. E10,694/74

Discussion of the various definitions of stress. Special attention is given to "stress (Selye)" but no definite recommendation is made (12 refs.).

Definition of Diseases of Adaptation

(See also our earlier stress monographs, p. xiii)

Godin, O., Blondiau, P., Lauwers, P., Gonze, A.: "La pathergie à l'humidité. Etude hydrogéologique de la région bruxelloise" (Pathergy in humidity. A hydrogeologic study of the Brussels region). *Acta Otorhinolaryngol. Belg.* **26**: 387-460 (1972). G99,747/72

While allergy is a hypersensitivity to chemicals, pathergy is defined as a comparable response to physical agents and considered to represent diseases of adaptation.

Principal Pathways Mediating the Response to a Stressor

The pathways through which the stress response is mediated are extremely complex and will be analyzed in depth later along with the pertinent literature. To gain perspective it may be useful to start with an overview; this will facilitate the task of the reader who is interested only in looking up a specific point but must nevertheless know exactly where it fits into the complicated network of interacting events that are triggered by confrontation with a stressor. In this presentation I shall follow the schematic outline given in Figure 2.

Apart from specific changes (which need not be discussed here), the first effect of a *stressor* acting upon the body, is to produce a nonspecific stimulus. This may be a nervous impulse, a chemical substance or lack of an indispensable metabolic factor, and it is referred to simply as the *first mediator* because we know nothing about its nature. We are not even certain that it has to be an excess or deficiency of any particular substance; it is possible that various derangements of homeostasis can initiate the stress response. Undoubtedly in man, with his highly developed central nervous system (CNS), emotional arousal is one of the most frequent initiators of somatic stress; yet it cannot be regarded as the only factor capable of causing stress, since stress reactions (that is, nonspecific responses common to all demands made upon a living organism) also occur in the most primitive animals in the absence of a nervous system. But even in man conscious psychic disturbances are not indispensable, since typical stress reactions can occur in patients exposed to stressors (for example, trauma, hemorrhage) while under deep anesthesia. Indeed, anesthetics themselves (for example, ether) are commonly used in experimental medicine to produce stress, and "the stress of anesthesia" is a serious problem in clinical surgery.

(For a detailed diagram of the common pathways mediating the stress response itself, see p. 25.)

When an *agent* acts upon the body (thick outer frame of the diagram) the effect will depend upon three factors (broad vertical arrows pointing to the upper horizontal border of the frame). All agents possess both nonspecific *stressor* effects (solid part of arrow) and *specific* properties (grey part of arrow). The latter are variable and characteristic of each individual agent; they will not be discussed here other than to state that they are inseparably attached to the stressor effect and invariably modify it. The other two heavy vertical arrows, pointing toward the upper border of the frame, represent exogenous and endogenous *conditioning factors* that largely determine the reactivity of the body. It is clear that since all stressors have some specific effects, they cannot elicit exactly the same response in all organs; furthermore, even the same agent will act differently on different individuals, depending upon the internal and external conditioning factors that determine their reactivity.

Although we have still to identify the first mediator(s), we do know that eventually stress acts upon the *hypothalamus* and particularly the ME. This action appears to be regulated largely by means of (mediated through or modified by) nervous stimuli coming from the cerebral cortex, the reticular formation and the limbic system (especially the hippocampus and amygdala).

The incoming nervous stimuli reach certain *neuroendocrine cells*, most of which are located in the ME. These act as "transducers," transforming nervous signals into a humoral messenger, the *corticotropin hormone-releasing factor (CRF)*, which can be demonstrated histochemically in the ME region and can also be extracted from it. Oddly enough, the posterior pituitary contains the highest concentration of CRF, and

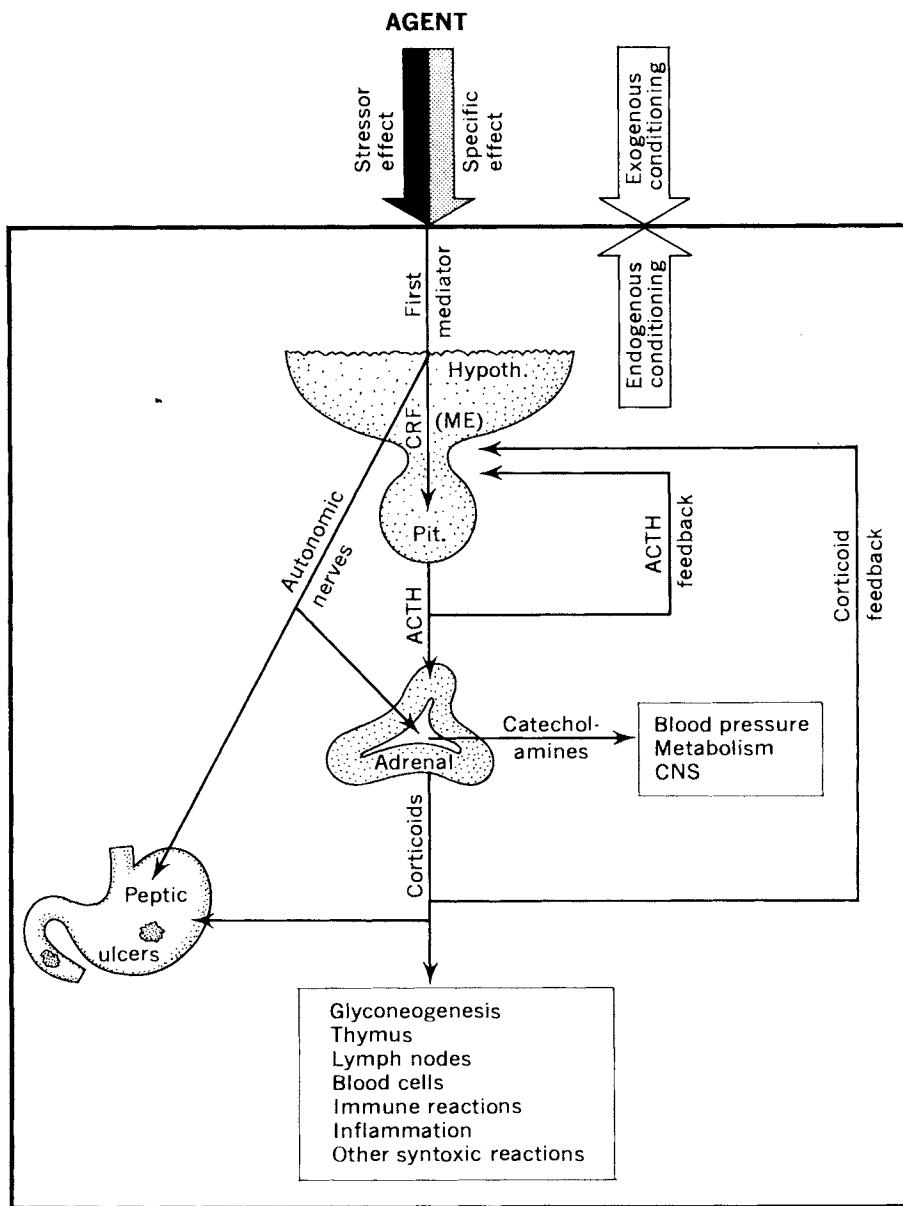


Figure 2. Principal pathways mediating the response to a stressor agent and the conditioning factors which modify its effect.

As soon as any *agent* acts upon the body (thick outer frame of the diagram) the resulting effect will depend upon three factors (broad vertical arrows pointing to the upper horizontal border of the frame). All agents possess both nonspecific *stressor* effects (solid part of arrow) and *specific* properties (grey part of arrow). The latter are variable and characteristic of each individual agent; they will not be discussed here other than to state that they are inseparably attached to the stressor effect and invariably modify it. The other two heavy vertical arrows, pointing toward the upper border of the frame, represent exogenous and endogenous *conditioning factors* which largely determine the reactivity of the body. It is clear that since all stressors have some specific effects, they cannot elicit exactly the same response in all organs; furthermore, even the same agent will act differently in different individuals, depending upon the internal and external conditioning factors which determine their reactivity.

it has been isolated from this source in pure form, thus permitting the determination of its chemical formula as a polypeptide which subsequently was synthesized. Yet we have no absolute proof that the CRF-active material extracted from the hypothalamus is identical with that obtained from the posterior lobe since only the structure of the latter has been definitely ascertained. Although vasopressin (the antidiuretic hormone or ADH) possesses considerable CRF activity it is not identical with CRF; this has been shown by the well-documented differences in their chemical structure and physiologic activity.

CRF reaches the anterior lobe through the *hypothalamo-hypophyseal portal system* that originates in the ME region within a network of capillaries into which CRF is discharged by the local neuroendocrine cells. It is then carried down through the larger veins of the pituitary stalk to a second capillary plexus in the pituitary.

The hypothalamus does not stimulate the *adrenocorticotrophic hormone (ACTH)* secretion of the anterior lobe through nervous pathways descending in the pituitary stalk but rather through blood-borne substances carried by way of the portal veins. That is why transection of the stalk inhibits the ACTH secretion only before vascular connections between the hypothalamus and the gland are reestablished; if regeneration of these vessels is prevented by interposing a plate between the cut ends of the stalk, this pathway is permanently blocked.

Both *in vivo* and *in vitro* experiments have proven that CRF elicits a discharge of ACTH from the adenohypophysis into the general circulation. Upon reaching the adrenal cortex, it causes secretion of corticoids, mainly *glucocorticoids*, such as cortisol or corticosterone. These induce glycogenesis, thereby supplying a readily available source of energy for the adaptive reactions necessary to meet the demands made by the stressors. In addition, they facilitate various other enzymatically regulated adaptive metabolic responses and suppress immune reactions as well as inflammation, assisting the body to coexist with potential pathogens (syntoxic reactions). Furthermore, the glucocorticoids are responsible for the thymic lymphatic involution, eosinopenia and lymphopenia characteristic of acute stress. Curiously, glucocorticoids are needed for the acquisition of adaptation primarily during the alarm reaction, but not so much to maintain the adjustment during the stage of resistance. ACTH plays a comparatively minor role in the secretion of *mineralocorticoids*, such as aldosterone, which is regulated mainly by the renin-hypertensin system and the blood electrolytes, whose homeostasis is in turn influenced by them.

This chain of events is cybernetically controlled by several *biofeedback* mechanisms. Whether an excess of CRF can inhibit its own endogenous secretion is still doubtful because its lifespan in the circulating blood is very short. On the other hand, there is definite proof of an ACTH feedback (short-loop feedback) by a surplus of the hormone, which returns to the hypothalamo-pituitary system and inhibits further ACTH production. We have even more evidence to substantiate the existence of a corticoid feedback mechanism (long-loop feedback) in that a high blood corticoid level similarly inhibits ACTH secretion. It is still not quite clear to what extent these feedbacks act upon the neuroendocrine cells of the hypothalamus, the adenohypophysis or both (hence, in Figure 2 the corresponding arrowheads merely point towards the hypothalamo-hypophyseal region in general, without specifying exactly where their target areas are situated).

A second important pathway that mediates the stress response is carried through the *catecholamines* liberated under the influence of an acetylcholine discharge, at autonomic nerve endings and in the adrenal medulla. The chromaffin cells of the latter

secrete mainly EP, which is of considerable value in that it stimulates mechanisms of general utility to meet various demands for adaptation. Thus it provides readily available sources of energy by forming glucose from glycogen depots and free fatty acids from the triglyceride stores of adipose tissue; it also quickens the pulse, raises the blood pressure to improve circulation into the musculature, and stimulates the CNS. In addition, EP accelerates blood coagulation and thereby protects against excessive hemorrhage should wounds be sustained in conflicts. All of this is helpful in meeting the demands of fight or flight.

The pathogenesis of the *stress ulcers* in the duodenum and stomach is not yet fully understood, but apparently glucocorticoids and autonomic nerve impulses cooperate to produce these characteristic manifestations of the stress syndrome.

Conditioning

How can different agents cause the same response (namely, stress) and this stereotyped response produce different lesions in various patients?

After the general characteristics and pathways of the stress reaction were clarified, there still remained two apparently insurmountable obstacles to our formulation of the concept that the Local Adaptation Syndrome (L.A.S.) and its derailments are all fundamentally dependent upon a single stereotyped response to stress:

- (1) Qualitatively different agents of equal toxicity (or stressor potency) do not necessarily elicit exactly the same syndrome in different people.
- (2) Even the same degree of stress, induced by the same agent, may produce different lesions in different individuals.

It took many years to show that qualitatively different agents can cause the same effects. They differ only in their specific actions, while their nonspecific stressor effects (such as ACTH secretion or corticoid secretion and thymic lymphatic involution) are essentially the same, although these are usually modified by the superimposed specific effects of the evocative agents.

The fact that the same stressor can cause different lesions in different individuals has been traced to "conditioning factors" that can selectively enhance or inhibit one or the other stress effect. This conditioning may be endogenous (genetic predisposition, age or sex) or exogenous (treatment with certain hormones, drugs, or dietary factors) (see Figure 2). Under the influence of such conditioning factors, a normally well-tolerated degree of stress can become pathogenic and cause diseases of adaptation. It then selectively affects those parts of the body that are particularly sensitized both by these conditioning factors and by the specific effects of the eliciting agent. This selectivity of damage is comparable to that in different chains, in each of which mechanical stress of identical tension will break the particular link that has become weakest as a result of internal or external factors.

Degrees of Specificity, Relationship between the G.A.S. and L.A.S.

We have seen that every agent capable of producing systemic stress with the manifestations of the G.A.S. also has some specific actions that primarily affect individual target regions.

In the case of local trauma, this leads to the development of what we have called the *Local Adaptation Syndrome* (L.A.S.) in the form of cell degeneration, necrosis, inflammation, wound healing, and so on at the site of injury. The local stress stimuli emanating from the primarily afflicted region will, in proportion to their intensity, mobilize the hypothalamus-pituitary-adrenal mechanism and elicit systemic stress of varying degrees of severity. However, even if the target is not a small area but instead the cerebral cortex (in the case of emotional arousal), the general metabolism, or the reticuloendothelial system (RES), there is a primary topical response. This corresponds to the L.A.S. and is superimposed upon the G.A.S. produced by the resulting systemic manifestations. Conversely, this secondary G.A.S. influences the L.A.S. through neurohumoral mechanisms (for example, anti-inflammatory hormones). That is one reason why the specificity of any agent acting upon the organism is never absolute but varies in degree. Some stimuli (for example, a small local burn or the effect of green light upon the retina) have virtually only specific local effects, whereas others (for example, whole body x-irradiation, antimitotic drugs, extreme neuromuscular exhaustion) are primarily characterized by their systemic stress effect.

To summarize these important points, let me reemphasize that it is not correct to speak of nervous stress, cold stress, traumatic stress and so on, as if each of these produced a different type of stress. By definition, the stress response is nonspecific and thus is common to all these stressors. What differs is only the manifest result of exposure to a particular type of demand; the primary specific and circumscribed effects (corresponding to the L.A.S.) are inseparably superimposed upon the stereotyped systemic G.A.S. manifestations. Specificity is never absolute; it is always a matter of degree.

Cross Resistance and Treatment with Stressors or Stress-Hormones

Stress is not invariably harmful but may actually have prophylactic or curative value under certain conditions. Thus, pretreatment with one stressor may induce resistance to another by mobilizing the body's nonspecific adaptive system. For example, syntoxic hormones (glucocorticoids) liberated during systemic stress can protect against various excessive and harmful inflammatory or immune reactions. This principle has been applied clinically in the treatment of inflammatory diseases and the suppression of graft rejection. However, other forms of cross-resistance may depend upon different mechanisms.

Before we knew anything about the mechanism of stress reactions, nonspecific treatment had to rely entirely upon the exposure of patients to stressors (cold, heat, hydrotherapy, bloodletting, exercise, fever therapy, electroshock, and so on). It was not known how these agents acted, but there could be no doubt that in many cases they were beneficial. It is still not clear why some nonspecific therapeutic procedures are more valuable in certain diseases than in others, but probably their specific effects are superimposed on—in some cases, even more important than—their nonspecific actions. Undoubtedly, all these treatments do produce stress and often act through the liberation of stress hormones such as ACTH, corticoids and catecholamines. Whenever this is the case, it is of course much more acceptable to the patient to receive the hormones themselves, rather than to count on their "auto-pharmacologic" endogenous production by exposure of the patient to drastic types of nonspecific treatments (for example, shock therapy).

The Diseases of Adaptation or Stress Diseases

Those maladies in whose development the nonspecific stressor effects of the eliciting pathogen play a major role are called *diseases of adaptation* or *stress diseases*. However, just as there is no pure stressor (that is, an agent that causes only nonspecific responses and has no specific actions of its own), so there are no pure diseases of adaptation. Some nonspecific components participate in the pathogenesis of every malady, but no disease is due to stress alone. The justification for placing a malady in this category is directly proportional to the role that maladjustment to stress plays in its development.

In the main text section on the diseases of adaptation I shall discuss this point at length in connection with a great many pathologic conditions. Here, suffice it to point out that in some instances (for example, peptic ulcers, hypertension, surgical shock, certain neuropsychiatric derangements) stress may be far the most important pathogenic factor. However, in other cases (instantly lethal intoxications, traumatic injuries to the spinal cord, most congenital malformations) it plays little or no role, either because the damage is inflicted so rapidly that there is no time for any adaptive process, or because the pathogen is highly specific. In the latter event, whatever develops represents a secondary result and not the primary component of the pathogenic process.

In typical diseases of adaptation, insufficient, excessive or faulty reactions to stressors (for example, inappropriate hormonal or nervous responses) are at the root of the disturbance. Yet as I have said before, there is no disease that can be attributed exclusively to maladaptation, since the cause of nonspecific responses will always be modified by various "conditioning factors" that enhance, diminish, or otherwise alter disease proneness. Most important among these are the specific effects of the primary pathogen, and the factors influencing the body's reactivity by endogenous (heredity, previously sustained damage to certain organs) or by exogenous (concurrent exposure to other pathogens and environmental agents, diet) conditioners. Hence, the diseases of adaptation cannot be ascribed to any one pathogen but to "pathogenic constellations;" they belong to what we have called the *pluricausal diseases* ("multifactorial maladies") that depend upon the simultaneous effect of several potentially pathogenic factors, among which, sometimes, none alone would produce disease.

Syntoxic and Catatoxic Responses

During the second half of the nineteenth century—well before anyone thought of stress—Claude Bernard first pointed out clearly that the internal medium of the living organism is not merely a vehicle for carrying nourishment to cells but that "it is the fixity of the *milieu intérieur* which is the condition of free and independent life." Some fifty years later, Cannon suggested the designation *homeostasis* (from the Greek *homoios* or similar and *stasis* or position, standing) for "the coordinated physiological processes which maintain most of the steady states in the organism," that is, the ability to stay the same or static.

What is meant by the "fixity of the *milieu intérieur*"? Everything inside the skin and even the skin itself constitutes the internal medium. To maintain a healthy life, nothing within the body must be allowed to deviate far from the norm; if something does, the individual will become sick or even die. There are many complex biochemical

mechanisms that ensure the fixity and steadiness of the *milieu intérieur*. Let us look briefly at how they work.

The biochemical analysis of the stress syndrome showed that homeostasis depends mainly upon two types of reactions: *syntoxic* (from the Greek *syn* or together) and *catatotoxic* (from the Greek *cata* or against). Apparently, to resist different stressors the organism can regulate its own reactions through chemical messengers and nervous stimuli that either pacify or incite to fight. Syntoxic stimuli act as tissue tranquilizers, creating a state of passive tolerance that permits a kind of symbiosis, or peaceful coexistence, with aggressors. The catatotoxic agents cause chemical changes (mainly through the production of hepatic microsomal enzymes) that lead to an active attack upon the pathogen, usually by accelerating its metabolic degradation.

Presumably, in the course of evolution the body learned to defend itself against all kinds of aggressors (whether arising in the organism or the environment) through mechanisms that help it tolerate the aggressor (*syntoxic*) or destroy it (*catatoxic*). Among the most effective syntoxic hormones are the *glucocorticoids*.

It is not immediately evident why it should be advantageous to inhibit inflammation or interfere with the rejection of foreign tissues, since both phenomena are essentially useful defense reactions. The main purpose of inflammation is to localize irritants (for example, microbes) by putting a barricade of inflammatory tissue around them to prevent their spread into the blood, which could lead to sepsis and even death. The suppression of this basic defense reaction is an advantage, however, when a foreign agent is in itself innocuous and causes trouble only by inciting inflammation. In such cases, inflammation itself is what we experience as a disease. Thus, in many patients who suffer from hay fever or extreme inflammatory swelling after an insect sting, suppression of defensive inflammation is essentially a cure, because the invading stressor agent is not in itself dangerous or likely to spread and kill. In the case of grafts, it may even be lifesaving.

At this point it is useful to distinguish between direct and indirect pathogens. Direct pathogens cause disease regardless of the body's reaction, whereas indirect pathogens cause damage only because they provoke exaggerated defensive responses.

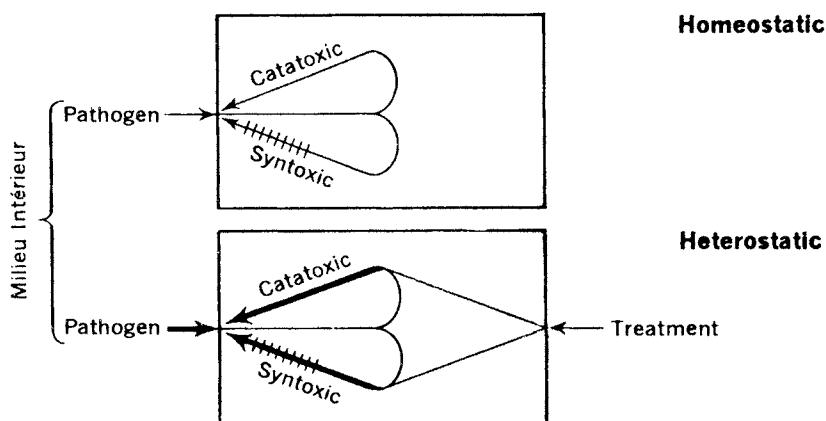


Figure 3. Comparison of homeostatic and heterostatic defense mechanisms (Reproduced from *Stress Without Distress*, Fig. 6, p. 56, 1974, by permission of the J B Lippincott Company).

If a man accidentally exposes his hand to a strong acid, alkali or boiling water, damage will occur regardless of his reactions, because these are all direct pathogens. They would damage even the hand of a dead man, who obviously could not put up any defense reactions. Most common inflammatory irritants, including allergens, are essentially indirect pathogens: they cause disease only through the purposeless defense reactions that they stimulate.

Immunologic reactions, which lead to the destruction of microbes, grafts and other foreign tissues, undoubtedly developed during evolution as useful defensive mechanisms against potentially dangerous foreign materials. When the attack against the foreign agent is unnecessary or even harmful—as in the case of many allergens, heart transplants, and so on—man can improve upon the wisdom of Nature by suppressing this hostility. When the aggressor is dangerous, the defensive reaction should not be suppressed but if possible increased beyond the normal level, which can be achieved, for example, by catatoxic substances that carry the chemical message to the tissues to destroy the invaders even more vigorously than would normally be the case.

The Concept of Heterostasis

Natural homeostatic mechanisms are usually sufficient to maintain a normal state of resistance; however, when the organism is faced with unusually heavy demands, ordinary homeostasis is not enough. The “thermostat of defense” must be raised to a heightened level. For this process, I proposed the term *heterostasis* (from the Greek *heteros* or other) as the establishment of a new steady state by treatment with agents that stimulate the physiologic adaptive mechanisms through the development of normally dormant defensive tissue reactions. Both in homeostasis and in heterostasis, the *milieu intérieur* participates actively.

We can stimulate the production of natural protective agents by treatment with chemicals that augment the induction of catatoxic or syntoxic enzymes, or by immunization with bacterial products (for example, vaccination) that increase the body's manufacture of serologic antibodies to combat infections.

In homeostatic defense the potential pathogen (which threatens the fixity of the *milieu intérieur*) automatically activates usually adequate catatoxic or syntoxic mechanisms; when these do not suffice, such natural catatoxic or syntoxic agents can also be administered readymade by the physician. Heterostasis depends upon treatment with artificial remedies that have no direct curative action, but which can precipitate the production of unusually high amounts of the body's own natural catatoxic or syntoxic agents so as to achieve fixity of the *milieu intérieur*, despite abnormally high demands that could not be met without outside help.

The most salient difference between homeostasis and heterostasis is that the former maintains a normal steady state by physiologic means, whereas the latter “resets the thermostat” of resistance to a heightened defensive capacity by artificial interventions from the outside (Figure 3). By chemical treatment, this process induces the body to raise the production of its own natural nonspecific (multipurpose) remedies. However, each type of planned or enforced training of the body through outside interventions also raises resistance from the homeostatic to the heterostatic level.

Heterostasis differs essentially from treatment with drugs (for example, antibiotics,

antacids, antidotes, pain killers) that act directly and specifically rather than by strengthening the body's own natural nonspecific defenses; in treatment with drugs, the *milieu intérieur* is passive.

Behavioral Implications

From what the laboratory and the clinical study of somatic diseases has taught me concerning stress, I have tried to arrive at a code of ethics based not on traditions of our society, inspiration, or blind faith in the infallibility of a particular prophet, religious leader or political doctrine, but on the scientifically verifiable laws that govern the body's reactions in maintaining homeostasis and living in satisfying equilibrium with its surroundings.

In a recent monograph (*Stress Without Distress*) on the behavioral implications of the stress concept, I attempted to show in more detail how we can adjust our personal reactions to enjoy fully the eustress of success and accomplishment without suffering the distress commonly generated by frustrating friction and purposeless aggressive behavior against our surroundings.

There I tried to illustrate this possibility by an example taken from daily life that shows how diseases can be produced indirectly by inappropriate or excessive adaptive reactions. When you meet a helpless drunk who showers you with insults but is obviously quite unable to do you any harm, nothing will happen if you take a syntoxic attitude—go past and ignore him. However, if you respond catatoxically and fight, or even only prepare to fight, the consequences may be tragic. You will discharge catecholamines that increase blood pressure and pulse rate, while your whole nervous system becomes alarmed and tense in anticipation of combat. If you happen to be a coronary candidate, the result may be a fatal brain hemorrhage or coronary accident. In this case, who is the murderer? The drunk didn't even touch you. This is biologic suicide! Death was caused by choosing the wrong reaction. If, on the other hand, the man who showers you with insults is a homicidal maniac with a dagger in his hand, evidently determined to kill you, you must take an aggressive catatoxic attitude. You must try to disarm him, even at the calculated risk of injury to yourself from the physical accompaniments of the alarm reaction in preparation for a fight. Contrary to common opinion, it is clear that Nature does not always know best, because on both the cellular and the interpersonal level, we do not always recognize what is and what is not worth fighting for.

Yet, it is a biologic law that man—like the lower animals—must fight and work for some goal that he considers worthwhile. We must use our innate capacities to enjoy the eustress of fulfillment. Only through effort, often aggressive egoistic effort, can we maintain our fitness and assure our homeostatic equilibrium with the surrounding society and the inanimate world. To achieve this state, our activities must earn lasting results; the fruits of work must be cumulative and must provide a capital gain to meet future needs. To succeed, we have to accept the scientifically established fact that man has an inescapable natural urge to work egoistically for things that can be stored to strengthen his homeostasis in the unpredictable situations with which life may confront him. These are not instincts we should combat or be ashamed of. We can do nothing about having been built to work, and it is primarily for our own good. Organs that are not used (muscles, bones, even the brain) undergo inactivity

atrophy, and every living being looks out first of all for itself. There is no example in Nature of a creature guided exclusively by altruism and the desire to protect others. In fact, a code of universal altruism would be highly immoral, since it would expect others to look out for us more than for themselves.

"Love thy neighbor as thyself" is a command filled with wisdom, but as originally expressed it is incompatible with biologic laws; no one needs to develop an inferiority complex if he cannot love all his fellow men on command. Neither should we feel guilty because we work for treasures that can be stored to ensure our future homeostasis. Hoarding is a vitally important biologic instinct that we share with animals such as ants, bees, squirrels and beavers.

How can we develop a code of ethics that accepts egoism and working to hoard personal capital as morally correct? That is what I attempted to do in *Stress Without Distress* and here I shall summarize the main conclusions in the form of three basic guidelines:

(1) *Find your own natural stress level.* People differ with regard to the amount and kind of work they consider worth doing to meet the exigencies of daily life and to assure their future security and happiness. In this respect, all of us are influenced by hereditary predispositions and the expectations of our society. Only through planned self-analysis can we establish what we really want; too many people suffer all their lives because they are too conservative to risk a radical change and break with traditions.

(2) *Altruistic egoism.* The selfish hoarding of the goodwill, respect, esteem, support and love of our neighbor is the most efficient way to give vent to our pent-up energy and create enjoyable, beautiful or useful things.

(3) *EARN thy neighbor's love.* This motto, unlike love on command, is compatible with man's structure, and although it is based on altruistic egoism, it could hardly be attacked as unethical. Who would blame him who wants to assure his own homeostasis and happiness by accumulating the treasure of other people's benevolence towards him? Yet this makes him virtually unassailable, for nobody wants to attack and destroy those upon whom he depends.

These are the three main principles derived from observations on the basic mechanisms that maintain homeostasis in cells, people and entire societies, and which help them face the stressors encountered in their constant fight for survival, security and well-being. Once understood and clearly formulated we can use them best by conscious control.

However, there remain many techniques whose value in improving the quality of life has been established by purely empirical observations. Although they are not directly related to attaining any particular goal, these techniques help us indirectly by improving our physical and mental fitness. Among these, I should mention muscular exercise, hot baths, saunas and a number of psychologic techniques such as Transcendental Meditation, yoga and Zen, whose beneficial effects upon general well-being and mental performance cannot yet be fully explained in somatic terms. With time, such explanation will undoubtedly become possible. Great progress has been made in this direction by demonstrations, for example, of the biochemical changes that accompany the refreshing relaxation induced by such different indirect means of improving well-being as athletics, relaxed meditation, a cup of coffee, or even psychotropic drugs (for example, tranquilizers). Of course, excessive or inappropriate use of any among these can cause considerable damage, and until we know more about their mechanisms

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of action, indications and contraindications cannot be clearly formulated for each individual in every situation. Yet in view of the great progress being made in our knowledge of the roles played by chemical compounds (catecholamines, 5-HT, hypothalamic neurohumors), it is in this field that we can see the greatest future for the further development of a code of behavior based upon biologic laws.

II. STRESSORS AND CONDITIONING AGENTS

The preceding chapter gave us an overview of the entire stress concept as we see it today, discussing its historical development, general outlines and special terminology. Now we shall have to turn our attention to a detailed résumé of the highlights of each point, namely:

1. the *stressors and conditioning agents*;
2. the *characteristic manifestations* of stress, including those that have diagnostic value;
3. the *diseases of adaptation*;
4. the *prophylaxis and treatment* of stress in general. (The management of diseases of adaptation will be discussed separately with each of these);
5. *theories* on the mechanism and general interpretation of stress reactions; and
6. *various other pertinent facts*, such as the legal and philosophic implications of the stress concept, as well as the societies, journals and institutes that deal with this subject.

In accordance with the principles of the analytico-synthetic style, in each instance we have started with a perusal of the entire pertinent literature, carefully collected by our library since the description of the stress syndrome in 1936. We have also included data published prior to 1936 that illustrate special aspects of the stress response, even though they were described before such implications could have been realized.

This analysis necessarily had to precede any attempt at a synthetic interpretation of the findings, and so in this volume we shall always begin with an analytic evaluation of the annotated references selected to illustrate each point. This résumé is meant only to act as a guide, assisting the reader in the selection of the individual papers he wishes to study in detail; it cannot pretend to offer a carefully reasoned evaluation of each point raised in the publications cited.

Trauma

Here, as in all subsequent sections of this guide to the stress literature, rapid orientation will be facilitated if we subdivide those topics about which an unusually large amount of data has been accumulated. This can be done according to various principles. For example, in the case of stressors, the material might be subdivided into separate observations on different species, age groups, the manifestations elicited in various targets, concurrent treatment with other stressors acting as conditioning agents, or even

just the chronologic order in which the observations were published. In this volume no uniform, rigid system has been adopted; instead, after the entire range of material available in each case had been studied, the subcategories were selected according to whatever system of classification appeared to be most convenient for the material at hand. Thus, in the present section, the subtitles refer to the most important target (which may be a chemical compound, or a morphologic or functional change); the section on Drugs classifies them alphabetically, while a later passage on Physical Agents used to elicit stress categorizes them according to their particular nature (for example, temperature variations, sound, rays, vibrations, electrical stimuli), and data on simple stressors, such as hemorrhage, are merely listed in chronologic order.

In most cases, the system of subdivision will be immediately obvious to the reader; any questions which might arise will be clarified by brief introductory explanations.

If the same publication deals with several especially important topics which must be considered in order to evaluate diverse aspects of stress, the publication will be included under each subdivision to which it is pertinent. To keep the synopsis of the stress literature as concise as possible, such duplications will be held to a minimum through the use of cross references in the event of heavily overlapping and inseparable subjects. For example, changes produced by stress in the ovaries should be considered under Sex as a conditioning factor which can influence stress susceptibility, and again under Sex in the section, Morphologic Changes. In all such instances, cross references will suffice to remind the reader of the additional sections under which he should search for relevant data.

However, those who really wish to gain access to as many data pertinent to their subject as possible are also advised to consult related sections using their own judgment, since even cross referencing has its practical limitations. For example, eosinopenia is listed as a morphologic characteristic of stress in general and also as a subdivision in almost all sections devoted to individual stressors, where this change has received special attention. It may be incidentally mentioned again in publications on any stressor, and of course, this cannot be indicated in every case by mere cross references. To illustrate, in the present section on Trauma, the subdivisions are arranged according to the stress manifestations that have received primary attention; eosinopenia may have been mentioned incidentally in almost any of these, and additional data will be found under the effect of trauma upon various Other Targets.

Finally, at the end of each section, we list data on the agent under study, when it is given in combination with some other agent which may modify its effect. However, relevant data will also be found under Multiple Stressors, when they illustrate cross-resistance or cross-sensitization in particular. Conversely, very general descriptions as well as reviews on the entire field are always listed under the name of the agent, characteristics, treatment, or theory under consideration.

Thus, in the present section, the subdivisions will be:

Generalities

ACTH and Corticoids

Catecholamines (EP, NEP)

STH

Insulin

Sex Hormones

Other Hormones

Histamine and 5-HT

Enzymes and Other Metabolites

Other Targets

Trauma + Other Agents

Generalities. Traumatic injury is one of the most commonly studied and most characteristic stressors, both in clinical and experimental medicine. Hence, the literature on its manifestations and prophylaxis has reached enormous proportions; nevertheless, the references given below will suffice for general orientation in this field. Acute and severe trauma causes typical alarm reaction changes in all species examined. In man, it is especially common, being an unavoidable consequence of surgery, in which case its manifestations are usually complicated by preoperative medication, anesthesia, anxiety, and loss of blood, making it quite impossible to determine the extent to which these associated factors have contributed to the production of any particular manifestation of surgical stress. (Hence, see also sections devoted to each of these agents.)

→**ACTH and Corticoids.** A rise in plasma ACTH and glucocorticoid levels is a very constant characteristic of stress; that it occurs regularly after traumatic injury has been well substantiated. ACTH is usually determined by bioassay on hypophysectomized rats, whereas corticoid levels are more accurately quantified by chemical methods. Data on 17-KS concentrations are difficult to interpret since these can be metabolites of either testosterone or corticoid hormones, whereas the levels of 11- or 17-hydroxycorticosteroids (11- or 17-OHCS), while not absolute, are more specific indicators of glucocorticoids in blood and urine.*

Since only the free steroids appear to be immediately effective in exerting their various biologic actions, a clear distinction should be made between these and their conjugates (for example, glucuronides or the transcortin-bound fraction).

The blood clearance of intravenously injected cortisol is delayed during surgical stress in man; this is perhaps partly due to impaired hepatic removal. Hence, a rise in blood corticoid levels cannot be ascribed solely to increased production.

In rats, traumatic stress (splenectomy) elicits an initial fall in the ACTH content of the pituitary within four hours, but after several days it reaches a peak of close to twice the normal level. Apparently, both the release and synthesis of ACTH are accelerated by surgical stress, the discharge being more rapid than resynthesis.

After gastrectomy, serum-free 17-OHCS levels in man rise more quickly than conjugated 17-OHCS, although the difference is not very impressive.

In adrenalectomized dogs given a constant intravenous infusion of cortisol, laparotomy induces a rise in free 17-OHCS, but this is not correlated with a fall in the plasma level of conjugated 17-OHCS, which either remains the same or is also increased. Presumably, the serum level of glucuronides is determined by multiple factors and is not an accurate index of their production or metabolism during surgery. In fact, there is good evidence that surgical interventions alter not only the absolute amount of corticoids excreted but also the rates of conjugation of free cortisol and cortisone.

Anesthesia and surgery decrease the binding of cortisol to albumin while the transcortin-binding capacity is unchanged.

→**Catecholamines (EP, NEP).** After surgical interventions in man, NEP is more constantly and significantly excreted in urine than is EP. However, the urinary excretion of both catecholamines rises significantly after serious surgical complications.

* At present, radioimmunologic techniques are being perfected.

→**STH.** In recent years, a good deal of evidence has been accumulated to support the view that plasma STH levels rise in the immediate postoperative period, reaching a peak after a few hours, as judged by radioimmunoassays. However, the response is often biphasic. Mere venipuncture can raise the blood STH level, especially in children. It has been postulated that STH may help to increase nonspecific resistance by providing a readily available source of energy in the form of FFA. Morphine anesthesia blocks not only cortisol but also STH production during surgical stress in man.

→**Insulin.** Several observations confirm that, in fasting men, plasma immunoreactive insulin concentrations are raised after surgical interventions simultaneously with the elevation of STH and cortisol. On the other hand, in rats the rise in plasma insulin caused by intravenous glucose is allegedly inhibited by trauma.

→**Sex hormones.** In general, traumatic as well as other stressors elicit a diminution of gonadotropic and gonadal hormones in both sexes, especially if exposure to the stressor is chronic. This is presumably a cause of the loss of libido and fertility in both sexes.

→**Other Hormones.** Plasma *vasopressin* levels rise in man following cardiac surgery and various cranial injuries. There is also some evidence that *thyroxine* metabolism and binding may be affected by trauma in the rat, and that, in patients after traumatic shocks, plasma *glucagon* and glucose levels rise considerably, often without any proportional increase in plasma *insulin*.

→**Histamine and 5-HT.** In mice, tourniquet shock allegedly activates 5-HT synthesis, which may interfere with the maintenance of circulatory homeostasis. In rats, some stressors deplete cerebral 5-HT and NEP, but this effect is produced neither by surgical shock nor by several other stressors, and is independent of the hypophysis.

→**Enzymes and Other Metabolites.** As compared with the many data on changes in cholesterol, glucose and enzyme mechanisms under the influence of various stressors, relatively little is known with regard to similar alterations during traumatic shock. Plasma renin activity in patients undergoing abdominal surgery is increased, but it remains to be shown that this is not a specific effect of interventions in the kidney region rather than a manifestation of stress.

→**Other Targets.** The other lesions ascribed to stress resulting from traumatic injuries are: eosinopenia, thrombocyte aggregation, and disseminated intravascular thromboembolism, as well as acceleration of fibrinolysis, circulatory disturbances, peptic ulcers, depression of RES activity, and psychologic changes related to the necessity of coping mentally with this form of stress.

+**Other Agents.** Age does not appear to play an important role in conditioning the hormonal response to traumatic injury. Adrenal ascorbic acid depletion following laparotomy in newborn rats is similar to that in adults, and children respond to cardiac catheterization with essentially the same corticoid excretion as adults.

Various *anesthetics* produce different intensities of 17-OHCS discharge in man but

subsequent surgery always causes a further rise. In rats, pentobarbital does not prevent tourniquet shock-induced ACTH discharge.

Mice survive tourniquet trauma better when kept at high rather than low *temperatures*.

Even *seasonal variations* in trauma sensitivity have been described, rats being more susceptible to trauma in November than in June or July.

Despite considerable work on the optimal *diet* needed to heighten resistance to trauma, all we can definitely say is that both excess and deficiency in food intake are detrimental.

Genetic factors also affect resistance to traumatic shock, but as yet, this subject has hardly been explored.

Trauma

(See also our earlier stress monographs, p. xiii)

Generalities. Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). A56,032/36

First detailed description of the "alarm reaction" characterized by adrenocortical enlargement with acute loss of lipids, thymic colymphatic atrophy and decreased body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP).

Noble, R. L., Collip, J. B.: "A quantitative method for the production of experimental traumatic shock without haemorrhage in unanaesthetized animals." *Q. J. Exp. Physiol.* **31**: 187-199 (1942). A56,106/42

Detailed description of the "Noble-Collip drum," which permits the production of graded degrees of shock in guinea pigs and rats by forcing them to run to avoid tumbling against projections and traumatizing themselves. This leads to typical thymus atrophy, adrenal hypertrophy, and other manifestations of the alarm reaction.

Hayes, M. A.: "Shock and the adrenocortex." *Surgery* **35**: 174-190 (1954). B93,820/54

Surgery produces various patterns of adrenocortical response depending "on the severity of the incurred stress and the availability of endogenous adrenocortical hormone to effect the necessary homeostatic readjustments."

Moore, F. D.: "Endocrine changes after anesthesia, surgery, and unanesthetized trauma in man." *Recent Prog. Horm. Res.* **13**: 511-582 (1957). C38,191/57

Review on the stressor effect of traumatic injuries, with special reference to their pathogenesis (126 refs.).

Selye, H., Bajusz, E.: "The stress concept as applied to traumatology. Part I." *Acta Chir. Acad. Sci. Hung.* **1**: 305-320; 347-362 (1960). C80,765/60

Extensive review on systemic and local stress in relation to traumatology (38 refs.).

Aho, A. J., Hormia, M.: "Effect of a mechanical abdominal stress on adrenal cortex. A comparison between the effects of ligation of the upper and lower part of the gastrointestinal tract." *Ann. Med. Fenn.* **38**: 367-380 (1960). D5,261/60

In rats, obstruction of the intestinal tract causes more intense and acute typical alarm reaction changes when placed near the pylorus than at lower levels (20 refs.).

Petri, G., Kovács, G. S., Kovács, B. M.: "The postoperative state as a stressor." *Bull. Soc. Int. Chir.* **20**: 183-189 (1961). D12,093/61

Bollobás, B.: "Experimentelle Untersuchung der Abwehr der bei otorhinolaryngologischen Eingriffen auftretenden Aggressionen mittels Blutdruckmessung" (Experimental study on the prevention of stress in otorhinolaryngologic surgery by blood pressure measurement). *H.N.O. (Berlin)* **9**: 327-331 (1961) (39 refs.). J23,042/61

Gasparetto, A.: "Evoluzione storica, valida teorica ed attualità pratica del concetto di stress chirurgico" (Historical evolution,

theoretical validity, and practical updating of the concept of surgical stress). *Acta Anesthesiol.* (Padova) **12**: 1-48 (1961).

D23,496/61

Johnston, I. D. A.: "Endocrine aspects of the metabolic response to surgical operation." *Ann. R. Coll. Surg. Engl.* **35**: 270-286 (1964).

G22,769/64

Hunterian Lecture on endocrine and metabolic responses to the stress of surgery.

Schumer, W.: "Metabolic considerations in the preoperative evaluation of the surgical patient." *Surg. Gynecol. Obstet.* **121**: 611-620 (1965).

F48,023/65

Review on the stress caused by surgical interventions, with special emphasis upon metabolic and hormonal changes (58 refs.).

Estep, H. L.: "Neuroendocrine aspects of surgical stress." In: Bajusz, E., *An Introduction to Clinical Neuroendocrinology*, p. 106. Basel and New York: S. Karger, 1967.

E6,578/67

Brief review on the principal factors involved in "surgical stress."

Schultis, K.: "Stress und Adaptions-syndrom aus chirurgischer Sicht" (Stress and the general adaptation syndrome in surgery). *Dtsch. Med. Wochenschr.* **96**: 1339-1342 (1971) (16 refs.).

H44,918/71

Warnes, H.: "Delayed after effects of medically induced abortion." *Can. Psychiatr. Assoc. J.* **16**: 537-541 (1971).

J20,188/71

Both the psychologic and somatic effects of abortion cause clearcut stress reactions (28 refs.).

Johns, M. W., Dudley, H. A. F., Master-ton, J. P.: "Psychosocial problems in surgery. A review." *J. Roy. Coll. Surg. Edinb.* **18**: 91-102 (1973).

J21,704/73

Strizhova, N. V., Makarova, L. D.: "State of the sympathico-adrenal system in the early post-operative period." *Eksp. Khir. Anesteziol.* No. 4: 44-49 (1974) (Russian).

H97,034/74

Day, S. B. (ed.): *Trauma*, p. 379. New York and London: Plenum Press, 1975.

E10,852/75

Monograph with a special chapter on homeostasis and heterostasis in relation to traumatic injuries.

→ **ACTH and Corticoids.** Forbes, A. P., Donaldson, E. C., Reifenstein, E. C. Jr., Al-

bright, F.: "The effect of trauma and disease on the urinary 17-ketosteroid excretion in man." *J. Clin. Endocrinol.* **7**: 264-288 (1947).

98,825/47

In normal individuals, 17-KS excretion usually rises for one to three days following injury and then almost always falls until convalescence. "In those debilitated patients where an alarm is not followed by a rise in 17-ketosteroids it is probable that, due to a previous alarm, they are already in the stage of resistance or even approaching the stage of exhaustion.... In chronically ill or debilitated individuals on the other hand, the initial level is subnormal and the response to injury usually small or absent. It is believed that these findings are further evidence that alterations in adrenal cortical function are an integral part of the adaptation syndrome of Selye and a link in our understanding of the part this syndrome plays in clinical medicine."

Franksson, C., Gemzell, C. A.: "Blood levels of 17-hydroxycorticosteroids in surgery and allied conditions." *Acta Chir. Scand.* **106**: 24-30 (1954).

E93,931/54

After surgical interventions and other traumatic procedures, plasma 17-OHCS greatly increase in man, reaching a peak on the first postoperative day and returning to normal within one to two weeks. Eosinopenia, 17-KS excretion, and erythrocyte sedimentation rates are less consistently altered by these stressors.

Moncrief, J. A., Weichselbaum, T. E., Elman, R.: "Changes in adrenocortical steroid concentration of peripheral plasma following surgery." *Surg. Forum* **4**: 469-473 (1954).

J11,248/54

Comparison of 17-OHCS levels in the plasma of chronically ill patients during fasting and in those with malignancies revealed higher levels in the latter group. After major operations, blood 17-OHCS levels rose in both groups, falling to normal within twenty-four hours.

Hume, D. M., Nelson, D. H.: "Adrenal cortical function in surgical shock." *Surg. Forum* **5**: 568-575 (1954).

E40,942/54

In the dog, surgical trauma markedly increases the 17-OHCS content of adrenal venous blood over that of convalescent animals, in which ACTH secretion drops considerably and shows intermittent variations. The cortex maintains high corticoid levels in severe shock despite substantially reduced blood

flow. However, when blood pressure drops to less than 35 mm. Hg, adrenal blood flow becomes so low that corticoid output is significantly diminished unless blood transfusions overcome the hypotension. Hemorrhage can increase corticoid output even above the level seen in surgical shock.

Sandberg, A. A., Eik-Nes, K., Samuels, L. T., Tyler, F. H.: "The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man." *J. Clin. Invest.* **33**: 1509-1516 (1954). B99,413/54

Surgical interventions cause a rapid increase in plasma 17-OHCS within the first hour. Intravenous cortisol is not cleared from the blood as rapidly during surgical stress as otherwise. Presumably, not only increased corticoid secretion but also decreased clearance contribute to the raised blood corticoid levels.

Franksson, C., Gemzell, C. A., Euler, U. S. von.: "Cortical and medullary adrenal activity in surgical and allied conditions." *J. Clin. Endocrinol. Metab.* **14**: 608-621 (1954).

B94,357/54

Immediately following surgery, all twenty-seven patients examined showed elevated 17-OHCS blood levels. The values were highest with shock or other complications. Urinary EP levels remained approximately within normal limits, but NEP values were occasionally high during the first seven days. The urinary concentration of both catecholamines were more often increased in patients with post-operative complications. "Determination of both the 17-OH blood level and catecholamine excretion may give valuable information as to the physiologic state of the patient."

Tyler, F. H., Schmidt, C. D., Eik-Nes, K., Brown, H., Samuels, L. T.: "The role of the liver and the adrenal in producing elevated plasma 17-hydroxycorticosteroid levels in surgery." *J. Clin. Invest.* **33**: 1516-1523 (1954). B99,414/54

Metabolic studies in man suggest that "the increased plasma levels of 17-hydroxycorticosteroid after surgery are the result of both increased adrenal secretion of these steroids and impaired hepatic removal."

Helmreich, M. L., Jenkins, D., Swan, H.: "The adrenal cortical response to surgery. II. Changes in plasma and urinary corticosteroid levels in man." *Surgery* **41**: 895-909 (1957) (25 refs.). C36,878/57

LeFemine, A. A., Marks, L. J., Teter, J. G., Leftin, J. H., Leonard, M. P., Baker, D. V.: "The adrenocortical response in surgical patients." *Ann. Surg.* **146**: 26-39 (1957).

D80,874/57

Hume, D. M.: "The secretion of epinephrine, norepinephrine and corticosteroids in the adrenal venous blood of the dog following single and repeated trauma." *Surg. Forum* **8**: 111-115 (1958).

D60,528/58

Hammond, W. G., Vandam, L. D., Davis, J. M., Carter, R. D., Ball, M. R., Moore, F. D.: "Studies in surgical endocrinology. IV. Anesthetic agents as stimuli to change in corticosteroids and metabolism." *Ann. Surg.* **148**: 199-211 (1958).

C57,405/58

"General anesthesia produced by Pentothal, nitrous oxide and d-tubo-curare in any combination was associated with significant changes in blood or urinary 17-hydroxycorticoid values. . . . Operation under Pentothal-N₂O-d-tubo-curare anesthesia was followed by an elevation of the free blood 17-OHCS, but the magnitude of the rise was not as great as that seen with operation under ether."

Fortier, C.: "Adenohypophyseal corticotrophin, plasma free corticosteroids and adrenal weight following surgical trauma in the rat." *Arch. Int. Physiol. Biochim.* **67**: 333-340 (1959).

C70,912/59

In rats, traumatic stress (splenectomy) caused a rapid fall in pituitary ACTH within four hours but after one to four days it rose to a peak of about twice the normal level. Plasma free corticoids rose to 600 percent of the baseline during the first hour and returned to normal within twenty-four hours. Adrenal weight increased to 120 percent of the controls within twelve hours and stabilized at this level until four days postoperatively, when it returned to normal values. It is suggested that "the rates of corticotrophin release and synthesis are accelerated, in successive and overlapping stages, by a mechanism triggered by stress, and depressed, in a similar fashion, by the elevation of the steroid level."

Steenburg, R. W., Smith, L. L., Moore, F. D.: "Conjugated 17-hydroxycorticosteroids in plasma: measurement and significance in relation to surgical trauma." *J. Clin. Endocrinol. Metab.* **21**: 39-52 (1961).

C98,414/61

In man, gastrectomy caused a rapid rise in the level of serum free 17-OHCS and a slower elevation of conjugated 17-OHCS, but

these differences were not statistically significant. In adrenalectomized dogs receiving constant intravenous infusion of cortisol, laparotomy elicited a rise in plasma free 17-OHCS, but this manifestation of a delay in steroid metabolism was not correlated with a fall in the plasma level of conjugated 17-OHCS, which remained the same or actually increased. "It is concluded that the serum concentration of glucuronide conjugates is determined by multiple factors, only one of which is the rate of their production. As such, their concentration in serum does not reflect the changes in the rate of steroid metabolism that often occur following surgical operations."

Cooper, C. E., Nelson, D. H.: "ACTH levels in plasma in preoperative and surgically stressed patients." *J. Clin. Invest.* **41**: 1599-1605 (1962) (33 refs.). D29,555/62

Espinier, E. A.: "Urinary cortisol excretion in stress situations and in patients with Cushing's syndrome." *J. Endocrinol.* **35**: 29-44 (1966). F66,914/66

Dörner, G., Stahl, F., Wendt, F., Schädlich, M.: "Beurteilung der Nebennierenrindenfunktion beim Operationsstress durch fluorimetrische Bestimmung von unkonjugiertem Kortisol und Kortikosteron im Plasma und Harn" (Evaluation of adrenal cortex function in surgical stress by fluorometric determination of unconjugated cortisol and corticosterone in plasma and urine). *Brunns Beitr. Klin. Chir.* **212**: 467-480 (1966).

G45,937/66

By use of an improved method for the fluorometric determination of unconjugated cortisol and corticosterone (11-OHCS), a distinct rise in blood and urine was noted. "The method easily allows to estimate quantitatively stress reactions of the hypothalamic-anterior lobe pituitary-suprarenal cortical system."

Olthoff, D., Gawellek, F.: "Die Ausscheidung von Nebennierenhormonen nach akuten Erkrankungen, Verletzungen und Operationen" (The excretion of adrenal gland hormones after acute diseases, injuries and surgery). *Zentralbl. Chir.* **92**: 1364-1367 (1967). F91,166/67

Hartenbach, W.: "Die Bedeutung der adreno-kortikalen Zusammenhänge für die allgemeine Chirurgie" (The importance of adrenocortical associations in general sur-

gery). *Zentralbl. Chir.* **92**: 1349-1355 (1967). F91,163/67

Review on the stressor effect of various operations with special emphasis upon urinary and blood corticoid levels.

Uozumi, T., Tanaka, H., Hamanaka, Y., Seki, T., Matsumoto, K., Akehi, A.: "Changes of urinary steroids following major surgical stress." *Endocrinol. Jap.* **14**: 7-10 (1967). F80,642/67

In patients who underwent pulmonary lobectomy, urinary excretion of 17-OHCS remained almost unchanged, but 17-KS clearance decreased gradually. Furthermore, "the ratios of etiocholanolone to androsterone and tetrahydrocortisone + tetrahydrocortisol + cortisol to allotetrahydrocortisol increased significantly following operation, even 6 to 8 months after surgical stress. It is suggested that these findings of urinary steroids following operation may reflect some of the non-specific metabolic responses to a major surgical stress."

Asfeldt, V. H., Elb, S.: "Hypothalamo-pituitary-adrenal response during major surgical stress." *Acta Endocrinol. (Kh.)* **59**: 67-75 (1968). H2,076/68

As indicated by the fall in plasma corticosteroids during surgical interventions in man, "suppression by dexamethasone has no influence on the hypothalamic pituitary adrenal response to major acute stress."

Gottfried, I., Lewenthal, H., Goldberg, S.: "Free 11-hydroxycorticosteroids in plasma and urine in pregnancy and in cases of stress." *Am. J. Obstet. Gynecol.* **102**: 924-927 (1968). G62,921/68

The free plasma and urinary 11-OHCS levels were measured in normal nonpregnant and normal pregnant women, those with a suspected fetal death, and in female patients after surgical stress.

Fossati, P.: "Manifestations endocrino-métaboliques de l'aggression cérébrale" (Endocrine-metabolic reactions to cranial injury). *Acta Anaesthesiol. Belg.* **19**: 284-307 (1968). G70,695/68

Cranial injuries produce general reactions to stress as well as other specific effects. The plasma cortisol level increases, as does the urinary output of 17-KS and 17-OHCS. "Production of ADH is also increased. A diencephalo-pituitary deficiency may be caused by the rupture of the pituitary stem or by ischaemic necrosis of the hypophysis" (49 refs.).

Plumpton, F. S., Besser, G. M.: "The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects." *Br. J. Surg.* **56**: 216-219 (1969). H9,868/69

In patients undergoing major surgery or experiencing insulin hypoglycemia, concurrent prednisolone administration usually (though not always) failed to produce the increase in plasma corticoids normally elicited by these stressors, but only for a limited length of time.

Sólyom, J., Sturcz, J., Spát, A., Mészáros, I., Ludwig, E.: "In vitro steroid production by the adrenal gland of intact rats and rats subjected to surgical stress." *Acta Physiol. Acad. Sci. Hung.* **36**: 371-377 (1969).

J22,416/69

Tanaka, H., Manabe, H., Koshiyama, K., Hamanaka, Y., Matsumoto, K., Uozumi, T.: "Excretion patterns of 17-ketosteroids and 17-hydroxycorticosteroids in surgical stress." *Acta Endocrinol. (Kbh.)* **65**: 1-10 (1970).

H30,321/70

Wendt, F.: "Die postoperative Stress-Reaktion bei relativer Nebennierenrindeninsuffizienz im Vergleich zum Standardverhalten" (Postoperative stress reaction with respect to relative adrenocortical insufficiency in comparison with standard behavior). *Endokrinologie* **56**: 339-346 (1970).

H33,161/70

Hamanaka, Y., Manabe, H., Tanaka, H., Monden, Y., Uozumi, T., Matsumoto, K.: "Effects of surgery on plasma levels of cortisol, corticosterone and non-protein-bound-cortisol." *Acta Endocrinol. (Kbh.)* **64**: 439-451 (1970). H27,377/70

In preoperative patients, plasma cortisol levels reached a peak at 06:00 and a low at 22:00. There was a steep rise in cortisol levels two to four hours after the end of the operation. Plasma corticosterone levels roughly paralleled these values. The percentage of nonprotein-bound plasma cortisol remained almost the same throughout the day, but it too increased postoperatively.

King, L. R., McLaurin, R. L., Lewis, H. P., Knowles, H. C. Jr.: "Plasma cortisol levels after head injury." *Ann. Surg.* **172**: 975-984 (1970). G80,265/70

Spandri, P., Ambrosio, G., Binda, F., Meo, A., Mingrino, S., Grandesso, R.: "Il comportamento dell'asse diencefalo-ipofiso-surrenale nel coma da trauma cranico" (The

function of the diencephalic-hypophyseal-adrenal axis in coma due to cranial trauma). *Minerva Med. Giul.* **10**: 26-30 (1970).

H25,551/70

In coma caused by cranial injury, the circadian rhythm of plasma corticoids, as well as their response to ACTH, vasopressin and metopyrone, are frequently abnormal (12 refs.).

Newsome, H. H., Rose, J. C.: "The response of human adrenocorticotrophic hormone and growth hormone to surgical stress." *J. Clin. Endocrinol. Metab.* **33**: 481-487 (1971).

H45,875/71

Observations on patients who have undergone various forms of surgery suggest that STH and ACTH plasma levels rise in a parallel fashion and are presumably mediated through a common afferent pathway in the spinal cord.

Wendt, F.: "Die überschüssende hypothalamo-hypophysär-adrenale Stress-Reaktion" (Excessive hypothalamo-hypophyseal-adrenal stress reaction). *Endokrinologie* **60**: 347-355 (1972).

H64,939/72

Funyu, T., Kudo, S., Shiraiwa, Y., et al.: "Changes in the fraction of urinary free 17-OHCS during surgical stress." *Folia Endocrinol. Jap.* **48**: 432-442 (1972) (Japanese).

J20,199/72

Kudo, S., Terayama, Y., Tamura, M., et al.: "Fluctuation of urinary 17-OHCS fractions in before and after surgical stress." *Clin. Endocrinol. (Tokyo)* **20**: 149-156 (1972) (Japanese).

J20,752/72

Kawamura, J.: "Clinical studies on the changes of blood and urinary glucocorticoid in renal failure. I. The change of blood glucocorticoid in acute renal failure with special regard to the plasma cortisol level and blood cell sodium and potassium under stress condition." *Acta Urol. (Kyoto)* **18**: 185-221 (1972) (Japanese). H81,033/72

In patients with acute renal failure treated by hemodialysis or peritoneal lavage, plasma cortisol levels rose, perhaps owing to a decrease in urinary 17-OHCS excretion. "Besides, in acute renal failure, stress such as surgery or trauma might have stimulated the hypothalamo-pituitary-adrenocortical system promoting cortisol excretion from the adrenal" (168 refs.).

Khomitskaya, L. F.: "Glucocorticoid function of the adrenals during surgery involving excision of the tumors of cerebral hemi-

spheres." *Vop. Neirokhir.* **36** No. 5: 27-32 (1972) (Russian). H81,437/72

After surgical interventions, urinary 17-OHCS excretion rose in sixty-two patients. Previous responses to ACTH did not correctly foretell the intensity of such stress reactions.

Spät, A., Józan, S.: "Displacement analysis of aldosterone and corticosterone in the rat adrenal venous blood." *J. Steroid Biochem.* **4**: 509-518 (1973). J9,302/73

Simultaneous determination of aldosterone and corticosterone levels in the adrenal venous blood of rats using a new technique. Even the mild stress of changing the environment caused consistent increases in corticosterone but rises in aldosterone were only irregularly observed, even after severe surgical stress.

Fossati, P., Lefebvre, J., Cappoen, J. P., Racadot, A., Lesaffre, J., Laine, E., Linquette, M.: "La fonction gluco-corticoïde du traumatisé crânien" (Glucocorticoid function in patients with cranial injury). *Ann. Endocrinol.* (Paris) **34**: 145-157 (1973).

H71,925/73

In patients with cranial injury, the increased values of plasma cortisol, corticosterone and dialysable cortisol diminish progressively within a week, as they do following surgery (41 refs.).

Funyu, T., Kudoh, S., Shiraiwa, Y., Terayama, Y., Nigawara, K., Hitomi, H.: "Changes in fractions of urinary free 17-hydroxy-corticosteroids before and after operation." *Tohoku J. Exp. Med.* **111**: 61-69 (1973). H81,184/73

The stress of surgical operations alters not only the absolute amount of corticoids excreted, but also the rates of conjugation of free cortisol and cortisone.

Allen, J. P., Kendall, J. W., McGilvra, R., Lamorena, T. L., Castro, A.: "Adrenocorticotrophic and growth hormone secretion. Studies during pneumoencephalography." *Arch. Neurol.* **31**: 325-328 (1974).

J17,778/74

"Associated with the stress of the procedure, both ACTH and growth hormone concentrations increased in the plasma without a corresponding change in CSF levels of these two hormones."

Kehlet, H., Binder, C., Engbaek, C.: "Cortisol binding capacity in plasma during

anaesthesia and surgery." *Acta Endocrinol.* (Kh.) **75**: 119-124 (1974). H81,710/74

In man, anesthesia and surgery decrease the binding of cortisol to albumin while transcortin binding capacity remains unchanged.

Hollmann, G., Fischer, A., Körner, J.: "Besonderheiten der Pathophysiologie des Operationstraumas im Kindesalter" (Peculiarities of the pathophysiology of surgical trauma in children). *Münch. Med. Wochenschr.* **116**: 1213-1218 (1974). H88,808/74

In children undergoing major operations the sympathetic adrenergic response is more manifest than in adults, and while the plasma cortisol levels often show little or no rise, indirect metabolic reactions suggest that excess aldosterone production occurs in response to a special need at an early age (20 refs.).

→**Catecholamines (EP, NEP).** Franksen, C., Gemzell, C. A., Euler, U. S. von.: "Cortical and medullary adrenal activity in surgical and allied conditions." *J. Clin. Endocrinol. Metab.* **14**: 608-621 (1954).

B94,357/54

Immediately following surgery, all twenty-seven patients examined showed elevated 17-OHCS blood levels. The values were highest in patients with shock or other complications. Urinary EP levels remained within approximately normal limits, but NEP values were occasionally high during the first seven days. The urinary concentration of both catecholamines increased more often in patients with postoperative complications. "Determination of both the 17-OH blood level and catecholamine excretion may give valuable information as to the physiologic state of the patient" (21 refs.).

Klensch, H.: "Der basale Noradrenalin-spiegel im peripheren venösen Blut des Menschen" (The basal noradrenaline content in the peripheral venous blood of man). *Pflügers Arch.* **290**: 218-224 (1966).

F69,584/66

Insertion of a cannula into the cubital vein raises blood pressure and pulse rate for only about ten minutes, whereas NEP levels remain elevated for about twenty minutes.

Carruthers, M., Taggart, P., Conway, N., Bates, D., Somerville, W.: "Validity of plasma-catecholamine estimations." *Lancet* July 11, 1970, pp. 62-67. H27,193/70

In man, venipuncture raises the blood catecholamine content. When several samples

are taken through an indwelling catheter, the results are not significantly altered although strong individual variations make interpretation difficult.

Klensch, H., Gött, U.: "Liquor-Adrenalin und -Noradrenalin im Operationsstress" (CSF-adrenaline and -noradrenaline in surgical stress). *Klin. Wochenschr.* **48**: 853-855 (1970). H27,637/70

In man, the stress of surgical operations causes a more pronounced rise in the NEP content of the CSF than in that of the plasma, whereas the EP level does not vary significantly.

Nikki, P., Takki, S., Tammisto, T., Jäätelä, A.: "Effect of operative stress on plasma catecholamine levels." *Ann. Clin. Res.* **4**: 146-151 (1972). G92,448/72

Rao, L. N., Bhatt, H. V.: "Stress response during surgery and anesthesia indicated by norepinephrine concentration in plasma of surgical patients." *Int. Surg.* **57**: 294-298 (1972). H54,659/72

Eisele, R., Lohmann, F. W., Kötter, D., Nasseri, M.: "Das Verhalten der Plasmakatecholamine nach Bauchoperationen beim Menschen" (Plasma catecholamine levels after abdominal operations in man). *Langenbecks Arch. Chir.* **336**: 103-113 (1974) (27 refs.). J17,952/74

Takki, S., Tammisto, T.: "The effect of operative stress on plasma catecholamine levels in chronic alcoholics." *Acta Anaesthesiol. Scand.* **18**: 127-132 (1974).

J15,791/74

In chronic alcoholics tolerance to anesthetics is reflected in an increased sympathetic activity during operative stress.

Hashimoto, Y., Kurobe, Y., Hirota, K.: "Effect of delivery on serum dopamine- β -hydroxylase activity and urinary vanillyl mandelic acid excretion of normal pregnant subjects." *Biochem. Pharmacol.* **23**: 2185-2187 (1974). H89,340/74

"The emotional and physiological stress of delivery" produced an increase in serum dopamine- β -hydroxylase and VMA.

→**STH.** Ross, H., Johnston, I. D. A., Wellborn, T. A., Wright, A. D.: "Effect of abdominal operation on glucose tolerance and serum levels of insulin, growth hormone, and hydrocortisone." *Lancet* September 10, 1966, pp. 563-566. F69,882/66

In man, abdominal operations produce high fasting blood glucose levels and reduced tolerance to intravenous glucose. Fasting plasma insulin levels are raised postoperatively, and intravenous glucose produces greater elevations of serum insulin and STH in the immediate postoperative period.

Ketterer, H., Powell, D., Unger, R. H.: "Growth hormone response to surgical stress." *Clin. Res.* **14**: 65 (1966). F82,744/66

Radioimmunoassays show that human plasma STH levels rise within an hour after surgery, reach a peak after two to four hours, and may remain elevated for days postoperatively.

Krulich, L., McCann, S. M.: "Influence of stress on the growth hormone (GH) content of the pituitary of the rat." *Proc. Soc. Exp. Biol. Med.* **122**: 612-616 (1966).

F67,299/66

In rats, pituitary STH activity (epiphysial cartilage test) was initially decreased and then increased after splenectomy. Formalin injections and the ringing of a doorbell raised pituitary STH, cold (3°C) depleted it and fasting caused a biphasic reaction with an initial depletion and a return to normal followed by a secondary depletion after about three days. These and other data suggest that STH secretion in the rat "is very labile and influenced by a variety of stresses as well as by alterations in the supply of available carbohydrate."

Copinschi, G., Hartog, M., Earll, J. M., Havel, R. J.: "Effect of various blood sampling procedures on serum levels of immunoreactive human growth hormone." *Metabolism* **16**: 402-409 (1967). F83,864/67

Arterial catheterization caused a rise in serum immunoreactive STH. For unknown reasons, infusion of NEP and a cold-pressor test elicited no similar change although the literature shows many examples of such a rise in man and animals after exposure to various stressors (28 refs.).

Helge, H., Weber, B., Quabbe, H. J.: "Growth-hormone release and venipuncture." *Lancet* January 25, 1969, p. 204.

H7,240/69

After a brief review of the literature on stress-induced increases in plasma STH, the authors report personal observations showing that venipuncture produces this effect more commonly in children than in adults or in newborns. "These observations suggest that, for children more often than for newborns or

adults, a rather harmless medical procedure can represent an iatrogenic stress."

Newsome, H. H., Rose, J. C.: "The response of human adrenocorticotropic hormone and growth hormone to surgical stress." *J. Clin. Endocrinol. Metab.* **33**: 481-487 (1971). H45,875/71

Observations on patients who have undergone various forms of surgery suggest that STH and ACTH plasma levels rise in a parallel fashion and are presumably mediated through a common afferent pathway in the spinal cord.

Geser, C. A., Felber, J. P., Brand, E., Schultis, K.: "Untersuchungen zur Glucagon-induzierten Sekretion von Wachstumshormon und Insulin und deren Einfluss auf Parameter des Kohlenhydrat- und Fettstoffwechsels nach einem Operationsstress" (Studies on glucagon-induced secretion of growth hormone and insulin and its influence on the parameters of carbohydrate and lipid metabolism following surgical stress). *Klin. Wochenschr.* **49**: 1175-1182 (1971). H48,219/71

Carey, L. C., Cloutier, C. T., Lowery, B. D.: "Growth hormone and adrenal cortical response to shock and trauma in the human." *Ann. Surg.* **174**: 451-460 (1971).

G86,425/71

In U.S. Marines injured during battle plasma STH levels rose markedly and constantly, whereas cortisol concentrations remained normal or were only slightly elevated. It is possible that STH provides an additional energy source in the form of FFA. The literature on STH secretion during various other types of stress is briefly reviewed. In the discussion following this paper it is mentioned that cortisol excretion apparently is minimal in stress associated with severe shock. However, some investigators have found very high cortisol levels following fatal traumatic injury (26 refs.).

Salter, C. P., Fluck, D. C., Stimmmer, L.: "Effect of open-heart surgery on growth hormone levels in man." *Lancet* October 21, 1972, pp. 853-854. H59,995/72

Plasma STH levels rose dramatically during open-heart surgery and fell to virtually normal within seven days.

George, J. M., Reier, C. E., Lanese, R. R., Rower, J. M.: "Morphine anesthesia blocks cortisol and growth hormone response to sur-

gical stress in humans." *J. Clin. Endocrinol. Metab.* **38**: 736-741 (1974). H86,212/74

Singh, A. K., Chansouria, J. P. N., Singh, R. K., Wahi, R. S., Udupa, K. N.: "Hormonal and metabolic alterations following surgical trauma." *Fifth Asia & Oceania Congr. Endocr.*, pp. 50-51. Chandigarh, India, 1974. H82,068/74

In man, the stress of major surgery caused an increase in plasma STH, cortisol and FFA, and a decrease in plasma insulin.

Allen, J. P., Kendall, J. W., McGilvra, R., Lamorena, T. L., Castro, A.: "Adrenocorticotropic and growth hormone secretion. Studies during pneumoencephalography." *Arch. Neurol.* **31**: 325-328 (1974).

J17,778/74

"Associated with the stress of the procedure, both ACTH and growth hormone concentrations increased in the plasma without a corresponding change in CSF levels of these two hormones."

→**Insulin.** Ross, H., Johnston, I. D. A., Welborn, T. A., Wright, A. D.: "Effect of abdominal operation on glucose tolerance and serum levels of insulin, growth hormone, and hydrocortisone." *Lancet* September 10, 1966, pp. 563-566. F69,882/66

In man, abdominal operations are followed by high fasting blood glucose levels and reduced tolerance to intravenous glucose. Fasting plasma insulin levels are raised post-operatively, and intravenous glucose produces greater elevations of serum insulin and STH in the immediate postoperative period.

Geser, C. A., Felber, J. P., Brand, E., Schultis, K.: "Untersuchungen zur Glucagon-induzierten Sekretion von Wachstumshormon und Insulin und deren Einfluss auf Parameter des Kohlenhydrat- und Fettstoffwechsels nach einem Operationsstress" (Studies on glucagon-induced secretion of growth hormone and insulin and its influence on the parameters of carbohydrate and lipid metabolism following surgical stress). *Klin. Wochenschr.* **49**: 1175-1182 (1971). H48,219/71

Vigaš, M., Németh, S., Jurčovičová, J.: "Stress-induced inhibition of insulin release in non-conditioned and conditioned rats." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 143-150. Bratislava: Slovak Academy of Sciences, 1973. E10,464/73

Whereas normal rats responded to 1 gm. per kg. intravenous glucose by a prompt rise

in plasma immunoreactive insulin, this reaction was completely suppressed after traumatization in the Noble-Collip drum. The blockade was prevented by bilateral adrenalectomy or by repeating the injury daily for 7 days (13 refs.).

Koch, G.: "Vergleichende Untersuchungen über das Blutglukose- und Plasmainsulinverhalten am traumatisierten Kaninchen" (Blood glucose and plasma insulin levels of traumatized rabbits, an experimental study). *Bruns Beitr. Klin. Chir.* **221**: 158-163 (1974). J17,605/74

In rabbits, surgical trauma causes hyperglycemia and an increase in plasma insulin, both of which are ascribed to the G.A.S.

Singh, A. K., Chansouria, J. P. N., Singh, R. K., Wahi, R. S., Udupa, K. N.: "Hormonal and metabolic alterations following surgical trauma." *Fifth Asia & Oceania Congr. Endocr.*, pp. 50-51. Chandigarh, India, 1974. H82,068/74

In man, the stress of major surgery caused an increase in plasma STH, cortisol and FFA, and a decrease in plasma insulin.

Vigaš, M., Németh, S., Jurčovičová, J.: "Effect of trauma on insulin response to glucose in thyroidectomized rats." *Endocrinol. Exp.* **8**: 147-151 (1974). H88,658/74

The degree of posttraumatic decrease in insulin secretion following glucose administration is diminished by thyroidectomy.

→**Sex Hormones.** Eiff, A. W. von, Plötz, E. J., Beck, K. J., Czernik, A.: "The effect of estrogens and progestins on blood pressure regulation of normotensive women." *Am. J. Obstet. Gynecol.* **109**: 887-892 (1971). G81,851/71

Both folliculoids and luteoids enhance the rise in blood pressure, respiratory rate and muscle tone in ovariectomized women performing a simple arithmetic task with or without noise.

Monden, Y., Koshiyama, K., Tanaka, H., Mizutani, S., Aono, T., Hamanaka, Y., Uozumi, T., Matsumoto, K.: "Influence of major surgical stress on plasma testosterone, plasma LH and urinary steroids." *Acta Endocrinol. (Kbh.)* **69**: 542-552 (1972). H52,372/72

Aono, T., Kurachi, K., Mizutani, S., Hamanaka, Y., Uozumi, T.: "Influence of major surgical stress on plasma levels of testosterone, luteinizing hormone and follicle-

stimulating hormone in male patients." *J. Clin. Endocrinol. Metab.* **35**: 535-542 (1972). H59,966/72

→**Other Hormones.** Goldenberg, I. S., Hayes, M. A., Greene, N. M.: "Endocrine responses during operative procedures." *Ann. Surg.* **150**: 196-201 (1959). C72,662/59

In man, *thyroid* activation has been observed after surgery, as reflected by circulating PBI-131.

Gejrot, T., Notter, G.: "Effects of surgical stress on thyroid function in man." *Acta Otolaryngol. (Stockh.)* **55**: 2-10 (1962). D57,721/62

The uptake of radioiodide by the *thyroid* was decreased during the first forty-eight hours after surgery but increased thereafter.

Fossati, P.: "Manifestations endocrinométaboliques de l'agression cérébrale" (Endocrine-metabolic reactions to cranial injury). *Acta Anaesthesiol. Belg.* **19**: 284-307 (1968). G70,695/68

Cranial injuries produce general reactions to stress. Plasma cortisol increases and so does the urinary output of 17-KS and 17-OHCS. "Production of *ADH* is also increased. A diencephalo-pituitary deficiency may be caused by the rupture of the pituitary stem or by ischaemic necrosis of the hypophysis" (49 refs.).

Richards, J. R., Harland, W. A., Orr, J. S.: "Factors affecting thyroid hormone metabolism in experimental trauma." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 151-161. Bratislava: Slovak Academy of Sciences, 1973. E10,465/73

In rats, fractures of the femur cause a transient increase in *thyroxine* secretion without any change in serum thyroxine or protein-bound iodine. Others have shown that plasma levels of free thyroxine and triiodothyronine rise rapidly after injuries, whereas the thyroxine-binding capacity of prealbumin decreases. "These alterations in the peripheral metabolism and transport of thyroxine may well play an important role in the metabolic consequences of injury."

Soliman, M. G., Brindle, G. F.: "Plasma levels of anti-diuretic hormone during and after heart surgery with extra corporeal circulation." *Can. Anaesth. Soc. J.* **21**: 195-204 (1974). J10,760/74

Plasma vasopressin increased in seven patients during cardiac surgery with extracor-

poreal circulation. This was "probably due to changes in serum osmolalities, surgical trauma and the action of anaesthetic drugs." The literature on the effects of various stressors upon plasma vasopressin is discussed (25 refs.).

Lindsey, A., Santeusanio, F., Braaten, J., Falloona, G. R., Unger, R. H.: "Pancreatic alpha-cell function in trauma." *J.A.M.A.* **227**: 757-761 (1974). H82,359/74

Following traumatic shock, patients' plasma glucagon levels rose far above normal and blood glucose averaged 188 mg. per 100 ml. whereas insulin remained unchanged. "In three patients undergoing major surgery without associated hypotension, glucagon concentrations did not rise comparably. Hyperglucagonemia without a proportional rise in insulin may be the usual islet cell response to severe trauma and possibly could contribute to survival."

Meguid, M. M., Brennan, M. F., Aoki, T. T., Muller, W. A., Ball, M. R., Moore, F. D.: "Hormone-substrate interrelationships following trauma." *Arch. Surg.* **109**: 776-783 (1974). J19,976/74

Observations in man lead to the conclusion that "in trauma, the gradual rise in glucagon contributes to the increase in concentration of glucose and FFA, and that the cortisol rise synergizes with the elevated glucagon concentration to favor gluconeogenesis from muscle amino acids. Relatively low circulating insulin levels favor these metabolic changes" (62 refs.).

Russell, R. C. G., Walker, C. J., Bloom, S. R.: "Hyperglucagonaemia in the surgical patient." *Br. Med. J.* January 4, 1975, pp. 10-12. H97,996/75

→**Histamine and 5-HT.** Schayer, R. W.: "Role of induced histamine in tourniquet shock in mice." *Am. J. Physiol.* **203**: 412-416 (1962). D32,955/62

Observations on mice traumatized with a tourniquet "suggest that the fundamental process leading to shock after fluid loss is activation of histamine synthesis in or near cells of the capillaries to restore an adequate supply of blood to the tissues. Since induced histamine synthesis is controlled by local conditions, opening of the capillary beds proceeds independently of the over-all circulatory picture; finally, homeostasis can no longer be maintained."

Barchas, J. D., Freedman, D. X.: "Brain amines: response to physiological stress." *Biochem. Pharmacol.* **12**: 1232-1238 (1963). E29,915/63

In rats, swimming to exhaustion especially in cold water caused depletion of brain 5-HT and NEP. Similar changes could not be obtained by having the rats run in a revolving cage, for under the conditions of the experiment the rats soon gave up and just allowed themselves to be dragged. Immersion in cold water did reproduce the catecholamine depletion whereas several other stressors (electroshock, starvation, hypoxia, surgery, adrenalectomy) were ineffective in this respect. The response is not dependent upon the pituitary-adrenocortical system, since active stressors deplete brain catecholamines even after hypophysectomy, as does LSD. It is noteworthy that drugs which induce a similar change in brain amines produce a unique pattern of central excitation, acting on brain mechanisms concerned with metabolic and physiologic temperature regulation. "If the stressors have such a central action, a role for the biogenic amines in central as well as in peripheral aspects of temperature regulation should be sought."

→**Enzymes.** Németh, Š.: "Plasma glucocorticoid and liver enzyme responses in the stressed rat." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 229-241. Bratislava: Slovak Academy of Sciences, 1973. E10,471/73

In rats subjected to stress in the Noble-Collip drum "no acute or long-term changes of glucose-6-phosphatase and phosphoenol-pyruvate carboxykinase were found after single or repeated injury. An increased activity of tyrosine aminotransferase was observed, 90 minutes as well as 3 hours after a first injury and evidence is presented indicating that the enzymic response is dependent on increased plasma corticosterone levels. The plasma corticosterone and transaminase responses of the repeatedly injured rats were of substantially shorter duration than those of rats injured for the first time."

Németh, Š., Vigaš, M., Straková, A.: "Effect of trauma and hydrocortisone on liver tyrosine-alpha-ketoglutarate transaminase activity of rats adapted to Noble-Collip drum trauma." *Physiol. Bohemoslov.* **22**: 355-358 (1973). J9,812/73

In rats adapted to trauma in a Noble-

Collip drum, the increase in hepatic tyrosine-alpha-ketoglutarate transaminase was not changed by subsequent minor traumas of the same kind although hypercorticosteronemia, which probably induces this enzyme activity, was substantially diminished by adaptation. Adrenalectomy prevented the enzyme response irrespective of adaptation.

Galvin, M. J. Jr., Bunce, R., Reichard, S. M.: "Histidine decarboxylase activity in traumatic shock." *Proc. Soc. Exp. Biol. Med.* **146**: 653-657 (1974). H89,001/74

In rats, trauma (Noble-Collip drum) increases histidine decarboxylase activity in the lung and spleen but not in plasma. Literature is cited to show that the RES "is altered by similar types of stress and by histamine."

Moore, T. C., Sinclair, M. C., McAlpin, C. D., Weber, G. A., Lemmi, C. A. E.: "Effect of aging, organ allografting, and surgical stress on rat thymus histidine decarboxylase activity." *Surgery* **76**: 733-740 (1974). J17,862/74

Oehler, G., Wolf, H., Schmahl, F. W., Roka, L.: "Veränderungen der Lipoproteinfatlipase nach experimenteller Femurfraktur" (Changes in lipoprotein-lipase after experimental fracture of the femur). *Z. Gesamte Exp. Med.* **163**: 31-38 (1974). H87,841/74

In rabbits, fracture of the femur caused a significant decrease in heparin-insoluble lipoprotein-lipase with a concurrent increase in serum glycerides and in the excretion of catecholamines during the first twenty-four hours. There was also histologic evidence of pulmonary fat embolism. It is concluded "in addition to the increased synthesis of triglycerides during the post-traumatic phase (lipid mobilization syndrome) the elimination of blood lipids is impaired by decreased LPL [lipoprotein-lipase] activity. The elevated release of catecholamine is probably of essential significance for both effects."

→**Other Metabolites.** Zarafonetis, C. J. D., Seifter, J., Baeder, D., Kalas, J. P.: "Lipid mobilization as a consequence of surgical stress." *Am. J. Med. Sci.* **237**: 418-433 (1959). C67,041/59

Goodman, J. R., Kellogg, F., Porter, R. W., Liechti, R.: "Decrease in serum cholesterol with surgical stress." *Calif. Med.* **97**: 278-280 (1962). D55,584/62

Serum cholesterol decreased in patients as

a result of surgery. "A presurgical drop was noted and considered to be related to psychological stress."

Ross, H., Johnston, I. D. A., Welborn, T. A., Wright, A. D.: "Effect of abdominal operation on glucose tolerance and serum levels of insulin, growth hormone, and hydrocortisone." *Lancet* September 10, 1966, pp. 563-566. F69,882/66

Abdominal operations are followed by high fasting blood glucose levels and reduced tolerance to intravenous glucose. Fasting plasma insulin levels are raised postoperatively, and intravenous glucose produces greater elevations of serum insulin and STH in the immediate postoperative period.

Szantay, I., Acalovschi, I.: "Aspects du métabolisme de la ³⁵S-méthionine au cours du stress opératoire" (Aspects of ³⁵S-methionine metabolism during surgical stress). *Agressologie* **11**: 389-394 (1970). H32,849/70

Studies with ³⁵S-methionine revealed an increased metabolism in patients, following various operations.

Stremmel, W.: "Die Bedeutung des Blutglykogens nach stressinduzierten Stoffwechselstörungen" (The importance of blood glycogen concentration after stress-induced metabolic disturbances). *Brunn's Beitr. Klin. Chir.* **220**: 297-305 (1973). J3,874/73

In man, the stress of surgical interventions raises blood glycogen. A similar change is seen after exposure to various stressors and may be responsible for increased platelet adhesiveness and stress-induced thrombosis.

Turton, M. B., Deegan, T.: "Central and peripheral levels of plasma catecholamines, cortisol, insulin and non-esterified fatty acids." *Clin. Chim. Acta* **48**: 347-352 (1973). J8,031/73

In patients undergoing cardiac catheterization, elevated levels of EP, NEP, FFA and cortisol with lowered concentrations of insulin are ascribed to stress. However, certain differences are noted in the concentrations of these substances in various vascular territories.

Koch, G.: "Vergleichende Untersuchungen über das Blutglukose- und Plasmainsulinverhalten am traumatisierten Kaninchen" (Blood glucose and plasma insulin levels of traumatized rabbits, an experimental study). *Brunn's Beitr. Klin. Chir.* **221**: 158-163 (1974). J17,605/74

In rabbits, surgical trauma causes *hyperglycemia* and an increase in plasma insulin, both of which are ascribed to the G.A.S.

→**Other Targets.** Laragh, J. H., Almy, T. P.: "Changes in circulating eosinophils in man following epinephrine, insulin, and surgical operations." *Proc. Soc. Exp. Biol. Med.* **69**: 499-501 (1948).

B31,814/48

In man, surgical trauma and injections of EP or insulin caused *eosinopenia*.

Gabrilove, J. L.: "The level of the circulating eosinophils following trauma." *J. Clin. Endocrinol.* **10**: 637-640 (1950).

B48,579/50

In man, the stress of surgical trauma or of coronary occlusion causes *eosinopenia* followed by a rise in blood eosinophils above the normal level, the curve running approximately parallel to corticoid secretion and resembling that elicited by ACTH or glucocorticoids.

Hamburg, D. A.: "Psychological adaptive processes in life-threatening injuries." In: *Symposium on Stress*, pp. 222-235. Washington, D.C.: Army Medical Service Graduate School, 1953.

B89,532/53

Detailed discussion of the various *mental defense* reactions with which people having different psychologic characteristics meet the challenge of life-threatening situations, particularly severe injuries and imminent stress. Among these responses, there are three general types: "those which tend to make the patient feel that his life is not really in danger; those which tend to make him feel unafraid of impending death; and those which tend to make him feel that he will recover. All of these emergency defenses are usually facilitated by the diffuse impairment of brain function often associated with severe injury. This impairment makes it easier for the patient to restrict his awareness, to perceive only what he wants to perceive, and to delay recognition of the threat to life."

Engquist, A., Winther, O.: "Variations of plasma cortisol and blood fibrinolytic activity during anaesthetic and surgical stress." *Br. J. Anaesth.* **44**: 1291-1297 (1972).

J672/72

In man, during thirty to ninety-three minutes of "surgical stress, enhancement of *fibrinolysis* was significantly correlated with increase of plasma cortisol levels."

Cohen, F., Lazarus, R. S.: "Active coping processes, coping disposition, and recovery

from surgery." *Psychosom. Med.* **35**: 375-389 (1973).

J7,262/73

Mainly *psychologic* studies on coping processes in preoperative and postoperative patients, with statistical data on the effect of avoidant and vigilant behavior upon recovery (37 refs.).

Scovill, W. A., Saba, T. M.: "Humoral recognition deficiency in the etiology of reticuloendothelial depression induced by surgery." *Ann. Surg.* **178**: 59-64 (1973).

J4,221/73

The phagocytic activity of the *RES* is greatly depressed in dogs during and after major abdominal surgery. This depression can be prevented by passive opsonin administration. "The potential depletion of opsonic protein by the entrance of damaged tissue or denatured protein in the circulation or the consumption of opsonin at the site of tissue injury may trigger this state of 'hypo-opsonemia.' In addition, preliminary findings suggest a role for the pituitary-adrenal axis in this response."

Stremmel, W.: "Stressinduzierte Stoffwechselveränderungen und gesteigerte Thrombozyten-Aggregation nach Operationen und Traumen" (Stress-induced metabolic changes and enhanced thrombocyte aggregation after surgery and trauma). *Münch. Med. Wochenschr.* **115**: 416-421 (1973).

H68,723/73

In man, various operations and other traumatic injuries enhance thrombocyte aggregation and may cause postoperative thromboembolism or disseminated *intravascular coagulation*. The stress-induced increase in FFA may play a role in this response (40 refs.).

Mazurkevich, G. S.: "Distribution of fractions of circulating and deposited blood in the hypothalamus, hypophysis, and the adrenal glands, and their oxygen regimen in traumatic shock." *Probl. Endokrinol.* **20** No. 1: 59-62 (1974) (Russian).

H85,172/74

In rats subjected to severe traumatic shock "under conditions of pronounced hypotension and hypovolemia, the capacity of the functioning *vascular* bed and the oxygen tension in the adrenal glands decreased more than in the adenohypophysis and the area of the median eminence. Circulatory disturbances and hypoxia of the adrenal cortex could serve as one of the causes of depressed production of corticosteroids during this process."

Galvin, M. J. Jr., Bunce, R., Reichard, S. M.: "Histidine decarboxylase activity in traumatic shock." *Proc. Soc. Exp. Biol. Med.* **146**: 653-657 (1974). H89,001/74

In rats, trauma (Noble-Collip drum) increased histidine decarboxylase activity in the lung and spleen but not in plasma. Literature is cited to show that the RES "is altered by similar types of stress and by histamine."

Letheby, B. A., Davis, R. B., Larsen, A. E.: "The effect of major surgical procedures on plasma and platelet levels of factor XIII." *Thromb. Diath. Haemorrh.* **31**: 20-29 (1974). H87,866/74

+Age. Rinfret, A. P., Hane, S.: "Depletion of adrenal ascorbic acid following stress in the infant rat." *Endocrinology* **57**: 497-499 (1955). B29,292/55

In four- to seven-day-old rats, adrenal ascorbic acid depletion in response to a stressor (laparotomy) is the same as in more mature animals and occurs between two and six hours following the initiation of stress.

Franks, R. C.: "Urinary 17-hydroxycorticosteroid and cortisol excretion in childhood." *J. Clin. Endocrinol. Metab.* **36**: 702-705 (1973). H68,183/73

The increase in urinary corticoid excretion is approximately the same in both adults and children exposed to various stressors, such as cardiac catheterization.

Hollmann, G., Fischer, A., Körner, J.: "Besonderheiten der Pathophysiologie des Operationstraumas im Kindesalter" (Peculiarities of the pathophysiology of surgical trauma in children). *Münch. Med. Wochenschr.* **116**: 1213-1218 (1974). H88,808/74

In children undergoing major operations the sympathetic adrenergic response to stress was more manifest than in adults, and while the plasma cortisol levels often showed little or no rise, indirect metabolic reactions suggested that excess aldosterone production occurs in response to a special need at an early age (20 refs.).

+Anesthesia. Virtue, R. W., Helmreich, M. L., Gainza, E.: "The adrenal cortical response to surgery. I. The effect of anesthesia on plasma 17-hydroxycorticosteroid levels." *Surgery* **41**: 549-566 (1957). C36,876/57

In patients, various anesthetics (ether, thiopental and so on) produce different de-

gresses of 17-OHCS discharge, and subsequent surgical operations are always highly effective in this respect.

Brunt, E. E. van, Ganong, W. F.: "The effects of preanesthetic medication, anesthesia and hypothermia on the endocrine response to injury." *Anesthesiology* **24**: 500-514 (1963). E23,121/63

Detailed review of the literature on the influence of preanesthetic medication and hypothermia upon the stressor effects of surgical injuries.

Purves, H. D., Sirett, N. E.: "Time course for corticotrophin release from ectopic pituitary grafts." *Endocrinology* **83**: 1377-1380 (1968). H5,737/68

Tourniquet shock produces an ACTH discharge in rats even when they are under pentobarbital anesthesia.

+Temperature. Brunt, E. E. van, Ganong, W. F.: "The effects of preanesthetic medication, anesthesia and hypothermia on the endocrine response to injury." *Anesthesiology* **24**: 500-514 (1963). E23,121/63

Detailed review of the literature on the influence of preanesthetic medication and hypothermia upon the stressor effects of surgical injuries.

Markley, K., Smallman, E., Thornton, S. W.: "The effect of environmental temperature on mortality and metabolism after burn and tourniquet trauma." *Fed. Proc.* **31**: 817 (1972). H53,564/72

An environmental temperature of 31°C significantly reduced the mortality rate of mice after burn and tourniquet trauma.

Markley, K., Smallman, E., Thornton, S. W., Evans, G.: "The effect of environmental temperature and fluid therapy on mortality and metabolism of mice after burn and tourniquet trauma." *J. Trauma* **13**: 145-160 (1973). J1,495/73

Partially shaved and congenitally hairless mice survive burn and tourniquet trauma better when kept at 31°C than at 25°C.

+Season. Ankier, S. I., Dawson, W., Karady, S., West, G. B.: "Seasonal variation in the resistance of rats." *J. Pharm. Pharmacol.* **17**: 187-188 (1965). G26,781/65

In the rat, traumatic (Noble-Collip drum) and tourniquet shock elicited greater mortality in November than in June or July. The

cause of this seasonal variation in stress resistance could not be determined.

+Diet. Cuthbertson, D. P.: "Physical injury and its effects on protein metabolism." In: Munro, H. N. and Allison, J. B., *Mammalian Protein Metabolism*, Vol. 2, pp. 373-414. New York and London: Academic Press, 1964. G79,175/64

Review on the effect of stress upon protein metabolism. In man, protein loss within ten days of physical injury may amount to about 12 percent of the total body protein. In general, there is a catabolic loss during the first ten days and a maximum at about the third day with a secondary peak on the eighth day. With regard to dietary treatment, most observers hold that "during the first few days following the injury in the previously adequately nourished person it is probably unwise to push the intake of a well-balanced diet beyond appetite as this may fail during this early postinjury phase in severe injuries. Further, kidney function may not be normal for a day or two. Thereafter the patient should be encouraged, but not forced, to take as much as he can of a well-balanced diet, relatively rich in protein."

Sakai, S.: "Effect of protein content of rat diet on amount of corticosterone in tooth ex-

traction." *Folia Pharmacol. Jap.* **68**: 66-72 (1972) (Japanese). H79,322/72

In rats on a low protein diet, the adrenals are comparatively small but show a pronounced increase in size during the stress of tooth extraction, which is ineffective in this respect in controls given normal amounts of protein.

+Genetics. James, V. H. T., Horner, M. W., Moss, M. S., Rippon, A. E.: "Adrenocortical function in the horse." *J. Endocrinol.* **48**: 319-335 (1970). H32,502/70

In the horse, surgical trauma or hypoglycemia increases plasma cortisol whereas exercise is much less effective in this respect. The cortisol variations are not necessarily associated with changes in the eosinophil count. "It is concluded that the mechanisms of control of adrenocortical function in the horse are not dissimilar to those described for other mammalian species."

Halevy, S., Altura, B. M.: "Sex and genetics as factors influencing resistance to traumatic shock." *Fed. Proc.* **33**: 298 (1974). H84,061/74

Certain "strains of mice could be used as models to explore further the roles of sex and genetics in resistance to traumatic shock."

Drugs

In this section, the stressor and conditioning effects of drugs will be enumerated conjointly in alphabetic order. When considered to be convenient for comparative purposes, class names, marked with asterisks (for example, *Anesthetics, *Tranquilizers), will be used in the alphabetic order of their class designations. This was done particularly whenever the same paper discussed several members of the same class; unnecessary repetition is avoided by conjoint grouping.

Most of the data in this section do not lend themselves to comparative evaluation in the form of an introduction, and so, for individual findings, the reader is referred to the abstracts. Whenever two or more drugs are combined, data on the treatment are listed under each drug heading.

Amphenone-induced adrenal hypertrophy is "sometimes" inhibited by destruction of the ME, whereas posterior hypothalamic lesions do not affect ACTH secretion although they curtail TTH production. This is important, since it furnishes additional evidence to support the view that the regulation of ACTH and TTH depends upon distinct centers, only the former being located in the ME.

In hypophysectomized rats with several ectopic adenohypophyseal grafts, amphenone still causes adrenal enlargement, presumably through depression of corticoid production. Hence, these pituitary grafts must remain subject to corticoid feedback control, at least to some extent.

Amphetamine, cf CNS Stimulants

Anesthetics differ in their ability to produce an alarm reaction, particularly a corticoid discharge. However, preanesthetic medication and anesthesia never appear to suffice for a complete inhibition of additional ACTH release following subsequent surgical intervention. In general, ether stimulates, whereas pentobarbital inhibits increased ACTH secretion resulting from trauma, but in dogs with isolated pituitaries (bilateral decortication), this barbiturate no longer depresses corticoid excretion; indeed, it appears to have an inverse augmenting effect.

Preliminary observations suggest that STH secretion in rats is diminished by ether anesthesia.

In rats with hypothalamic-pituitary islands, the high resting plasma corticosterone levels are further elevated by ether, but this response is blocked by pentobarbital. Yet the latter allegedly fails to prevent ACTH release after trauma.

Pentobarbital anesthesia blocks the stress-induced stimulation of the hypothalamus-hypophysis-adrenal axis. This and other barbiturates are frequently used, therefore, as "antistress agents." It has been claimed that even fatal doses of barbiturates fail to produce an adrenal reaction in the rat. However, here again, conditioning circumstances appear to influence the results, since the findings of various investigators were by no means uniform, some having claimed that, in dogs, pentobarbital fails to block an increased corticoid response after whole body vibration or exposure to trauma. Still, the majority of observations suggest that, under usual conditions, barbiturates differ essentially in this respect from other anesthetics, especially ether, which causes a marked ACTH discharge and is often used as a standard stressor agent. This fact is of special importance in connection with the hypothesis according to which, at least in man, stressor effects are invariably mediated through emotional arousal that evidently becomes impossible under anesthesia. It is undoubtedly true, however, that moderate treatment with nervous depressants, particularly neuroleptanesthesia and tranquilizers, tends to counteract the stressor effect of emotional arousal.

When administered intraperitoneally, ketamine, a centrally acting nonbarbiturate anesthetic, raises plasma corticosterone levels in the rat; this effect can be prevented by hypophysectomy or dexamethasone, but only slightly or not at all by atropine, phentolamine, propranolol or haloperidol. Presumably, the response to ketamine is mediated through facilitatory β -adrenergic and/or dopaminergic pathways. The drug also predisposes rats to restraint ulcers.

Antiadrenergics. β -adrenergic blocking agents diminish the tachycardia produced by automobile driving without affecting performance. On the other hand, the rise in FFA and triglycerides noted in people watching exciting films is not prevented by β -blockade, presumably because it is mediated through STH or other hormones causing lipolysis.

The tachycardia, extrasystoles and other unpleasant emotional side effects that develop in some persons when addressing an audience can be abolished by β -adrenergic blocking agents.

In man, the tachycardia produced by increased gravity is diminished by propranolol

but subjective gravity tolerance is maintained. There is some evidence that propranolol also suppresses endogenous renin release in response to various stressors. This effect might play some role in its antihypertensive action.

In adrenalectomized rats, resistance to formalin, hemorrhage, forced muscular exercise and cold was enhanced by various autonomic blocking agents. Perusal of the pertinent literature leaves the definite impression that these drugs offer great promise as "antistress agents," at least under certain conditions.

Anticholinergics such as atropine can produce an alarm reaction in the rat when administered in large doses. Yet, in adrenalectomized rats, resistance to various stressors is increased by autonomic blocking agents, including atropine. Apparently, in the absence of adrenals, autonomic blockade is beneficial. Stress ulcers produced in the rat by immersion in cold water can be prevented by atropine and other anticholinergic agents, although this effect may be associated with ulcer formation in the proventriculus.

Antihistamines. Various antihistaminics have been shown not to interfere significantly with the discharge of adrenal ascorbic acid during stress.

Asiaticoside has recently been claimed to be an "antistress agent," but the few relevant observations are still badly in need of confirmation on a larger scale.

Cannabis allegedly may either inhibit stress-induced corticosterone release in the rat, or actually cause stress reactions, depending upon conditioning circumstances and particularly dosage.

CNS Stimulants. Amphetamine—like various other stressors—depletes the rat brain of its NEP stores but does not significantly affect dopamine concentrations. The drug enhances the toxicity of several other stressors. In mice, radioamphetamine accumulates in synaptic particles of the brain, a response allegedly increased by the stress of isolation.

Among the CNS stimulants, amphetamine has received the greatest attention. It has been claimed that various stressors increase its toxicity, perhaps through the depletion of brain NEP. On the other hand, it appears to augment the 5-HT content of the brain stem. However, the pertinent literature is far from unanimous.

Chlorpromazine does not inhibit ACTH release in surgical shock or following EP injection; in fact, the drug may increase ACTH secretion by itself. Presumably, the response depends upon experimental conditions since some investigators obtained opposite results. The circadian plasma corticoid variations, as well as the stress ulcers produced by restraint in the rat, are inconstantly affected by chlorpromazine.

Colchicine elicits extremely severe manifestations of the alarm reaction including adrenal enlargement and thymicolympathic atrophy, but these effects are prevented by adrenalectomy and presumably mediated through the suprarenals.

Cysteamine produces selective duodenal ulcers in the rat. These serve as a good model for the testing of antiulcer agents, also effective against stress ulcers in man. It is not known, however, why cysteamine is particularly conducive to duodenal ulcers rather than to the gastric lesions characteristic of stress. Additional data on cysteamine-induced ulcers, especially in the study of antiulcer drugs, will be found in the section devoted to stress ulcers in the chapter on Diseases of Adaptation.

Electrolytes, Water, Osmotic Pressure. Various electrolytes, particularly if they produce changes in osmotic pressure, are highly potent stressors.

Ethanol, especially if consumed in large doses, is a typical alarming stimulus. Chronic

alcoholics allegedly drink most when stress and "socialization" coincide. In dogs, mortality following repeated hemorrhage is increased by daily gavages of ethanol.

Ethyltryptamine (a MAO inhibitor), in doses which restore blood pressure, prevents the increase in ACTH secretion produced by hemorrhage in dogs. Presumably, inhibition of ACTH secretion is related to the blockade of hypotension. α -*Methyltryptamine* has a similar effect, which is shared by several other pressor amines, but not by MAO inhibitors. In dogs, α -ethyltryptamine also decreases 17-OHCS output after surgical stress. This is true even when "hypothalamic islands" are created; hence, the compound may prevent stimulation of CRF-secreting neurons.

Formaldehyde injections served as stressors in the first experiments on the alarm reaction, and since then have been frequently employed as typical stressors. The lymphopenic effect of formaldehyde injections can be completely blocked by circumscribed lesions in the ME region of the rat hypothalamus.

Glucose given orally can prevent stress ulcer formation in the rat, especially during starvation, which would otherwise sensitize the gastric mucosa to this type of damage. In monkeys, an exaggerated STH response following intravenous glucose is seen during acute infection.

6-Hydroxydopamine, which causes a "chemical sympathectomy," diminishes the resistance of the rat to cold. There is a marked rise in urinary EP but not in NEP because, presumably, the adrenal medulla largely compensates for the loss of sympathetic nerve activity after treatment with this drug.

6-Hydroxydopamine-induced depletion of catecholamines in the rat brain does not significantly affect the pituitary-adrenal system. "These findings raise serious doubts with regard to the theory of the existence of a noradrenergic inhibitory system acting on pituitary-adrenal regulatory processes in the brain."

MAO inhibitors are discussed under the names of the individual compounds.

Methamphetamine (Desoxyephedrine), a CNS stimulant, inhibits the rise of urinary EP excretion in students undergoing examinations. Curiously, this blocking effect is shared by pentobarbital. The circadian variation of plasma corticoid levels is deranged by methamphetamine as well as by chlorpromazine.

Metyrapone increases ACTH discharge through its action upon the adenohypophysis and is therefore currently used to test the ACTH-secreting capacity of this gland. In epileptics treated with diphenylhydantoin, the normal circadian rhythm of ACTH release is maintained, yet they respond poorly to metyrapone, or to the suppression of ACTH secretion by dexamethasone as a result of deranged feedback controls. In Cushing's syndrome, urinary 17-OHCS excretion as well as plasma ACTH activity are inconsistently influenced by metyrapone.

Morphine was used as one of the first stressors in the original description of the alarm reaction. However, for this purpose, very large doses had to be given. Smaller amounts of it block ACTH secretion induced by various stressors, including histamine, EP, vasopressin and laparotomy; this is true even after unilateral adrenalectomy. On the other hand, the effect of exogenous ACTH is not blocked by morphine, showing that the drug does not interfere directly with adrenocortical reactivity. The blockade of ACTH secretion by morphine is so constant that it has even been used as a basis for the bioassay of CRF which overcomes this blockade. Although chlorpromazine and reserpine may also inhibit ACTH secretion, only the action of morphine is striking and consistent.

Nicotinic acid prevents the elevation in plasma FFA and triglycerides induced in man by emotional stressors, but not the increase in catecholamine elimination and the associated tachycardia and hypertension. In rats, gastric ulcers produced by restraint are more effectively inhibited by nicotinic acid than by chlorpromazine.

PCPA (p-Chlorophenylalanine), a potent tryptophan hydroxylase inhibitor, diminishes brain 5-HT in rats. A number of experiments suggest that "serotonergic" neurons affected by PCPA play an important part in responses of the hypothalamus-hypophysis-adrenal system during stress and the circadian cycle. The volitional increase in ethanol intake is likewise enhanced in rats by PCPA.

Reserpine curtails not only anxiety and fear but also the associated 17-OHCS rises in plasma and urine. On the other hand, large doses of reserpine produce a transient elevation of 17-OHCS levels and hypersecretion of ACTH concurrently with a lowering of brain NEP and 5-HT. At the same time, the ACTH content of the pituitary is sufficiently depleted to prevent a detectable discharge in response to stressors.

Reserpine decreases body temperature in the rat by diminishing heat production rather than by increasing heat loss. Restraint further augments this type of hypothermia.

In rats, reserpine, like dexamethasone or cortisol implants into the ME, inhibits the compensatory hypertrophy of the remaining adrenal after unilateral suprarenalecotomy. However, reserpine implanted into the ME or injected subcutaneously shows no evidence of substituting for glucocorticoids in the feedback regulation of ACTH secretion.

In hares, fear causes regressive changes in the internal nuclear habenular ganglion which can be prevented by reserpine. This was taken to suggest that the "habenular-pineal complex has an important role in the neuroendocrinology of the general adaptation syndrome." EM studies have revealed an increase in electron-dense large granules (presumably carriers of neurohypophyseal hormones) and a decrease in small granules (carriers of catecholamines) in the ME axons of the rat after reserpine treatment.

Reserpine enhances the *in vivo* toxicity of various stressors under most experimental conditions. Large doses can produce stress ulcers in the rat, especially at low surrounding temperatures. These will be discussed at length in the section on the experimental Diseases of Adaptation.

Extensive studies with various *tranquillizers* in psychiatric patients have already been reported in connection with the individual drugs of this group, and complex comparative investigations will have to be consulted in the original publications cited herein.

Drugs

(See also our earlier stress monographs, p. xiii)

Actinomycin. (See Antibiotics)

Adenosine Monophosphate (AMP), Adenosine Diphosphate (ADP), Adenosine Triphosphate (ATP). Rotondo, G.: "Sull'impiego dell'acido adenosintrifosforico e della cocarbossilasi in piloti affetti da lieve o iniziale fatica di volo" (The use of adenosine triphosphate and cocarboxylase in pilots suffering from light or initial flying fatigue).

Riv. Med. Aeronaut. Spaz. **27:** 172-192 (1964).
G19,344/64

Flying fatigue in jet pilots is ascribed to the exhaustion of adaptation energy. Treatment with a combination of ATP and co-carboxylase is beneficial (19 refs.).

Adrenergic Blocking Agents. (See Anti-adrenergics)

Alloxan. (See also Insulin, Diabetes) Kraus, S. D.: "Impairment of the pituitary-adrenal response to acute stress in al-

loxan diabetes." *Acta Endocrinol.* (Kbh.) **54**: 328-334 (1967). F77,713/67

Ivanova, I. I., Lapshina, V. F., Tsaplin, V. M.: "Corticosterone content in the peripheral blood and adrenal glands during stress in rats with alloxan diabetes." *Probl. Endokrinol.* **20** No. 3: 94-97 (1974) (Russian). H92,322/74

In rats, alloxan diabetes did not significantly influence the typical stress reaction to trauma. The rats showed adrenal enlargement, thymus involution and elevated corticosterone levels in plasma and the adrenals.

Altrinolol. (See **Antiadrenergics**)

Aminoglutethimide. Loscalzo, B., Nisticò, G., Preziosi, P.: "A possible dissociation of ACTH effects on the adrenal glands as revealed by aminoglutethimide." *Pharmacol. Res. Commun.* **2**: 55-62 (1970).

G80,104/70

In rats, aminoglutethimide inhibits an increase in plasma corticosterone levels after stress (swimming in cold water until exhaustion). The compound also dissociates the effect of ACTH (following failure of the negative feedback mechanism and hypophyseal activation by stress) at the adrenocortical level in that a decrease in adrenal ascorbic acid and an increase in adrenal cholesterol occur without any relation to enhanced corticosterone synthesis.

Greer, M. A., Allen, C. F.: "Failure to detect excessive stress-induced adrenal corticosterone secretion following amino-glutethimide withdrawal in the rat." *Endocrinology* **91**: 600-602 (1972). H58,083/72

Aminoglutethimide is chemically related to amphenone and inhibits corticosterone synthesis, presumably by depressing conversion of cholesterol to pregnenolone. In rats, the "plasma corticosterone concentration was measured 20 min after an ether stress before and on various days during and after amino-glutethimide feeding. There was a significant depression of the corticosterone concentration within two days after starting the experimental diet which persisted throughout the period of drug administration. Within 1-2 days after drug withdrawal, plasma corticosterone response to ether had returned to control levels. There was no supranormal response up to 8 days after drug withdrawal, indicating that a marked increase in available cholesterol in the adrenal does not per se lead to an increase in hormone secretion."

Amphenone. (See also **Aminoglutethimide**) Greer, M. A., Erwin, H. L.: "Evidence of separate hypothalamic centers controlling corticotropin and thyrotropin secretion by the pituitary." *Endocrinology* **58**: 665-670 (1956). C14,624/56

In rats, destruction of the ME "sometimes" inhibited amphenone-induced adrenal hypertrophy whereas posterior hypothalamic lesions did not significantly affect ACTH secretion, but did curtail TTH production. Presumably, the centers for ACTH and TTH excretions are distinct and the former is limited to the ME.

Hertz, R.: "Gonadotropin and adrenocorticotropic from rat pituitary homografts as manifested by host response to chorionic gonadotropin and amphenone." *Endocrinology* **66**: 842-844 (1960). C87,506/60

In hypophysectomized rats bearing four adenohypophyseal grafts under the renal capsule, amphenone caused adrenal enlargement that was lacking in hypophysectomized controls. "Since the adrenomegalic response to amphenone is mediated through suppression of corticoid production by the rat adrenal, these pituitary grafts apparently also maintain a degree of reciprocal functional relationship with the adrenal cortex."

Amphetamine. (See **CNS Stimulants**)

***Anesthetics and Analgesics.** (See also under the names of specific anesthetics and analgesics) Ronzoni, E.: "Sodium pentobarbital anesthesia and the response of the adrenal cortex to stress." *Am. J. Physiol.* **160**: 499-505 (1950). B47,024/50

In rats, *pentobarbital* anesthesia blocked the depletion of adrenal ascorbic acid and the hyperglycemia normally produced by cold. "With hemorrhage or heat as the form of stress, anesthetic sufficient to prevent the normally observed increase in blood glucose failed to influence the lowering of adrenal ascorbic. Apparently even light anesthesia is sufficient to inhibit epinephrine release due to this mild form of stimulation."

Heldt, T. J.: "Effect of agents inducing deliria on the course of certain bodily reactions to stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 477-519. Baltimore: Williams & Wilkins, 1950. B51,923/50

Gori, E.: "Les hypnotiques et le stress" (Hypnotic drugs and stress). *20e Congr. Int.*

Physiol., pp. 357-358. Brussels, July 30-August 4, 1956. C23,393/56

Even fatal doses of *barbiturates* fail to produce an alarm reaction (adrenal ascorbic acid depletion) in the rat, and they actually inhibit the stressor effects of various agents. On the other hand, many hypnotics and anesthetics stimulate ACTH secretion and may thereby overcome their own antistress actions which might be due to depression of the reticular formation. [The brief abstract does not lend itself to critical analysis (H.S.).]

Virtue, R. W., Helmreich, M. L., Gainza, E.: "The adrenal cortical response to surgery. I. The effect of anesthesia on plasma 17-hydroxycorticosteroid levels." *Surgery* 41: 549-566 (1957). C36,876/57

In patients, various anesthetics (*ether*, *thiopental*, and so on) produce different degrees of 17-OHCS discharge, and subsequent surgical operations are always highly effective in this respect.

Hammond, W. G., Vandam, L. D., Davis, J. M., Carter, R. D., Ball, M. R., Moore, F. D.: "Studies in surgical endocrinology. IV. Anesthetic agents as stimuli to change in corticosteroids and metabolism." *Ann. Surg.* 148: 199-211 (1958). C57,405/58

"General anesthesia produced by *Pentothal*, *nitrous oxide* and *d-tubo-curare* in any combination was associated with significant changes in blood or urinary 17-hydroxycorticoid values.... Operation under Pentothal-N₂O-d-tubo-curare anesthesia was followed by an elevation of the free blood 17-OHCS, but the magnitude of the rise was not as great as that seen with operation under ether."

Brunt, E. E. van, Ganong, W. F.: "The effects of preanesthetic medication, anesthesia and hypothermia on the endocrine response to injury." *Anesthesiology* 24: 500-514 (1963). E23,121/63

Detailed review of the literature on the influence of *preanesthetic medication* and hypothermia upon the stressor effects of surgical injuries.

Matsuda, K., Duyck, C., Kendall, J. W. Jr., Greer, M. A.: "Pathways by which traumatic stress and ether induce increased ACTH release in the rat." *Endocrinology* 74: 981-985 (1964). F12,792/64

In rats, following removal of all prosencephalon anterior to the superior colliculus, with an isolated ME, stalk and pituitary left intact, there is still ACTH release (corti-

costerone in adrenal effluent) in response to *ether* anesthesia with or without additional traumatic stress (fracture of foreleg). However, after *Nembutal* anesthesia traumatic stress is no longer active in this respect. Bone fracture distal to a section of the spinal cord in otherwise intact rats also fails to raise adrenal cortical secretion under Nembutal but not under ether anesthesia. "Ether apparently directly stimulates the median eminence to cause increased ACTH release. Traumatic stress induces ACTH release through ascending neural pathways feeding to the hypothalamus through the dorsal mesencephalon."

Blivaiss, B. B., Litta-Modignani, R., Priede, I.: "Plasma 17-hydroxycorticosteroids in dogs after whole body vibration." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 511-516. New York and London: Academic Press, 1965.

E5,495/65

In dogs anesthetized with *pentobarbital*, whole body vibration still causes a "stress-like response" in that it increases plasma 17-OHCS elimination although this reaction is even more pronounced in nonanesthetized animals. Evidently, emotional factors are important but consciousness is not indispensable for typical adrenal stress reactions.

Egdahl, R. H.: "Studies on the effect of ether and pentobarbital anesthesia on pituitary adrenal function in the dog." *Neuroendocrinology* 1: 184-191 (1966).

F65,750/66

In dogs, the rise in plasma 17-OHCS caused by the trauma of adrenal vein cannulation was the same under ether and *pentobarbital* anesthesia. Neither anesthetic altered cortical sensitivity to ACTH. Ether was a potent but variable stimulus of corticoid secretion, and its effect could be depressed by concurrent administration of pentobarbital. In dogs with isolated pituitaries (bilateral decortication), this barbiturate failed to depress cortical hypersecretion and appeared to have an inverse, increasing effect.

Schalch, D. S., Reichlin, S.: "Plasma growth hormone concentration in the rat determined by radioimmunoassay: influence of sex, pregnancy, lactation, anesthesia, hypophysectomy and extrasellar pituitary transplants." *Endocrinology* 79: 275-280 (1966).

F69,338/66

In hypophysectomized rats, plasma STH levels become undetectable and intraocular pituitary transplants fail to raise them. Brief periods of *ether* anesthesia decrease STH only in male rats.

Dobkin, A. B., Byles, P. H., Neville, J. F. Jr.: "Neuroendocrine and metabolic effects of general anaesthesia and graded haemorrhage." *Can. Anaesth. Soc. J.* **13**: 453-475 (1966). G41,075/66

In dogs, various parameters of the stress reaction were compared following anaesthesia induced by different agents in combination with severe bleeding, and after pretreatment with methylprednisolone and ampicillin. Individual parameters of the stress response varied depending upon the *anesthetic* used. "It is likely that the rapid recovery from the stress of the combination of haemorrhage and general anaesthesia may be attributed to the use of a relatively large dose of the corticoid and antibiotic drugs." [Lack of adequate controls makes it difficult to identify the relative role of each factor in this complicated procedure (H.S.).]

Greer, M. A., Rockie, C.: "Inhibition by pentobarbital of ether-induced ACTH secretion in the rat." *Endocrinology* **83**: 1247-1252 (1968). H5,714/68

In rats, ether anesthesia stimulated ACTH release, apparently acting through the ME. *Pentobarbital* anesthesia actually blocked this release, as indicated by plasma corticosterone levels. Rats with hypothalamic-pituitary islands (Halász knife) had high resting plasma corticosterone concentrations which were further increased by ether. Pentobarbital also blocked this response. Presumably, "pentobarbital acts on the basal hypothalamus to prevent ether from inducing ACTH release but does not prevent ACTH release following trauma."

Purves, H. D., Sirett, N. E.: "Time course for corticotrophin release from ectopic pituitary grafts." *Endocrinology* **83**: 1377-1380 (1968). H5,737/68

In rats, tourniquet shock increased ACTH discharge even under *pentobarbital* anesthesia.

Shephard, D. A. E.: "The anxious surgical patient and anaesthesia." *N.S. Med. Bull.* **47**: 107-111 (1968). G58,805/68

Practical hints on ways to avoid the stressor effect of *anaesthesia* in anxious patients.

Oyama, T., Saito, T., Isomatsu, T., Samejima, N., Uemura, T., Arimura, A.: "Plasma

levels of ACTH and cortisol in man during *diethyl ether* anaesthesia and surgery." *Anesthesiology* **29**: 559-564 (1968).

G57,525/68

Jégo, P., Lescoat, G., Beraud, G., Maniez, J.: "Etude des modalités de réponse du complexe hypothalamo-hypophysio-surrénalien à l'agression par l'éther chez le rat: cas d'une injection intraperitoneale" (Study on the responsiveness of the hypothalamo-hypophysio-adrenal axis to stress by ether in the rat: effects of intraperitoneal injection). *C.R. Soc. Biol. (Paris)* **164**: 2117-2121 (1970). H41,303/70

The increase in blood corticosterone produced in rats by *ether* is diminished by previous *pentobarbital* anaesthesia. However, intraperitoneal injection of ether causes marked rises in blood corticosterone in pentobarbital-anesthetized females, but not in males.

Theye, R. A.: "Effects of *halothane*, anoxia, and hemorrhage upon canine whole-body, skeletal muscle, and splanchnic excess lactate production." *Anesthesiology* **35**: 394-400 (1971) (18 refs.). J20,012/71

Dechezleprêtre, S., Lechat, P.: "Influence du jeûne, du stress et de la narcose sur le taux de corticostérone plasmatique chez le rat" (Effect of fasting, stress and anaesthesia on plasma corticosterone levels in the rat). *Arch. Sci. Physiol.* **25**: 247-259 (1971). G85,426/71

In rats, *ether*, *chloral*, *hydroxydione* and *ethylurethane* considerably increase blood corticosterone levels. Since pentobarbital is comparatively ineffective in this respect, it is a suitable anesthetic for experiments in which a virtually normal baseline of blood corticoids is desirable.

Tarhan, S., Fulton, R. E., Moffitt, E. A.: "Body metabolism during general anaesthesia without superimposed surgical stress." *Anesth. Analg. (Cleve.)* **50**: 915-923 (1971). J11,008/71

Patients briefly anesthetized for renal arteriograms by four combinations of agents (*halothane*, *nitrous oxide*, *thiopental* and *Innovar*) showed no evidence of stress, judging from plasma STH, FFA and glucose levels (26 refs.).

Lidbrink, P., Corrodi, H., Fuxé, K., Olson, L.: "Barbiturates and meprobamate: decreases in catecholamine turnover of central dopamine and noradrenaline neuronal sys-

tems and the influence of immobilization stress." *Brain Res.* (Amst.) **45**: 507-524 (1972). G95,413/72

Buchel, L., Prioux-Guyonneau, M., Liblau, L., Murawsky, M.: "Influence de la contrainte du rat blanc sur l'activité, la pénétration et le métabolisme de l'hexobarbital et du barbital" (Influence of restraint on the activity, penetration and metabolism of hexobarbital and barbital in white rats). *Thérapie* **27**: 609-625 (1972). G92,849/72

"The potentiation of the hypnotic effects, increases of the sleeping time with *hexobarbital*, shortening of the latent period with barbital, in relation with short or long lasting restraint in rats, are attributable to two different mechanisms: inhibition of hexobarbital metabolism; increase of barbital penetration into the brain."

Dobkin, A. B., Pieloch, P. A.: "The metabolic effects of neuroleptanesthesia." *Int. Anesthesiol. Clin.* **11**: 155-169 (1973).

J9,286/73

Brief résumé of the literature and personal observations on the metabolic changes associated with anesthesia, particularly *neuroleptanesthesia* in man. The alterations in blood sugar, plasma cortisol, catecholamines and so on are clearly characteristic of systemic stress. Furthermore, in the case of concurrent surgical interventions, "balanced anesthesia, with or without the neuroleptic component, does not block the stress response. Associated rises in blood sugar, plasma cortisol, and catecholamines during anesthesia and surgery appear to be well documented" (31 refs.).

Cheney, D. H., Slogoff, S., Allen, G. W.: "Ketamine-induced stress ulcers in the rat." *Anesthesiology* **40**: 531-535 (1974).

J13,522/74

In rats, restraint produced stress ulcers whereas *ketamine* alone, at the dose levels given, did not although it did increase the incidence of restraint-induced ulcers from 35 percent to almost 100 percent. This sensitization was counteracted by phenoxybenzamine and halothane, "suggesting that the action of ketamine is mediated by vasoconstriction. Antihistamine pretreatment with promethazine was without effect."

Fahringer, E. E., Foley, E. L., Redgate, E. S.: "Pituitary adrenal response to ketamine and the inhibition of the response by catecholaminergic blockade." *Neuroendocrinology* **14**: 151-164 (1974). H86,423/74

Ketamine, a centrally acting nonbarbiturate anesthetic given intraperitoneally, caused a rise in the blood corticosterone content of rat plasma which was abolished by hypophysectomy or dexamethasone. This response was only slightly altered by pretreatment with atropine or phentolamine but significantly diminished by propranolol or haloperidol. The authors assume that the "response to ketamine is mediated through a facilitatory β -adrenergic and/or dopaminergic pathway or some hybrid thereof, and that ketamine is a convenient and useful agent for testing pituitary adrenal responsiveness in the rat."

Roizen, M. F., Moss, J., Henry, D. P., Kopin, I. J.: "Effects of halothane on plasma catecholamines." *Anesthesiology* **41**: 432-439 (1974). J17,763/74

Cunitz, G., Plötz, J., Michel, B.: "Untersuchungen über den Einfluss der Narkose auf das Hypophysenvorderlappen-Nebennierenrinden-System anhand von Ascorbinsäurebestimmungen" (Investigations on the influence of *anesthesia* on the anterior pituitary gland-adrenocortical system using ascorbic acid determinations). *Anaesthetist* **23**: 520-524 (1974). J21,846/74

Nakashima, A., Koshiyama, K., Uozumi, T., Monden, Y., Hamanaka, Y., Kurachi, K., Aono, T., Mizutani, S., Matsumoto, K.: "Effects of general *anesthesia* and severity of surgical stress on serum LH and testosterone in males." *Acta Endocrinol. (Kbh.)* **78**: 258-269 (1975). H96,576/75

***Antiadrenergics.** Goldstein, M. S., Ramey, E. R., Fritz, I., Levine, R.: "Reversal of effects of stress in adrenalectomized animals by autonomic blocking agents. Use of atropine, Banthine and Dibenamine." *Am. J. Physiol.* **171**: 92-99 (1952). B75,440/52

In adrenalectomized rats resistance to formalin, hemorrhage, forced muscular exercise and cold was increased by autonomic blocking agents such as *atropine*, *Banthine*, *Dibenamine* and *Thephorin*. Apparently, in the absence of adrenals, blockade of autonomic stimuli is beneficial.

Eliasch, H., Rosen, A., Scott, H. M.: "Systemic circulatory response to stress of simulated flight and to physical exercise before and after propranolol blockade." *Br. Heart J.* **29**: 671-683 (1967). G50,658/67

Heart rate, blood pressure and cardiac output increased in pilots during a Link

trainer simulated flight, and also after intense physical exercise on a bicycle ergometer. Comparisons with similar tests after *propranolol* administration "indicate that beta adrenergic receptor activity is extensively involved in the circulatory reaction to emotional stress. In contrast, this activity appears to be involved but less essential in the achievement of the circulatory adjustments during moderate physical exercise."

Goldman, V., Comerford B., Hughes, D., Nyberg, G.: "Effect of β -adrenergic blockade and alcohol on simulated car driving." *Nature* **224**: 1175-1178 (1969). H19,740/69

The β -adrenergic blocking agent *alprenolol* diminishes the tachycardia produced by an exciting ride in a fast roller coaster or a simulated car driving machine without significantly affecting driving performance.

Pettinger, W. A., Augusto, L., Leon, A. S.: "Alteration of renin release by stress and adrenergic receptor and related drugs in unanesthetized rats." *Adv. Exp. Med. Biol.* **22**: 105-117 (1972). G94,419/72

Renin release, noted after exposure to various stressors, can be influenced by diverse drugs. "The beta-adrenergic blocking drug *propranolol* suppressed endogenous release of renin and inhibited renin release induced by stresses of swimming and anesthesia... Suppression of endogenous renin release by *propranolol* could play a role in the antihypertensive properties of this drug in man."

Palmer, B.: "The influence of stress on the survival of experimental skin flaps. A study on rats." *Scand. J. Plast. Reconstr. Surg.* **6**: 110-113 (1972). G99,625/72

In rats with very long skin flaps that normally undergo partial necrosis, stress (restraint) distinctly diminished skin survival, but this could be inhibited by α -adrenergic blocking agents presumably because they prevent vasoconstriction. [Since the skin flap, even at the end farthest removed from its attachment to normal skin, was equivalent to an autotransplant which usually heals without necrosis in the absence of all vascular connections, it is difficult to understand why this was not the case here (H.S.).]

Gorizontov, P. D., Belousova, O. I., Zimin, I. I.: "Role of adrenalin and exclusion of α -receptors in reactions of the hemopoietic organs to stress." *Biull. Eksp. Biol. Med.* **73** No. 12: 23-26 (1972) (Russian).

J20,143/72

Clasing, D., Machtens, E.: "The effect of beta adrenergic blocking agents on the heart rate during psychic stress." *Proc. Biotelemetry Int. Symp.*, pp. 246-250 (1972).

H80,196/72

Carruthers, M., Taggart, P.: "Vagotonicity of violence: biochemical and cardiac responses to violent films and television programmes." *Br. Med. J.* August 18, 1973, pp. 384-389. H74,499/73

Description of the changes in blood EP, glucose, FFA, triglycerides and STH that occurred in men and women watching films and television programs depicting violence, humor or suspense. "Groups of people taken to see two particularly violent films showed similar evidence suggesting vagal overactivity, together with increases in plasma free fatty acids and decreases in triglycerides. As these changes occurred even with β -blockade, it is suggested that they might be caused by non-sympathetically mediated changes in the levels of hormones, such as growth hormone, producing lipolysis."

Taggart, P., Carruthers, M., Somerville, W.: "Electrocardiogram, plasma catecholamines and lipids, and their modification by *oxprenolol* when speaking before an audience." *Lancet* August 18, 1973, pp. 341-346.

H74,091/73

In normal subjects and patients with coronary heart disease, speaking before an audience caused tachycardia (up to 180 per minute), and an increase in plasma catecholamines and FFA. Ectopic heartbeats were noted in about 25 percent of these subjects. A single dose of the β -adrenergic blocker *oxprenolol* suppressed most of the cardiac anomalies in both normal and coronary subjects, although plasma NEP levels were not significantly affected. Presumably, "emotional challenges may produce conspicuous cardiovascular effects, especially in susceptible persons. It is suggested that β -blockade could be used to alleviate the unpleasant symptoms associated with speaking before an audience."

Taylor, S. H., Meenan, M. K.: "Different effects of adrenergic beta-receptor blockade on heart rate response to mental stress, catecholamines and exercise." *Br. Med. J.* November 3, 1973, pp. 257-259.

H77,497/73

In normal people a single oral tablet of *oxprenolol* relieves the tachycardia associated with automobile driving and isoproterenol, whereas exercise tachycardia is substantially

less influenced. "Thus relatively small doses of beta-receptor antagonists will suppress the increase in heart rate induced by mental stress or catecholamines with relatively little effect on the response to everyday exercise. Possibly smaller doses of these drugs would relieve emotionally-induced anginal pain and tachycardia."

Bergamaschi, M., Caravaggi, A. M., Mandelli, V., Shanks, R. G.: "The role of beta adrenoceptors in the coronary and systemic hemodynamic responses to emotional stress in conscious dogs." *Am. Heart J.* **86**: 216-226 (1973). H72,433/73

In dogs, "emotional stress produced by firing a gun increased heart rate, cardiac output, and left ventricular work." The responses were reduced by *propranolol* and *practolol*, and abolished by *alprenolol*.

Winchester, J. F.: "Drug profile: Trasistor." *J. Int. Med. Res.* **2**: 448-457 (1974). H97,640/74

In man, *oxprenolol* is allegedly the most effective β -blocker in simulated emotional stress situations, and can be highly recommended in the treatment of hypertension and angina pectoris.

Bjurstedt, H., Rosenhamer, G., Tydén, G.: "Acceleration stress and effects of propranolol on cardiovascular responses." *Acta Physiol. Scand.* **90**: 491-500 (1974).

J12,120/74

In man, after treatment with *propranolol*, "the heart rate response to increased G at rest averaged 38 percent of that observed without blockade, indicating that G-induced cardioacceleration is predominantly due to sympathetic stimulation." However, subjective gravity tolerance was well preserved; hence, sympathetic chronotropic stimulation of the heart is not essential for the circulatory defense against gravitational stress.

*Antiadrenocortical Compounds. (See *Amphenone, Metyrapone*)

*Antibiotics. Renaud, S.: "Action du stress et de NaCl sur les effets toxiques et bactériostatiques de la néomycine" (Action of stress and NaCl on the toxic and bacteriostatic effects of neomycin). *Presse Méd.* **69**: 281-283 (1961). C94,493/61

Various antibiotics, especially *neomycin*, become particularly pathogenic if applied to rats simultaneously with some stressors. Cer-

tain sodium salts offer protection against this combined treatment.

Arimura, A., Bowers, C. Y., Schally, A. V., Saito, M., Miller, M. C.: "Effect of corticotropin-releasing factor, dexamethasone and actinomycin D on the release of ACTH from rat pituitaries in vivo and in vitro." *Endocrinology* **85**: 300-311 (1969). H15,815/69

Comparative in vivo and in vitro studies on rats given *actinomycin D* to inhibit DNA-dependent RNA synthesis led to the following conclusions: 1) Dexamethasone suppresses the action of CRF at the pituitary level, 2) this dexamethasone blockade does not develop immediately, 3) dexamethasone-blockade of CRF requires a process which involves DNA-dependent RNA synthesis, and 4) the process of ACTH release by CRF does not require RNA synthesis" (34 refs.).

Cannon, R. E., Shane, M. S.: "The effect of antibiotic stress on protein synthesis in the establishment of lysogeny of *Plectonema boryanum*." *Virology* **49**: 130-133 (1972). G92,363/72

Evidence is presented for the establishment of lysogeny in *Plectonema boryanum* by LPP-1D and LPP-2 phycoviruses after treatment of the alga with *chloramphenicol*.

Walton, J. R.: "Indirect consequences of low-level use of antimicrobial agents in animal feeds." *Fed. Proc.* **34**: 205-208 (1975). H98,529/75

In mammals treated with *antimicrobial agents*, "one form of stress may be defined in terms of a disturbance of intestinal flora brought on by relocation, group mixing, change of diet, or travel."

*Anticholinergics. Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction" characterized by adrenocortical enlargement with acute loss of lipids, thymic-lymphatic atrophy, and decreased body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for 48 hours or more, large doses of *atropine*, morphine, formaldehyde or EP). Adrenalectomy and, to a lesser extent, hypophsectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug," but greatly

shorten survival. Perhaps the adrenal enlargement, loss of body weight and other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Goldstein, M. S., Ramey, E. R., Fritz, I., Levine, R.: "Reversal of effects of stress in adrenalectomized animals by autonomic blocking agents. Use of atropine, Banthine and dibenamine." *Am. J. Physiol.* **171**: 92-99 (1952). B75,440/52

In adrenalectomized rats resistance to formalin, hemorrhage, forced muscular exercise and cold was increased by autonomic blocking agents such as *atropine*, Banthine, Dibenamine and Thephorin. Apparently, in the absence of adrenals, blockade of autonomic stimuli is beneficial.

Takagi, K., Okabe, S.: "An experimental gastric ulcer of the rat produced with anticholinergic drugs under stress." *Eur. J. Pharmacol.* **5**: 263-271 (1969). H9,358/69

In rats, the stress ulcers produced by immersion in cold water are prevented by *atropine* and other anticholinergic agents, but at the same time another type of ulcer appears in the proventriculus.

***Antihistamines.** Tepperman, J., Rakieten, N., Birnie, J. H., Diermeier, H. F.: "Effect of antihistamine drugs on the adrenal cortical response to histamine and to stress." *J. Pharmacol. Exp. Ther.* **101**: 144-152 (1951). B59,242/51

In rats, various *antihistaminics* (Phenoxyadrine, Benadryl, Pyribenzamine) did not significantly alter adrenal ascorbic acid, but intraperitoneal injection of histamine reduced it remarkably. On the other hand, "pretreatment with an antihistamine drug did not prevent or modify the adrenal ascorbic acid response to the stress of intraperitoneal carbon tetrachloride administration."

Asiaticoside. Ravokatra, A., Loiseau, A., Ratsimamanga-Urverg, S., Nigeon-Dureuil, M., Ratsimamanga, A. R.: "Action de l'asiaticoside (triterpène pentacyclique) retiré de l'Hydrocotyle Madagascariensis sur les ulcères duodénaux créés par la mercaptoéthylamine chez le rat Wistar mâle" (The effects of asiaticoside [pentacyclic triterpene] extracted from Hydrocotyle Madagascariensis on mercaptoethylamine-induced duodenal ulcers in the Wistar male rat). *C. R. Acad.*

Sci. (Paris) **278**: 2317-2321 (1974).

J13,441/74

In rats, cysteamine-induced duodenal ulcers can be prevented by asiaticoside. A similar protective effect is exerted by this compound against peptic ulcers caused by stress.

Atropine. (See **Anticholinergics**)

Barbiturates. (See **Anesthetics and Analgesics**)

Benzene. Bartolini, G., Berti, P.: "Istopatologia del timo di 'Mus ratus albinus' nel benzolismo cronico sperimentale" (Thymus histopathology in "Mus ratus albinus" after chronic experimental benzolism). *Arch. Vecchi Anat. Patol.* **63**: 777-786 (1964).

G32,118/64

Chronic benzol intoxication produces a typical G.A.S. with conspicuous thymus involution in the rat.

Cannabis. "Cannabis and driving skills." *Can. Med. Assoc. J.* **107**: 269-270 (1972). J16,956/72

Retterstøl, N.: "Cannabis og bilkjøring" (Cannabis and car driving). *T. Norske Laegeforen.* **93**: 2121-2122 (1973) (Norwegian). J16,347/73

Pertwee, R. G.: "Tolerance to the effect of Δ^1 -tetrahydrocannabinol on corticosterone levels in mouse plasma produced by repeated administration of cannabis extract or Δ^1 -tetrahydrocannabinol." *Br. J. Pharmacol.* **51**: 391-397 (1974). H92,479/74

"Pretreatment with cannabis extract or Δ^1 -THC can produce tolerance to the effect of Δ^1 -THC on corticosterone levels in mouse plasma and does so without impairing the effect of immobilization stress on corticosterone release. In addition, both the rise in corticosterone plasma levels produced by cannabis or Δ^1 -THC and the development of tolerance to this effect can still take place in the absence of hypothermia."

Klonoff, H.: "Marijuana and driving in real-life situations. The effect of marijuana on driving is bidirectional and dependent on compensatory ability and dose." *Science* **186**: 317-324 (1974). H93,920/74

Kokka, N., Garcia, J. F.: "Effects of Δ^9 -THC on growth hormone and ACTH secre-

tion in rats." *Life Sci.* **15**: 329-338 (1974).

J15,591/74

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) "acts as a pharmacological stressor of hypothalamo-pituitary function in rats since the same changes in plasma corticosterone and GH concentrations are elicited in response to many stimuli that are commonly of a stressful nature" (23 refs.).

Carbohydrates. (See under names of individual carbohydrates)

Chloramphenicol. (See Antibiotics)

Chlorpromazine. (See also Tranquilizers) Holzbauer, M., Vogt, M.: "The action of chlorpromazine on diencephalic sympathetic activity and on the release of adrenocorticotropic hormone." *Br. J. Pharmacol.* **9**: 402-407 (1954). C7,651/54

In rats, ACTH release following surgical shock or EP injection was not prevented by chlorpromazine which in fact caused some ACTH secretion by itself. These observations contradict certain earlier claims.

Sevy, R. W., Ohler, E. A., Weiner, A.: "Effect of chlorpromazine on stress-induced adrenal ascorbic acid depletion." *Endocrinology* **61**: 45-51 (1957). C37,515/57

In experiments on rats, chlorpromazine did not cause adrenal ascorbic acid depletion but actually inhibited this change when produced by sham adrenalectomy, unilateral adrenalectomy or by EP. The adrenal ascorbic acid depletion elicited by vasopressin or ACTH was not influenced.

DeBias, D. A., Paschkis, K. E., Cantarow, A.: "Effects of chlorpromazine and autonomic nervous system blocking agents in combating heat stress." *Am. J. Physiol.* **193**: 553-556 (1958). C54,401/58

Personal observations and brief review of the literature on the effects of various drugs upon resistance to diverse stressors in intact and adrenalectomized rats. Since different drugs are effective against different stressors, the mechanism of protection must be dissimilar.

Mahfouz, M., Ezz, E. A.: "The effect of reserpine and chlorpromazine on the response of the rat to acute stress." *J. Pharmacol. Exp. Ther.* **123**: 39-42 (1958). C53,654/58

In rats, both chlorpromazine and reserpine inhibit the stressor effect (adrenal ascorbic acid depletion) of cold, heat and hemorrhage

under ether anesthesia. Neither drug prevents the adrenal ascorbic acid depletion caused by ACTH, but may act upon the hypothalamus.

Juszkiewicz, T., Jones, L. M.: "The effects of chlorpromazine on heat stress in pigs." *Am. J. Vet. Res.* **22**: 553-557 (1961).

J10,364/61

As indicated by adrenal ascorbic acid determinations, "chlorpromazine diminishes stressful response of the pituitary-adrenal axis in pigs due to hyperthermia, increases the survival rate at 40°C., and decreases the body weight loss."

Juszkiewicz, T.: "Effects of chlorpromazine, reserpine, and ascorbic acid in resisting heat stress in rats." *Am. J. Vet. Res.* **22**: 537-543 (1961).

J11,417/61

In rats, pretreatment with chlorpromazine, reserpine or ascorbic acid failed to prevent but did somewhat diminish the loss of adrenal ascorbic acid produced by heat (43°C.).

Betz, D., Ganong, W. F.: "Effect of chlorpromazine on pituitary-adrenal function in the dog." *Acta Endocrinol. (Kbh.)* **43**: 264-270 (1963).

D68,211/63

Bohus, B., Endrőczi, E.: "Untersuchungen über die Wirkung von Chlorpromazin auf das Hypophysen-Nebennierenrinden-System bei Ratten" (Studies on the effect of chlorpromazine on the hypophysis-adrenal cortex system in rats). *Endokrinologie* **46**: 126-133 (1964).

F16,012/64

In rats, large doses of subcutaneous chlorpromazine, particularly when injected into the reticular formation of the brain, produced high corticosterone secretion. It was not possible to inhibit the blood corticosterone rise normally caused by stressors (formalin, restraint) through pretreatment with chlorpromazine.

Yamashita, I., Moroji, T., Yamazaki, K., Kato, H., Sakashita, A., Onodera, I., Ito, K., Okada, F., Saito, Y., Tamakoshi, M., Suwa, N.: "Neuroendocrinological studies in mental disorders and psychotropic drugs. I. On the circadian rhythm of the plasma adrenocortical hormone in mental patients and methamphetamine- and chlorpromazine-treated animals." *Folia Psychiatr. Neurol. Jap.* **23**: 143-158 (1969).

G72,651/69

The circadian plasma corticosteroid rhythm was deranged in rats treated with methamphetamine or chlorpromazine.

Lindenbaum, E. S., Diamond, B., Yaryura-Tobías, J. A.: "Nicotinic acid and restraint induced ulcers." *Acta Physiol. Lat. Am.* **23**: 288-292 (1973). J9,059/73

In rats, the gastric ulcers produced by restraint with food and water deprivation are more effectively inhibited by nicotinic acid than by chlorpromazine.

p-Chlorophenylalanine. (See PCPA)

***CNS Stimulants.** (See also Methamphetamine) Weiss, B., Laties, V. G., Blanton, F. L.: "Amphetamine toxicity in rats and mice subjected to stress." *J. Pharmacol. Exp. Ther.* **132**: 366-371 (1961).

D6,968/61

The toxicity of *amphetamine* is increased in rats and mice exposed to aversive electroshock. This effect can be counteracted by chlorpromazine and phenoxybenzamine.

Moore, K. E., Lariviere, E. W.: "Effects of stress and D-amphetamine on rat brain catecholamines." *Biochem. Pharmacol.* **13**: 1098-1100 (1964). G17,075/64

Various stressors enhanced the toxicity of *d-amphetamine*, perhaps through the release of NEP. Among the stressors examined (restraint, swimming, electroshock, sound and so on), only some caused a significant increase in amphetamine toxicity and a decrease in brain NEP. In the latter respect, grid-shocked rats were particularly responsive. The depletion of brain NEP by stressors and *d-amphetamine* might be due to release through excessive stimulation, and subsequent destruction at a rate faster than its synthesis. "Dopamine, on the other hand, is not affected by these particular stimuli. This differential depletion of catecholamines in response to various stimuli can perhaps be explained by the fact that they are distributed differently within the brain. Norepinephrine is primarily located in the hypothalamus and other brain stem areas that are believed to represent the central component of the sympathetic nervous system; dopamine is primarily located in the basal ganglia-areas associated with the extrapyramidal system."

Goldberg, M. E., Salama, A. I.: "Amphetamine toxicity and brain monoamines in three models of stress." *Toxicol. Appl. Pharmacol.* **14**: 447-456 (1969).

G66,997/69

In the mouse and rat, a significant rise in the level of brain stem 5-HT was caused by

trauma or electroshock but not by cold. "This increase was obtained in animals subjected to stress alone, or those given the highest possible nonlethal dose of *amphetamine*. These same doses did not augment the catecholamine-releasing properties of amphetamine in drum- or electric shock-stressed animals. It does not appear that stress potentiates the effects of amphetamine, as no evidence of excitation was obtained in stressed animals given amphetamine. It is postulated that amphetamine enhances the effects of stress."

Welch, B. L., Welch, A. S.: "Chronic social stimulation and tolerance to amphetamine: interacting effects of amphetamine and natural nervous stimulation upon brain amines and behavior." In: Ellingwood, E. H. Jr. and Cohen, S., *Current Concepts in Amphetamine Abuse*, pp. 107-115. Washington, D. C.: U. S. Government Printing Office, 1973. J11,597/73

Review of the literature on the enhancement of *amphetamine* toxicity by various acute stressors. Chronic stress appears to have an inverse effect as shown by experiments in mice (22 refs.).

DeFeudis, F. V., Marks, J. H.: "Studies on the time course of entry and subcellular distribution of radioactivity of (³H) *d*-amphetamine in the brains of differentially-housed mice." *Experientia* **29**: 1518-1520 (1973). H81,970/73

In mice, the accumulation of radio-marked *d-amphetamine* in synaptic particles of the brain was increased after prolonged isolation. [The authors do not specifically relate this to stress (H. S.).]

Colchicine. Leblond, C. P., Segal, G.: "Action de la cochinicine sur la surrénale et les organes lymphatiques" (Effect of colchicine on the adrenals and the lymphatic organs). *C. R. Soc. Biol. (Paris)* **128**: 995-996 (1938). A50,424/38

In rats, colchicine produces extremely severe manifestations of the alarm reaction, including adrenal enlargement and thymic-lymphatic atrophy. Adrenalectomy suppresses these actions.

Cysteamine. Flemming, K., Geierhaas, B.: "Hemmung von Cysteamin auf den Corticosterongehalt der Nebennieren von Ratten nach Stress-Einwirkung" (Inhibitory effect of cysteamine on the corticosterone content of rat adrenal glands after stress).

Experientia **28**: 965-966 (1972).

H61,481/72

In rats, cysteamine inhibits the rise in corticosterone elicited in the adrenals and plasma by various stressors.

Robert, A., Lancaster, C., Nezamis, J., Badalamenti, J.: "A new model to test antiulcer agents, cysteamine-induced duodenal ulcers." *Fed. Proc.* **33**: 310 (1974).

H84,075/74

The cysteamine-induced duodenal ulcers of rats generally respond to the same therapeutic agents as do the spontaneous duodenal ulcers of man. Hence "they represent a useful model to detect antiulcer agents, and to study the mechanism of duodenal ulcer formation."

DDD. Reznikov, A. G., Kravtsova, E. L.: "Effect of o,p'-DDD on the secretion of 11- and 17-hydroxy-corticosteroids in dogs during stress." *Patol. Fiziol. Eksp. Ter.* **14** Nos. 7-8: 38-40 (1970) (Russian).

J21,368/70

In dogs, o,p'-DDD diminished the 17-OHCS and 11-OHCS content of adrenal venous blood. They also showed decreased corticoid production when exposed to stress. o,p'-DDD disturbed the synthesis of corticosterone and cortisol to the same extent.

Hamid, J., Sayeed, A., McFarlane, H.: "The effect of 1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane (o,p'-DDD) on the immune response in malnutrition." *Brit. J. exp. Pathol.* **55**: 94-100 (1974).

H86,118/74

In rats, o,p'-DDD caused loss of body weight as well as involution of the thymus, spleen and adrenals. In malnourished rats, adrenal atrophy was particularly marked and was associated with diminution of plasma corticoids and a decrease in the impairment of the immune response normally occasioned by this drug.

DDT. Wassermann, D., Wassermann, M.: "Adrenocortical zona fasciculata in rats receiving p,p'-DDT." *Environ. Physiol. Biochem.* **3**: 274-280 (1973). J11,455/73

EM studies suggest that "the inhibition of adrenal hyperplasia after surgical stress in rats receiving p,p'-DDT...as well as the lack of clear-cut morphological features of hyperactivity expected in zona fasciculata cells (as a result of an enhanced glucocorticoid clearance rate in the presence of p,p'-DDT) raise the problem of the influence of

p,p'-DDT on the chain of biochemical events of the adaptation of zona fasciculata activity to the needs."

Deoxyephedrine. (See **Methamphetamine**)

Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA). Day, E. D., Fletcher, D. C., Naimark, G. M., Mosher, W. A.: "Sonic radiation effects on rats." *J. Aviat. Med.* **22**: 316-318 (1951). B63,927/51

In rats, exposure to an intense sound imitating that of turbojet engines caused death with typical manifestations of the G.A.S. The DNA content of the hepatic and adrenal nucleus remained unchanged.

Dibenzylamine. Ohler, E. A., Sevy, R. W.: "Inhibition of stress induced adrenal ascorbic acid depletion by morphine, dibenzylamine, and adrenal cortex extract." *Endocrinology* **59**: 347-355 (1956). C23,020/56

In rats the adrenal ascorbic acid depletion produced by sham adrenalectomy, uniadrenalectomy, EP, hydroxyamphetamine or vasopressin could be inhibited by morphine. Adrenal cortical extract blocked the response to operative stress and to catecholamines, but not to vasopressin. Dibenzylamine abolished only the reaction to catecholamines.

Diphenylhydantoin. Bliss, E. L., Migeon, C. J., Nelson, D. H., Samuels, L. T., Branch, C. H. H.: "Influence of E. C. T. and insulin coma on level of adrenocortical steroids in peripheral circulation." *Arch. Neurol. Psychiatry* **72**: 352-361 (1954). C1,997/54

In schizophrenics, electroconvulsive therapy as well as insulin coma increased the plasma level of 17-OHCS. When diphenylhydantoin was used to eliminate cyanosis, apnea and violent muscular movements, seizures still resulted in a corticoid increase but of shortened duration.

Asfeldt, V. H., Buhl, J.: "Inhibitory effect of diphenylhydantoin on the feedback control of corticotrophin release." *Acta Endocrinol. (Kbh.)* **61**: 551-560 (1969).

H15,117/69

Epileptic patients receiving diphenylhydantoin retain a normal circadian rhythm of ACTH release but respond poorly to the increase in ACTH normally produced by metyrapone or to the suppression of ACTH secretion by dexamethasone, presumably as

a result of deranged ACTH feedback controls.

DMSO. Allen, J. P., Allen, C. F.: "The effect of dimethyl sulfoxide on hypothalamic pituitary-adrenal functions in the rat." *Ann. N.Y. Acad. Sci.* **243**: 325-336 (1975).

H98,565/75

Experimental observations suggesting that dimethyl sulfoxide (DMSO) acts either directly on the hypothalamic-anterior pituitary complex to cause secretion of ACTH (presumably through the release of CRF), or that it potentiates the effect of circulating ACTH on the adrenal cortex to stimulate the secretion of corticosterone. DMSO significantly raises plasma corticosterone even in adrenalectomized or deafferented animals.

DOPA. Loon, G. R. van, Hilger, L., King, A. B., Boryczka, A. T., Ganong, W. F.: "Inhibitory effect of L-dihydroxyphenylalanine on the adrenal venous 17-hydroxycorticosteroid response to surgical stress in dogs." *Endocrinology* **88**: 1404-1414 (1971).

H39,650/71

In dogs, the adrenal venous 17-OHCS elevation after surgical stress was curtailed by L-dopa but not by NEP or intravenous dopamine. "The minimum effective dose of L-dopa that inhibited the 17-OHCS response to stress was decreased by the monoamine oxidase inhibitor, pargyline, and increased by the catecholamine synthesis inhibitor, α -methyl-p-tyrosine. These data support the hypothesis of a central adrenergic neural system which inhibits ACTH secretion in dogs" (42 refs.).

Lovinger, R. D., Connors, M. H., Kaplan, S. L., Ganong, W. F., Grumbach, M. M.: "Effect of L-dihydroxyphenylalanine (L-dopa), anesthesia and surgical stress on the secretion of growth hormone in the dog." *Endocrinology* **95**: 1317-1321 (1974).

H94,147/74

In dogs, pentobarbital anesthesia and surgical stress failed to cause significant alterations in plasma STH, whereas L-dopa elicited a pronounced rise as it did in man.

***Electrolytes, Water, Osmotic Pressure.** (See also **Osmotic Pressure under Physical Agents**) Lawzewitsch, I. von, Sarrat, R.: "Das neurosekretorische Zwischenhirn-Hypophysensystem von Vögeln nach langer osmotischer Belastung" (The neurosecretory hypothalamo-hypophyseal system of birds

after long-term osmotic stress). *Acta Anat.* (Basel) **77**: 521-539 (1970).

G84,461/70

It is concluded that "the hypothalamohypophyseal neurosecretory system of cocks under a chronic stress of a 0.3 m NaCl solution ad libitum, resulting in an exhaustion of the system, enters into a period of adaptation during which new neurosecretory material is stored by the cells of the nucleus. This adaptation could either result from the synthesizing ability of the neurosecretory cells being increased by a prolonged stress or from the decrease in hormonal demand due to functional changes in the periphery."

Levine, A. M., Higgins, J. A., Barrnett, R. J.: "Biogenesis of plasma membranes in salt glands of *salt*-stressed domestic ducklings: localization of acyltransferase activity." *J. Cell Sci.* **11**: 855-873 (1972).

J19,377/72

Funkhouser, D., Goldstein, L.: "Urea response to pure *osmotic* stress in the aquatic toad *Xenopus laevis*." *Am. J. Physiol.* **224**: 524-529 (1973).

H67,004/73

Nevis, A. H., Thursby, M. H.: "Paradoxical quantitative electroencephalographic changes in rats stressed *osmotically*." *Int. J. Neurosci.* **5**: 75-80 (1973).

H80,333/73

Ellis, R. A., Goertemiller, C. C. Jr.: "Cytological effects of *salt*-stress and localization of transport adenosine triphosphatase in the lateral nasal glands of the desert Iguana, *Dipsosaurus dorsalis*." *Anat. Rec.* **180**: 285-298 (1974).

J17,759/74

Pospíšil, M.: "Electrolyte balance of the internal environment as a factor conditioning individual differences in metabolic, cellular and stress activities of the organism. Hypothesis and experimental evidence." *Agresologie* **15**: 169-177 (1974).

H97,226/74

Ethanol. (See also **Toxicomanias under Diseases of Adaptation**) Bass, A. D., Feigelson, M.: "Response of normal and malignant lymphoid tissue to non specific tissue damage." *Proc. Soc. Exp. Biol. Med.* **69**: 339-341 (1948).

B28,259/48

In mice, "ethyl alcohol is an alarming stimulus.... Fasting begun thirty hours after the initial stimulus gives an additional 'lympholytic' effect. It has been shown that stimuli which are known to produce an alarm reaction with resulting atrophy of the normal thymus and normal spleen produce a similar

type of reaction in tissue composed of malignant lymphocytes."

Mardones, J., MacLeod, L. D.: "The 'craving' for alcohol. A symposium by members of the WHO expert committees on mental health and on alcohol." *Q. J. Stud. Alcohol* **16**: 34-66 (1955). B56,097/55

Review on the effects of stress and corticoids upon alcohol craving in experimental animals and man.

Myers, R. D., Cicero, T. J.: "Effects of serotonin depletion on the volitional alcohol intake of rats during a condition of psychological stress." *Psychopharmacologia* **15**: 373-381 (1969). G70,679/69

In rats PCPA (a potent tryptophan hydroxylase inhibitor) diminishes brain 5-HT. The stress of electroshock avoidance increases ethanol intake but this preference is reduced through depletion of brain 5-HT by PCPA.

Rappaport, M.: "NAD effects on the biochemistry and psychological performance of alcoholics under ethanol stress." *Q. J. Stud. Alcohol* **30**: 570-584 (1969). J22,892/69

Allman, L. R., Taylor, H. A., Nathan, P. E.: "Group drinking during stress: effects on drinking behavior, affect, and psychopathology." *Am. J. Psychiatry* **129**: 669-678 (1972). G96,807/72

A group of three chronic alcoholics "drank most when stress and socialization periods coincided; they drank least when stress and periods of isolation occurred together."

Smith, J. F. B., Lucie, N. P.: "Alcohol—a cause of stress erythrocytosis?" *Lancet* March 24, 1973, pp. 637-638.

H67,158/73

In man, high ethanol intake causes "stress erythrocytosis" due to a reduced plasma volume.

Beard, J. D., Knott, D. H., Simpson, J. R., Sargent, W. Q.: "Cardiovascular response to hemorrhage in dogs after alcohol." *Q. J. Stud. Alcohol* **34**: 1303-1314 (1973).

J9,037/73

In dogs, mortality owing to repeated hemorrhage was considerably higher after daily gavages of an ethanol solution than following treatment with an isocaloric glucose solution. This decrease in resistance may be due to depletion of cardiac reserves caused by stress, but other stressors have not yet been examined under similar circumstances.

Ether. (See Anesthetics)

Ethionine. Marks, B. H., Vernikos-Danellis, J.: "Effect of acute stress on the pituitary gland: action of ethionine on stress-induced ACTH release." *Endocrinology* **72**: 582-587 (1963). D60,686/63

In rats, "ethionine produced a marked suppression of ACTH release following ether-laparotomy stress."

α -Ethyltryptamine, α -Methyltryptamine. Ganong, W. F., Wise, B. L., Shackleford, R., Boryczka, A. T., Zipf, B.: "Site at which α -ethyltryptamine acts to inhibit the secretion of ACTH." *Endocrinology* **76**: 526-530 (1965). F33,025/65

In dogs, α -ethyltryptamine decreased 17-OHCS output after surgical stress even if most of the CNS was removed except for "hypothalamic islands." However, direct stimulation of the ME increased 17-OHCS secretion which could not be blocked by α -ethyltryptamine. Perhaps the compound "may prevent stimulation of the CRF-secreting neurons by impulses in the incoming afferent fibers." Although α -ethyltryptamine is a MAO inhibitor, its blockade of ACTH secretion is so transient that it seems unlikely to be related to MAO inhibition. Besides, other MAO inhibitors do not share this effect.

Ganong, W. F., Boryczka, A. T., Lorenzen, L. C., Egge, A. S.: "Lack of effect of α -ethyltryptamine on ACTH secretion when blood pressure is held constant." *Proc. Soc. Exp. Biol. Med.* **124**: 558-559 (1967).

F77,622/67

In dogs, the increased ACTH secretion produced by hemorrhage is prevented by α -ethyltryptamine in doses that restore the blood pressure. Presumably, it is the latter effect of α -ethyltryptamine that causes the inhibition of ACTH secretion.

Lorenzen, L. C., Ganong, W. F.: "Effect of drugs related to α -ethyltryptamine on stress-induced ACTH secretion in the dog." *Endocrinology* **80**: 889-892 (1967).

F83,263/67

In dogs, α -methyltryptamine suppressed ACTH secretion as effectively as did α -ethyltryptamine. Corresponding tests with numerous indole derivatives, MAO inhibitors, antidepressants and pressor amines revealed that the ACTH-blocking activity of α -methyltryptamine is correlated only with its pressor action since it is shared by vasopressors. The

effect is unrelated to any other chemical or pharmacologic property of the drugs used for comparison.

Formaldehyde. Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction" characterized by adrenocortical enlargement with acute loss of lipids, thymic-lymphatic atrophy and decreased body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and to a lesser extent hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug," but greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Weisz, P., Kádas, T., Köves, P., Ritter, L.: "Einwirkung der chronischen Formalinbehandlung auf die Corticosteronausscheidung der Nebennieren bei weissen Ratten" (Effect of chronic formalin treatment on the corticosterone secretion of the adrenals in white rats). *Endocrinologie* **38**: 80-85 (1959).

C74,539/59

In rats, chronic treatment with formaldehyde caused enlargement of the adrenals, but a pronounced increase in corticosterone excretion was not observed. Apparently, the functional and morphologic stimulation of the adrenal cortex may depend upon independent factors.

Ahrén, C.: "Effects of diencephalic lesions on acute and chronic stress responses in male rabbits." *Acta Endocrinol. (Kbh.)* **41** Suppl. 69: 1-92 (1962). D38,126/62

Monograph on the effect of variously placed diencephalic lesions upon the stress response of rabbits given formalin subcutaneously. "The results indicate that the lymphopenic response was completely blocked by small, circumscribed lesions in the region of the dorsomedial and ventromedial nuclei as well as by lesions in the posterior border of the mammillary bodies and the region dorso-

caudal thereto, whilst it remained unaffected by lesions in the premammillary area or in the anterior half or all the mammillary bodies. Lesions in the anterior preoptic area and posterior orbitofrontal cortex, in the ventro-caudal septum or in the anterior hypothalamic area dorsocaudal to the optic chiasm were associated with partial inhibition, and occasionally even with total blockage, of the lymphopenic response." The findings do not permit conclusions concerning any particular region which would represent a "center" of such stress responses in the limbic structures or mesencephalon.

Glucose. (See also other carbohydrates) Selye, H., MacLean, A.: "Prevention of gastric ulcer formation during the alarm reaction." *Am. J. Dig. Dis.* **11**: 319-322 (1944).

A75,010/44

In rats, the gastric ulcers produced by transection of the spinal cord at the height of the seventh cervical vertebra may be prevented by the prophylactic administration of various food substances, aluminum hydroxide gel and especially by comparatively small doses of dextrose given orally or intravenously. Even in doses insufficient to raise the glucose content of the blood above the normal level, dextrose inhibited gastric ulcer formation for the duration of the experiment. Its prophylactic effect is nonspecific in the sense that it prevents the formation of gastric ulcers in animals exposed to a wide variety of stressors such as formaldehyde injections, exposure to cold or spinal cord transection.

Pyant, R. L. Jr., Mullane, J. F.: "Starvation, glucose ingestion and stress ulcer formation in the rat." *Clin. Res.* **20**: 872 (1972).

H62,440/72

Stress ulcer production by restraint is facilitated in rats by four but not by two days of previous starvation. Oral administration of glucose has a protective effect.

Rayfield, E. J., George, D. T., Beisel, W. R.: "Altered growth hormone homeostasis during acute bacterial sepsis in the rhesus monkey." *J. Clin. Endocrinol. Metab.* **38**: 746-754 (1974). H86,214/74

Studies on monkeys demonstrate an exaggerated STH response following an intravenous glucose load during the stress of acute infection, and suggest that this reaction may be suppressed with chlorpromazine.

Halothane. (See Anesthetics)

Histamine. (See Hormones and Hormone-like Substances)

6-Hydroxydopamine. Delft, A. M. L. van, Nyakas, C., Kaplanski, J., Tilders, F. J. H.: "The effect of 6-hydroxydopamine administration to neonatal rats on some endocrine and behavioral parameters." *Arch. Int. Pharmacodyn. Ther.* **206:** 403-404 (1973). H82,629/73

Depletion of catecholamines in the rat brain by 6-hydroxydopamine caused severe anorexia, impairment of growth, and delayed vaginal opening, but curiously, the stressor activity of the pituitary-adrenal system did not appear to be significantly affected. "Adrenal weights were normal when expressed per 100 g body weight. Diurnal peak and trough activities of adrenocortical activity as determined by measuring both plasma corticosterone levels and corticoid production of excised adrenal tissue in vitro were comparable to the activities found in control rats. Also the response of the pituitary-adrenal system when animals were exposed to strange environment or ether stress was completely within the normal range. These findings raise serious doubts with regard to the theory of the existence of a noradrenergic inhibitory system acting on pituitary-adrenal regulatory processes in the brain."

Leduc, J.: "Effet de la sympathectomie chez le rat exposé au froid" (Effect of sympathectomy on rats exposed to cold). *Ann. ACFAS* **40:** 128 (1973). H87,897/73

6-Hydroxydopamine, which causes a "chemical sympathectomy," greatly diminished resistance to cold. There was a marked rise in urinary EP but not NEP. Apparently, the adrenal medulla can largely compensate for the loss of sympathetic nerve activity.

Insecticides. (See individual agents, e.g., DDT) Murphy, S. D.: "Some relationships between effects of insecticides and other stress conditions." *Ann. N.Y. Acad. Sci.* **160:** 366-377 (1969). G78,902/69

Isethionate. Bennett, J., Dave, C.: "Effect of intravenous infusion of isethionate on rats." *Proc. Soc. Exp. Biol. Med.* **146:** 170-175 (1974). H87,184/74

Isethionate, a metabolite of taurine found in various tissues, caused only very mild stress manifestations when chronically infused into rats. It is probable that even these were largely the result of immobilization and

the infusion procedure rather than of the drug.

Ketamine. (See Anesthetics)

***MAO inhibitors.** (See also α -ethyltryptamine) Ostow, M.: "Orthostatic hypotension and psychic energizers: a clinical note." *Psychosomatics* **7:** 224-225 (1966).

F68,735/66

In patients treated with MAO inhibitors, both stressors and glucocorticoids combat the resulting orthostatic hypotension. Endogenous glucocorticoid liberation may have a therapeutic effect on this condition.

Vermesh, I., Ryzhenkov, V. E.: "Functional condition of the hypophysis-adrenal system in rats with deafferentated hypothalamus; the action of dexamethasone and nialamide." *Probl. Endokrinol.* **20** No. 3: 67-70 (1974) (Russian). H92,315/74

In rats with a completely deafferented medio-basal hypothalamus, the basal plasma corticosterone level rose but could be curtailed by dexamethasone or nialamide. "At the same time suppression of corticosterone secretion in stress by nialamide was stronger in comparison with dexamethasone. Nialamide potentiated the depressive action of dexamethasone on the basal corticosterone secretion, but not under stress [restraint]."

Marijuana. (See Cannabis)

Meprobamate. (See also Tranquilizers) Mäkelä, S., Näätänen, E., Rinne, U. K.: "The response of the adrenal cortex to psychic stress after meprobamate treatment." *Acta Endocrinol.* **32:** 1-7 (1959).

C75,051/59

In rats "meprobamate is able under acute experimental conditions to inhibit the ascorbic acid depletion caused by psychic stress although in the meprobamate plus psychic stress group the adrenal ascorbic acid quantity was highly significantly less than in the controls." After chronic treatment the effect of meprobamate gradually disappears. Curiously, the drug alone stimulates the adrenal cortex in intact and in unilaterally adrenalectomized rats.

Myers, R. D.: "Effects of meprobamate on alcohol preference and on the stress of response extinction in rats." *Psychol. Rep.* **8:** 385-392 (1961). J12,455/61

Frankenhaeuser, M., Kareby, S.: "Effect of meprobamate on catecholamine excretion

during mental stress." *Percept. Mot. Skills* **15**: 571-577 (1962). E30,225/62

In students psychogenic stress (problem solving, and to a lesser extent even anticipation of such tests) augmented EP and NEP excretion. After simultaneous administration of meprobamate, EP output increased but NEP decreased during stress. Thus, "meprobamate in moderate doses counteracted the increase in the catecholamine response of normal individuals subjected to mental stress in a laboratory situation."

Methadone. Farmer, R. W., Harrington, C. A., Fabre, L. F. Jr.: "Inhibition of steroid biosynthesis in isolated rat adrenal cells by methadone." *Fed. Proc.* **33**: 288 (1974).

H84,044/74

Methamphetamine. (See also CNS Stimulants). Frankenhaeuser, M., Post, B.: "Catecholamine excretion during mental work as modified by centrally acting drugs." *Acta Physiol. Scand.* **55**: 74-81 (1962).

D35,589/62

In medical students the stress of various "intellectual tests" increased urinary EP excretion, and this change could be suppressed by methamphetamine and pentobarbital. It appears that "urinary excretion of adrenaline provides a sensitive measure of reactions to mental stress, and that centrally acting drugs may influence adrenaline excretion during mental work."

Yamashita, I., Morojo, T., Yamazaki, K., Kato, H., Sakashita, A., Onodera, I., Ito, K., Okada, F., Saito, Y., Tamakoshi, M., Suwa, N.: "Neuroendocrinological studies in mental disorders and psychotropic drugs. I. On the circadian rhythm of the plasma adrenocortical hormone in mental patients and methamphetamine- and chlorpromazine-treated animals." *Folia Psychiatr. Neurol. Jap.* **23**: 143-158 (1969). G72,651/69

The circadian plasma corticosteroid rhythm was deranged in rats treated with methamphetamine or chlorpromazine.

α -Methyl-p-tyrosine. (See α -MT)

α -Methyltryptamine. (See α -Ethyltryptamine)

Metrazol. Palfai, T., Kurtz, P., Gutman, A.: "Effect of metrazol on brain norepinephrine: a possible factor in amnesia produced by the drug." *Pharmacol. Biochem. Behav.* **2**: 261-262 (1974). J12,891/74

In mice, metrazol-induced seizures diminish brain NEP.

Metyrapone. Kaplan, N. M.: "Assessment of pituitary ACTH secretory capacity with Metopirone: II. Comparison with other tests." *J. Clin. Endocrinol. Metab.* **23**: 953-960 (1963). E27,529/63

Observations in man "confirm the impression that the Metopirone test is the most sensitive measure now available for assessing pituitary ACTH secretory capacity. Discrepancies between the Metopirone and insulin tolerance tests were noted, indicating that the Metopirone test should be considered a measure of only one aspect of pituitary ACTH secretory capacity, and not necessarily a measure of total reserve."

French, F. S., Macfie, J. A., Williams, T. F., Wyk, J. J. van: "Cushing's syndrome with a paradoxical response to dexamethasone." *Am. J. Med.* **47**: 619-624 (1969).

G70,061/69

In a patient with Cushing's syndrome (due to a basophil hypophyseal adenoma) dexamethasone increased urinary 17-OHCS and 17-KS excretion as well as plasma ACTH activity. Metyrapone caused the expected initial rise in urinary 17-KS (due to augmentation of tetrahydro-11-deoxycortisol), but a much larger increase in adrenal corticoid excretion occurred on the second and third days and was associated with the reappearance of urinary cortisol metabolites.

Asfeldt, V. H., Buhl, J.: "Inhibitory effect of diphenylhydantoin on the feedback control of corticotrophin release." *Acta Endocrinol. (Kbh.)* **61**: 551-560 (1969). H15,117/69

Epileptic patients receiving diphenylhydantoin retain a normal circadian rhythm of ACTH release but respond poorly to the increase in ACTH normally produced by metyrapone or to the suppression of ACTH secretion by dexamethasone, presumably as a result of deranged ACTH feedback controls.

Jensen, H. K., Blichert-Toft, M.: "Investigation of pituitary-adrenocortical function in the elderly during standardized operations and postoperative intravenous metyrapone test assessed by plasma cortisol, plasma compound S and eosinophil cell determinations." *Acta Endocrinol. (Kbh.)* **67**: 495-507 (1971). H42,510/71

During the postoperative stage, elderly patients show a significantly stronger response to intravenous metyrapone than do young persons.

Morphine. (See also **Anesthetics and Analgesics**) Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). *C36,032/36*

First detailed description of the "alarm reaction" characterized by adrenocortical enlargement with acute loss of lipids, thymicolympathic atrophy and decreased body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and to a lesser extent hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug," but will greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Briggs, F. N., Munson, P. L.: "Studies on the mechanism of stimulation of ACTH secretion with the aid of morphine as a blocking agent." *Endocrinology* **57**: 205-219 (1955). *C7,791/55*

In rats, morphine blocks the ACTH secretion induced by various stressors (histamine, EP, vasopressin, laparotomy) or unilateral adrenalectomy, whereas these stimuli were effective in anesthetized controls. The effect of exogenous ACTH was not blocked by morphine, showing that the drug fails to interfere directly with the response of the adrenal cortex.

Ohler, E. A., Sevy, R. W.: "Inhibition of stress induced adrenal ascorbic acid depletion by morphine, dibenzylidine, and adrenal cortex extract." *Endocrinology* **59**: 347-355 (1956). *C23,020/56*

In rats, the adrenal ascorbic acid depletion produced by sham adrenalectomy, unilateradrenalectomy, EP, hydroxyamphetamine or vasopressin could be inhibited by morphine. Adrenal cortical extract blocked the response to operative stress and to catecholamines but not to vasopressin. Dibenzylidine blocked only the reaction to catecholamines.

Epstein, S., Burdette, H., Munson, P. L.: "Effect of nalorphine on inhibition of ACTH release by morphine in the rat." *Fed. Proc.* **16**: 294 (1957). *C33,192/57*

Leeman, S. E., Munson, P. L.: "In vivo

system for detection of the neural hormone responsible for ACTH secretion in stress." *Fed. Proc.* **17**: 387 (1958). *C51,861/58*

In rats, blockade of ACTH secretion by morphine is used as a basis for the bioassay of CRF.

Tanabe, T., Cafruny, E. J.: "Adrenal hypertrophy in rats treated chronically with morphine." *J. Pharmacol. Exp. Ther.* **122**: 148-153 (1958). *C48,625/58*

In rats, chronic morphine treatment caused adrenal enlargement that was prevented by hypophysectomy, although "the ability of hypophysectomized rats to tolerate large doses of morphine and morphine-withdrawal stresses did not seem to be impaired."

Wied, D. de, Bouman, P. R., Smelik, P. G.: "The effect of a lipide extract from the posterior hypothalamus and of Pitressin on the release of ACTH from the pituitary gland." *Endocrinology* **62**: 605-613 (1958). *C52,310/58*

In rats, various lipid extracts of bovine hypothalamus and vasopressin stimulated ACTH secretion. Blockade with morphine or cortisol inhibited the effect of the lipid extracts, but only morphine prevented ACTH discharge by vasopressin, which was obtained even after destruction of the ME. "It is concluded that the lipide extract requires the intactness of hypothalamic structures for its action, and that Pitressin contains the specific neurotransmitter."

Doepfner, W., Stürmer, E., Berde, B.: "On the corticotrophin-releasing activity of synthetic neurohypophysial hormones and some related peptides." *Endocrinology* **72**: 897-902 (1963). *D67,095/63*

In rats, the ACTH-releasing activity of vasopressin and oxytocin preparations was tested after blockade of ACTH release by morphine. "The pressor and the CRF activities of peptides related to the neurohypophysial hormones need not be strictly correlated."

Munson, P. L.: "Pharmacology of neuroendocrine blocking agents." In: Nalbandov, A. V., *Advances in Neuroendocrinology*, pp. 427-444. Urbana, Ill.: University of Illinois Press, 1963. *J12,674/63*

A review of the literature shows that chlorpromazine, reserpine and morphine may inhibit ACTH secretion, but only the action of morphine is striking and consistent. Yet, in extremely high doses morphine stimulates adrenocortical activity, and in fact was one

of the first stressors described in the original publication on the alarm reaction (117 refs.).

Stevens, M. W., Domer, F. R.: "Alterations in morphine-induced analgesia in mice exposed to pain, light or sound." *Arch. Int. Pharmacodyn. Ther.* **206**: 66-75 (1973).

H82,603/73

In mice, pain stimuli significantly increased both the rate of onset and the intensity of morphine analgesia. This was not so in animals exposed to photic or auditory stimuli.

Brown, W. A., Krieger, D. T., Woert, M. H. van, Ambani, L. M.: "Dissociation of growth hormone and cortisol release following apomorphine." *J. Clin. Endocrinol. Metab.* **38**: 1127-1130 (1974). H87,291/74

In man, apomorphine-induced STH release is probably not mediated through systemic stress but through a specific effect on dopamine receptor sites in the ME, since dopaminergic stimulation is not associated with cortisol release.

α -MT. Scapagnini, U., Loon, G. R. van, Moberg, G. P., Ganong, W. F.: "Effect of α -methyl-p-tyrosine on the circadian variation of plasma corticosterone in rats." *Eur. J. Pharmacol.* **11**: 266-268 (1970).

H27,438/70

α -MT increased plasma corticosterone in most rats at all times of the day. Hypothalamic catecholamine content fell in rats in which α -MT increased plasma corticosterone but not in others. "The data are consistent with the hypothesis that an adrenergic neural system inhibits ACTH secretion."

Halawani, M. E. el, Waibel, P. E., Appel, J. R., Good, A. L.: "Effects of temperature stress on catecholamines and corticosterone of male turkeys." *Am. J. Physiol.* **224**: 384-388 (1973). H65,841/73

In male turkeys, neither heat nor stress had any pronounced effect upon adrenal, brain or heart catecholamine concentrations; however, plasma corticosterone levels rose. When α -MT (an inhibitor of catecholamine synthesis) was given prior to stress exposure, catecholamine concentrations fell markedly unless the birds had been previously adapted to hot or cold environments. "These findings indicate that an increased rate of catecholamine and corticosterone release seems to be required during the initial response to temperature stress, and may be associated with the adaptive changes leading to temperature acclimation" (20 refs.).

*Mustards. Karnofsky, D. A., Graef, I., Smith, H. W.: "Studies on the mechanism of action of the nitrogen and sulfur mustards in vivo." *Am. J. Pathol.* **24**: 275-291 (1948). J8,918/48

Observations on rats showed that the systemic intoxication produced by mustard compounds "resembles in many respects a pattern of organic changes that has been termed by Selye the 'alarm reaction.' "

*Narcotics and Other Psychotropic Drugs. (See Anesthetics and CNS Stimulants) Franzén, G.: "Serum cortisol in chronic schizophrenia. Changes in the diurnal rhythm and psychiatric mental status on withdrawal of drugs." *Psychiatr. Clin. (Basel)* **4**: 237-246 (1971). G86,703/71

Farmer, R. W., Harrington, C. A., Fabre, L. F. Jr.: "Inhibition of steroid biosynthesis in isolated rat adrenal cells by methadone." *Fed. Proc.* **33**: 288 (1974). H84,044/74

Neuroleptics. (See CNS Stimulants and Methamphetamine)

Nialamide. Vermes, I., Telegdy, G.: "Adrenal function following drug-induced alterations of the hypothalamic serotonin content." *Acta Physiol. Acad. Sci. Hung.* **43**: 105-114 (1973). J12,928/73

In rats PCPA lowered the hypothalamic 5-HT level and facilitated stimulation of corticosterone secretion by "ether stress." Nialamide increased hypothalamic 5-HT but blocked the adrenal response to stress. Reserpine lowered hypothalamic 5-HT and augmented basal corticoid secretion; however, after "ether stress" there was no response either in hypothalamic 5-HT content or adrenal function. In any event the results suggest that "the changes induced in the stress mechanism by different drugs are related to their action on the hypothalamic serotonin level. Its increase inhibits, while its decrease facilitates, the stress-induced activation of pituitary-adrenal function."

Vermesh, I., Ryzhenkov, V. E.: "Functional condition of the hypophysis-adrenal system in rats with deafferentated hypothalamus; the action of dexamethasone and nialamide." *Probl. Endokrinol.* **20** No. 3: 67-70 (1974) (Russian). H92,315/74

In rats with a completely deafferented MBH, the basal plasma corticosterone level rose; this elevation could be inhibited by dexamethasone or nialamide. "At the same

time suppression of corticosterone secretion in stress [restraint] by nialamide was stronger in comparison with dexamethasone. Nialamide potentiated the depressive action of dexamethasone on the basal corticosterone secretion, but not under stress."

Nicotine. Schechter, M. D.: "Effect of nicotine on response to frustrative non-reward in the rat." *Eur. J. Pharmacol.* **29:** 312-315 (1974). H96,851/74

"Rats were subjected to frustrative non-reward in the Amsel double runway after administration of nicotine and saline. Results revealed that nicotine decreases the magnitude of the frustrative effect when compared to saline."

Nicotinic Acid. Carlson, L. A., Levi, L., Orö, L.: "Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid." *J. Clin. Invest.* **47:** 1795-1805 (1968). H1,440/68

In male volunteers, emotional stressors (dazzling light, standardized criticism, sorting steel balls of different sizes) caused a rise in plasma FFA and triglycerides as well as increased catecholamine excretion. Concurrent treatment with nicotinic acid prevented the elevation of FFA and triglycerides, but not the stressor-induced increase in catecholamine elimination, or the associated rise in heart rate and blood pressure.

Lindenbaum, E. S., Diamond, B., Yaryura-Tobías, J. A.: "Nicotinic acid and restraint induced ulcers." *Acta Physiol. Lat. Am.* **23:** 288-292 (1973). J9,059/73

In rats, the gastric ulcers produced by restraint with food and water deprivation are more effectively inhibited by nicotinic acid than by chlorpromazine.

Nitrous Oxide. (See also **Anesthetics and Analgesics**) Steinberg, H.: "Effects of nitrous oxide on reactions to stress." *Bull. Br. Psychol. Soc.* **24:** 12 (1954). J13,306/54

In man inhalation of small amounts of nitrous oxide (sufficient to cause euphoria) reduced the stress elicited by being asked to solve insoluble problems. [The brief abstract gives no details about how this was measured (H.S.).]

Russell, R. W., Steinberg, H.: "Effects of nitrous oxide on reactions to 'stress.'" *Q. J. Exp. Psychol.* **7:** 67-73 (1955).

D81,503/55

"The present investigation using insoluble and soluble problems has demonstrated that both nitrous oxide and exposure to stress impair learning; but that, when subjects are exposed to stress while under the influence of the drug, the effects of the stress on subsequent learning are abolished."

Oxprenolol. (See **Antiadrenergics**)

PCPA. Myers, R. D., Cicero, T. J.: "Effects of serotonin depletion on the volitional alcohol intake of rats during a condition of psychological stress." *Psychopharmacologia* **15:** 373-381 (1969). G70,679/69

In rats PCPA (a potent tryptophan hydroxylase inhibitor) diminishes brain 5-HT. The stress of electroshock avoidance increases ethanol intake but this preference is reduced by depletion of brain 5-HT by PCPA.

Scapagnini, U., Moberg, G. P., Loon, G. R. van, Groot, J. de, Ganong, W. F.: "Relation of brain 5-hydroxytryptamine content to the diurnal variation in plasma corticosterone in the rat." *Neuroendocrinology* **7:** 90-96 (1971). H36,747/71

The 5-HT content of the hippocampus and amygdala exhibits a circadian rhythm in rats which roughly parallels that of plasma corticosterone. PCPA, which blocks 5-HT synthesis, increases the a.m. and decreases the p.m. plasma corticosterone levels so that circadian variations are largely eliminated. "The results suggest that 'serotonergic' neurons play a role in the diurnal fluctuation in pituitary-adrenal function."

Vermes, I., Telegdy, G.: "Adrenal function following drug-induced alterations of the hypothalamic serotonin content." *Acta Physiol. Acad. Sci. Hung.* **43:** 105-114 (1973). J12,928/73

In rats PCPA lowered the hypothalamic 5-HT level and facilitated stimulation of corticosterone secretion by "ether stress." Nialamide increased hypothalamic 5-HT but blocked the adrenal response to stress. Reserpine lowered hypothalamic 5-HT and augmented basal corticoid secretion; however, after "ether stress" there was no response either in hypothalamic 5-HT content or adrenal function. In any event the results suggest that "the changes induced in the stress mechanism by different drugs are related to their action on the hypothalamic serotonin level. Its increase inhibits, while its

decrease facilitates, the stress-induced activation of pituitary-adrenal function."

Hill, S. Y., Goldstein, R.: "Effect of p-chlorophenylalanine and stress on alcohol consumption by rats." *Q. J. Stud. Alcohol* **35**: 34-41 (1974). J13,259/74

PCPA caused a marked depletion of brain 5-HT and reduced volitional alcohol intake in the rat. These effects could be inhibited under certain conditions by stressors (for example, electroshock). Indeed, there is no evidence that PCPA ordinarily induces avoidance of alcohol (20 refs.).

Pimozide. Mierlo, P. J. van: "Open pilot trial of pimozide in patients suffering from psychic stress." *Arzneim. Forsch.* **22**: 2147-2148 (1972). H64,912/72

Polychlorinated Biphenyls. Wassermann, D., Wassermann, M., Cucos, S., Djavaherian, M.: "Function of adrenal gland-zona fasciculata in rats receiving polychlorinated biphenyls." *Environ. Res.* **6**: 334-338 (1973). J6,552/73

In rats given toxic polychlorinated biphenyls, plasma corticosterone levels rose sharply and characteristic structural changes developed in the fasciculata of the adrenal. "The results are interpreted as evidence of the need for a higher level of glucosteroids in defense against the stressor character of PCBs-1221 and perhaps also of the need for catatotoxic activity of glucosteroids."

Propranolol. (See **Antiadrenergics**)

Psychotropic Drugs. (See also individual psychotropic and psychotomimetic agents) Meltzer, H. Y.: "Muscle toxicity produced by phencyclidine and restraint stress." *Res. Commun. Chem. Path. Pharmacol.* **3**: 369-382 (1972). H52,159/72

In rats stressed by restraint, the toxicity of *phencyclidine* (a potent psychotomimetic agent) is greatly enhanced.

Glass, G. S.: "Psychedelic drugs, stress, and the ego. The differential diagnosis of psychosis associated with *psychotomimetic* drug use." *J. Nerv. Ment. Dis.* **156**: 232-241 (1973). J2,562/73

Wray, S. R.: "Interaction of stress and psychotomimetic drug-action: possible implication for psychosis." *Psychopharmacologia* **30**: 263-268 (1973). J4,950/73

From experiments on rats concerning the effect of avoidance responses to electroshock

upon the psychotomimetic drug *cyclazocine*, it is concluded that "environmental stress can play a crucial role in the genesis and underlying mechanism of schizophrenia."

Reserpine. (See also **Tranquilizers**) Mason, J. W., Brady, J. V.: "Plasma 17-hydroxycorticosteroid changes related to reserpine effects on emotional behavior." *Science* **124**: 983-984 (1956).

C25,425/56

In rhesus monkeys, moderate doses of reserpine inhibited not only experimentally induced anxiety and fear responses, but also the associated increase in plasma 17-OHCS levels. This fact is all the more interesting since, in themselves, comparable doses of reserpine produced a transient increase in 17-OHCS.

Wells, H., Briggs, F. N., Munson, P. L.: "The inhibitory effect of reserpine on ACTH secretion in response to stressful stimuli." *Endocrinology* **59**: 571-579 (1956).

G21,910/56

Miline, R., Stern, P.: "Effect of reserpine on the stressogenic reactivity of habenular-pineal complex." *Anat. Rec.* **136**: 243-244 (1958).

C95,318/58

In hares, fear caused regressive changes in the internal nuclear habenular ganglion which could be prevented by reserpine. Allegedly, the results "show that the habenular-pineal complex has an important role in the neuroendocrinology of the general adaptation syndrome."

Knigge, K. M., Penrod, C. H., Schindler, W. J.: "In vitro and in vivo adrenal corticosteroid secretion following stress." *Am. J. Physiol.* **196**: 579-582 (1959).

C65,769/59

In rats, scalding or restraint produced an initial biphasic response in ACTH and corticosterone secretion. The decrease was not due to adrenal exhaustion, for it occurred at the time when the pituitary contained approximately twice the normal amount of ACTH. "The low level of hormone secretion was replaced by very high levels by treatment of the stressed rat with reserpine or by placement of hypothalamic lesions. At a variable time after stress, corresponding to time of least corticosteroid secretion, there appears to exist an inability of the pituitary to release ACTH, which may be due to cessation of the initial hypothalamic stimulation or to a neural mechanism which temporarily

suppresses or inhibits the secretion of endogenous ACTH."

Blackman, J. G., Campion, D. S., Fastier, F. N.: "Mechanism of action of reserpine in producing gastric haemorrhage and erosion in the mouse." *Br. J. Pharmacol.* **14**: 112-116 (1959). C68,958/59

Gastric hemorrhage and erosion are produced in mice by reserpine through a mechanism involving liberation of 5-HT.

Kitay, J. I., Holub, D. A., Jailer, J. W.: "'Inhibition' of pituitary ACTH release after administration of reserpine or epinephrine." *Endocrinology* **65**: 548-554 (1959).

C74,892/59

In rats, single injections of EP or reserpine produced an ACTH discharge, yet "the acute release of ACTH in response to the stress of ether anesthesia was found to be diminished or absent after a single injection of epinephrine or after multiple injections of either reserpine or epinephrine. These data are consistent with the hypothesis that the amount of pituitary ACTH available for immediate release in response to acute stress is reduced after administration of reserpine or epinephrine, whereas chronic hypersecretion of ACTH remains unimpaired."

Maickel, R. P., Westermann, E. O., Brodie, B. B.: "Effects of reserpine and cold-exposure on pituitary-adrenocortical function in rats." *J. Pharmacol. Exp. Ther.* **134**: 167-175 (1961). D48,441/61

Reserpine and those reserpine derivatives which decrease brain NEP and 5-HT produced sedation and ACTH hypersecretion in rats. Large doses of reserpine or prolonged cold exposure decreased the ACTH content of the pituitary sufficiently to prevent a detectable discharge in response to other stressors.

Damrau, F.: "Peptic ulcers induced in white rats by reserpine and stress. The protective action of roterized bismuth subnitrate." *Am. J. Gastroenterol.* **35**: 612-618 (1961). D92,441/61

Efron, D. H.: "Reserpine toxicity and 'nonspecific stress.'" *Life Sci.* **1**: 561-564 (1962). D59,758/62

"The increased toxicity of reserpine in adrenalectomized rats is related to the absolute lack of certain adrenal steroids, which in some way may condition the nervous system to the effects of the drug, rather than to the inability of the pituitary-adrenal system to

respond to so-called 'nonspecific stress' caused by the drug."

Taylor, R. E. Jr., Fregly, M. J.: "Effect of reserpine on body temperature regulation of the rat." *J. Pharmacol. Exp. Ther.* **138**: 200-207 (1962). D41,319/62

In rats, intraperitoneal reserpine diminishes body temperature much more at low than at high environmental temperatures. It acts by decreasing heat production rather than by increasing heat loss. Restraint augmented the reserpine-induced decrease in body temperature.

Dasgupta, S. R., Mazumder, R. C.: "A study of the effect of reserpine (Serpasil) on lymphocytopenia of stress in rabbits." *Arch. Int. Pharmacodyn. Ther.* **138**: 120-124 (1962). D30,286/62

In rabbits, "reserpine not only failed to prevent lymphocytopenia of stress, but appeared to enhance the lymphocytopenia, indicating a stimulant type action of reserpine on the hypothalamus."

Girod, C.: "Influence de la réserpine sur l'axe hypophysocorticosurrénalien, chez le singe *Macacus sylvanus L.*" (The influence of reserpine on the pituitary-adrenal cortex axis in the *Macacus sylvanus L.* monkey). *C.R. Acad. Sci. (Paris)* **256**: 1600-1602 (1963). D62,899/63

In the monkey *Macacus sylvanus L.*, reserpine causes adrenal hyperactivity with pituitary changes suggestive of increased ACTH secretion.

Halkerston, I. D. K., Feinstein, M., Hechter, O.: "Increased responsiveness of adrenals from reserpine-treated or stressed rats to steroidogenic activity of ACTH." *Proc. Soc. Exp. Biol. Med.* **115**: 292-295 (1964). F2,446/64

Feldman, S., Conforti, N., Davidson, J. M.: "Adrenocortical responses in rats with corticosteroid and reserpine implants." *Neuroendocrinology* **1**: 228-239 (1966).

F68,591/66

Dexamethasone or cortisol pellets implanted into the ME of rats inhibited compensatory hypertrophy of the remaining adrenal following unilateral adrenalectomy. Dexamethasone implants into the pituitary itself exerted only a slight inhibition. Similar implants of reserpine or subcutaneous injections of the substance could not be shown "to be involved in the negative feedback regulation of ACTH secretion by corticosteroids."

Smelik, P. G.: "ACTH secretion after depletion of hypothalamic monoamines by reserpine implants." *Neuroendocrinology* **2**: 247-254 (1967). F90,175/67

Implantation of reserpine into the rat hypothalamus depleted the regional 5-HT and catecholamine content. Nevertheless, after subsequent systemic administration of reserpine, chlorpromazine and vasopressin, as well as emotional and traumatic stress, the pituitary-adrenal response was not modified by the depletion of hypothalamic monoamines. Presumably, "under these experimental conditions there is no indication that monoamines present in the hypothalamus are involved in the control of pituitary ACTH secretion."

Doteuchi, M.: "Studies on the experimental gastrointestinal ulcers produced by reserpine and stress. I. Relationship between production of ulcers and changes in tissue monoamines." *Jap. J. Pharmacol.* **17**: 638-647 (1967). F96,238/67

Kobayashi, T., Kobayashi, T., Yamamoto, K., Kaibara, M., Ajika, K.: "Electron microscopic observation on the hypothalamo-hypophyseal system in the rat. III. Effect of reserpine treatment on the axonal inclusions in the median eminence." *Endocrinol. Jap.* **15**: 321-335 (1968). H4,331/68

In reserpine-treated rats, EM studies of the ME revealed an increase in electron-dense large granules (thought to be carriers of neurohypophyseal hormones) and a decrease in small granules (presumably carriers of catecholamines).

Doteuchi, M.: "Studies on the experimental gastrointestinal ulcers produced by reserpine and stress. II. Ulcerogenic activities of reserpine and its analogues." *Jap. J. Pharmacol.* **18**: 130-138 (1968). J16,601/68

Observations on cats suggest that a decrease in peripheral and central monoamines is involved in gastric ulcer formation caused by reserpine and its analogues in combination with electroshock.

Doteuchi, M.: "Studies on the experimental gastrointestinal ulcers produced by reserpine and stress. III. Effects of monoamines and their precursors." *Jap. J. Pharmacol.* **18**: 175-184 (1968). J16,602/68

In cats, gastric ulcer formation by reserpine plus electroshock could be inhibited by 5-hydroxytryptophane, dopa and atropine. These and other observations suggested that

a decrease in monoamine content of the CNS was involved in the development of stress ulcers.

Carr, L. A., Moore, K. E.: "Effects of reserpine and α -methyltyrosine on brain catecholamines and the pituitary-adrenal response to stress." *Neuroendocrinology* **3**: 285-302 (1968). H3,332/68

The brain content of NEP and dopamine was markedly reduced in rats given reserpine (which depletes catecholamine stores) or α -MT (which blocks catecholamine synthesis). Plasma corticosterone was essentially unchanged in the rats at rest as well as after treatment with stressors (ether, histamine, formalin, restraint, changes in environment). "The results suggest that brain catecholamines do not play an essential role in stress-induced activation of the pituitary-adrenal system."

Boulu, R., Schwartz, J. C.: "Ulcères gastriques médicamenteux et température environnante" (Drug-induced gastric ulcers and environmental temperature). *C. R. Acad. Sci. (Paris)* **268**: 2507-2510 (1969).

G67,252/69

The production of gastric ulcers in rats by reserpine, phenylbutazone and desoxy-2-glucose is much higher at 20°C than at 37°C.

Blaszkowski, T. P., DeFeo, J. J., Guarino, A. M.: "Central vs. peripheral catecholamines in rats during adaptation to chronic restraint stress." *Pharmacology* **4**: 321-333 (1970). H36,516/70

Reserpine pretreatment increases the mortality of rats exposed to the stress of restraint, presumably because of its central rather than peripheral NEP-depleting action.

Purchas, R. W.: "The response of circulating cortisol levels in sheep to various stresses and to reserpine administration." *Aust. J. Biol. Sci.* **26**: 477-489 (1973). J3,638/73

Vermes, I., Telegdy, G.: "Adrenal function following drug-induced alterations of the hypothalamic serotonin content." *Acta Physiol. Acad. Sci. Hung.* **43**: 105-114 (1973).

J12,928/73

In rats, PCPA lowered the hypothalamic 5-HT level and facilitated stimulation of corticosterone secretion by "ether stress." Nialamide increased hypothalamic 5-HT but blocked the adrenal response to stress. Reserpine lowered hypothalamic 5-HT and augmented basal corticoid secretion; however, after "ether stress" there was no response

either in hypothalamic 5-HT content or adrenal function. In any event, the results suggest that "the changes induced in the stress mechanism by different drugs are related to their action on the hypothalamic serotonin level. Its increase inhibits while its decrease facilitates the stress-induced activation of pituitary-adrenal function."

Hara, M.: "Gastroduodenal ulcers in dogs produced by electric stress after reserpinization." *Nihon Univ. J. Med.* **16**: 119-128 (1974). J15,282/74

The production of gastroduodenal ulcers by electric stimulation in reserpine-pretreated dogs is ascribed to the peptic action of gastric juice upon a mucosa damaged by angiotensin. Special attention is given to Japanese literature that is unavailable in English (24 refs.).

Johnson, T. H., Tharp, G. D.: "The effect of chronic exercise on reserpine-induced gastric ulceration in rats." *Med. Sci. Sports* **6**: 188-190 (1974). J16,755/74

A study on cross-resistance in rats, using reserpine-induced gastric ulcers as an indicator of stress, and using forced running in a treadmill or swimming as a second stressor. "The degree of ulceration of the glandular portion of the stomach produced by administration of reserpine was significantly lower in treadmill runners than in their controls, however, the degree of ulceration for the swimmers was not significantly different from that of their controls.... It might be that the swimmers were still in Selye's 'stage of resistance' and not quite in the 'trained state.' Thus, the corticosterone level may have still been higher than normal and may have contributed to the increased ulceration in the swimmers" (19 refs.).

Ricin. Balint, G. A.: "Examination of the inflammatory effect of ricin with special reference to the endogenous corticosteroid mobilisation." *Toxicology* **1**: 329-336 (1973). J10,650/73

Topical arthritis is produced by injection of ricin into the hind foot pad of the rat. If ricin is injected intraperitoneally it increases plasma corticoids and causes degranulation of the adrenals with inhibition of the anaphylactoid edema induced by dextran.

***Salicylates.** George, R., Way, E. L.: "The hypothalamus as an intermediary for pituitary-adrenal activation by aspirin." *J. Pharmacol. Exp. Ther.* **119**: 310-316 (1957). C34,580/57

In rats, lesions of the ME completely blocked adrenal ascorbic acid depletion following treatment with large doses of acetylsalicylic acid.

***Tranquilizers.** (See also under names of individual tranquilizers) Sabshin, M., Eisen, S. B.: "The effects of ward tension on the quality and quantity of tranquilizer utilization." *Ann. N.Y. Acad. Sci.* **67**: 746-757 (1956). J10,382/56

Riley, H., Spinks, A.: "Biological assessment of tranquillisers. Part I." *J. Pharm. Pharmacol.* **10**: 657-671 (1958). G79,395/58

Review on the assay of tranquilizers with an extensive section on their effect upon stress reactions (202 refs.).

Oyama, T., Kimura, K., Takazawa, T., Takiguchi, H.: "An objective evaluation of tranquillizers as preanaesthetic medication: effect on adrenocortical function." *Can. Anaesth. Soc. J.* **16**: 209-216 (1969). J11,007/69

"While placebo had no measurable effects, diazepam and nitrazepam clearly decreased plasma free cortisol levels at 8:30 am. and hydroxyzine significantly reduced the value at 8:00 am. The sedative effects of these tranquillizing agents and the ineffectiveness of the placebo definitely correlated with the alterations in plasma cortisol levels" (11 refs.).

Lidbrink, P., Corrodi, H., Fuxé, K., Olson, L.: "Barbiturates and meprobamate: decreases in catecholamine turnover of central dopamine and noradrenaline neuronal systems and the influence of immobilization stress." *Brain Res.* **45**: 507-524 (1972). G95,413/72

Costa, E., Meek, J. L.: "Regulation of biosynthesis of catecholamines and serotonin in the CNS." *Ann. Rev. Pharmacol.* **14**: 491-511 (1974). J12,127/74

Review on catecholamine and 5-HT synthesis in the nervous system under various conditions including stress. "Benzodiazepines (minor tranquilizers) block the increase in NEP turnover produced by stress, in doses devoid of any effect on amine turnover in normal animals. One of the mechanisms discussed above might be directly affected by the benzodiazepines, but they might directly affect another system of neurons that in stress influence noradrenergic neurons" (161 refs.).

***Vitamins.** Thayer, W. R., Toffler, A. H., Chapo, G., Spiro, H. M.: "Inhibition of restraint ulcers in the rat by pyridoxine deficiency." *Yale J. Biol. Med.* **38**: 257-264 (1965). G37,375/65

In rats, pyridoxine deficiency decreases the incidence of restraint ulcers and depresses gastric secretion. "It is suggested that since pyridoxine deficiency lowers histamine-forming capacity, this reduction in endogenous histamine leads to a decrease in acid production which then protects against restraint ulcers."

Moritz, E., Zacherl, H., Onderscheka, K., Helsberg, A.: "Vitamin A und Stressulkus-Prophylaxe" (The effect of vitamin A on endotoxin-induced stress ulcers). *Brunn Beitr. Klin. Chir.* **221**: 208-221 (1974).

J13,239/74

In rats, the incidence of endotoxin-induced stress ulcers of the stomach can be reduced by vitamin A. Despite virtually unchanged plasma and liver levels of the vitamin, its concentration in the gastric wall was significantly increased after treatment.

***Various Drugs or Drug Combinations**
not previously mentioned. Brenner, R. M.: "Radioautographic studies with tritiated thymidine of cell migration in the mouse adrenal after a carbon tetrachloride stress." *Am. J. Anat.* **112**: 81-86 (1963). D56,443/63

In mice stressed by subcutaneous carbon tetrachloride, ^3H -thymidine was given to study its incorporation into DNA-synthesizing cells by stripping film autoradiography. "Labeled cells were initially distributed at the periphery of the cortex scattered between the glomerulosa and the upper fasciculata, but within four to six weeks heavily labeled cells were found deep within the cortex indicating that centripetal migration had occurred. The upper fasciculata was judged to be a region of maximum cell turnover from which cells had migrated centripetally, but migration of cells from the glomerulosa seemed to be minimal."

Lorenzen, L. C., Ganong, W. F.: "Effect of drugs related to α -ethyltryptamine on stress-induced ACTH secretion in the dog." *Endocrinology* **80**: 889-892 (1967). F83,263/67

In dogs, α -methyltryptamine suppressed ACTH secretion as effectively as did α -ethyltryptamine. Corresponding tests with numerous indole derivatives, MAO inhibitors, antidepressants and pressor amines revealed

that the ACTH blocking activity of α -methyltryptamine is correlated only with its pressor action, since it is shared by vasopressors. The effect is unrelated to any other chemical or pharmacologic property of the drugs used for comparison.

Scapagnini, U., Preziosi, P.: "Role of brain norepinephrine and serotonin in the tonic and phasic regulation of hypothalamic-hypophyseal adrenal axis." *Arch. Int. Pharmacodyn. Ther.* **196** Suppl.: 205-220 (1972).

H56,654/72

Survey of the literature plus the extensive experiments of the authors and their co-workers led to the following main conclusions: (1) there is an adrenergic system in the brain which inhibits ACTH secretion. Drugs that release active catecholamines from nerve endings block ACTH discharge if they can pass the blood-brain barrier or are injected directly into the third ventricle or ME. Stressors deplete brain NEP and increase ACTH secretion. Admittedly, the amount of drugs necessary for inhibition is large compared to the normal catecholamine levels present in the brain; hence, their action is of doubtful physiologic significance. They may act merely by constricting the portal vessels so that CRF cannot reach an adequate concentration in the adenohypophysis. Among the drugs used to explore the ACTH inhibitory adrenergic mechanism were: amphetamine, α_1 -ethyltryptamine, L-dopa, tyramine, α -MT, guanethidine, FLA-63 (an inhibitor of dopamine- β -oxidase), L-threo-dihydroxy-phenyl-serine or DOPS (which selectively repletes NEP after depletion of NEP and dopamine by α -MT), phenolamine (an α -blocking agent) and so on. (2) 5-HT appears to regulate the circadian variations of ACTH secretion by the limbic system. Its concentration is especially high in the raphé nuclei (containing the greatest number of serotonergic cell bodies), particularly the amygdala and hippocampus in which it shows circadian variations. Destruction of these nuclei abolishes the circadian plasma corticosterone rhythm.

Mogilner, B. M., Freeman, J. S., Blashar, Y., Pincus, F. E.: "Reye's syndrome in three Israeli children. Possible relationship to warfarin toxicity." *Isr. J. Med. Sci.* **10**: 1117-1125 (1974). H96,872/74

On the basis of clinical observations, "warfarin is added to the list of factors predisposing to or causing the extreme acute stress."

Hormones and Hormone-like Substances

Catecholamines, particularly EP and NEP, are strong stressors when given in large doses. They elicit all the characteristic manifestations of the stress syndrome, such as eosinopenia, adrenocortical stimulation with an increase in adrenal size, loss of cortical lipids, and a rise in blood ACTH levels. Most of these effects are discussed at greater length in the section on the mechanism of the stress response, since catecholamine discharge (from the sympathetic nerve endings, the adrenal medulla, from extra-adrenal and particularly from hypothalamic cells) is an essential part of it.

Suffice it to mention here a few unconfirmed special observations which at first sight appear to be paradoxical. Allegedly, in mice, EP-induced adrenocortical lipid discharge can be prevented by small doses of vasopressin. This is all the more unexpected since vasopressin itself is a strong activator of the pituitary-adrenocortical axis.

In eviscerated and decapitated dogs, EP has been said to stimulate corticoid secretion despite the absence of the hypophysis and independently of any change in the vascularization of the adrenals. This claim was based on insufficient evidence and has never been confirmed.

Large doses of *mineralocorticoids* produce experimental replicas of cardiovascular diseases and hypertension, such as are also elicited by prolonged exposure to certain stressors, especially in animals receiving proper conditioning (for example, high sodium chloride diets, unilateral nephrectomy). An excess of *glucocorticoids* usually enhances the production of stress ulcers. All these effects will be dealt with in greater detail in the section on experimental models of diseases of adaptation. It is worth mentioning here, however, that under certain conditions restraint ulcers can be prevented in rats by glucocorticoids. The mechanism of this apparently paradoxical effect is not known.

Glucagon, added to rat pituitary homogenates, inhibits ACTH concentration in the medium, perhaps because of ACTH destruction or a diminution of its production.

Gonadotropic and *gonadal hormones* do not exert any conspicuous stressor effect, although they may influence the stress response elicited by other agents. Estrogens are especially notorious for their marked adrenocortical stimulating action and the thymicolympathic and splenic involution which they produce at relatively low dose levels.

Prepubertal ovariectomy decreases ACTH secretion, allegedly through a diminution of pituitary sensitivity to CRF stimulation and a decreased capacity to synthesize ACTH. Precocious puberty induced by gonadotropic hormones in female rats stimulates adrenocortical function and sensitivity to "ether stress."

Insulin, given in hypoglycemic doses, is a strong stressor which causes eosinopenia, adrenocortical stimulation and a rise in plasma STH. On the other hand, the pituitary concentration of STH is diminished by insulin (as it is by various other stressors, such as EP, vasopressin, cold). This effect of insulin hypoglycemia is prevented by dexamethasone and is ascribed to the stressor action of hypoglycemia.

In rats with chronic ME lesions, the *thyroid hormones*, T_3 and T_4 , increase adrenal weight without correcting pituitary or ovarian atrophy. Basal ACTH secretion remains appreciable after ME destruction and can be enhanced by hyperthyroidism. The fact that thiouracil interferes with TTH secretion without inhibiting the production of ACTH shows that the two mechanisms are independent.

Vasopressin is almost as potent as CRF in stimulating ACTH discharge and acts as a strong stressor. This is true both of natural and of synthetic preparations. The matter will be discussed at length in the section on the mechanism of stress responses.

Large doses of both *histamine* and *5-HT* produce definite stress responses.

Hormones and Hormone-like Substances

(See also our earlier stress monographs, p. xiii)

Angiotensin. (See Renin)

Catecholamines. Marañon, G.: "Contribution à l'étude de l'action émotive de l'adrénaline" (Contribution to the study of emotive actions of adrenaline). *Rev. Fr. Endocrinol.* **2**: 301-325 (1924). 87,752/24

Description of various emotional responses to EP in man. Depending upon individual variations, these responses may be characterized by trembling, crying, salivation, sweating, blushing, pallor, palpitations, moaning, shivering, polyuria, diarrhea, gastrointestinal spasms, hypertension, hyperglycemia, glycosuria and other somatic manifestations.

Landis, C., Hunt, W. A.: "Adrenalin and emotion." *Psychol. Rev.* **39**: 467-485 (1932). 8,333/32

Early observations on emotional changes produced by EP in some but not in other individuals, depending upon their predisposition.

Vogt, M.: "Observations on some conditions affecting the rate of hormone output by the suprarenal cortex." *J. Physiol. (Lond.)* **103**: 317-332 (1944). B897/44

In eviscerated dogs and cats, intravenous infusion of EP causes intense stimulation of corticoid secretion which is allegedly direct and not mediated through the pituitary. [The latter statement is based on observations on a single decapitated dog (H.S.).] This effect is obtained with physiologic doses of EP and is of the order of several times the normal corticoid output. The action is independent of blood pressure and blood flow.

Vogt, M.: "Cortical lipids of the normal and denervated suprarenal gland under conditions of stress." *J. Physiol. (Lond.)* **106**: 394-404 (1947). B26,537/47

Repeated injections of EP in rats and cats caused conspicuous degranulation of the adrenal cortical cells. This degranulation is ascribed to stress and cannot be prevented by adrenal denervation.

Laragh, J. H., Almy, T. P.: "Changes in circulating eosinophils in man following epinephrine, insulin, and surgical operations." *Proc. Soc. Exp. Biol. Med.* **69**: 499-501 (1948). B31,814/48

In man, surgical trauma and injections of EP and insulin caused eosinopenia.

Recant, L., Hume, D. M., Forsham, P. H.,

Thorn, G. W.: "Studies on the effect of epinephrine on the pituitary-adrenocortical system." *J. Clin. Endocrinol.* **10**: 187-229 (1950). B47,003/50

"A simple clinical test for the evaluation of pituitary-adrenocortical integrity is presented, based on the four-hour fall in circulating eosinophils following the subcutaneous injection of 0.3 mg. of epinephrine or the intravenous administration of 0.2 mg. in 200 cc. of saline over a one-hour period. A fall exceeding 50 per cent excludes both adrenocortical and pituitary ACTH deficiency."

Humphreys, R. J., Raab, W.: "Response of circulating eosinophils to norepinephrine, epinephrine and emotional stress in humans." *Proc. Soc. Exp. Biol. Med.* **74**: 302-303 (1950). B49,646/50

In medical students, the stress of an examination caused profound eosinopenia. This reaction was much more readily duplicated by EP than by NEP.

Farrell, G. L., McCann, S. M.: "Detectable amounts of adrenocorticotropic hormone in blood following epinephrine." *Endocrinology* **50**: 274-276 (1952). B69,080/52

In rats, EP causes a particularly rapid and pronounced increase in blood ACTH.

Nelson, D. H., Sandberg, A. A., Palmer, J. G., Glen, E. M.: "Levels of 17-hydroxycorticosteroids following intravenous infusion of epinephrine into normal men." *J. Clin. Endocrinol. Metab.* **12**: 936 (1952). B71,939/52

Basowitz, H., Korchin, S. J., Oken, D., Goldstein, M. S., Gussack, H.: "Anxiety and performance changes with a minimal dose of epinephrine." *Arch. Neurol. Psychiatry* **76**: 98-105 (1956). J12,074/56

Medical interns receiving constant infusions of EP (5γ per kg. body weight per hour) showed moderate increases in pulse rate and blood pressure. Among performance tests only motor tasks were significantly affected. The emotional responses demonstrated considerable individual variations.

Kitay, J. I., Holub, D. A., Jailer, J. W.: "'Inhibition' of pituitary ACTH release after administration of reserpine or epinephrine." *Endocrinology* **65**: 548-554 (1959). C74,892/59

In rats, single injections of EP or reserpine produced an ACTH discharge, yet "the acute release of ACTH in response to the stress of ether anesthesia was found to be diminished or absent after a single injection

of epinephrine or after multiple injections of either reserpine or epinephrine. These data are consistent with the hypothesis that the amount of pituitary ACTH available for immediate release in response to acute stress is reduced after administration of reserpine or epinephrine, whereas chronic hypersecretion of ACTH remains unimpaired."

Frankenhaeuser, M., Järpe, G.: "Psychophysiological changes during infusions of adrenaline in various doses." *Psychopharmacologia* **4**: 424-432 (1963). E26,806/63

Kurokawa, M.: "Effect of posterior pituitary hormone on adrenal cortical lipids." *Nagoya J. Med. Sci.* **20**: 23-30 (1967).

E53,885/67

In mice, the adrenal cortical lipid depletion produced by EP or cold could be prevented by pretreatment with small doses of vasopressin. The lipid-depleting effect of ACTH was not affected by such pretreatment.

Dechezleprêtre, S., Lechat, P.: "Effets comparés de l'adrénaline et d'un stress aigu sur la glycémie, la lactacidémie et la corticostérone plasmatique et surrénalienne du rat" (Comparison of the effects of epinephrine and acute stress on glycemia, lactacidemia and the corticosterone levels of plasma and the adrenals of the rat). *Aggressologie* **15**: 117-123 (1974). H93,830/74

In rats, acute exposure to cold causes marked hyperlactacidemia and mild hyperglycemia, with a considerable increase in plasma and adrenal corticosterone levels. These changes reach their maximum within ten minutes. EP exerts a similar effect due to the stressor action of the injection procedure, since it is also produced by injection of the solvent alone. The changes elicited by combined treatment with cold and EP are not greater than those caused by the two agents separately.

Zachariassen, R. D., Newcomer, W. S.: "Phenylethanolamine-N-methyl transferase activity in the avian adrenal following immobilization or adrenocorticotropin." *Gen. Comp. Endocrinol.* **23**: 193-198 (1974).

H88,608/74

In cockerels, ACTH or immobilization resulted in an increase of plasma EP and NEP with an accompanying decrease in the adrenal levels of these catecholamines; plasma corticosterone also rose as did the phenylethanolamine-N-methyl transferase (PNMT) content of the adrenals without affecting adrenal

corticosterone. "It is suggested that the rapid increase in PNMT activity, occurring with the acute application of stressors in chickens, may provide a means of sustaining an increased outflow of EP in times of 'stress.'" Corticosterone may play a role in the elevation of PNMT during the avian stress response.

Corticoids. Selye, H.: "Effect of desoxycorticosterone upon the toxic actions of somatotrophic hormone." *Proc. Soc. Exp. Biol. Med.* **76**: 510-515 (1951).

B54,470/51

In uninephrectomized rats kept on a high sodium intake, STH produces cardiac hypertrophy, myocarditis, hypertension, nephrosclerosis and polyuria similar to the syndrome elicited by DOC. When STH and DOC are given simultaneously, all these effects are greatly increased, except for the hypertension which may be inhibited as a consequence of the pronounced edema and obvious physical deterioration. It is possible that even purified STH stimulates the adrenal cortex or activates mineralocorticoids.

Schapiro, S.: "Androgen treatment in early infancy: effect upon adult adrenal cortical response to stress and adrenal and ovarian compensatory hypertrophy." *Endocrinology* **77**: 585-587 (1965). F49,822/65

One-day-old female rats given 1 mg. testosterone subsequently developed the expected persistent estrus syndrome. The response to stress (ether) was normal in both sexes although the extent of compensatory adrenal hypertrophy appeared to be less after testosterone pretreatment. An addendum notes that "neonatal treatment with 1 mg cortisol has been subsequently observed to produce a fertile 'corticoid runt' with a normal adrenal cortical response to stress."

Robert, A., Phillips, J. P., Nezamis, J. E.: "Production, by restraint, of gastric ulcers and of hydrothorax in the rat." *Gastroenterology* **51**: 75-81 (1966). G40,473/66

In rats, restraint produced gastric ulcers and hydrothorax within four to six hours. Overnight fasting prevented the hydrothorax and reduced gastric ulcerations (contrary to previous reports). Restraint ulcers and hydrothorax "were also inhibited by crowding of the animals, a rise in ambient temperature, or administration of prednisolone."

Glucagon. Barrett, A. M., Sayers, G.: "Loss of ACTH activity following incubation

of pituitary tissue: inhibition by glucagon and by pitressin." *Endocrinology* **62**: 637-645 (1958). C52,314/58

In rat pituitary homogenates, ACTH activity rapidly disappears, presumably owing to destruction of the hormone by proteolytic enzymes. Addition of glucagon or vasopressin to the incubates inhibits this effect. In tests for CRF activity it must be kept in mind that "substances added to the medium of incubated pituitaries may increase the quantity of ACTH in the medium by inhibition of ACTH destruction as well as by stimulation of release from adenohypophyseal cells."

Hinterberger, H., Wilcken, D. E. L.: "The effect of prolonged glucagon infusions on the urinary excretion of catecholamines and 4-hydroxy-3-methoxymandelic acid and on adrenal medullary tissue levels of catecholamines in patients with severe cardiac disease." *Clin. Chim. Acta* **52**: 153-161 (1974). J12,410/74

In patients with congestive heart failure, unphysiologically high doses of glucagon promote catecholamine synthesis and storage in the adrenal medulla (26 refs.).

Gonadotropic and Gonadal Hormones. Schapiro, S.: "Androgen treatment in early infancy: effect upon adult adrenal cortical response to stress and adrenal and ovarian compensatory hypertrophy." *Endocrinology* **77**: 585-587 (1965). F49,822/65

One-day-old female rats given 1 mg. testosterone subsequently developed the expected persistent estrous syndrome. The response to stress (ether) was normal in both sexes although the extent of compensatory adrenal hypertrophy appeared to be less after testosterone pretreatment. An addendum notes that "neonatal treatment with 1 mg cortisol has been subsequently observed to produce a fertile 'corticoid runt' with a normal adrenal cortical response to stress."

Coyne, M. D., Kitay, J. I.: "Effect of ovariectomy on pituitary secretion of ACTH." *Endocrinology* **85**: 1097-1102 (1969). H19,815/69

Experiments on rats "indicate that prepuberal ovariectomy results in decreased pituitary secretion of ACTH. The hyposecretion is related to a decreased sensitivity of the pituitary to CRF stimulation and a decreased pituitary capacity to synthesize ACTH. Moreover, the lower levels of plasma ACTH in adrenalectomized, ovariectomized

rats suggest that the effects of estradiol are independent of corticosteroid feedback."

Eiff, A. W. von, Plotz, E. J., Beck, K. J., Czernik, A.: "The effect of estrogens and progestins on blood pressure regulation of normotensive women." *Am. J. Obstet. Gynecol.* **109**: 887-892 (1971). G81,851/71

Both folliculoids and luteoids enhance the rise in blood pressure, respiratory rate and muscle tone in ovariectomized women performing a simple arithmetic task with or without noise.

Rodier, W. I., Kitay, J. I.: "The influence of progesterone on adrenocortical function in the rat." *Proc. Soc. Exp. Biol. Med.* **146**: 376-380 (1974). H87,653/74

In rats treated in vivo with progesterone, production of corticosterone in their adrenal homogenates was decreased.

Ramaley, J. A., Olson, J.: "Adrenal function in rats given PMS before puberty: response to ether stress." *Neuroendocrinology* **14**: 1-13 (1974). H83,081/74

Induction of precocious puberty by gonadotropic hormone in female rats stimulates adrenocortical function as indicated by an increase in blood corticosterone after "ether stress."

Schlein, P. A., Zarrow, M. X., Denenberg, V. H.: "The role of prolactin in the depressed or 'buffered' adrenocorticosteroid response of the rat." *J. Endocrinol.* **62**: 93-99 (1974). H90,051/74

The diminished corticosterone secretion of lactating rats under stress is due to a blockade produced by increased LTH levels.

Dunn, J. D.: "Pituitary-adrenal function in adult androgenized female rats." *Proc. Soc. Exp. Biol. Med.* **146**: 75-77 (1974). H87,171/74

Neonatal treatment with testosterone did not markedly affect the pituitary-adrenal response of female rats to ether stress in adult life.

Histamine and 5-HT. Weltman, A. S., Sackler, A. M.: "Effect of lysergic acid diethylamide (LSD-25) on growth, metabolism and the resistance of male rats to histamine stress." *J. Pharm. Sci.* **54**: 1382-1384 (1965). F49,487/65

Kawai, A., Yates, R. E.: "Interference with feedback inhibition of adrenocorticotropin release by protein binding of corticoste-

rone." *Endocrinology* **79**: 1040-1046 (1966).
F74,052/66

In rats, intravenous histamine causes nearly maximal ACTH release, as indicated by plasma and adrenal corticosterone. If given intravenously before histamine, unbound corticosterone impairs ACTH secretion, but does not if injected in the presence of corticosterone-binding plasma proteins. It is not certain, however, that impairment of the negative feedback action of corticosterone by its binding proteins is present at low corticosterone concentrations.

Kakihana, R., Blum, S., Kessler, S.: "Developmental study of pituitary-adrenocortical response in mice: plasma and brain corticosterone determination after histamine stress." *J. Endocrinol.* **60**: 353-358 (1974).

H83,418/74

In newborn mice, histamine caused a rise in plasma corticosterone between the sixteenth and twenty-first days of life but not between the third and eleventh days. In the younger group, corticosterone levels in the brains of nonstressed controls were much higher than those in the older animals. Histamine significantly increased brain corticosterone during both periods, particularly in the stress-responsive older mice.

Insulin. Laragh, J. H., Almy, T. P.: "Changes in circulating eosinophils in man following epinephrine, insulin, and surgical operations." *Proc. Soc. Exp. Biol. Med.* **69**: 499-501 (1948).
B31,814/48

In man, surgical trauma and injections of EP or insulin caused eosinopenia.

Hales, W. M., Simon, W.: "Minnesota multiphasic personality inventory patterns before and after insulin shock therapy." *Am. J. Psychiatry* **105**: 254-258 (1948).

B59,134/48

Bliss, E. L., Migeon, C. J., Nelson, D. H., Samuels, L. T., Branch, C. H. H.: "Influence of E.C.T. and insulin coma on level of adrenocortical steroids in peripheral circulation." *Arch. Neurol. Psychiatry* **72**: 352-361 (1954).
C1,997/54

In schizophrenics, electroconvulsive therapy as well as insulin coma increased the plasma level of 17-OHCS. When diphenylhydantoin was used to eliminate cyanosis, apnea and violent muscular movements, seizures still resulted in a rise of corticoids, but of shortened duration.

Bliss, E. L., Migeon, C. J., Branch, C.

H. H., Samuels, L. T.: "Reaction of the adrenal cortex to emotional stress." *Psychosom. Med.* **18**: 56-76 (1956). C13,032/56

In normal people and psychiatric patients emotional stress (subjectively estimated by manifestations of anxiety and tension), whether occurring spontaneously or elicited experimentally, caused consistent but very modest increases of 17-OHCS in blood and urine. These changes were always much less pronounced than those produced by ACTH, Piromen, insulin, electroshock or moderate physical exercise.

Skaug, O. E., Lingjaerde, P.: "The effect of insulin on blood sugar, electrolytes, plasma 17-hydroxycorticosteroids, and circulating eosinophils in adult women." *Scand. J. Clin. Lab. Invest.* **12**: 71-75 (1960).

C86,714/60

Landon, J., Wynn, V., James, V. H. T.: "The adrenocortical response to insulin-induced hypoglycemia." *J. Endocrinol.* **27**: 183-192 (1963). E33,724/63

The rise in plasma cortisol induced in man by insulin is recommended as a quick and simple test for stress responsiveness.

Roth, J., Glick, S. M., Yalow, R. S., Berzon, S. A.: "Hypoglycemia: a potent stimulus to secretion of growth hormone." *Science* **140**: 987-988 (1963). D66,637/63

Hunter, W. M., Clarke, B. F., Duncan, L. J. P.: "Plasma growth hormone after an overnight fast and following glucose loading in healthy and diabetic subjects." *Metabolism* **15**: 596-607 (1966). F68,199/66

In healthy and diabetic patients glucose loading diminishes plasma STH concentrations, but this is followed by a rise during the subsequent drop in blood sugar. [These observations suggest that insulin-induced increases in plasma STH may not be true stress effects but are specific results of hypoglycemia (H.S.).]

Müller, E. E., Saito, T., Arimura, A., Schally, A. V.: "Hypoglycemia, stress and growth hormone release: blockade of growth hormone release by drugs acting on the central nervous system." *Endocrinology* **80**: 109-117 (1967). F75,362/67

The pituitary STH content (tibia test) was diminished by various stressors (EP, vasoressin, urecholine, cold, insulin). This effect of insulin hypoglycemia was prevented by dexamethasone, and it was assumed that the discharge of pituitary STH "observed after

insulin administration may reflect a nonspecific stress effect of the hypoglycemic stimulus."

Marks, V., Greenwood, F. C., Howorth, P. J. N., Samols, E.: "Plasma growth hormone levels in spontaneous hypoglycemia." *J. Clin. Endocrinol. Metab.* **27**: 523-528 (1967). F82,109/67

In patients with insulinomas, fasting hypoglycemia raises plasma STH levels. On the other hand, "spontaneous hypoglycemia" and that produced by overnight fasting cause no rise in plasma STH even if blood sugar concentrations are very low. "Insulin-induced hypoglycemia may therefore be interpreted as a 'stress' stimulus." This might explain why the highest values for fasting plasma STH were more closely related to the presence of subjective symptoms than to the absolute blood glucose concentrations. Possibly, the stressor effect of insulin hypoglycemia depends on a deficit in cerebral glucose, since other investigators have shown that glucocorticoids, well known to increase cerebral tolerance to hypoglycemia, tend to diminish STH secretion after insulin.

Plumpton, F. S., Besser, G. M.: "The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects." *Br. J. Surg.* **56**: 216-219 (1969). H9,868/69

In patients undergoing major surgery or experiencing insulin hypoglycemia, concurrent prednisolone administration usually, but not always, failed to develop the increase in plasma corticoids normally elicited by these stressors, but only for a limited length of time.

Daly, J. R., Fleisher, M. R., Chambers, D. J., Bitensky, L., Chayen, J.: "Application of the cytochemical bioassay for corticotrophin to clinical and physiological studies in man." *Clin. Endocrinol. (Oxford)* **3**: 335-345 (1974). H88,166/74

In rheumatoid arthritics chronically treated with ACTH, insulin hypoglycemia causes a subnormal rise in plasma ACTH, and yet the plasma cortisol level is identical to that in control subjects. Presumably, the adrenal in ACTH-treated patients is hypersensitive and responds to subnormal amounts of ACTH with an enhanced cortisol secretion. However, the difference is very slight, and only the rate of response measured by the slope of the steepest part of the curve differs significantly. Hence, strong ACTH treatment

alters only the rate of ACTH release in response to hypoglycemia, not the total amount secreted. In contrast, prolonged corticoid treatment greatly reduces the ACTH secretion following insulin hypoglycemia.

Pineal Hormones. Golikov, P. P., Konushko, S. D.: "The effect of the extracts of the epiphysis on the content of 11-OCS in the peripheral blood of rats." *Probl. Endokrinol.* **20** No. 3: 81-85 (1974) (Russian). H92,319/74

In rats, pineal extracts administered intraperitoneally increased plasma 11-OHCS levels but only in the presence of the pituitary. [Presumably, they produced distress (H.S.).]

Renin, Angiotensin. Gal, T. J., Cooperman, L. H., Berkowitz, H. D.: "Plasma renin activity in patients undergoing surgery of the abdominal aorta." *Ann. Surg.* **179**: 65-69 (1974). J9,433/74

Surgical anesthesia sufficed to increase plasma renin activity, but a further rise was noted following subsequent insertion of an aortic bifurcation graft and release of the cross clamped aorta. [The observations do not permit differentiation between the relative roles of stress and the specific operative procedure (H.S.).]

STH. Selye, H.: "Effect of desoxycorticosterone upon the toxic actions of somatotrophic hormone." *Proc. Soc. Exp. Biol. Med.* **76**: 510-515 (1951). B54,470/51

In uninephrectomized rats kept on a high sodium intake, STH produces cardiac hypertrophy, myocarditis, hypertension, nephrosclerosis and polyuria similar to the syndrome elicited by DOC. When STH and DOC are given simultaneously all these effects are greatly increased, except for hypertension, which may be inhibited as a consequence of the pronounced edema and obvious physical deterioration. It is possible that even purified STH stimulates the adrenal cortex or activates mineralocorticoids.

Thymus Hormones. Deschaux, P., Flores, J. L., Fontanges, R.: "Influence de la thymectomie sur les glandes surrenales. Opothérapie de substitution à l'aide d'extraits thyminiques" (Influence of thymectomy on the adrenals. Substitutive ootherapy with thymus extracts). *Arch. Int. Physiol.* **82**: 115-121 (1974). J13,829/74

Neonatal thymectomy in mice causes decreased adrenal activity (as indicated by

oxygen consumption of the gland in vitro). This effect is allegedly compensated for by administration of the thymus extract "thymosine," and is interpreted to show a regulatory effect of the thymus upon the adrenals. [This interpretation requires confirmation (H.S.).]

Thyroid Hormones. Bogdanov, E. M., Halmi, N. S.: "Effects of hypothalamic lesions and subsequent propylthiouracil treatment on pituitary structure and function in the rat." *Endocrinology* **53**: 274-292 (1953).

B86,246/53

In rats with lesions in diverse parts of the hypothalamus, administration of thiouracil inhibited adrenal and/or thyroid enlargement, but the number of animals was small and adrenal size was too variable to draw definite conclusions on the exact location of the various regulating centers.

McGuire, J. S. Jr., Tomkins, G. M.: "The effects of thyroxin administration on the enzymic reduction of Δ^4 -3-ketosteroids." *J. Biol. Chem.* **234**: 791-794 (1959).

E90,938/59

In vitro observations in rats suggest that thyroxine increases Δ^4 -3-ketosteroid reduction "(a) by causing an increase in available reduced triphosphopyridine nucleotide which is a rate-determining reactant in this process, and (b) by causing an increase in a steroid 5α -hydrogenase in liver microsomes.

D'Angelo, S. A., Young, R.: "Chronic lesions and ACTH: effects of thyroid hormones and electrical stimulation." *Am. J. Physiol.* **210**: 795-800 (1966). F63,559/66

In rats with chronic ME lesions, T_3 and T_4 increased adrenal weight without correcting pituitary and ovarian atrophy, decreased the adrenal and ovarian ascorbic acid contents, and elevated the plasma and adrenal corticoids. Electric stimulation of the anterior hypothalamus in intact rats caused ACTH release and this was blocked by the ME lesions. Basal ACTH discharged following destruction of the ME remained appreciable and could be enhanced by hyperthyroidism. Presumably, "neural stimuli from the rostral hypothalamus mediate their effects on ACTH release via the median eminence; and augmentation of ACTH secretion in severe hyperthyroidism involves a non-neural, humoral metabolic pathway."

Labrie, F., Raynaud, J. P., Pelletier, G., Ducommun, P., Fortier, C.: "Corticosterone-

binding by transcartin and pituitary-thyroid-adrenocortical interactions in the rat." In: Jasmin, G., *Endocrine Aspects of Disease Processes*, pp. 20-26. St. Louis, Mo.: Warren H Green, 1968. E7,614/68

In rats, graded doses of thyroxine cause progressive increases in adrenal weight, presumably as a consequence of augmented ACTH secretion. At the same time, there is a stepwise elevation of total plasma corticosterone without a significant alteration in the absolute level of the unbound fraction. Presumably, only free corticosterone is responsible for the feedback mechanism, while the binding capacity of transcartin accounts for adjustments in the rate of corticosterone secretion to changes in thyroid activity. Furthermore, "thyroxine alone has a direct enhancing effect on the binding capacity of transcartin" and "the stimulating effect of estrogen and progesterone is exerted through the pituitary-thyroid axis."

Németh, S., Vigáš, M., Mikulaj, L.: "Changed response of the plasma corticosterone level to Noble-Collip drum trauma in non conditioned and conditioned rats after treatment with thyroxine and after thyroidectomy." *Endocrinol. Exp.* **5**: 179-184 (1971). H47,156/71

In rats pretreated with thyroxine, plasma corticosterone levels were high and showed an exaggerated increase after Noble-Collip drum trauma. The reverse was true after thyroidectomy.

Meserve, L. A., Leathem, J. H.: "Hypothyroidism and the maturation of the hypothalamo-hypophyseal-adrenal axis." *Dev. Psychobiol.* **6**: 123-129 (1973).

J2,516/73

In rats made hypothyroid by feeding thiouracil to the mothers during pregnancy and lactation, the adrenal and serum corticosterone levels were normal. However, "ether stress" failed to elicit an increased synthesis of corticosterone in the hypothyroid rat, although the response to ACTH was normal. Presumably, neonatal hypothyroidism retards the maturation of the hypothalamus-pituitary axis.

Rosolovskii, A. P.: "The effect of the thyroid gland on the appearance of trophic afflictions of the stomach during the action of stress and steroids." *Probl. Endokrinol.* **20** No. 5: 70-72 (1974) (Russian).

H95,571/74

In rats, "the ulcerogenic action of stress and steroids increased considerably in experimental hyperthyroidism, and was markedly diminished in hypothyroidism."

Vasopressin. Bertelli, A., Martini, L.: "Caduta dell'acido ascorbico surrenalico in animali trattati con ormoni postipofisari—Nota 3" (Adrenal ascorbic acid depletion in animals treated with posthypophyseal hormones—Note 3). *Atti Soc. Lomb. Sci. Med. Biol.* 7: 430-432 (1952). B77,331/52

In intact rats both oxytocin and vasopressin cause adrenal ascorbic acid depletion, but since this response is inhibited by hypophsectomy it must be ascribed to a discharge of pituitary ACTH.

Arimura, A.: "The effect of posterior-pituitary hormone on the release of ACTH." *Jap. J. Physiol.* 5: 37-44 (1955).

C6,604/55

Although large doses of vasopressin cause adrenal ascorbic acid depletion in the rat, pretreatment with small doses actually prevents the release of ACTH provoked by EP, histamine or cold.

Kurokawa, M.: "Effect of posterior pituitary hormone on adrenal cortical lipids."

Nagoya J. Med. Sci. 20: 23-30 (1967).

E53,885/67

In mice, the adrenal cortical lipid depletion produced by EP or cold could be prevented by pretreatment with small doses of vasopressin. The lipid-depleting effect of ACTH was not affected by such pretreatment.

Simionescu, S.: "L'action pharmacodynamique non spécifique de l'ADH (8-lysine-vasopressine)" (Nonspecific pharmacodynamic effects of ADH [8-lysine-vasopressin]). *Rev. Roum. Physiol.* 10: 349-352 (1973).

J8,130/73

Brief survey of the stressor effects of synthetic lysine-vasopressin (15 refs.).

Pai, S. R.: "Influence of oxytocin on pituitary-adrenal-gonad relationship and on the development of mammary tumours in C₃H mice." *Indian J. Med. Res.* 61: 1810-1817 (1973).

J13,044/73

The synthetic oxytocin, Syntocinon, failed to cause morphologic changes in the gonads and adrenals of two strains of mice. Yet "loss of weight of thymus was seen in intact C₃H mice immediately after Syntocinon treatment, however, in C₁₇ thymus was not responsive to this treatment."

Diet

The fact that acute and complete starvation produces a typical stress response was emphasized in the first publications on the alarm reaction, and this has been fully confirmed by subsequent investigators. It has also been noted that starvation sensitizes the rat and other species to superimposed stressors such as cold, restraint or trauma. On the other hand, chronic partial starvation produces a singular syndrome of "*pseudohypophsectomy*" which exhibits many of the typical manifestations of stress but is associated with adrenal atrophy. The mechanism of this singular response is still not clear, but a considerable amount of confusion has arisen in the literature by disregard of the essential difference between acute total starvation and chronic under-nutrition.

The frequent combination of *Kwashiorkor* and undernutrition, especially in India, has led to numerous studies on the relationship between these two conditions. It has been suggested that adrenocortical failure to respond adequately to stressors may be a crucial step in the "dysadaptation or breakdown of adaptation resulting in the characteristic biochemical and clinical picture of Kwashiorkor."

Data on *hormonal* changes caused by nutritional factors are comparatively scarce and largely contradictory. It has been claimed that in undernourished children with emotional deprivation, the serum STH levels are usually increased, though the STH

and ACTH response to hypoglycemia is diminished. The STH content of the adenohypophysis decreases during starvation in the rat, and apparently, there is a reduced synthesis and release of this hormone owing to a diminution in the production of STH-releasing factor (SRF). The blood glucagon level decreases during starvation in man just as it does after various other treatments that cause an increased need for glucose. In rats, swimming to exhaustion in cold water causes depletion of brain 5-HT and NEP; similar changes have been observed after exposure to some but not all stressors tested. (The voluminous literature on the effects of malnutrition upon *psychologic reactions, cardiovascular diseases*, and so on should be consulted in the original publications.)

+Other Agents

We have already mentioned the fact that malnutrition sensitizes to the damaging effects of various stressors. This has been shown especially as regards resistance to *cold*, because starvation appears to interfere with thermoregulation. In rats, cold causes considerable proliferation of brown adipose tissue (the so-called hibernating gland). In rabbits, ordinary adipose tissue is used as a readily available source of caloric energy during starvation, whereas brown fat is not as easily accessible. Starvation appears to have a particularly facilitating effect upon the production of gastric ulcers by cold or restraint, and these combinations have therefore extensively been used in studies on experimental "stress ulcers."

Restraint is another stressor to which starvation considerably sensitizes, and as previously mentioned, manifests itself especially in the frequent and severe development of gastroduodenal ulcers. Vitamin B₁₅ (calcium pangamate) allegedly diminishes some characteristic metabolic stress manifestations of restraint in rats.

Resistance to *traumatic* injuries appears to be particularly dependent upon the protein content of the diet.

Electroshock aggravates hypercholesterolemia, hyperlipemia and atherosclerosis in rats kept on a high-fat, high-cholesterol diet. Combativeness upon exposure to electric shock does not seem to be affected by undernutrition in rats.

Among *other stressors* whose dependence upon dietary factors has been the subject of special studies we may mention: infections, hypoxia, crowding, hemorrhage, drugs, circadian variations, and muscular exercise. There is as yet no confirmation of the claim that vitamin C supplements, when given with a standard amount of adrenocortical extract, increase the resistance of adrenalectomized rats to the mild stress of ether anesthesia.

Generalities

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction" characterized by adrenocortical en-

largement with acute loss of lipids, thymic-colymphatic atrophy and decreased body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and, to a lesser extent, hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the

first time will subside later in spite of the continued administration of this drug" but greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937).

38,798/37

In rats, "hunger and cold are very active factors in aggravating the effects of alarming stimuli. In fact, cold or any other stimulus which is able to cause an alarm reaction by itself acts in a similar way. Thus it is possible, for instance, to obtain a typical alarm reaction by giving one quarter of the alarming dose of 4 different drugs within 48 hours, although one quarter of the alarming dose of any one of these drugs has no effect by itself."

Mulinos, M. G., Pomerantz, L., Smelser, J., Kurzrok, R.: "Estrus-inhibiting effects of inanition." *Proc. Soc. Exp. Biol. Med.* **40**: 79-83 (1939). A17,221/39

Various agents that cause loss of weight (adrenalectomy, dietary deficiencies, vitamin B₁-avitaminosis, dinitrophenol, thyroid extract) had been shown by others to produce anestrus in the rat. Other potentially toxic treatments (insulin, manganese-free diets, morphine, nicotine) which under the employed experimental conditions did not cause loss of weight also failed to elicit anestrus. The authors' own experiments on partially starved rats "support the conclusion that in the investigations alluded to above, the loss of estrus was either wholly or at least in part due to the concomitant inanition." Since both gonadotropic hormone and estradiol did elicit estrus changes in underfed rats, the cause of the derangement was seen in the malfunction of the pituitary resulting from inanition.

Mulinos, M. G., Pomerantz, L.: "Pseudohypophysectomy. A condition resembling hypophysectomy produced by malnutrition." *J. Nutr.* **19**: 493-504 (1940). A33,348/40

Mulinos, M. G., Pomerantz, L.: "The reproductive organs in malnutrition. Effects of chorionic gonadotropin upon atrophic genitalia of underfed male rats." *Endocrinology* **29**: 267-275 (1941). A36,530/41

Mulinos, M. G., Pomerantz, L.: "Hormonal influences on the weight of the adrenal

in inanition." *Am. J. Physiol.* **132**: 368-374 (1941). A36,788/41

Mulinos, M. G., Pomerantz, L.: "Pituitary replacement therapy in pseudohypophysectomy. Effect of pituitary implants upon organ weights of starved and underfed rats." *Endocrinology* **29**: 558-563 (1941).

A36,729/41

In chronically underfed rats, loss of body weight was accompanied by atrophy of the adrenals, ovaries, spleen, testes, thyroids, hypophysis, thymus, liver and kidneys. Anterior pituitary implants restored the weight of the endocrines. This syndrome of "pseudohypophysectomy" is in sharp contrast to that produced by acute stressors during the alarm reaction.

Mulinos, M. G., Pomerantz, L., Lojkin, M. E.: "Effects of pseudohypophysectomy (underfeeding), starvation, hormones and aging upon the ascorbic acid content of the adrenal glands and liver of the rat." *Endocrinology* **31**: 276-281 (1942). A38,469/42

In chronically underfed rats, the adrenals undergo atrophy as well as a decrease in adrenal ascorbic acid content and concentration. These changes can be corrected by pituitary implants. On the other hand, complete starvation causes an acute increase in the weight and ascorbic acid content of the adrenals. It is concluded that chronic underfeeding causes adenohypophyseal deficiency and adrenocortical changes quite opposite to those characteristic of the alarm reaction; the changes are designated by the authors as the "pseudohypophysectomy" of starvation.

Mitchell, H. H., Edman, M.: *Nutrition and Climatic Stress*, p. 235. Springfield, Ill.: Charles C Thomas, 1951. B65,070/51

Technical discussion of observations on stress caused by cold, heat, high altitude and acceleration in relation to the nutrition of man (more than 750 refs.).

Baker, B. L.: "A comparison of the histological changes induced by experimental hyperadrenocorticalism and inanition." *Recent Prog. Horm. Res.* **7**: 331-373 (1952). B68,657/52

Careful review of the morphologic changes induced in rats by starvation, many of which strikingly resemble those elicited by excess ACTH or glucocorticoids. Yet it is considered unlikely that they are actually due to increased corticoid secretion (81 refs.).

Mitchell, M. L.: "Stress factors and nutri-

tion." *J. Am. Diet. Assoc.* **29**: 753-757 (1953). B79,353/53

Brief review on the roles of stress factors in nutrition.

Galdston, I.: *Beyond the Germ Theory*, p. 182, New York and Minneapolis: Health Education Council, 1954. C1,722/54

Very readable book with major emphasis upon the disease-producing effects of "deprivation stress" in relation to the G.A.S. Special sections on deprivation of food and emotional stimuli.

Lipman, D. G.: "Stress and hypertension: use of antistress diet and antihistamine." *J. Am. Geriatr. Soc.* **8**: 177-184 (1960).

C81,912/60

Detailed description of a diet which allegedly alleviates stress-induced hypertension, especially when given in combination with an antihistaminic.

Ershoff, B. H.: "Unidentified nutritional factors and resistance to stress." *J. Dent. Med.* **16**: 71-75 (1961). D5,818/61

Review on nutritional factors affecting resistance to stress during the G.A.S. (51 refs.).

Khaleque, K. A., Muazzam, M. G., Chowdhury, R. I.: "Stress in Ramadhan fasting." *J. Trop. Med. Hyg.* **64**: 277-279 (1961). D16,879/61

No consistent change in blood eosinophils was found during the first day of the religious practice of Ramadhan fasting.

Slater, G. G.: "Adrenal ascorbic acid, plasma and adrenal corticoid response to fasting in young rats." *Endocrinology* **70**: 18-23 (1962). D16,636/62

Kollar, E. J., Slater, G. R., Palmer, J. O., Docter, R. F., Mandell, A. J.: "Measurement of stress in fasting man. A pilot study." *Arch. Gen. Psychiatry* **11**: 113-125 (1964) (31 refs.). G18,898/64

Angel, C.: "Starvation, stress and the blood-brain barrier." *Dis. Nerv. Syst.* **30**: 94-97 (1969). G64,873/69

Matsumoto, Y. S.: "Social stress and coronary heart disease in Japan." *Milbank Mem. Fed. Q.* **48**: 9-36 (1970). G73,150/70

In Japan the incidence of arteriosclerotic CHD is extremely low as compared to that of the white North American population. "Although the diet factor remains dominant in current thinking, the stress hypothesis merits the most intensive probing as alternate

or associated explanations of observed relations and differentiations" (87 refs.).

Godard, C.: "Review: the endocrine glands in infantile malnutrition." *Helv. Paediatr. Acta* **29**: 5-26 (1974) (113 refs.).

J13,622/74

Jaya Rao, K. S.: "Evolution of kwashiorkor and marasmus." *Lancet* April 20, 1974, pp. 709-711. H85,623/74

Studies on kwashiorkor and marasmus in India show that the two are only different facets of the same disease. "It is suggested that marasmus, characterised by severe growth retardation, but remarkably well-preserved metabolic processes, represents a state of good adaptation to the stress of protein-calorie malnutrition. The response of the adrenal cortex may be crucial for this adaptation, a normal increase in plasma-cortisol helping in adequate mobilisation of muscle protein and in maintenance of metabolic integrity. The failure of the adrenal cortex to respond adequately may represent the crucial step in dysadaptation or breakdown of adaptation, resulting in the characteristic biochemical and clinical picture of kwashiorkor" (25 refs.).

→Hormones

Barchas, J. D., Freedman, D. X.: "Brain amines: response to physiological stress." *Biochem. Pharmacol.* **12**: 1232-1238 (1963).

E29,915/63

In rats, swimming to exhaustion, especially in cold water, caused depletion of brain 5-HT and NEP. Similar changes could not be obtained by having them run in a revolving cage because under the conditions of the experiment the rats soon gave up and just allowed themselves to be dragged. On the other hand, immersion in cold water did reproduce the catecholamine depletion whereas several other stressors (electroshock, starvation, hypoxia, surgery, adrenalectomy) were ineffective in this respect. The response is not dependent upon the pituitary-adrenocortical system since active stressors deplete brain catecholamines even after hypophysectomy, as does LSD. It is noteworthy that drugs that induce a similar change in brain amines produce a unique pattern of central excitation acting on brain mechanisms concerned with metabolic and physiologic temperature regulation. "If the stressors have such a central action, a role for the biogenic amines in central as well as in peripheral

aspects of temperature regulation should be sought."

Friedman, R. C., Reichlin, S.: "Growth hormone content of the pituitary gland of starved rats." *Endocrinology* **76**: 787-788 (1965). F35,443/65

The STH content of the adenohypophysis of rats decreases progressively during starvation for twenty-four to ninety-six hours.

Meites, J., Fiel, N. J.: "Effect of starvation on hypothalamic content of 'somatotropin releasing factor' and pituitary growth hormone content." *Endocrinology* **77**: 455-460 (1965). F49,805/65

In rats, starvation reduces the synthesis and secretion of STH-releasing factor (SRF) by the hypothalamus, which results in a decreased STH discharge from the adenohypophysis.

Aguilar-Parada, E., Eisentraut, A. M., Unger, R. H.: "Effects of starvation on plasma pancreatic glucagon in normal man." *Diabetes* **18**: 717-723 (1969).

H18,441/69

Through the use of relatively specific anti-serum for pancreatic glucagon, it was found that blood levels of the latter rose considerably during starvation in man. Literature is cited showing that insulin, phlorhizin, certain sulfonylurea derivatives, arginine and various other amino acids likewise cause hyperglucagonemia, and apparently the hormone is secreted in excess whenever a glucose need arises (23 refs.).

Krieger, I., Mellinger, R. C.: "Pituitary function in the deprivation syndrome." *J. Pediatr.* **79**: 216-225 (1971). G85,342/71

In children with food and emotional deprivation, fasting serum STH was usually increased but the STH and ACTH response to hypoglycemia was diminished.

Aboul-Dahab, Y. K. W., Zaki, K., Wishahi, A., Fahmi, L. F.: "Plasma cortisol, total bound and unbound in severe malnutrition in children." *J. Egypt. Med. Assoc.* **55**: 89-96 (1972). J12,086/72

Shoemaker, W. J., Wurtman, R. J.: "Effect of perinatal undernutrition on the metabolism of catecholamines in the rat brain." *J. Nutr.* **103**: 1537-1547 (1973). J7,704/73

Job, J. C., Rappaport, R.: "Somatomédines et croissance" (Somatomedins and growth). *Arch. Fr. Pédiatr.* **31**: 333-338 (1974).

J12,952/74

The plasma level of somatomedin is greatly

diminished in various types of malnutrition, especially in protein deficiencies causing kwashiorkor.

Merimee, T. J., Fineberg, S. E.: "Growth hormone secretion in starvation: a reassessment." *J. Clin. Endocrinol. Metab.* **39**: 385-386 (1974). H89,326/74

In man seventy-two hours of fasting increased STH levels in blood.

Bassett, J. M.: "Diurnal patterns of plasma insulin, growth hormone, corticosteroid and metabolite concentrations in fed and fasted sheep." *Austral. J. Biol. Sci.* **27**: 167-181 (1974). J13,836/74

→Varia

Mulinos, M. G., Pomerantz, L., Smelser, J., Kurzrok, R.: "Estrus-inhibiting effects of inanition." *Proc. Soc. Exp. Biol. Med.* **40**: 79-83 (1939).

A17,221/39

Various agents that cause loss of weight (adrenalectomy, dietary deficiencies, vitamin B₁-avitaminosis, dinitrophenol, thyroid extract) had been shown by others to produce anestrus in the rat. Other potentially toxic treatments (insulin, manganese-free diets, morphine, nicotine) which under the employed experimental conditions did not cause loss of weight also failed to elicit anestrus. The authors' own experiments on partially starved rats "support the conclusion that in the investigations alluded to above, the loss of estrus was either wholly or at least in part due to the concomitant inanition." Since both gonadotropic hormone and estradiol did elicit estrus changes in underfed rats, the cause of the derangement was seen in the malfunction of the pituitary resulting from inanition.

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A36,729/41

In chronically underfed rats, loss of body weight was accompanied by atrophy of the adrenals, ovaries, spleen, testes, thyroid, hypophysis, thymus, liver and kidneys. Anterior pituitary implants restored the weight of the endocrines. This syndrome of "pseudohypophysectomy" is in sharp contrast to that produced by acute stresses during the alarm reaction.

Bajusz, E.: *Nutritional Aspects of Cardiovascular Diseases*, p. 244. London: Crosby Lockwood & Son, 1965.

E5,013/65

Monograph on the influence of diet upon the development of *cardiovascular disease*, with special emphasis on nutritional factors determining predisposition to stress-induced experimental cardiac necroses.

Kim, Y. S., Lambooy, J. P.: "Riboflavin deficiency and gastric ulcer production in the rat: a procedure for the study of susceptibility to stress-induced gastric ulcers." *J. Nutr.* **91**: 183-188 (1967). G45,068/67

Riboflavin deficiency increased the susceptibility of rats to stress-induced (rocking cage) *gastric ulcers*. A comparable degree of general inanition did not have this effect.

Pegelman, S. G., Kanarik, U. K.: "Adaptive responses in guinea pigs under conditions of a prolonged cooling." *Sechenov Physiol. J. U.S.S.R.* **53** No. 10: 1212-1217 (1967).

J13,141/67

Exposure of guinea pigs to cold causes marked *adrenal hypertrophy* and ascorbic acid depletion with eosinopenia. Pretreatment with ascorbic acid reverses the *eosinophil response* and virtually blocks loss of ascorbic acid from the adrenals.

Hocking, F.: "Extreme environmental stress and its significance for psychopathology." *Am. J. Psychother.* **24**: 4-26 (1970).

G72,373/70

Review on "some of the immediate and possible long-term [*psychologic*] effects of a number of situations involving severe to extreme stress, including semistarvation, sensory deprivation, natural disasters, military combat, concentration camps, Russian labor camps, and nuclear bombings" (78 refs.).

+Temperature Variations. Horst, K., Mendel, L. B., Benedict, F. G.: "The metabolism of the albino rat during prolonged fasting at two different environmental temperatures." *J. Nutr.* **3**: 177-200 (1930).

6,639/30

Rats fasting at 26°C lived an average of 16.5 days and lost 49 percent of their initial body weight, whereas those fasting at 16°C survived an average of eleven days and lost 44 percent of their weight.

Leduc, J.: "Catecholamine production and release in exposure and acclimation to cold." *Acta Physiol. Scand.* **53** Supp. 183: 1-101 (1961). D42,829/61

Review of personal observations indicating that "warm- and cold-acclimated rats could

not withstand prolonged exposure to cold after restriction of food. Their catecholamine excretion rapidly attained maximal values and animals died in hypothermia. The same happened with warm-acclimated rats whose insulation has been reduced by removal of the fur. Cold-acclimated clipped rats survived in the cold, but their catecholamine response was much more intense than that of intact cold-acclimated animals." Allegedly these experiments suggest that acclimation to cold is limited by the body's finite capacity to produce catecholamines and thereby maintain thermal balance. EP is considered to be a defense hormone against cold.

Boulouard, R.: "Effects of cold and starvation on adrenocortical activity of rats." *Fed. Proc.* **22**: 750-754 (1963).

E20,995/63

In rats, starvation brings about a very significant increase in plasma corticosterone that is even more considerable in the event of simultaneous exposure to cold. The relationship between these findings and Porter-Silber chromogens is discussed. The strongest adrenocortical response occurs during the first few days of exposure to cold; secretion diminishes later despite the continued maintenance of adrenocortical hypertrophy.

Heim, T., Kellermayer, M.: "The effect of environmental temperature on brown and white adipose tissue in the starving newborn rabbit." *Acta Physiol. Acad. Sci. Hung.* **31**: 339-346 (1967). G50,688/67

The effect of stress upon fat mobilization was studied in newborn rabbits starved to death at different environmental temperatures. "Brown fat is mobilized in response to cold but not during starvation in a thermoneutral environment, whereas white fat apparently serves as a general metabolic reserve and is used during starvation both in the absence and the presence of a cold-induced increase in heat production."

Buchel, L., Gallaire, D.: "Ulcères de contrainte chez le rat. I. Influence, sur la fréquence des ulcères, du jeûne et de la température de l'environnement associés à des immobilisations de durées variables" (Restraint ulcers in the rat. I. Influence of fasting and environmental temperature associated with restraint of variable duration on the incidence of restraint ulcers). *Arch. Sci. Physiol.* **21**: 527-536 (1967). G53,615/67

In rats, twenty-four hours of fasting increases the incidence of gastric ulcers pro-

duced by subsequent restraint. Concurrent exposure to cold further sensitizes the stomach to the development of these stress ulcers.

Hale, H. B., Mefferd, R. B. Jr.: "Influence of chronic heat exposure and prolonged food deprivation on excretion of magnesium, phosphorus, calcium, H^+ and ketones." *Aerospace Med.* **39**: 919-926 (1968).

G63,858/68

Description of the metabolic changes produced in rats by "interplay of two stressors, chronic heat exposure and prolonged food deprivation."

Brooke, O. G., Harris, M., Salvosa, C. B.: "The response of malnourished babies to cold." *J. Physiol. (Lond.)* **233**: 75-91 (1973).

J5,659/73

Malnourished Jamaican children failed to raise their heat production and had decreased rectal temperature when environmental temperature was reduced from 28 to 25° C.

+Restraint. Frisone, J. D., Essman, W. B.: "Stress-induced gastric lesions in mice." *Psychol. Rep.* **16**: 941-946 (1965).

G41,731/65

"Immobilization-induced stress contributed little more to the incidence and severity of gastric lesions in mice than did food deprivation alone." Apparently, the gastric ulcers produced by immobilization are essentially due to fasting.

Buchel, L., Gallaire, D.: "Influence de la température ambiante sur la production d'ulcères de contrainte chez le rat" (Influence of surrounding temperature on the production of restraint ulcers in rats). *C.R. Soc. Biol. (Paris)* **160**: 1817-1820 (1966).

F78,016/66

A decrease of the surrounding temperature from 24 to 14° C facilitates the production of restraint ulcers in rats, whether or not they are previously exposed to twenty-four hours of fasting. The latter accelerates the development of such restraint ulcers. On the other hand, body temperature does not appear to be the only important factor since rats kept at warm temperatures (28-32° C) still show gastric erosions, whereas treatment with phenobarbital or chloral hydrate during restraint aggravates the hypothermia and yet diminishes ulcer frequency.

Robert, A., Phillips, J. P., Nezamis, J. E.: "Production, by restraint, of gastric ulcers and of hydrothorax in the rat." *Gastroenterology* **51**: 75-81 (1966).

G40,473/66

In rats, restraint produced gastric ulcers and hydrothorax within four to six hours. Overnight fasting prevented the hydrothorax and reduced gastric ulcerations (contrary to previous reports). Restraint ulcers and hydrothorax "were also inhibited by crowding of the animals, a rise in ambient temperature, or administration of prednisolone."

Rasche, R., Butterfield, W. C.: "Vitamin A pretreatment of stress ulcers in rats." *Arch. Surg.* **106**: 320-321 (1973).

J641/73

Studies on rats receiving 10,000 international units of vitamin A prior to an eight-hour period of immobilization in a wire gauze device suggest that this vitamin "exerts a negligible, if any, protective effect on the occurrence of gastric ulceration."

Khomulo, P. S., Mytareva, L. V., Zakrinichnaya, G. A.: "Oxygen and glucose utilization by aortic tissue with administration of cholesterol and nervous system stress." *Kardiologija* **13** No. 1: 116-120 (1973) (Russian).

H80,123/73

In rats, vitamin B₁₅ (calcium pangamate) allegedly diminishes certain metabolic changes produced by restraint.

Sibilly, A., Krivošič, I., Foucher, G., Fresnel, P. L., Bouteiller, P.: "Prévention locale de l'ulcère gastrique expérimental. (Etude préliminaire)" (Topical prevention of experimental gastric ulcer. [Preliminary study]). *J. Chir. (Paris)* **106**: 521-534 (1973).

J10,151/73

In rats, the stress ulcers produced by restraint are aggravated by fasting and prevented by oral administration of glucose or aluminum gel. Neutralization of the gastric acid does not seem to be decisive since aluminum gel protects less than hypertonic glucose; perhaps the latter helps to maintain cell metabolism and the gastric barrier.

+Other Stressors. Lazovik, A. D., Patton, R. A.: "The relative effectiveness of *auditory stimulation* and *motivational stress* in precipitating convulsions associated with magnesium deficiency." *J. Comp. Physiol. Psychol.* **40**: 191-202 (1947).

B26,573/47

Malmros, H.: "The relation of nutrition to health. A statistical study of the effect of the war-time on arteriosclerosis, cardiosclerosis, tuberculosis and diabetes." *Acta Med. Scand.* **138**: 137-153 (1950).

B60,638/50

During the postwar years, starvation increased the incidence of tuberculosis in Germany.

Quaife, M. L., Harris, P. L.: "Relation of vitamin E to acute physiological stress." *Proc. Soc. Expt. Biol. Med.* **78**: 188-191 (1951).

B63,658/51

The vitamin E content of the diet had no significant effect upon the adrenal ascorbic acid concentration of rats exposed to stressors (*EP* and *cold*). Furthermore, stress was not associated with any conspicuous change in tissue vitamin E levels.

Ryer, R., Grossman, M. I., Friedemann, T. E., Best, W. R., Consolazio, C. F., Kuhl, W. J., Insull, W. Jr., Hatch, F. T.: "The effect of vitamin supplementation on soldiers residing in a cold environment. Part II. Psychological, biochemical, and other measurements." *J. Clin. Nutr.* **2**: 179-194 (1954).

C8,720/54

In soldiers receiving large supplements of vitamin B complex and ascorbic acid, exposure to *cold* caused biochemical changes characteristic of stress that did not differ significantly from those in the controls. The higher incidence of eosinopenia during forced marches in the supplemented group was statistically significant.

Myasnikov, A. L.: "Influence of some factors on development of experimental cholesterol atherosclerosis." *Circulation* **17**: 99-113 (1958).

C68,103/58

In rabbits, the development of cholesterol atherosclerosis can be delayed by such stressors as *hypoxia* or *physical exercise*. "These effects may be considered useful to some degree in preventing atherosclerosis in man as well."

Uhley, H. N., Friedman, M.: "Blood lipids, clotting and coronary atherosclerosis in rats exposed to a particular form of stress." *Am. J. Physiol.* **197**: 396-398 (1959).

C73,763/59

In rats kept on a high-fat, high-cholesterol diet in a cage that periodically delivered *electric shocks*, unusually pronounced hypercholesterolemia, hyperlipemia and coronary atherosclerosis developed at the end of ten months.

Bhagat, B., Lockett, M. F.: "The failure of the adrenals to respond to cold stress during thiamine deficiency." *J. Endocrinol.* **23**: 237-241 (1961).

D16,943/61

"The adrenal glands of thiamine-deficient mice weighed more than those of normal mice and responded to *adrenocorticotropic hormone*, but not to *cold stress*, by further hypertrophy."

Hodges, J. R., Vernikos-Danellis, J.: "Pitu-

itary and blood corticotrophin changes in adrenalectomized rats maintained on physiological doses of corticosteroids." *Acta Endocrinol.* **39**: 79-86 (1962). D16,314/62

In adrenalectomized rats, ACTH discharge after mild stress (*ether*) was greater than in the controls. This hyperexcitability of the pituitary was not diminished by corticoids alone, but was considerably reduced by adrenocortical extracts plus ascorbic acid. Perhaps corticoids control the rate of ACTH synthesis, but other factors including ascorbic acid regulate pituitary responsiveness to stress-induced ACTH secretion.

Cuthbertson, D. P.: "Physical injury and its effects on protein metabolism." In: Munro, H. N. and Allison, J. B., *Mammalian Protein Metabolism*, Vol. 2, pp. 373-414. New York and London: Academic Press, 1964.

G79,175/64

Review on the effect of stress upon protein metabolism. In man, protein loss within ten days of *physical injury* may amount to about 12 percent of the total body protein. In general, there is a catabolic loss during the first ten days and a maximum at about the third day with a secondary peak on the eighth day. With regard to dietary treatment, most observers hold that "during the first few days following the injury in the previously adequately nourished person it is probably unwise to push the intake of a well-balanced diet beyond appetite as this may fail during this early postinjury phase in severe injuries. Further, kidney function may not be normal for a day or two. Thereafter the patient should be encouraged, but not forced, to take as much as he can of a well-balanced diet, relatively rich in protein."

Essman, W. B., Frisone, J. D.: "Isolation-induced facilitation of gastric ulcerogenesis in mice." *J. Psychosom. Res.* **10**: 183-188 (1966).

G41,114/66

Isolation facilitates the gastric ulcerogenesis induced by fasting in mice. "The data suggest that isolation contributes to food intake and food disposition and differences in the duration of aggregation or isolation and resulting ulcer development may be accounted for in terms of: (1) differences in motor activity, or (2) age [of the mice at the time] of change in population density."

Kies, C., Fox, H. M., Williams, E. R.: "Time, stress, quality, and quantity as factors in the nonspecific nitrogen supplementation of corn protein for adult men." *J. Nutr.* **93**: 377-385 (1967).

H6,953/67

In man, nitrogen retention after the stress of *hemorrhage* can be improved by a nitrogen-supplemented corn diet, but a similarly supplemented milk diet is even more effective.

Freiman, M., Seifter, E., Connerton, C., Levenson, S. M.: "Vitamin A deficiency and surgical stress." *Surg. Forum* **20**: 81-82 (1970). H64,565/70

It is suggested that "impaired glucose mobilization may be associated with the reduced ability of the vitamin A deficient rat to survive *surgical stress*."

Langlois, P., Williams, H. B., Gurd, F. N.: "Effect of an elemental diet on mortality rates and gastrointestinal lesions in experimental burns." *J. Trauma* **12**: 771-777 (1972). G94,742/72

Rats fed an "elemental diet" in which amino acids replaced all the protein showed improved survival and diminished gastrointestinal lesions after *burns*.

Hartzell, W. G., Newberry, P. D.: "Effect of fasting on tolerance to moderate hypoxia." *Aerospace Med.* **43**: 821-826 (1972).

H80,194/72

In man, "acute fasting significantly increases the orthostatic, hypotensive response to moderate *hypoxia*. This synergistic effect was sufficient to induce a syncopal attack in one normal individual during stress by moderate hypoxia while fasting, and this subject's recovery was delayed for more than 20 minutes after return to breathing room air."

Sakai, S.: "Effect of protein content of rat diet on amount of corticosterone in tooth extraction." *Folia Pharmacol. Jap.* **68**: 66-72 (1972) (Japanese). H79,322/72

In rats on a low-protein diet the adrenals are comparatively small but show a pronounced increase in size during the stress of *tooth extraction*, which is ineffective in this respect in controls given normal amounts of protein.

Creer, T. L.: "Hunger and thirst in shock-induced aggression." *Behav. Biol.* **8**: 433-437 (1973). H80,353/73

Hunger and *thirst* did not affect the mean of fighting among rats who initially showed a considerable rate of combativeness after electric shocks to the feet. Fasting likewise failed to alter the frequency of fighting in low-aggression rats but water deprivation increased it.

Paisey, R. B., Angers, M., Frenk, S.: "Plasma cortisol levels in malnourished children with and without superimposed acute

stress." *Arch. Dis. Child.* **48**: 714-716 (1973). J6,618/73

Plasma cortisol levels in malnourished children with marasmus or kwashiorkor were essentially normal unless superimposed stress (*infection, hypoglycemia, acidosis*) caused a rise.

Hamid, J., Sayeed, A., McFarlane, H.: "The effect of 1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane (o,p'-DDD) on the immune response in malnutrition." *Br. J. Exp. Pathol.* **55**: 94-100 (1974).

H86,118/74

In rats, *o,p'-DDD* caused loss of body weight as well as involution of the thymus, spleen and adrenals. In malnourished rats, adrenal atrophy was particularly marked and was associated with diminution of plasma corticoids and a decrease in the impairment of the immune response normally occasioned by this drug.

Pintar, K., Schulte, W. J., Barboriak, J. J.: "Histologic study of gastric lesions in food-restricted rats." *Proc. Soc. Exp. Biol. Med.* **145**: 1353-1358 (1974). H86,412/74

"Rats limited to food intake of 1 hr a day and allowed to run in an *activity wheel* developed gastric lesions which, on histologic examination, resembled human stress ulcers."

Bruckdorfer, K. R., Kang, S. S., Khan, I. H., Bourne, A. R., Yudkin, J.: "Diurnal changes in the concentrations of plasma lipids, sugars, insulin and corticosterone in rats fed diets containing various carbohydrates." *Horm. Metab. Res.* **6**: 99-106 (1974).

H86,042/74

Menguy, R., Masters, Y. F.: "Mechanism of stress ulcer. IV. Influence of fasting on the tolerance of gastric mucosal energy metabolism to ischemia and on the incidence of stress ulceration." *Gastroenterology* **66**: 1177-1186 (1974). J13,618/74

Fasting greatly sensitizes the gastric mucosa of the rabbit to the induction of stress ulcers by *hemorrhage*. These and many other observations suggest that "stress ulceration complicating hemorrhagic shock results from a gastric mucosal energy deficit due to shock-induced mucosal ischemia."

Wells, A., Jones, A., Williams, M., Geist, C. R.: "Noise, vitamin A deficiency, and emotional behavior in rats." *Percept. Mot. Skills* **38**: 392-394 (1974). J17,474/74

In rats, aversive stimulation (*noise*) appears to have a greater effect during food deprivation or vitamin A deficiency than otherwise.

*PHYSICAL AGENTS**Temperature Variations (including Frostbite)*

Exposure to cold was one of the first stressors used in animal experiments to prove the nonspecificity of agents capable of eliciting an alarm reaction with the typical thymicolumphatic involution, adrenal enlargement and gastrointestinal ulcers. Many review articles summarize the response of animals and man to short- or long-term exposure to cold, including adaptation to this stressor and "cross sensitization," in which adaptation to cold increases sensitivity to subsequent exposure to heat and vice versa. The relationship between the effects of cold upon nonhibernating animals, natural hibernation and "artificial hibernation" induced by cooling after pretreatment with various drugs, has likewise been the subject of extensive studies which yielded widely differing results.

The special problems arising from temperature variations in different climates, such as, the tropics, the Arctic, and Antarctic regions are discussed at greater length in the sections, Climate, Environment, and Biorhythms, and the section on Occupations, although there the role of temperature variations as such is difficult to distinguish from associated factors, such as the loneliness of the polar regions, or the noise, vibrations and muscular fatigue in overheated factories.

We will consider the effects of frostbite conjointly with systemic undercooling since the two are often combined, whereas burns, which usually occur as a consequence of local heat application at normal surrounding temperatures, will be discussed separately in the next section.

→**Morphology.** Even localized frostbite, from cooling the tails of rats, produces typical G.A.S. changes (for example, loss of secretory granules from the adrenal cortex and medulla) as well as a discharge of thyroid colloid. However, the latter is usually considered to be a specific effect of systemic heat loss, against which increased thyroid hormone secretion can protect by raising the BMR. Of course, systemic exposure to cold is even more effective as a stressor in some species in that it produces eosinopenia, lymphopenia and the discharge of histologically visible secretory granules from the adrenal cortex and medulla. Exposure to heat acts similarly but for hitherto unexplained reasons, it appears to be much less effective in this respect within the temperatures compatible with survival.

Upon chronic exposure to extremes of temperature, experimental animals go through the three characteristic stages of the G.A.S. and eventually exhibit pronounced loss of body weight and gonadal atrophy.

→**Hormones.** The endocrine changes produced by heat or cold are very similar to those elicited by other stressors, except for the characteristic increase in TTH and thyroid hormone secretion, which is a specific compensatory mechanism for heat loss during exposure to cold.

In rats, graded doses of thyroxine increase adrenal weight as a consequence of a rise in ACTH secretion. This is accompanied by an increase in total plasma corticosterone without significant alteration in the unbound fraction of the hormone. Presumably, only free corticosterone is responsible for the feedback inhibition, and the

binding capacity of transcartin is stimulated only by thyroxine, which can thus adjust corticoid production to thyroid activity at different temperatures.

In man, intense muscular work in hot environments increases the corticoid excretion in sweat even more than in urine. Allegedly, under these conditions a significant fraction of the total corticoid elimination is accounted for in sweat.

It has also been claimed that aldosterone excretion is particularly augmented in man exposed to heat, perhaps because this mineralocorticoid plays an important defensive role in protecting against heat-induced electrolyte anomalies.

Catecholamines have been thought to play a specific protective role against cold, and the finite capacity of the body to produce them may sometimes be the decisive factor in determining the limits of cold resistance. The excretion of NEP is more markedly augmented by cold than that of EP. Enzymologic studies suggest that the increase of NEP biosynthesis during cold is due to excess dopamine formation.

The urinary elimination of corticoids allegedly rose while that of EP and NEP remained unchanged in men exposed to the cold of Antarctic regions.

Very acute cold, sufficient to lower rectal temperatures and increase plasma cortisol and catecholamine excretion, does not change the TTH or thyroid hormone levels of the blood presumably because, in man, relatively severe but acute cold of a few hours duration acts mainly as a physical and emotional stressor, without effectively mobilizing heat regulation through the thyroid.

In adults, allegedly, even short-term exposure to cold suffices to raise plasma STH, whereas this is not the case in full-term or premature babies whose plasma STH, TTH, insulin, and glucagon levels are not significantly affected by cold.

In unacclimatized subjects, exposure to heat for two hours increases plasma cortisol and corticosterone concentrations as well as the urinary elimination of 17-OHCS. Studies with radiocortisol suggest that most of the corticoid rise is due to increased secretion, but this is accompanied by accelerated blood clearance in hot environments. In obese men, exposure to hot air for one hour after an overnight fast elevates body temperature and increases plasma STH and FFA levels without causing significant changes in plasma cortisol, thyroxine or glucose.

→**Metabolites.** In adult men exposed to cold of an intensity sufficient to raise plasma cortisol and diminish body temperature, the total plasma amino acid content is said to be unaffected, but tryptophane and tyrosine levels are lowered, and the excretion of two major tryptophane metabolites (kynurenic and xanthurenic acids) suggests an increase in hepatic tryptophane oxygenase activity. This may make the two amino acids more readily available for protein, hormone and biogenic amine synthesis during stress.

In mice, exposure to cold increases hepatic tryptophane oxygenase and tyrosine amino transferase activity. However, there are no strict correlations between these changes and the reduced plasma tryptophane, tyrosine and brain NEP or 5-HT. Apparently, under these conditions, alternative pathways can maintain homeostasis.

Cold also appears to increase cholesterol-7α-hydroxylase activity in the liver as well as the phosphatidyl glycerol and FFA levels in plasma.

→**Varia.** Fibrinolytic activity is increased in both whole blood and plasma in man exposed to heat. During and after a sauna bath, 17-OHCS excretion is raised in normal

but not, or at least much less, in allergic people, although the initial values are essentially the same in both groups.

The EEG changes noted in men kept in water of varying temperatures suggest that the arousal level is not determined exclusively by the ambient temperature.

In sheep, fertility is diminished by exposure to heat, but the nonspecificity of this response has not been proven.

+Restraint. There is unanimity among various authors on the fact that cold increases sensitivity to the stressor effect of restraint, and particularly enhances the production of stress ulcers. In fact, combined treatment with cold and restraint has been commonly used as a standard technique for the induction of such lesions. Heat tends to have an opposite effect, but only if it is of moderate intensity.

In rats, restraint during the active phase of their circadian cycle is particularly effective in producing gastric ulcers, and of course, cold augments wakefulness which may be a factor of pathogenic importance.

In guinea pigs overheated up to twenty-one days, there appears to be no significant rise in the normal plasma levels of corticoids, but the corticoid discharge during restraint is reduced. Since they continue to respond normally to ACTH, their insensitivity is attributed to decreased ACTH production.

Antiadrenergic drugs diminish cold-induced gastric ulcers in the rat, suggesting that the increased turnover of NEP may be causally related to their development. Yet, 6-hydroxydopamine-induced "chemical sympathectomy" raises cold resistance in this species.

The muscle relaxant effect of zoxazolamine is enhanced by restraint plus cold in the rat, presumably owing primarily to the increased sensitivity of the nervous system, and perhaps only secondarily to augmented zoxazolamine metabolism during stress.

+Genetics. Somewhat unexpectedly, it has been claimed that both hibernating and nonhibernating Syrian hamsters exhibit no enlargement or other morphologic evidence of adrenal hyperactivity when exposed to cold. Yet, some investigators have stated that the hamster adrenal is sensitive to other stressors and shows distinct histologic changes in the adrenal medulla and cortex during hibernation, upon awakening from hibernation, and during "anesthesia" induced by cold.

In piglets, cold or starvation causes typical G.A.S. changes in the adrenal as well as hypoglycemia and eosinopenia. Certain strains of pigs are particularly stress sensitive.

Female sheep are more resistant to cold than males, but daily "cold shocks" reduce cold resistance and inhibit acclimatization in females though not in males.

The Somali donkey is especially resistant to the stress of heat and dehydration.

+Drugs. In rats, large doses of reserpine—like previous prolonged exposure to cold—decrease the ACTH content of the adenohypophysis sufficiently to prevent a detectable discharge in the response to other stressors. Reserpine reduces body heat much more at low than at high environmental temperatures, presumably by decreasing heat production rather than by increasing heat loss. In rats, chlorpromazine, reserpine and ascorbic acid only slightly inhibit the loss of adrenal ascorbic acid elicited by exposure to heat. In pigs, chlorpromazine diminishes pituitary-adrenocortical hormone discharge and increases the survival rate at 40°C.

Disulfiram, a potent dopamine hydroxylase inhibitor, greatly accentuates the loss

of cardiac NEP in rats exposed to cold, presumably because utilization of NEP is increased at low temperatures. This becomes particularly evident when repletion by biosynthesis is blocked. In rats, cold raises the urinary excretion of NEP, with a concurrent increase in thyroid activity. If cold-acclimated rats are given the antithyroid drug methimazole, the excretion of free EP and NEP doubles, presumably as a result of an effort to compensate for the decreased metabolic activity necessary for heat production.

The stress ulcers elicited in the rat by immersion in cold water can be prevented by atropine and other anticholinergic drugs, whereas reserpine, phenylbutazone and desoxy-2-glucose augment their incidence.

Most α -adrenergic-blocking agents (as well as the depletion of endogenous monoamines by reserpine and tetrabenazine) aggravate, while β -adrenergic-blocking agents inhibit, the production of stress ulcers in rats restrained while immersed in cold water. Fusaric acid, a potent dopamine- β -hydroxylase inhibitor, exerts an antiulcerogenic effect under similar conditions, presumably because of a decrease in the release of NEP from the CNS.

+Trauma. Cold diminishes, whereas moderate heat of a reasonable intensity increases, resistance to the stressor effect of diverse types of trauma in various species.

+Age. Adaptation to cold is less readily acquired by old than by young mice. In contradiction to earlier reports, it has been shown that the pituitary-adrenocortical mechanism is responsive to various stressors, including heat, in neonatal rats, as indicated by the rise in plasma corticosterone, although adrenal ascorbic acid depletion appears to be subnormal.

In premature babies exposed to cold, urinary NEP excretion drops but EP elimination is normal. Possibly, in neonates, cold rapidly depletes the NEP stores and thereby interferes with chemical thermogenesis.

+Diet. The extensive studies on the effect of various diets upon resistance to temperature fluctuations did not lead to any clearcut results which would permit us to formulate an optimal diet for defense against thermal stressors. However, fasting undoubtedly diminishes cold resistance in various species and increases corticoid production beyond the levels elicited by cold or starvation alone.

Malnourished Jamaican children failed to raise heat production and developed hypothermia easily when the surrounding temperature was diminished.

+Ionizing Rays. Allegedly, cold protects the rat against total body irradiation, whereas the latter has a detrimental effect on survival upon subsequent exposure to cold.

+Varia. The literature contains data on the effects of variations in ambient temperature upon resistance to many other stressors, but these observations are too numerous, and the data on each one too scarce to warrant detailed discussion here. Hence, the reader is referred to the corresponding abstract section. There he will find data on the effects of external temperature upon resistance to burns, electric shocks, hypoxia, diving, muscular work, gravitational forces, infections, the demands made by aerospace performance, the menstrual cycle and so on.

Temperature, including Frostbite

(See also our earlier stress monographs, p. xiii, and **Climate**)

Generalities. Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). C38,798/37

In rats, "hunger and cold are very active factors in aggravating the effects of alarming stimuli. In fact, cold or any other stimulus which is able to cause an alarm reaction by itself acts in a similar way. Thus, it is possible, for instance, to obtain a typical alarm reaction by giving one quarter of the alarming dose of 4 different drugs within 48 hours, although one quarter of the alarming dose of any one of these drugs has no effect by itself."

Stein, H. J., Bader, R. A., Eliot, J. W., Bass, D. E.: "Hormonal alterations in men exposed to heat and cold stress." *J. Clin. Endocrinol.* **9**: 529-547 (1949).

B37,251/49

Kuhl, W. J. Jr., Wilson, H., Ralli, E. P.: "Measurements of adrenal cortical activity in young men subjected to acute stress." *J. Clin. Endocrinol. Metab.* **12**: 393-406 (1952).

B69,085/52

Normal men immersed in cold water for eight minutes exhibited significant eosinopenia, lymphopenia and hypochloremia with increased ascorbic acid and uric acid excretion. Serum sodium, potassium, blood sugar and blood ascorbic acid were not significantly altered.

Booker, W. M., DaCosta, F. M., Tureman, J. R., Froix, C., Jones, W.: "The relation of ascorbic acid to adrenocortical function during cold stress." *Endocrinology* **56**: 413-419 (1955).

C3,562/55

Laborit, H.: *Stress and Cellular Function*, p. 255. Philadelphia and Montreal: J. B. Lippincott, 1959. C93,896/59

Cellular and biochemical aspects of stress phenomena, especially in relation to artificial hibernation and resuscitation.

Fleischner, J. R., Sargent, F.: "Effects of heat and cold on the albino rat: crossed resistance or crossed sensitization?" *J. Appl. Physiol.* **14**: 789-797 (1959).

C74,884/59

Under the conditions of these experiments, a typical stress reaction could be produced in rats by cold but not by heat. In rats adapted to heat, subsequent exposure to cold elicited

particularly severe stress manifestations, ascribed to "crossed sensitization."

Smith, R. E., Hoijer, D. J.: "Metabolism and cellular function in cold acclimation." *Physiol. Rev.* **42**: 60-142 (1962).

D16,425/62

Review on adaptation to cold in various species with special sections on the roles of the adrenal cortex and medulla (664 refs.).

Bedford, T.: *Basic Principles of Ventilation and Heating*. London: H. K. Lewis, 1964; (abstracted) Staff Century Res. Corp.: *Pamphlet No. 2* Arlington, Va. 1973.

J16,134/64

Review of the early literature concludes that the endurable "heat stress" limits for men are a bulb temperature of 88° F in calm air and 93° F in air currents of about 150 feet per minute.

Leitch, C. S., Lind, A. R.: *Heat Stress and Heat Disorders*, p. 304. London: Cassell, 1964

E4,166/64

Review of the literature and personal observations on the assessment, management and control of heat stress and the diseases that may result from exposure to high temperatures.

Budd, G. M.: "General acclimatization to cold in men studied before, during and after a year in Antarctica." *ANARE Rep. Ser. B. 4*: 1-84 (1964).

G43,355/64

The results of an expedition showed that "in Antarctica a highly significant improvement occurred in the men's ability to maintain rectal temperature during acute cold stress." Heat production and skin temperature did not change significantly (114 refs.). [Various metabolic studies have been performed, but alterations characteristic of non-specific stress have not been reported; hence, it is difficult to draw general conclusions beyond those applicable to the polar climate as such (H.S.).]

Edholm, O. G., Bacharach, A. L. (eds.): *The Physiology of Human Survival*, p. 581. New York and London: Academic Press, 1965.

E6,283/65

A monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal and muscular exercise. Each chapter is written by a specialist in the corresponding field, and numerous references indicate the difference

between specific defense mechanisms and the stressor effects of the agents used.

Findikyan, N., Duke, M., Sells, S. B.: *Thermal Stress—Cold*. Technical Rep. No. 8, Inst. Behav. Res. Contract No. 3436(00), Off. Naval Res., 1966. J13,072/66

Henderson, A. R.: "Induced hypothermia is not 'artificial hibernation,'" *J.A.M.A.* **198**: 1074-1078 (1966). F73,930/66

So-called "artificial hibernation" is not identical with that which occurs naturally. "The hibernating hibernator is unhampered and unmenced by any physiological sequence comparable to Selye's 'stress syndrome.'" The designations *artificial* or *induced* hibernation are not applicable to man and other homeotherms; these and similar terms should be discarded, as they are applied to induced hypothermia.

Budd, G. M., Warhaft, N.: "Body temperature, shivering, blood pressure and heart rate during a standard cold stress in Australia and Antarctica." *J. Physiol. (Lond.)* **186**: 216-232 (1966). G43,353/66

Wyndham, C. H., Allan, A. M., Bredell, G. A. G.: "Assessing the heat stress and establishing the limits for work in a hot mine." *Br. J. Ind. Med.* **24**: 255-271 (1967). F90,710/67

Collins, K. J., Weiner, J. S.: "Endocrinological aspects of exposure to high environmental temperatures." *Physiol. Rev.* **48**: 785-839 (1968). H3,548/68

Review on the various hormonal changes elicited by exposure to heat with a special section on the role of stress (453 refs.).

Wyndham, C. H.: "Adaptation to heat and cold." *Environ. Res.* **2**: 442-469 (1969) (27 refs.). H37,557/69

Bar-Or, O., Lundegren, H. M., Buskirk, E. R.: "Heat tolerance of exercising obese and lean women." *J. Appl. Physiol.* **26**: 403-409 (1969) (23 refs.). J14,817/69

Ramanathan, N. L., Chatterjee, B. B.: "An analytical study of the indices of thermal stress with respect to human body temperature." *Indian J. Med. Res.* **58**: 1104-1112 (1970). G82,560/70

Adams, T., Morgan, M. L., Hunter, W. S., Holmes, K. R.: "Temperature regulation of the unanesthetized cat during mild cold and severe heat stress." *J. Appl. Physiol.* **29**: 852-858 (1970) (24 refs.). G80,331/70

Raven, P. R., Horvath, S. M.: "Variability of physiological parameters of unacclimatized males during a two-hour cold stress of 5°C." *Int. J. Biometeorol.* **14**: 309-320 (1970). J20,824/70

Hall, S. A.: "Heat stress in outdoor manual workers in East Africa." *Ergonomics* **14**: 91-94 (1971). J19,719/71

Parker, J. T., Boone, M. A.: "Thermal stress effects on certain blood characteristics of adult male turkeys." *Poultry Sci.* **50**: 1287-1295 (1971). J20,533/71

Riccio, D. C., Hamm, R. J.: "Increased resistance to punishment produced by adaptation to a cold stressor." *Physiol. and Behav.* **9**: 209-212 (1972). G97,853/72

Kerslake, D. M.: *The Stress of Hot Environments*, p. 316. (Monogr. Physiol. Soc. No. 29). Cambridge: The University Press, 1972. E10,278/72

Monograph on the somatic effects of life in hot environments (about 400 refs.). [The title is somewhat misleading since characteristic stress effects are only briefly considered (H.S.).]

MacPherson, R. K.: "Thermal stress and thermal comfort." *Ergonomics* **16**: 611-623 (1973). J8,262/73

Personal observations and review of the literature showing that heat stress interferes with sleep and increases mortality in the aged. Means for mitigating stress in hot climates are surveyed.

Vanjani, S., Sharma, V. N., Lauria, P.: "Blood glucose, cardiac and skeletal muscle glycogen, electrocardiogram and haematological changes in acute heat stress. Modification by physostigmine and atropine." *Indian J. Physiol. Pharmacol.* **17**: 261-265 (1973). J13,454/73

In rats exposed to heat, stress manifests itself by hyperglycemia, a decrease in myocardial and skeletal muscle glycogen, eosinopenia and an accelerated pulse rate. These changes can be modified by drugs.

Horvath, S. M., Colwell, M. O.: "Heat stress and the new standards." *J. Occup. Med.* **15**: 524-528 (1973). J17,239/73

Hellstrøm, B.: "Adjustment of the peripheral circulation in human cold acclimatization: a critical review." *J. Hum. Evol.* **2**: 93-104 (1973). H91,967/73

Marple, D. N., Jones, D. J., Alliston, C. W., Forrest, J. C.: "Physiological and

endocrinological changes in response to terminal heat stress in swine." *J. Anim. Sci.* **39**: 79-82 (1974). J21,596/74

Héroux, O.: "Physiological adjustments responsible for metabolic cold adaptation and possible deleterious consequences." *Rev. Can. Biol.* **33**: 209-222 (1974).

H97,110/74

Review of metabolic changes produced by cold in various mammals. Increased energy utilization may participate in stress-induced myocardial necroses.

Fröberg, J., Karlsson, C.-G., Lennquist, S., Levi, L., Mathé, A. A., Theorell, T.: "Renal and adrenal function: a comparison between responses to cold and to psychosocial stressors in human subjects. A pilot study." *Rep. Lab. Clin. Stress Res. (Stockh.)* **40**: 1-27 (1974). J18,098/74

In man, "psychosocial stressors can elicit a renal response which is fully analogous to the response to cold, including increased diuresis accompanied by significant increases in osmolal clearance and excretion of sodium, chloride, calcium, phosphate and uric acid along with a significant decrease in the tubular reabsorption of sodium and calcium. This seems to indicate that cold-induced diuresis is not a response specific to cold, since the same response can also be elicited by other forms of stimuli, e.g. psychosocial ones."

Hales, J. R. S., Brown, G. D.: "Net energetic and thermoregulatory efficiency during panting in the sheep." *Comp. Biochem. Physiol.* **49A**: 413-422 (1974).

H93,878/74

Smith, J. J., McDermott, D. J., Kamper, D. G., Gotshall, R. W., Stekiel, W. J.: "Factors affecting the response of human subjects to postural and cold pressor tests" (abstracted). *Physiologist* **17**: 333 (1974).

H89,958/74

Singer, M., Angelakos, E. T.: "Adrenergic and cardiovascular responses to acute heat stress in the anesthetized dog" (abstracted). *Physiologist* **17**: 331 (1974). H89,956/74

Costill, D. L., Fink, W., Handel, P. van: "Muscle metabolism during exercise in the heat and cold" (abstracted). *Physiologist* **17**: 201 (1974). H89,883/74

→Morphology. Zenow, Z. I.: "Über Veränderungen im endokrinen System bei experimenteller örtlicher Erfrierung" (Changes in

the endocrine system caused by experimental localized frostbite). *Virchows Arch. [Pathol. Anat.]* **312**: 486-500 (1944). B28,100/44

In rats, localized frostbite from cooling the tails causes typical G.A.S. changes with an initial depletion and subsequent increase in adrenocortical lipids, discharge of medullary EP and loss of colloid from thyroid.

Elmadjian, F., Pincus, G.: "The adrenal cortex and the lymphocytopenia of stress." *Endocrinology* **37**: 47-49 (1945).

B366/45

In mice, both restraint and exposure to cold produce a typical stress lymphopenia.

Pincus, G., Elmadjian, F.: "The lymphocyte response to heat stress in normal and psychotic subjects." *J. Clin. Endocrinol.* **6**: 295-300 (1946). B1,243/46

Normal men exposed to 40.5-44.0° C at 85 to 95 percent relative humidity exhibited marked "stress lymphocytopenia" attributed to increased corticoid secretion. "With the short-time stress employed here it is entirely likely that we are dealing with the first stage of the adaptation syndrome which involves adrenocortical hypersecretion as the result of the pituitary stimulation." By contrast, twenty out of twenty-one psychotic (mostly schizophrenic) subjects exhibited a rise in blood lymphocytes after heat exposure.

Robinson, F. B., Yoffey, J. M.: "Histochemical changes produced by cold and adrenaline in the suprarenal cortex of the adult male rat." *J. Anat.* **84**: 32-37 (1950).

B48,448/50

In rats, intraperitoneal EP or exposure to cold causes cholesterol depletion from the zona reticularis and inner fasciculata of the adrenal cortex within five minutes. The gland returns to normal after three days. "The 3 stages of Selye's adaptation syndrome can be readily demonstrated by: (a) varying the length of time an animal is exposed to cold, and (b) giving repeated injections of adrenaline over long periods."

Louch, C., Meyer, R. K., Emlen, J. T.: "Effect of stress on diurnal fluctuations in eosinophils of the laboratory mouse." *Proc. Soc. Exp. Biol. Med.* **82**: 668-671 (1953).

B82,222/53

In mice, there are pronounced circadian variations in eosinophil counts, with peaks during the day and drops during the night, presumably owing to the characteristic nocturnal activity of this species. Exposure to cold decreases the eosinophil count but does

not eliminate the circadian fluctuations. Presumably, nocturnal activity in these experiments acts as a secondary stress superimposed upon the sustained stress of exposure to cold, and the adrenal gland "is capable of responding further to the daily stress of nocturnal activity."

Vašku, J.: "Die Beeinflussung der experimentellen diphtherischen Intoxikation durch den künstlichen Winterschlaf" (The influence of artificial hibernation on experimental diphtheria intoxication). *Z. Gesamt. Inn. Med.* **16**: 885-894 (1961).

D80,395/61

Hibernation did not protect guinea pigs against the adrenal changes elicited by diphtheria toxins but it did increase their sensitivity as indicated by a rise in mortality. The "artificial hibernation" (drugs plus cold) used in these experiments acted as a stressor.

Ouellette, R., Perrault, H. J., Dugal, L. P.: "Effet du froid sur le testicule endocrinien: chronologie des événements" (Effect of cold on the endocrine testis: chronology of events). *Rev. Can. Biol.* **24**: 7-21 (1965).

F42,194/65

In male rats, "a time study of the response of the sexual accessories reveals the succession of events as distinct phases related to the duration of the stress and reminiscent of the three stages of the General Adaptation Syndrome."

Skinner, J. D., Louw, G. N.: "Heat stress and spermatogenesis in Bos indicus and Bos taurus cattle." *J. Appl. Physiol.* **21**: 1784-1790 (1966).

G42,859/66

Even short-term exposure of bulls to "heat stress" can adversely affect spermatogenesis and fertility. [Since heat is known to have a specific damaging effect upon the testis, it remains to be shown that this is a non-specific or stress action (H.S.).]

Ambud, L., Agid, R.: "Cold-induced fatty liver and hypothermia in a hibernator, the garden dormouse (*Eliomys quercinus* L.)." *Arzneim. Forsch.* **24**: 967 (1974).

H89,300/74

→**Hormones.** Nichols, J., Miller, A. T. Jr.: "Excretion of adrenal corticoids in the sweat." *Proc. Soc. Exp. Biol. Med.* **69**: 448-449 (1948).

B28,608/48

In man, exposure to heat and intense muscular exercise increase the rate of corticoid excretion in sweat more than in urine. Hence, "it is a reasonable assumption that

it indicates an activation of the adrenal cortex in response to the stresses of heat and strenuous exertion. Our results also emphasize the fact that in stresses associated with sweating, a significant fraction of the total corticoid excretion is accounted for in the sweat."

Hellmann, K., Collins, K. J., Gray, C. H., Jones, R. M., Lunnon, J. B., Weiner, J. S.: "The excretion of urinary adrenocortical steroids during heat stress." *J. Endocrinol.* **14**: 209-216 (1956).

C25,981/56

In men exposed to heat, "while there was no significant change in the excretion of 17-hydroxycorticoids, cortisone and cortisol or of tetrahydrocortisone and tetrahydrocortisol, there was a significant increase in the output of aldosterone."

Egdahl, R. H., Richards, J. B.: "Effect of extreme cold exposure on adrenocortical function in the unanesthetized dog." *Am. J. Physiol.* **185**: 239-242 (1956).

D97,431/56

In dogs with polyethylene cannulas in the right lumboadrenal vein, exposure to cold or heat caused an increase in the 17-OHCS content of the collected blood similar to that produced by intravenous ACTH.

Robinson, K. W., MacFarlane, W. V.: "The influence of environmental temperature on the level of plasma antidiuretic substances in the rat." *Aust. J. Biol. Sci.* **9**: 130-138 (1956).

J12,293/56

Schapiro, S., Marmorston, J., Sobel, H.: "Mobilization of the antidiuretic hormone and the secretion of ACTH following cold stress." *Endocrinology* **62**: 278-282 (1958).

C48,916/58

In both hydrated and dehydrated guinea pigs, exposure to cold produced a "normal stress response" as indicated by the rise in urinary corticoid excretion. The vasopressor activity of the hypothalamus and posterior pituitary was markedly diminished by dehydration. "Apparently, conditions which induce alterations in mobilization of the antidiuretic hormone do not necessarily induce parallel alterations in the secretion of ACTH in response to stress."

Knigge, K. M.: "Neuroendocrine mechanisms influencing ACTH and TSH secretion and their role in cold acclimation." *Fed. Proc.* **19**: 45-51 (1960) (127 refs.).

C97,819/60

Leduc, J.: "Catecholamine production and release in exposure and acclimation to cold."

Acta Physiol. Scand. **53** Supp. 183: 1-101 (1961). D42,829/61

Review of personal observations indicating that "warm- and cold-acclimated rats could not withstand prolonged exposure to cold after restriction of food. Their catecholamine excretion rapidly attained maximal values and animals died in hypothermia. The same happened with warm-acclimated rats whose insulation had been reduced by removal of the fur. Cold-acclimated clipped rats survived in the cold, but their catecholamine response was much more intense than that of intact cold-acclimated animals." These experiments suggest that acclimation to cold is limited by the finite capacity of the body to produce catecholamines and thereby maintain thermal balance. EP is considered to be a defense hormone against cold.

Gwóździak, B.: "The effect of thermal stress on the level of 17-hydroxycorticosteroids in the blood serum of man." *Endokrinol. Pol.* **13**: 275-286 (1962) (Polish).

D31,024/62

Studies on miners exposed to dry heat (29 refs.).

Frommel, E., Fleury, C., Ledebur, I. von, Beguin, M.: "On the differential mobilisation of adrenalin and cortisone in the progress of stress under hypothermic conditions of external cause and of vaccine fever." *Med. Exp.* **6**: 261-264 (1962). D27,769/62

In guinea pigs, hypothermia "due to refrigeration, mobilizes adrenalin with an ephemeral action and brief duration, whereas vaccine fever stimulates the hormones of the adrenal cortex, possessing a slower and more lasting effect."

Euler, U. S. von: "Quantitation of stress by catecholamine analysis." *Clin. Pharmacol. Ther.* **5**: 398-404 (1964). G18,238/64

Review of the literature and personal observations on man suggest that "gravitational stress and exposure to cold are mainly associated with an increase in the norepinephrine excretion, indicating the importance of this hormone in circulatory and temperature controlling homeostatic mechanisms. Mental stress involving exhilarating or aggressive reactions is also associated with an increase in the norepinephrine excretion. The types of emotional stress which are mainly characterized by apprehension, anxiety, pain, or general discomfort are regularly accompanied by an increase in the epinephrine excretion." Special sections are devoted to catecholamine

elimination associated with flying, mental work and exposure to cold.

Chowers, I., Hammel, H. T., Eisenman, J., Abrams, R. M., McCann, S. M.: "Comparison of effect of environmental and pre-optic heating and pyrogen on plasma cortisol." *Am. J. Physiol.* **210**: 606-610 (1966). F62,277/66

Kotby, S., Johnson, H. D.: "Rat adrenal cortical activity during exposure to a high (34°) ambient temperature." *Life Sci.* **6**: 1121-1132 (1967). G47,329/67

In rats, after exposure to high surrounding temperatures, "the increase in plasma corticosterone, a calorigenic hormone, may serve as a precursor for increased aldosterone production during acclimation to heat."

Sundberg, M., Kotovirta, M.-L., Pesola, E.-L.: "Effect of the Finnish sauna-bath on the urinary excretion of 17-OH-corticosteroids and blood eosinophil count in allergic and healthy persons." *Acta Allergol. (Kbh.)* **23**: 232-239 (1968). G61,502/68

Urinary 17-OHCS elimination was essentially the same in allergic and normal individuals. "During the sauna day and 24 hours after the sauna bath the healthy subjects showed a statistically significant increase in the excretion of 17-OHCS. This kind of reaction was not found in the allergics and the difference between allergics and healthy subjects was also significant." The weak reaction of allergics was attributed to decreased reactivity to stressors. The eosinophil count was not consistently affected by the sauna.

Collins, K. J., Few, J. D., Forward, T. J., Giec, L. A.: "Stimulation of adrenal glucocorticoid secretion in man by raising the body temperature." *J. Physiol. (Lond.)* **202**: 645-660 (1969). G68,085/69

Plasma cortisol and corticosterone concentrations increased significantly in eleven resting, unacclimatized subjects after two hours of exposure to heat. At the same time, the urinary elimination of 17-OHCS showed no significant change. Alteration in plasma cortisol specific activity after intravenous injection of radiocortisol indicated that the raised plasma concentrations were due mainly to increased adrenal secretion, although this was accompanied by more rapid removal of cortisol from the circulation in hot environments.

Budd, G. M., Warhaft, N.: "Urinary excretion of adrenal steroids, catecholamines and electrolytes in man, before and after ac-

climatization to cold in Antarctica." *J. Physiol. (Lond.)* **210**: 799-806 (1970).

G79,783/70

The urinary excretion of corticoids and 17-KS rose while that of EP and NEP remained unchanged in men exposed to cold in Antarctic regions. Comparable studies during previous Antarctic expeditions are reviewed.

Wilson, O., Hedner, P., Laurell, S., Nosslin, B., Rerup, C., Rosengren, E.: "Thyroid and adrenal response to acute cold exposure in man." *J. Appl. Physiol.* **28**: 543-548 (1970).

G76,132/70

In man, acute exposure to cold sufficient to cause a .5°C decrease in rectal temperature as well as a rise in plasma cortisol and catecholamine excretion did not change the thyroid hormone level in blood, thyroid hormone turnover, thyroid hormone binding protein or plasma TTH. Presumably, "in man a relatively severe cold exposure of 3 hours does not measurably stimulate the pituitary-thyroid axis, but seems to increase the adrenal activity by moderately increasing the corticosteroid as well as the catecholamine output." It remains to be seen whether the activation of the pituitary-adrenocortical axis is due to the physical or emotional effects of cold (40 refs.).

Golstein-Golaire, J., Vanhaelst, L., Bruno, O. D., Leclercq, R., Copinschi, G.: "Acute effects of cold on blood levels of growth hormone, cortisol, and thyrotropin in man." *J. Appl. Physiol.* **29**: 622-626 (1970).

G79,353/70

In man, two hours' exposure to a temperature of 4° C caused no change in plasma STH concentrations and only moderate variations in plasma cortisol, but TTH values rose as expected.

Bertin, R.: "Influence de l'adaptation à la température sur quelques hormones surrénales du rat" (Influence of adaptation to temperature upon some adrenal hormones in the rat). *J. Physiol. (Paris)* **63**: 204-207 (1971).

G85,537/71

Adaptation to cold increases NEP production in rats and at the same time augments the plasma and adrenal concentration of corticosterone in a lasting manner. However, adaptation to heat diminishes the level of both corticoid and catecholamine. Adaptation to fluctuating temperatures does not augment NEP secretion but persistently raises plasma corticosterone.

Fekete, M., Milner, R. D. G., Soltész, G.,

Assan, R., Mestyán, J.: "Plasma glucagon, thyrotropin, growth hormone and insulin response to cold exposure in the human newborn." *Acta Paediatr. Scand.* **61**: 435-441 (1972).

G92,222/72

In full-term and premature babies, exposure to cold caused no significant change in plasma insulin, glucagon, STH or TTH concentrations.

Okada, Y., Matsuoka, T., Kumahara, Y.: "Human growth hormone secretion during exposure to hot air in normal adult male subjects." *J. Clin. Endocrinol. Metab.* **34**: 759-763 (1972).

H54,871/72

In four obese adult males exposed to hot air (48° C) for one hour after an overnight fast, elevation of body temperature was associated with increased plasma STH and FFA levels. No significant changes in cortisol, total thyroxine-iodine, blood glucose or hematocrit were noted during heat exposure. In two subjects, administration of glucose before heat prevented the rise in plasma STH.

Lamke, L. O., Lennquist, S., Liljedahl, S. O., Wedin, B.: "The influence of cold stress on catecholamine excretion and oxygen uptake of normal persons." *Scand. J. Clin. Lab. Invest.* **30**: 57-62 (1972).

H61,015/72

In young men, exposure to cold caused greatly increased urinary excretion of EP and NEP and a concurrent rise in oxygen uptake. "This indicates that the catecholamines play an important part in the regulation of the heat balance."

Panareto, B. A., Vickery, M. R.: "The distribution of cortisol and its rate of turnover in normal and cold-stressed shorn sheep." *J. Endocrinol.* **55**: 519-531 (1972).

H64,137/72

Mitra, R., Johnson, H. D.: "Growth hormone response to acute thermal exposure in cattle." *Proc. Soc. Exp. Biol. Med.* **139**: 1086-1089 (1972).

H54,712/72

In cattle, exposure to heat causes a rise in blood STH.

Tal, E., Sulman, F. G.: "Rat thyrotrophin levels during heat stress and stimulation by thyrotrophin releasing factor." *J. Endocrinol.* **57**: 181-182 (1973).

H69,590/73

Stott, G. H., Wiersma, F.: "Climatic thermal stress, a cause of hormonal depression and low fertility in bovine." *Int. J. Biometeorol.* **17**: 115-122 (1973).

H93,300/73

Leppäläluoto, J., Lybeck, H., Ranta, T., Virkkunen, P.: "Effect of acute exposure to cold on blood thyrotrophin (TSH) and corticosterone concentrations in the rabbit." *Acta Physiol. Scand.* **89**: 423-428 (1973).

J9,165/73

Parkhie, M. R., Johnson, H. D.: "Hypothalamic growth hormone releasing factor: release and synthesis after exposure to a high ambient temperature." *Proc. Soc. Exp. Biol. Med.* **142**: 311-315 (1973). H64,888/73

Studies on the release and synthesis of hypothalamic STH-releasing factor in rats exposed to heat. In general, resynthesis keeps pace with the discharge of the releasing factor (27 refs.).

Wilkerson, J. E., Raven, P. B., Bolduan, N. W., Horvath, S. M.: "Adaptations in man's adrenal function in response to acute cold stress." *J. Appl. Physiol.* **36**: 183-189 (1974). J10,302/74

In man, exposure to temperatures of 15°C or less acted as a "cold stress." "Because of increased circulating levels of cortisol, epinephrine, and norepinephrine, it was concluded that sympathoadrenal function in unacclimatized males was markedly altered" (45 refs.).

Panarett, B. A.: "Relationship of visceral blood flow to cortisol metabolism in cold-stressed sheep." *J. Endocrinol.* **60**: 235-245 (1974). H83,404/74

As long as sheep exposed to cold are capable of maintaining their body temperature, plasma cortisol levels are raised conjointly with cortisol metabolic clearance rates (radiocortisol). With continued exposure the animals lose their ability to maintain normal rectal temperatures, and plasma cortisol levels rise still further, but the metabolic clearance rates fall significantly below normal. The latter change is largely ascribed to reductions in hepatic and renal blood flow.

Mueller, G. P., Chen, H. T., Dibbet, J. A., Chen, H. J., Meites, J.: "Effects of warm and cold temperatures on release of TSH, GH, and prolactin in rats." *Proc. Soc. Exp. Biol. Med.* **147**: 698-700 (1974). H98,469/74

In rats, exposed to heat or cold, the fact that TTH and LTH secretion "responded oppositely to the same temperature changes suggests that different mechanisms regulate release of these two hormones under these conditions. The possible role of stress, and the interactions of the hypothalamic hypo-

physiotropic hormones and biogenic amines in the temperature-induced changes remain to be evaluated."

Cyberman, A., Francesconi, R., Robinson, S.: "Alteration of diurnal rhythmicities of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) and vanillylmandelic acid (VMA) in man during cold exposure." *Fed. Proc.* **33**: 245 (1974). H83,908/74

S trosser, M. T., Bucher, B., Briaud, B., Lutz, B., Koch, B., Mialhe, C.: "Effet de la chaleur sur la sécrétion de l'hormone de croissance et sur l'activité du cortex surréalien du Rat" (Effects of heat on growth hormone secretion and on adrenal cortex activity in rats). *J. Physiol. (Paris)* **68**: 181-191 (1974). J14,464/74

In rats, a sudden change of the ambient temperature from 20 to 34°C produces a rapid increase in ACTH and a decrease in STH content of the plasma. The literature on STH secretion during stress is partially reviewed.

→ Metabolites. Thoenen, H.: "Induction of tyrosine hydroxylase in peripheral and central adrenergic neurones by cold-exposure of rats." *Nature* **228**: 861-862 (1970). H32,295/70

Kato, M.: "Sensitivity of cholesterol turnover in rat liver to cold environmental stress." *Am. J. Physiol.* **221**: 1255-1259 (1971). J19,652/71

Francesconi, R. P., Boyd, A. E. III, Mager, M.: "Human tryptophan and tyrosine metabolism: effects of acute exposure to cold stress." *J. Appl. Physiol.* **33**: 165-169 (1972). J11,247/72

In men exposed to cold stress, the circadian variations of plasma cortisol were diminished and body temperature dropped. Although the total plasma amino acid content was not affected, tryptophan and tyrosine levels were lowered. An associated increase in the excretion of two major tryptophan metabolites (*kynurenic* and *xanthurenic acids*) suggested enhanced activity of hepatic tryptophan oxygenase, presumably in order to make these two amino acids more readily available for protein, hormone, and biogenic amine synthesis during stress.

Okada, Y., Matsuoka, T., Kumahara, Y.: "Human growth hormone secretion during exposure to hot air in normal adult male subjects." *J. Clin. Endocrinol. Metab.* **34**: 759-763 (1972). H54,871/72

In four normal obese adult males exposed to hot air (48°C) for one hour after an overnight fast, elevation of body temperature was associated with increased plasma STH and FFA levels. No significant changes in cortisol, total thyroxine-iodine, blood glucose or hematocrit were noted during heat exposure. In two subjects, administration of glucose before heat prevented the rise in plasma STH.

Cantfort, J. van: "Influence du 'stress' sur l'activité de la cholestérol- 7α -hydroxylase" (Effects of "stress" on cholesterol- 7α -hydroxylase activity). *C.R. Acad. Sci. (Paris)* **277**: 345-348 (1973). J6,396/73

In normal animals, the *cholesterol-7 α -hydroxylase* activity of the liver shows a circadian rhythm with a maximum at the beginning of the night. This is controlled by the hypothalamus-pituitary-adrenal axis and is abolished by adrenalectomy. Corticoids and various stressors increase this enzyme activity in the rat.

Polis, B. D., Polis, E., Schwarz, H. P., Dreisbach, L.: "The effect of cold on the composition of the phospholipids of the blood plasma of healthy athletes." *Proc. Soc. Exp. Biol. Med.* **145**: 70-73 (1974). J21,416/74

In athletes, the *phosphatidyl glycerol* content of plasma was very significantly elevated immediately after and for seven minutes following exposure to cold.

Sabbot, I., Costin, A.: "Cold stress induced changes in the uptake and distribution of radiolabelled *magnesium* in the brain and pituitary of the rat." *Experientia* **30**: 905-906 (1974). H92,909/74

Chirpaz, F., Lafrance, L., Leblanc, J.: "Effets de la noradrénaline sur le métabolisme des acides gras libres du plasma chez des rats adaptés au froid" (Effects of noradrenaline on plasma *free fatty acid* metabolism in rats adapted to cold). *Ann. ACFAS* **41**: 175 (1974). H88,198/74

Francesconi, R. P., Mager, M.: "Cold exposure: effect on hepatic tryptophan oxygenase and tyrosine aminotransferase, plasma tryptophan and tyrosine, and brain monoamines." *Experientia* **30**: 233-235 (1974). H86,502/74

In mice, exposure to "cold stress" rapidly enhances the production of *tryptophan oxygenase* and *tyrosine aminotransferase*. However, "there are no general correlations between increased activity of these catabolic enzymes and reduced levels of plasma trypto-

phan, tyrosine, and brain norepinephrine and serotonin.... Our results indicate that if the rate limiting enzymes in serotonin and norepinephrine biosynthesis, tryptophan and tyrosine hydroxylases respectively, are stimulated by cold stress, then homeostatic conditions are maintained by increased levels of catabolic activity."

→Varia. Cooke, R. E.: "The behavioral response of infants to heat stress." *Yale J. Biol. Med.* **24**: 334-340 (1952).

D86,749/52

In infants, "an increase in *water intake* and fall in *milk intake* were noted on exposure to heat stress. The converse occurred when the room temperature fell."

Thomson, A. G.: "The effect of temperature and humidity on the *working efficiency* of miners." *Mining J.* **240**: 98-100 (1953).

E53,354/53

Bedrak, E., Beer, G., Furman, K. I.: "Fibrinolytic activity and heat stress." *Isr. J. Exp. Med.* **11**: 1-6 (1963). G9,119/63

"Single acute exposures of normal resting men to environmental heat stress without physical activity caused increased *fibrinolytic activity* in both whole blood and plasma systems. With more prolonged heat stress exposures, proportionately greater activity was observed in the whole blood system." The literature on the fibrinolytic activity of various stressors is reviewed.

Nair, C. S., Malhotra, M. S., Gopinath, P. M.: "Effect of altitude acclimatization and simultaneous acclimatization to altitude and cold on critical flicker frequency at 11,000 ft. altitude in man." *Aerosp. Med.* **43**: 1097-1100 (1972). H81,634/72

In healthy men, acclimatization to high altitude did not significantly affect *critical flicker frequency*, whereas "cold stress produced a profound deterioration."

Leibowitz, H. W., Abernethy, C. N., Buskirk, E. R., Bar-Or, O., Hennessy, R. T.: "The effect of heat stress on *reaction time* to centrally and peripherally presented stimuli." *Hum. Factors* **14**: 155-160 (1972).

J19,859/72

Provins, K. A., Glencross, D. J., Cooper, C. J.: "Thermal stress and arousal." *Ergonomics* **16**: 623-631 (1973). J8,263/73

Studies on healthy young men kept in a water bath of varying temperature "suggested that the *arousal level* as indicated by

both the subjective and EEG records is not determined solely by either the body temperature or ambient conditions but is a resultant of their combined influences."

Hales, J. R. S.: "Effects of heat stress on blood flow in respiratory and non-respiratory muscles in the sheep." *Pflüegers Arch.* **345**: 123-130 (1973). J9,044/73

This article describes obviously specific effects of heat. [These are quite unrelated to nonspecific changes; hence the word stress in the title is superfluous and misleading (H.S.).]

Needham, A. D., Dawson, T. J., Hales, J. R. S.: "Forelimb blood flow and saliva spreading in the thermoregulation of the red kangaroo, *Megaleia rufa*." *Comp. Biochem. Physiol.* **49A**: 555-565 (1974).

H93,882/74

Rowell, L. B.: "Human cardiovascular adjustments to exercise and thermal stress." *Physiol. Rev.* **54**: 75-159 (1974).

H81,278/4

Review on cardiovascular adjustments to the stress caused by heat or exercise (422 refs.).

Neville, W. E. Jr., Neathery, M. W.: "Effect of temperature under field conditions on the reproductive performance of ewes." *J. Reprod. Fertil.* **36**: 423-426 (1974).

H80,745/74

In sheep, "heat stress" diminishes fertility. [Other stressors have not been used for comparison to determine the nonspecificity of this result (H.S.).]

+Restraint. Lange, K., Gold, M. M. A., Weiner, D., Kramer, M.: "Factors influencing resistance to cold environments." *Bull. U.S. Army* **8**: 849-859 (1948).

B23,962/48

The survival time of restrained rabbits is greatly diminished at -20° C and their body temperature drops precipitously.

Bartlett, R. G., Miller, M. A.: "The adrenal cortex in restraint hypothermia and in adaptation to the stress of restraint." *J. Endocrinol.* **14**: 181-187 (1956).

C25,043/56

In rats, mild restraint for one week increased the ascorbic acid and to a lesser extent the cholesterol content of the adrenals. Restraint sufficiently severe to reduce body temperature produced inverse changes. Loss of adrenal cholesterol and ascorbic acid from

the adrenals was particularly severe in animals restrained while exposed to cold.

Frankel, H. M.: "Effects of restraint on rats exposed to high temperature." *J. Appl. Physiol.* **14**: 997-999 (1959). J11,919/59

Restraint diminishes the resistance of rats to high temperatures, although the final rectal temperatures are not greatly different.

Brodie, D. A., Valitski, L. S.: "Production of gastric hemorrhage in rats by multiple stresses." *Proc. Soc. Exp. Biol. Med.* **113**: 998-1001 (1963). E28,039/63

"Gastric hemorrhage was produced in 93% of rats subjected to cold + restraint stress for 60 minutes." This combination of stressors also elicited a marked depression of body temperature lasting three hours after the stress. "Anticholinergics, ganglionic blocking agents, certain central nervous system depressants and epinephrine reduced the incidence of hemorrhage."

Robert, A., Phillips, J. P., Nezamis, J. E.: "Production, by restraint, of gastric ulcers and of hydrothorax in the rat." *Gastroenterology* **51**: 75-81 (1966). G40,473/66

In rats, restraint produced gastric ulcers and hydrothorax within four to six hours. Overnight fasting prevented the hydrothorax and reduced the gastric ulcerations (contrary to previous reports). Restraint ulcers and hydrothorax "were also inhibited by crowding of the animals, a rise in ambient temperature, or administration of prednisolone."

Buchel, L., Gallaire, D.: "Influence de la température ambiante sur la production d'ulcères de contrainte chez le rat" (Influence of surrounding temperature on the production of restraint ulcers in rats). *C.R. Soc. Biol. (Paris)* **160**: 1817-1820 (1966).

F78,016/66

A decrease of the surrounding temperature from 24 to 14° C facilitates the production of restraint ulcers in rats, whether or not they are previously exposed to twenty-four hours of fasting. Yet starvation accelerates the development of such restraint ulcers. Body temperature does not appear to be the only important factor, for rats kept at warm temperatures (28-32° C) still show gastric erosions, whereas treatment with phenobarbital or chloral hydrate during restraint aggravates the hypothermia and yet diminishes ulcer frequency.

Buchel, L., Gallaire, D.: "Ulcères de contrainte chez le rat. I. Influence, sur la fréquence des ulcères, du jeûne et de la tempér-

ature de l'environnement associés à des immobilisations de durées variables" (Restraint ulcers in the rat. I. Influence of fasting and environmental temperature associated with restraint of variable duration on the incidence of restraint ulcers). *Arch. Sci. Physiol.* **21**: 527-536 (1967).

G53,615/67

In rats, twenty-four hours of fasting increases the incidence of gastric ulcers produced by subsequent restraint. Concurrent exposure to cold further sensitizes the stomach to the development of these stress ulcers.

Senay, E. C., Levine, R. J.: "Synergism between cold and restraint for rapid production of stress ulcers in rats." *Proc. Soc. Exp. Biol. Med.* **124**: 1221-1223 (1967).

F83,370/67

The authors present a technique for the acute production of gastric ulcers in rats within two hours by combined exposure to restraint and cold.

Martin, M. S., André, C., Martin, F., Lambert, R.: "Rôle du froid dans l'ulcère de contrainte chez le Rat" (Effects of cold on restraint ulcers in rats). *C.R. Soc. Biol. (Paris)* **163**: 158-161 (1969).

H14,537/69

In rats, restraint at 5°C is highly effective in producing gastric ulcers within three hours and a concurrent drop in rectal temperature.

Martin, M. S., Martin, F., Lambert, R.: "The effect of ambient temperature on restraint ulcer in the rat." *Digestion* **3**: 331-337 (1970).

H34,597/70

In rats, the incidence of gastric ulcers produced by restraint increased considerably as the ambient temperature was lowered from 28 to 19°C. However, no strict correlation was observed between body temperature and frequency of gastric lesions. Restraint during the active phase of their diurnal cycle was particularly effective in producing gastric ulcers in the rats, and cold augmented wakefulness.

Ivanova, G. N., Altukhova, V. I., Kenig, E. E., Skebelskaia, I. B.: "Functional condition of the adrenal cortex of guinea pigs under conditions of prolonged and continuous overheating." *Probl. Endokrinol.* **18** No. 5: 98-103 (1972) (Russian).

H60,926/72

In guinea pigs, overheating at 35°C from five hours up to twenty-one days reduced the adrenocortical response to the stress of restraint, but did not alter blood 17-OHCS levels or reactivity to exogenous ACTH. "A conclusion could be drawn that reduced re-

sponse to stress in these animals was associated with a lesser excretion of endogenous ACTH."

Djahanguiri, B., Taubin, H. L., Landsberg, L.: "Increased sympathetic activity in the pathogenesis of restraint ulcer in rats." *J. Pharmacol. Exp. Ther.* **184**: 163-168 (1973).

H65,010/73

In rats, exposure to cold greatly increased the production of gastric ulcers by restraint. α -Methyldopa, bretylium, phenoxybenzamine and phentolamine all reduced the incidence of such gastric ulcerations. "The results suggest that the increased turnover of norepinephrine may be causally related to the development of restraint ulcers."

Yano, S., Harada, M.: "A method for the production of stress erosion in the mouse stomach and related pharmacological studies." *Jap. J. Pharmacol.* **23**: 57-64 (1973).

H85,804/73

Stress ulcers of the stomach can be most reliably produced in mice by immersing them in water of 25°C for eighteen hours while they are enclosed in a restraint cage of special design. The technique is said to be particularly useful in the assay of drugs inhibiting such erosions. Curiously, immersion at lower or higher temperatures causes less severe gastric ulcers.

Buchel, L., Murawsky, M.: "Métabolisme et activité de la zoxazolamine chez le rat blanc au cours de l'immobilisation forcée accompagnée ou non d'hypothermie" (Zoxazolamine metabolism and activity in white rats during restraint with or without hypothermia). *Arch. Sci. Physiol.* **27**: 37-53 (1973).

J7,077/73

In rats, the muscle-relaxing effect of zoxazolamine is considerably enhanced by the stress of restraint, especially in cold surroundings. This is ascribed mainly to increased sensitivity of the nervous system and (to a lesser extent) to impaired zoxazolamine metabolism during stress.

Hadjiolova, I.: "Veränderungen des Plasma- und Nebennierenrindencorticosterons bei Ratten während Hypokinesie und zusätzlicher Stress-Einwirkungen" (Influence of hypokinesia and subsequent stress upon rat plasma and adrenal corticosterone levels). *Int. Arch. Arbeitsmed.* **33**: 59-70 (1974).

J17,473/74

Studies on plasma and adrenal corticosterone in rats exposed to different stressors (heat, restraint, noise) alone or in combina-

tion. "A moderate increase in the levels of both plasma and adrenal corticosterone was observed after 24 hours of hypokinesia. In a subsequent period of 60 days the corticosterone levels did not differ significantly from the levels found in the control animals. However, a marked decrease in adrenal weight and a slighter response to additional thermal stress were demonstrated after 60 days of hypokinesia. Differences between the restrained and the control animals were also found in the adaptation to chronic auditory stress."

+**Genetics.** Deane, H. W., Lyman, C. P.: "Body temperature, thyroid and adrenal cortex of hamsters during cold exposure and hibernation, with comparisons to rats." *Endocrinology* **55**: 300-315 (1954).

B97,428/54

In both hibernating and nonhibernating Syrian hamsters, exposure to cold causes no significant adrenal enlargement or histologic evidence of hyperactivity similar to that produced in rats. However, the hamster adrenal is sensitive to other stressors.

Raths, P., Schulze, W.: "Die Nebennieren des Goldhamsters im Winterschlaf und bei anderen Aktivitätszuständen" (The adrenals of the golden hamster during hibernation and other activities). *Z. Biol.* **109**: 233-243 (1957). C36,859/57

Detailed description of histologic changes in the adrenal medulla and cortex of the golden hamster during hibernation, awakening from hibernation, and during anesthesia induced by cold.

D'Angelo, S. A.: "Adenohypophyseal function in the guinea pig at low environmental temperature." *Fed. Proc.* **19** Supp. 5: 51-56 (1960). C97,820/60

The relationship between adrenal and thyroid stimulation was studied in cold-exposed guinea pigs after electrocautery of the hypothalamus.

Yoon, Y. H.: "Pathological studies on the baby pig with hypoglycemia." *J. Kor. Vet. Med. Assoc.* **6**: 1222-1232 (1962) (Korean with English summary). G16,777/62

In baby pigs, stress induced by exposure to cold or starvation caused changes typical of the G.A.S., such as loss of adrenal lipids, hypoglycemia and eosinopenia (24 refs.).

Schwarz, D.: "Die Änderung der unspezifischen Reaktion des Organismus unter Hitzeanpassung" (Changes in the nonspecific

reaction of the organism during heat adaptation). *Dtsch. Versuchsanstalt für Luft- und Raumfahrt No. 441*: 1-71 (1965).

F72,209/65

Doctoral thesis containing a detailed analysis of the roles of stress and stress hormones in man's adaptive reactions to heat, with particular emphasis on aerospace medicine (242 refs.).

Pegelman, S. G., Kanarik, U. K.: "Adaptive responses in guinea pigs under conditions of a prolonged cooling." *Sechenov Physiol. J. U.S.S.R.* **53** No. 10: 1212-1217 (1967) (Russian).

J13,141/67

In guinea pigs, exposure to cold causes marked adrenal hypertrophy and ascorbic acid depletion with eosinopenia. Pretreatment with ascorbic acid reverses the eosinophil response and virtually blocks the loss of ascorbic acid from the adrenals.

Henschel, A.: "Obesity as an occupational hazard." *Can. J. Public Health* **58**: 491-493 (1967) (15 refs.). E71,837/67

Strydom, N. B., Williams, C. G.: "Effect of physical conditioning on state of heat acclimatization of Bantu laborers." *J. Appl. Physiol.* **27**: 262-265 (1969) (15 refs.).

J14,803/69

Slee, J.: "Resistance to body cooling in male and female sheep, and the effects of previous exposure to chronic cold, acute cold and repeated short cold shocks." *Anim. Prod.* **12**: 13-21 (1970). J10,493/70

The resistance of shorn female sheep to cold can be greatly increased by a single previous exposure of a few hours. Females are more resistant to cooling than males. Daily short cold shocks reduced cold resistance and inhibited acclimatization in females but not in males.

Maloiy, G. M. O.: "The effect of dehydration and heat stress on intake and digestion of food in the Somali donkey." *Environ. Physiol. Biochem.* **3**: 36-39 (1973).

H79,366/73

+**Drugs or Hormones.** Maickel, R. P., Westermann, E. O., Brodie, B. B.: "Effects of reserpine and cold-exposure on pituitary-adrenocortical function in rats." *J. Pharmacol. Exp. Ther.* **134**: 167-175 (1961).

D48,441/61

Reserpine and those reserpine derivatives that decrease brain NEP and 5-HT produced sedation and ACTH hypersecretion in rats. Large doses of reserpine or prolonged cold

exposure decreased the ACTH content of the pituitary sufficiently to prevent a detectable discharge in response to other stressors.

Juszkiewicz, T.: "Effects of chlorpromazine, reserpine, and ascorbic acid in resisting heat stress in rats." *Am. J. Vet. Res.* **22**: 537-543 (1961). J11,417/61

In rats, pretreatment with chlorpromazine, reserpine or ascorbic acid failed to prevent, but did somewhat diminish, the loss of adrenal ascorbic acid produced by heat (43°C).

Juszkiewicz, T., Jones, L. M.: "The effects of chlorpromazine on heat stress in pigs." *Am. J. Vet. Res.* **22**: 553-557 (1961).

J10,364/61

As indicated by adrenal ascorbic acid determinations, "chlorpromazine diminishes stressful response of the pituitary-adrenal axis in pigs due to hyperthermia, increases the survival rate at 40°C, and decreases the body weight loss."

Taylor, R. E. Jr., Fregly, M. J.: "Effect of reserpine on body temperature regulation of the rat." *J. Pharmacol. Exp. Ther.* **138**: 200-207 (1962). D41,319/62

In rats, intraperitoneal reserpine diminishes body temperature much more at low than at high environmental temperatures. It acts by decreasing heat production rather than by increasing heat loss. Restraint augments the reserpine-induced decrease in body temperature.

Johnson, G. E., Flattery, K. V., Schönbaum, E.: "The influence of methimazole on the catecholamine excretion of cold-stressed rats." *Can. J. Physiol. Pharmacol.* **45**: 415-421 (1966). F66,195/66

In rats, exposure to cold increases urinary excretion of NEP and thyroid activity. Failure to secrete adequate amounts of NEP and, in its absence, of EP, results in hypothermia and death. If cold-acclimated rats are treated with the antithyroid drug methimazole, the excretion of free EP and NEP doubles. It is postulated that the increase in the secretion of EP and NEP after exposure to cold results from a decrease in the intrinsic metabolic activity of catecholamines, and is a compensatory mechanism for the maintenance of heat production.

Goldstein, M., Nakajima, K.: "The effect of disulfiram on the biosynthesis of catecholamines during exposure of rats to cold." *Life Sci.* **5**: 175-179 (1966). G36,828/66

In rats, increased catecholamine excretion during exposure to cold suggests increased activity of the sympatho-adrenal system. Disulfiram, a potent inhibitor of dopamine- β -hydroxylase, causes only a slight decrease in the cardiac NEP concentration in adrenalectomized rats at room temperature. In animals kept 2°C for one hour there is a 50 percent decrease in cardiac NEP concentration, as compared with NEP levels in the corresponding controls. The fact that cold decreases the cardiac NEP content following inhibition of dopamine- β -hydroxylase by disulfiram "suggests an increase in cardiac norepinephrine utilization during cold exposure." In otherwise untreated animals, cardiac NEP levels after cold exposure are sustained by an increase in the biosynthesis of these catecholamines. It is possible that the increase in NEP biosynthesis during cold is due to excess dopamine formation.

Takagi, K., Okabe, S.: "An experimental gastric ulcer of the rat produced with anticholinergic drugs under stress." *Eur. J. Pharmacol.* **5**: 263-271 (1969). H9,358/69

In rats, the stress ulcers produced by immersion in cold water are prevented by atropine and other anticholinergic agents but at the same time another type of ulcer appears in the proventriculus.

Boulu, R., Schwartz, J. C.: "Ulcères gastriques médicamenteux et température environnante" (Drug-induced gastric ulcers and environmental temperature). *C. R. Acad. Sci. (Paris)* **268**: 2507-2510 (1969). G67,252/69

In rats, the production of gastric ulcers by reserpine, phenylbutazone and deoxy-2-glucose is much higher at an environmental temperature of 20°C than at 37°C.

Leduc, J.: "Effet de la sympathectomie chez le rat exposé au froid" (Effect of sympathectomy in rats exposed to cold). *Ann. ACFAS* **40**: 128 (1973). H87,897/73

6-Hydroxydopamine, which causes a "chemical sympathectomy," greatly diminishes resistance to cold. There is a marked rise in urinary EP but not in NEP. Apparently, the adrenal medulla can largely compensate for the loss of sympathetic nerve activity.

Osumi, Y., Takaori, S., Fujiwara, M.: "Preventive effect of fusaric acid, a dopamine- β -hydroxylase inhibitor, on the gastric ulceration induced by water-immersion stress

in rats." *Jap. J. Pharmacol.* **23**: 904-906 (1973). H82,948/73

Earlier observations had shown that EP and NEP can inhibit the production of stress ulcers in the stomach of the rat. It had also been noted that most α -adrenergic-blocking agents as well as the release of endogenous monoamines by reserpine and tetrabenazine aggravate these lesions, while β -adrenergic-blocking agents inhibit them. In the present experiments rats immobilized in restraint cages were immersed up to the xyphoid in water at 21°C, which produced gastric ulceration within three hours. Tetrabenazine prior to the stress aggravated ulcer production, while concurrently eliciting a decrease in NEP and dopamine content. Fusaric acid (5-butylpicolinic acid), a potent inhibitor of dopamine- β -hydroxylase, exerted an antiulcerogenic effect that was presumably due to a decrease in the release of NEP from the CNS.

Dechezleprêtre, S., Lechat, P.: "Effets comparés de l'adrénaline et d'un stress aigu sur la glycémie, la lactacidémie et la corticostérone plasmatique et surrénaliennes du rat" (Comparison of the effects of epinephrine and acute stress on glycemia, lactacidemia and the corticosterone level of plasma in the adrenals of the rat). *Agressologie* **15**: 117-123 (1974). H93,830/74

In rats, acute exposure to cold causes marked hyperlactacidemia, mild hyperglycemia and a considerable increase in plasma and adrenal corticosterone levels. These changes reach their maximum within ten minutes. EP exerts a similar effect but this is due to the stressor action of the injection procedure, as it is also produced by injection of the solvent alone. The changes elicited by combined treatment with cold and EP are not greater than those caused by the two agents separately.

+**Trauma.** Brunt, E. E. van, Ganong, W. F.: "The effects of preanesthetic medication, anesthesia and hypothermia on the endocrine response to injury." *Anesthesiology* **24**: 500-514 (1963). E23,121/63

Detailed review of the literature on the influence of preanesthetic medication and hypothermia upon the stressor effects of surgical injuries.

Markley, K., Smallman, E., Thornton, S. W.: "The effect of environmental temperature on mortality and metabolism after burn

and tourniquet trauma." *Fed. Proc.* **31**: 817 (1972). H53,564/72

An environmental temperature of 31°C significantly reduced mortality in mice after burn and tourniquet trauma.

Markley, K., Smallman, E., Thornton, S. W., Evans, G.: "The effect of environmental temperature and fluid therapy on mortality and metabolism of mice after burn and tourniquet trauma." *J. Trauma* **13**: 145-160 (1973). J1,495/73

Partially shaved and hairless mice kept at 31°C survive burn and tourniquet trauma better than those kept at 25°C.

+**Age.** Cooke, R. E., Pratt, E. L., Darrow, D. C.: "The metabolic response of infants to heat stress." *Yale J. Biol. Med.* **22**: 227-249 (1950) (52 refs.). B30,242/50

Grad, B., Kral, V. A.: "The effect of senescence on resistance to stress: I. Response of young and old mice to cold." *J. Gerontol.* **12**: 172-181 (1957).

C33,287/57

Adaptation to cold was less readily acquired by old than by young mice. "The fatal failure of old mice to adapt to cold generally occurred early in the stress period, that is, in the alarm phase of the Selye's adaptation syndrome."

Haltmeyer, G. C., Denenberg, V. H., Thatcher, J., Zarrow, M. X.: "Response of the neonatal rat after subjection to stress." *Nature* (Lond.) **212**: 1371-1373 (1966).

F74,906/66

During the first five days of life, the stress of heat or electric shock raises the adrenal and plasma concentration of corticosterone in the rat. Manifestly, the neonatal rat adrenal can respond normally to stressors by both an increased synthesis and release of corticoids. These data contradict earlier reports of a "stress-non-responsive period" (SNR) in this species. When adrenal ascorbic acid depletion is used as an indicator the situation appears to be different. Reactivity also depends upon the stressor (20 refs.).

Riccio, D. C., Campbell, B. A.: "Adaptation and persistence of adaptation to a cold stressor in weanling and adult rats." *J. Comp. Physiol. Psychol.* **61**: 406-410 (1966).

F76,331/66

No major difference in adaptability to cold was observed between weanling and adult rats "when severity of the stressor was

equated on the basis of previously reported behavioral and physiological measures."

Campbell, B. A., Riccio, D. C.: "Cold-induced stress in rats as a function of age." *J. Comp. Physiol. Psychol.* **64**: 234-239 (1966). G39,214/66

Comparative studies in animals of different age groups exposed to cold showed that "initial colonic temperatures were lower and behavioral recovery times slower in weanling rats, whereas colonic temperature-recovery times did not vary with age."

Danilova, L. Y.: "The role of adrenal glands in the regulation of carbohydrate metabolism of undercooled animals having different degrees of thermoregulation." *Acta Biol. Med. Germ.* **21**: 625-634 (1968) (Russian). H7,143/68

In various premature (although not in mature) neonatal mammals, cooling is not accompanied by glycogenolysis due to an insufficient EP secretion. Glucocorticoids raise the hepatic glycogen reserves in newborns, but fail to increase their resistance to hypothermia.

Fennell, W. H., Moore, R. E.: "Peripheral vascular responses to heat stress in elderly men." *Int. J. Biometeorol.* **15**: 325-329 (1971). J20,332/71

Wagner, J. A., Robinson, S., Tzankoff, S. P., Marino, R. P.: "Heat tolerance and acclimatization to work in the heat in relation to age." *J. Appl. Physiol.* **33**: 616-622 (1972). H79,771/72

Males aged eleven to sixty-seven years were compared in standard work-heat stress (walking on a treadmill in dry heat). "The older men had lower coefficients of heat conductance and finger blood flow in the heat than the young men. During work in the heat the older men and preadolescent boys were more limited in the sensitivity and secretory capacity of the sweating mechanism than the young men and the older boys."

Lyle, J. G., Jonson, K. M., Edwards, M. J., Penny, R. H.: "Effect of prenatal heat stress at mid- and late gestation on the learning of mature guinea-pigs." *Dev. Psychobiol.* **6**: 483-494 (1973). J8,629/73

In guinea pigs subjected to "heat stress" prenatally, black-white serial discrimination was impeded, and often morphologic evidence of brain damage became detectable.

Anagnostakis, D., Economou-Mavrou, C.,

Agathopoulos, A., Matsaniotis, N.: "Neonatal cold injury: evidence of defective thermogenesis due to impaired norepinephrine release." *Pediatrics* **53**: 24-28 (1974). J9,386/74

In preterm neonates exposed to cold, urinary excretion of NEP was considerably lower than after recovery. Urinary excretion of EP was unaffected by cold stress. Possibly, exposure of the newborn to cold exhausts the NEP stores and thereby causes inability to stimulate and utilize chemical thermogenesis.

+Diet. Horst, K., Mendel, L. B., Benedict, F. G.: "The metabolism of the albino rat during prolonged fasting at two different environmental temperatures." *J. Nutr.* **3**: 177-200 (1930). 6,639/30

Rats fasting at 26°C lived on the average 16.5 days and lost 49 percent of their initial body weight, whereas those fasting at 16°C survived on the average eleven days and lost 44 percent of their weight.

Mitchell, H. H., Edman, M.: *Nutrition and Climatic Stress*, p. 235. Springfield, Ill.: Charles C Thomas, 1951. B65,070/51

Technical discussion of observations on stress caused by cold, heat, high altitude and acceleration in relation to the nutrition of man (more than 750 refs.).

Leduc, J.: "Catecholamine production and release in exposure and acclimation to cold." *Acta Physiol. Scand.* **53** Supp. 183: 1-101 (1961). D42,829/61

Review of personal observations indicating that "warm- and cold-acclimated rats could not withstand prolonged exposure to cold after restriction of food. Their catecholamine excretion rapidly attained maximal values and animals died in hypothermia. The same happened with warm-acclimated rats whose insulation has been reduced by removal of the fur. Cold-acclimated clipped rats survived in the cold, but their catecholamine response was much more intense than that of intact cold-acclimated animals." Allegedly, these experiments suggest that acclimation to cold is limited by the finite capacity of the body to produce catecholamines and thereby maintain thermal balance. EP is considered to be a defense hormone against cold.

Boulouard, R.: "Effects of cold and starvation on adrenocortical activity of rats." *Fed. Proc.* **22**: 750-754 (1963). E20,995/63

In rats, starvation brings about a very significant increase in plasma corticosterone which is even more considerable in the event of simultaneous exposure to cold. The relationship between these findings and Porter-Silber chromogens is discussed. The strongest adrenocortical response occurs during the first few days of exposure to cold; secretion diminishes later despite the continued maintenance of adrenocortical hypertrophy.

Heim, T., Kellermayer, M.: "The effect of environmental temperature on brown and white adipose tissue in the starving newborn rabbit." *Acta Physiol. Acad. Sci. Hung.* **31**: 339-346 (1967). G50,688/67

The effect of stress upon fat mobilization was studied in newborn rabbits starved to death at different environmental temperatures. "Brown fat is mobilized in response to cold but not during starvation in a thermo-neutral environment, whereas white fat apparently serves as a general metabolic reserve and is used during starvation both in the absence and the presence of a cold induced increase in heat production."

Hale, H. B., Mefford, R. B. Jr.: "Influence of chronic heat exposure and prolonged food deprivation on excretion of magnesium, phosphorus, calcium, H⁺ and ketones." *Aerospace Med.* **39**: 919-926 (1968). G63,858/68

Description of the metabolic changes produced in rats by the "interplay of two stressors, chronic heat exposure and prolonged food deprivation."

Brooke, O. G., Harris, M., Salvosa, C. B.: "The response of malnourished babies to cold." *J. Physiol. (Lond.)* **233**: 75-91 (1973). J5,659/73

In malnourished Jamaican children heat production was not increased and rectal temperature fell when environmental temperature was decreased from 28° to 25°C.

+Rays. Gambino, J. J., Bennett, L. R., Billings, M. S., Lamson, B. G.: "Biological effect of stress following ionizing radiation." *Aerospace Med.* **35**: 220-224 (1964).

G9,697/64

Review of the literature on the effect of hypothermia upon x-ray resistance. Rats given a single dose of 500 rads (total body irradiation) showed "reduced longevity; retarded growth; cataracts; accelerated onset of skin ulcers, greying, enlarged mammary glands and palpable tumors; and increased incidence of palpable tumors." Repeated ex-

posure to brief periods of cold did not significantly influence these changes with the possible exception of tumorigenesis (41 refs.).

Reinhardt, K.: "Bestrahlung, insbesondere lokal- und fraktionierte Bestrahlung in Hypothermie bei der Ratte" (Irradiation, especially local and fractionated irradiation, during hypothermia in rats). *Strahlentherapie* **132**: 274-283 (1967). G45,682/67

In rats, induced hypothermia protects against local and whole body x-irradiation.

Musacchia, X. J., Barr, R. E.: "Helium-cold induced hypothermia in the hamster and radio-resistance." *Physiologist* **10**: 257 (1967). F86,700/67

In hamsters rendered hypothermic by being placed in an 80 percent helium, 20 percent oxygen atmosphere at low temperatures, resistance to cobalt irradiation is increased.

Phillips, R. D., Kimeldorf, D. J.: "An immediate irradiation effect on resistance of rats to low temperature." *J. Appl. Physiol.* **24**: 768-772 (1968). G58,748/68

Phillips, R. D., Kimeldorf, D. J.: "Effect of X-irradiation on the resistance of rats to low temperature." *Fed. Proc.* **27**: 508 (1968). H565/68

In rats exposed to cold after whole body x-irradiation, survival time was diminished.

+Varia. Caldwell, F. T. Jr.: "Metabolic response to thermal trauma: II. Nutritional studies with rats at two environmental temperatures." *Ann. Surg.* **155**: 119-126 (1962).

G48,655/62

At an environmental temperature of 30°C rats with skin burns gained weight and maintained a positive nitrogen balance without mortality. At 20°C animals with similar wounds lost weight rapidly, showed negative nitrogen balance and had a 60 percent mortality rate, although in both groups food intake was maintained at a preburn level. When the rats were allowed free access to food, the striking difference between those kept at 20°C and those kept at 30°C after burn was not seen. Normally, the burned rats consumed more food than the controls.

Handler, E.: "Temperature effects on operator performance." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 321-352. Glencoe, Ill.: Free Press, 1963. E10,431/63

Review on the effect of high and low temperatures on performance with special reference to aerospace medicine.

Rosenberg, A.: "Production of gastric lesions in rats by combined cold and electrostress." *Am. J. Dig. Dis.* **12**: 1140-1148 (1967). G51,611/67

In rats, combined exposure to cold and *electrostress* was much more effective in producing gastric lesions than either of these stressors alone. "The cold-electrostress-induced gastric lesions were prevented by atropine sulfate, atropine methyl nitrate and propantheline." Several other central depressants were less effective or ineffective.

Morimoto, T., Slabochova, Z., Naman, R. K., Sargent, F.: "Sex differences in physiological reactions to thermal stress." *J. Appl. Physiol.* **22**: 526-532 (1967).

G45,267/67

Skreslet, S., Aarefjord, F.: "Acclimatization to cold in man induced by frequent scuba diving in cold water." *J. Appl. Physiol.* **24**: 177-181 (1968). G55,183/68

Scuba *divers* practicing in cold water go through three stages of acclimatization: 1) unacclimatized stage: cold stress is met with by an elevated metabolic rate compensating heat loss. 2) intermediate stage: there is a fall in the rectal (core) temperature as heat loss is not fully compensated for by metabolism, believed to be caused by habituation of the CNS. 3) acclimatized stage: a constant rectal temperature is maintained, although minor metabolic heat is produced. Conservation of heat is attributed to lowered heat transfer with the blood to the body surface." [It is difficult to establish to what extent these reactions are truly nonspecific and hence characteristic of stress as such rather than of cold (H.S.).]

Stone, E. A.: "Behavioral and neurochemical effects of acute swim stress are due to hypothermia." *Life Sci.* **9** No. 1: 877-888 (1970). G77,276/70

In rats, forced *swimming* at 15°C causes hypothermia, inactivity and reduction of brain NEP. These changes can be prevented by rapid rewarming or by swimming in 37°C water.

Patton, G. W. R.: "Combined autonomic effects of concurrently-applied stressors." *Psychophysiology* **6**: 707-715 (1970).

H47,514/70

In U.S. soldiers, the stress effects (pulse rate, blood pressure, skin conductance) of solving *anagrams* during exposure to cold were greater than when each stressor was applied alone.

Nair, C. S., Malhotra, M. S., Gopinath, P. M.: "Effect of altitude and cold acclimation on the basal metabolism in man." *Aerosp. Med.* **42**: 1056-1059 (1971).

H75,566/71

In man, cold and *hypoxia* exert an additive action in raising the BMR. This is ascribed to a combination of the stressor effects.

Kolanowski, J., Hausman, A., Crabbé, J.: "Répercussions hydro-électrolytiques et hormonales de l'effort physique selon la température ambiante" (Hydroelectrolytic and hormonal repercussions of physical effort in ambient temperatures). *Rev. Inst. Hyg. Mines* **26**: 159-180 (1971). H78,606/71

In mineworkers submitted to a standard *exercise*, cortisolemia remained uninfluenced at normal ambient temperatures, but was greatly increased at high temperatures.

Hertig, B. A.: "Human physiological responses to heat stress: males and females compared." *J. Physiol. (Paris)* **63**: 270-273 (1971).

J19,855/71

Wilson, S. P., Doolittle, D. P., Dunn, T. G., Malven, P. V.: "Effect of temperature stress on growth, reproduction and adrenocortical function of mice." *J. Hered.* **63**: 324-330 (1972). G99,980/72

Allan, J. R., Crossley, R. J.: "Effect of controlled elevation of body temperature on human tolerance to +G_x acceleration." *J. Appl. Physiol.* **33**: 418-420 (1972).

J19,375/72

"Fully acclimatized subjects may show a smaller adverse effect of thermal stress on *G tolerance*, attributable to the cardiovascular changes which characterize this adaptive response."

Davis, F. M., Charlier, R., Saumarez, R., Muller, V.: "Some physiological responses to the stress of aqualung diving." *Aerosp. Med.* **43**: 1083-1088 (1972).

G95,712/72

Scuba (aqualung) *diving* in British coastal waters caused hormonal changes characteristic of stress. "Plasma cortisol levels were significantly raised before and after 30-meter dives when compared with 3-meter dives. Raised urinary levels of adrenalin, with high adrenalin to noradrenalin excretion ratios, were seen in several divers. The average decrease in rectal temperature was 0.33°C and mean skin temperatures remained approximately 16°C above ambient water temperature. Cold stress was considered unlikely to contribute to the hormonal changes seen."

These changes are probably due to anxiety over deep open water diving in a 'stressful' diving situation" (22 refs.).

Hale, H. B., Williams, E. W., Ellis, J. P. Jr.: "Cross-adaptation in military trainees in a hot climate." *Aerosp. Med.* **43**: 978-983 (1972). J2,006/72

Young men were exposed to *hyperoxia*, heat or both agents combined. "Differences in the metabolic response patterns of the trainees studied in summer and winter strongly suggest that heat adaptation led to positive cross-adaptation."

Iampietro, P. F., Melton, C. E. Jr., Higgins, E. A., Vaughan, J. A., Hoffmann, S. M., Funkhouser, G. E., Saldivar, J. T.: *High Temperature and Performance in a Flight Task Simulator*, pp. 1-8. Washington, D.C.: Federal Aviation Administration, 1972.

G91,965/72

In a *flight task simulator*, performance definitely declined at high cockpit temperatures. Relationships to the classic manifestations of the stress syndrome are not discussed.

Tanaka, M.: "Experimental studies on human reaction to cold with reference to differences between males and females." *Bull. Tokyo Med. Dent. Univ.* **19**: 1-18 (1972).

H56,898/72

When they were exposed to cold, heat production was lower in *women* than in men, but the decrease in skin temperature was more pronounced in males. Urinary 17-KS concentrations increased in the male but not in the female.

Tillman, F. R., Miller, J. A. Jr.: "Hypothermia and resistance of mice to lethal exposures to high gravitational forces." *Aerosp. Med.* **43**: 860-866 (1972). H79,348/72

Senay, L. C. Jr.: "Body fluids and temperature responses of heat-exposed women before and after ovulation with and without rehydration." *J. Physiol. (Lond.)* **232**: 209-219 (1973). J4,529/73

Personal observations and review of the literature on *sex* differences in the response of men and women to "heat stress." No special mention is made of any typical stress phenomena.

Wells, C. L., Horvath, S. M.: "Heat stress responses related to the menstrual cycle." *J. Appl. Physiol.* **35**: 1-5 (1973). J4,516/73

The few changes occurring during the *menstrual cycle* had a minimal influence upon

the ability of normal women "to regulate body temperature when exposed to environmental heat stress."

Wyndham, C. H.: "The physiology of exercise under heat stress." *Ann. Rev. Physiol.* **35**: 193-220 (1973). H67,021/73

Review on the physiology of *muscular exercise* "under heat stress," with special reference to metabolic and vascular reactions. Very little attention is given to stress in general or to adaptive hormones (122 refs.).

Harrison, M. H.: "Comparison of the metabolic effects of centrifugation and heat stress in man." *Aerosp. Med.* **44**: 299-303 (1973). H80,109/73

In fasted men, the stress of *centrifugation* or exposure to heat increased blood lactate, glucose, FFA, glycerol and catecholamine levels, but these changes did not always parallel each other (30 refs.).

Claus-Walker, J., Halstead, L. S., Carter, R. E., Campos, R. J., Spencer, W. A., Canzoneri, J.: "Physiological responses to cold stress in healthy subjects and in subjects with *cervical cord injuries*." *Arch. Phys. Med.* **55**: 485-490 (1974) (20 refs.).

J19,762/74

Dechezleprêtre, S., Lechat, P.: "Effets comparés de l'adrénaline et d'un stress aigu sur la glycémie, la lactacidémie et la corticostérone plasmatique et surrénalienne du rat" (Comparison of the effects of epinephrine and acute stress on glycemia, lactacidemia, and the plasma and adrenal corticosterone levels in the rat). *Aggressologie* **15**: 117-123 (1974). H93,830/74

In rats, acute exposure to cold causes marked hyperlactacidemia and mild hyperglycemia, with a considerable increase in plasma and adrenal corticosterone levels. These changes reach their maximum within ten minutes. EP exerts a similar effect due to the stressor action of the injection procedure, since it is also produced by injection of the solvent alone. The changes elicited by combined treatment with cold and EP are not greater than those caused by the two agents separately.

Poulton, E. C., Edwards, R. S.: "Interactions and range effects in experiments on pairs of stresses: mild heat and low-frequency noise." *J. Exp. Psychol.* **102**: 621-628 (1974). J17,212/74

Review of the literature on the interaction between the stressor effects of heat and *noise* in man.

Morimoto, T., Shiraki, K., Asayama, M.: "Seasonal difference in responses of body fluids to heat stress." *Jap. J. Physiol.* **24**: 249-262 (1974). J15,690/74

Wessenberg, H.: "The pathogenicity of *Entamoeba histolytica*: is heat stress a factor?" *Perspect. Biol. Med.* **17**: 250-266 (1974).

H81,930/74

Review of the literature and personal observations suggest that heat stress, especially in combination with physical exertion and solar radiation, predisposes to *infection* with

Entamoeba invadens and *histolytica*. In military epidemics, the emotional factor of anxiety also plays an important role. "Whether or not heat stress is the directly antecedent cause of tissue invasion, the lesson seems clear regarding the danger of heat stress to carriers of the amoebae or to those exposed to infection" (66 refs.).

Chou, B. J., Besh, E. L.: "Feeding bio-rhythm alterations in heat-stressed rats." *Aerosp. Med.* **45**: 535-539 (1974).

J13,391/74

Burns

→**Morphology.** Among the morphologic changes now known to be primarily dependent upon stress, gastroduodenal ulcer formation in man was probably one of the first to be observed. As early as 1823 Swan, and in 1839 Cooper, clearly described the development of bleeding surface erosions or even deep ulcers in the gastric and duodenal mucosa of severely burned children. These findings were repeatedly confirmed in adults also, both before and after 1842 when Curling described the lesions which now bear his name.

Similar changes have been reproduced experimentally in animals, although it was not until the alarm reaction was described in 1936 that they were recognized as being part of the characteristic stress reaction, and not a specific effect of some "burn toxin." Following extensive superficial skin burns, gastrointestinal lesions were often associated with adrenal changes, particularly red discoloration, which was regarded as a sign of hyperemia or hemorrhagic infarction with necrosis, but later it was also ascribed to simple hyperactivity with discharge of the cortical lipid granules. Yet, very severe burns may also cause necrosis and hemorrhage as well as deplete medullary catecholamines, and in some cases treatment with corticoids and/or catecholamines has been considered to be of therapeutic value.

→**Hormones.** Burns, if sufficiently severe, can produce pronounced increases in ACTH, glucocorticoid and catecholamine secretion, both in experimental animals and in man. Despite the many claims to the contrary, there is no convincing evidence of an exhaustion of the hormone-producing capacity of the pituitary or adrenals after severe burns, although cortical necrosis may cause some degree of relative adrenal insufficiency. The increase in the urinary secretion of corticoids and catecholamines is most pronounced during the first twenty-four hours after burns. This is when the adrenal stores of these hormones are correspondingly most markedly depleted, since resynthesis is slower than discharge. It is at this time, not during the stage of exhaustion, that we may speak of a functional adrenal insufficiency, but it is usually transient and rarely the cause of death. The excess secretion of corticoids and catecholamines is generally associated with all the other classic signs of the G.A.S.

In patients with severe burns, an increase in immunoreactive plasma STH and in-

sulin allegedly may persist for several weeks, but eventual exhaustion of the β -cells can cause "dangerous burn stress pseudodiabetes."

The plasma renin and angiotensin II concentrations have also been claimed to exhibit a very high rise, persisting for days or weeks.

→Metabolites. The biochemical changes most characteristic of stress, that occur as a consequence of burns, have already been discussed in the previous section devoted to the metabolism of hormones and hormone-like substances. Since burns, especially if they are extensive, undoubtedly represent extremely powerful systemic stressors, they are also associated with all other chemical manifestations of the stress syndrome, including intense catabolism with the liberation of breakdown products from protein, fat and carbohydrate stores.

It is worth noting, however, that in burned patients the BMR rises even in the absence of fever. Furthermore, plasma renin and angiotensin II are often unusually high and this elevation may persist for weeks. It may be related to the renal and hepatic damage associated with burns, but its pathogenesis has not yet been established.

→Varia. The renal complications of severely burned patients have received considerable attention, but it remains to be shown to what extent they depend upon stress as such. On the other hand, the characteristic eosinopenia and lymphopenia are undoubtedly the consequences of increased glucocorticoid production elicited by burns. The hypercoagulability of the blood, often observed in burned or severely traumatized patients, appears to be a result of a stress-induced derangement in platelet function. In rats, skin burns reduce the radioiodine uptake by the thyroid within a few hours, but it remains unexplained why this and other stressors may cause either hyper- or hypothyroidism, depending upon circumstances.

Data on complex psychologic defense mechanisms mobilized by patients under life-threatening stress, including burns, are not yet sufficiently understood to justify detailed evaluation here.

+Varia. In certain cases, corticoids have been recommended for the treatment of burns (especially in children), but their efficiency is still dubious.

In rats with extensive skin burns, maintenance of a positive N balance and survival are certainly better at high than at low surrounding temperatures. Normally, burned rats consume more food than controls unless they are in extremely poor general condition. If the animals are given free access to food, a striking difference between those kept at low and high temperatures is less evident.

Burns

(See also our earlier stress monographs, p. xiii)

Generalities. Greenwald, H. M., Eliasberg, H.: "The pathogenesis of death from burns." *Am. J. Med. Sci.* 171: 682-696 (1926).

B26,710/26

In man and rabbits, extensive burns cause an initial state of shock with hyperglycemia, followed by hypoglycemia and adrenal

changes interpreted as due to the initial stimulation resulting in exhaustion.

Delarue, J., Chomette, G., Pinaudeau, Y., Abelanet, R., Monsaingeon, A.: "Les lésions viscérales des grands brûlés. Etude anatomo-pathologique de 50 cas de brûlures mortelles" (Visceral lesions in extensive burns. Anatomopathologic study of fifty cases of fatal burns in man). *Ann. Anat. Path.* (Paris) 7: 53-85 (1962). D33,096/62

Review on the pathologic changes of fatal burns in man, revealing their similarity to alterations characteristic of the alarm reaction (84 refs.).

Foss, D. L., Stavney, L. S., Haraguchi, T., Harkins, H. N., Nyhus, L. M.: "Pathophysiologic and therapeutic considerations of Curling's ulcer in the rat." *J.A.M.A.* **187**: 592-594 (1964). F1,660/64

Stress ulcers produced in rats by scalding could be prevented by antacids, bilateral vagotomies and anticholinergic agents.

Oliver, W. J., French, J. W., Venema, W. J.: "The burned child: fluid therapy, adrenal function, and infection." *Univ. Mich. Med. Center J.* **30**: 270-277 (1964).

G26,300/64

Review on the characteristic indices of stress in burned children (63 refs.).

Waters, W. R., Riddell, D. M.: "A review of the literature of burns and trauma September 1966 to August 1967." *Med. Serv. J. Can.* **23**: 1333-1386 (1967). H11,299/67

Annotated review of the literature on burns, quoting many observations on their relation to the G.A.S. (703 refs.).

→**Ulcers.** Swan, J.: "Burns." *Mth. Gaz. Health* **8**: 612-613 (1823). 6,901/1823

Swan, J. "Practical observations." *Edinb. Med. J.* **19**: 344-347 (1823). 11,389/1823

Probably the first descriptions of what is now known as a "stress ulcer," in a five-year-old child who died from severe burns. "At different times he vomited a blackish matter, and the day before he died, appeared so weak and cold, that a little wine and sago were given him. On opening the abdomen, every part appeared sound, except the stomach, in the villous coat of which were several black spots and stripes like sloughs, extending deep, and quite black.... There can be no doubt that the diseased appearances of the head of the stomach were produced by the irritation of the skin."

Cooper, S.: "Pathology of burns and scalds." *Lond. Med. Gaz.* **23**: 837-838 (1839). 72,145/1839

In an eight-year-old girl who died about five weeks after severe scalds of the chest, an ulcer "about the size of a shilling" was noted in the duodenum just beyond the pylorus. Duodenal ulcers were also found after scalds and burns in other children.

Long, J.: "On the post-mortem appearances found after burns." *Lond. Med. Gaz.* **25**: 743-750 (1840). B4,643/1840

One of the first detailed descriptions of perforating duodenal ulcers in patients who died from extensive burns. "I have been induced to give the two cases of perforation of the duodenum in detail, as I believe they are unique; indeed I am not aware of any case being recorded, of perforation of the gastrointestinal tube occurring after a burn, except the one I have quoted from Liston, which approximates to my two cases by the perforation being near the pylorus, and by the change which had taken place in the duodenum."

Pack, G. T.: "The pathology of burns." *Arch. Pathol.* **1**: 767-805 (1926).

A15,632/26

In a review on the pathology of burns it is stated that "the inconstant duodenal ulcer of burns is due either to the irritant action of the bile, which owes its injurious ability to its content of the presumptive burn toxin, or to the production of infarction of the duodenal mucosa by septic emboli."

McLaughlin, C. W.: "The Curling ulcer. Study of intestinal ulceration associated with suprarenal damage." *Arch. Surg.* **27**: 490-505 (1933). 92,906/33

In man as in animals, superficial burns can produce peptic ulcers as well as adrenal lesions. Experiments on the dog show that extensive partial adrenalectomies are often conducive to duodenal ulcers, and hence the adrenal lesions may predispose to burn-induced peptic ulcerations (42 refs.).

Harkins, H. N.: "Acute ulcer of the duodenum (Curling's ulcer) as a complication of burns: relation to sepsis." *Surgery* **3**: 608-641 (1938) (134 refs.). E87,072/38

Friesen, S. R.: "The genesis of gastroduodenal ulcer following burns. An experimental study." *Surgery* **28**: 123-158 (1950).

B60,268/50

Review of the literature and personal observations in dogs and rabbits concerning the factors (hemoconcentration, thromboembolic phenomena, histamine, gastric acidity, infection, sepsis, stress) influencing gastroduodenal ulcer formation following burns (139 refs.).

Weigel, A. E., Artz, C. P., Reiss, E., Davis, J. H., Amspacher, W. H.: "Gastrointestinal ulcerations complicating burns. A report of five cases and a review of seventeen cases re-

- ported from 1942 to 1952." *Surgery* **34**: 826-836 (1953). G99,960/53
- Moncrief, J. A., Switzer, W. E., Teplitz, C.: "Curling's ulcer." *J. Trauma* **4**: 481-494 (1964). J11,165/64
- Review of 103 patients having peptic ulcers following burns.
- Ryan, R. F., Gay, J. S., Vincent, V., Longnecker, C. G.: "Stress ulcers of the upper gastrointestinal tract after burns: Curling's ulcer." *Plast. Reconstr. Surg.* **35**: 385-390 (1965). G28,093/65
- Sevitt, S.: "Duodenal and gastric ulceration after burning." *Br. J. Surg.* **54**: 32-41 (1967). J10,423/67
- Oosterhout, D. K., Feller, I.: "Occult gastrointestinal hemorrhage in burned patients." *Arch. Surg.* **96**: 420-422 (1968). J11,182/68
- Stone, H. H.: "Stress ulcers in patients with major burns." *Am. Surg.* **38**: 107-110 (1972). G88,727/72
- "The review of a 20-year experience in the management of 3,164 patients with major burns revealed 88 instances of stress ulcer developing in the gastroduodenal region. Massive upper gastrointestinal hemorrhage was the usual presenting feature, although perforation and obstruction did occur. Predisposing factors were sepsis, an extensive burn, prior peptic ulcer disease and severe wasting" (7 refs., all to articles published between 1964-1967).
- Drüner, H. U., Grözinger, K. H.: "Stress-Ulzena nach Verbrennungen" (Stress ulcer following burns). *Med. Welt* (Stuttg.) **23**: 707-708 (1972). H55,300/72
- Newsome, T. W., Asch, M. J., McGuigan, J. E., Pruitt, B. A. Jr.: "Gastrin levels following thermal injury." *Arch. Surg.* **107**: 622-624 (1973). J6,788/73
- Serum gastrin levels in patients with extensive skin burns show no strict correlation with the size of the burn, sepsis or the occurrence of gastroduodenal ulcer. Presumably, "Curling ulcer diathesis is determined primarily by defects in the barrier function of the gastric mucosa rather than by abnormal acid production" (35 refs.).
- Mathur, P. N., Singh, P. P., Rathore, A. S., Shastri, K. D.: "Gastric acidity uropepsin and urinary 17-ketosteroids in burns." *Indian J. Med. Res.* **61**: 1618-1624 (1973). J12,445/73
- Czaja, A. J., McAlhany, J. C., Pruitt, B. A. Jr.: "Acute gastroduodenal disease after thermal injury. An endoscopic evaluation of incidence and natural history." *N. Engl. J. Med.* **291**: 925-929 (1974). H94,314/74
- Adrenals. Kolosko: "Über Befunde an der Nebennieren bei Verbrennungstod" (Adrenal changes in patients dying after suffering severe burns). *Vierteljschr. Gerichtl. Med.* **47** Supp: 217 (1914). 3,525/14
- Weiskotten, H. G.: "Fatal superficial burns and the suprarenals. Note on the occurrence of suprarenal lesions in uncomplicated fatal cases of extensive superficial burns." *J. A. M. A.* **69**: 776 (1917). 92,580/17
- In patients with widespread, fatal superficial burns, the adrenals are usually swollen and deep red, exhibiting hemorrhages, necroses and polymorphonuclear cell infiltrations. Kolosko described similar changes in a number of cases of extensive superficial burns, and he interpreted them as hemorrhagic infarction.
- McLaughlin, C. W.: "The Curling ulcer. Study of intestinal ulceration associated with suprarenal damage." *Arch. Surg.* **27**: 490-505 (1933). 92,906/33
- In man as in animals superficial burns can produce peptic ulcers as well as adrenal lesions. Experiments on the dog show that extensive partial adrenalectomies are often conducive to duodenal ulcers, and hence the adrenal lesions may predispose to burn-induced peptic ulcerations (42 refs.).
- Hilgenfeldt, O.: "Die Behandlung und die pathogenetischen Grundlagen der Verbrennungen" (The treatment and pathogenesis of burns). *Ergeb. Chir. Orthop.* **29**: 102-210 (1936). 38,008/36
- Review, especially of the old literature, and personal observations on the histologic changes induced by severe surface burns in man. These changes may be due to shock, or to the resorption of protein decomposition products and bacteria from the damaged areas. "It may be assumed that after several weeks exhaustion of the adrenals may become equivalent to their total elimination."
- Lorthioir, J.: "Etude expérimentale et traitement des brûlés" (Experimental study and treatment of burns). *Acta Chir. Belg.* **60**: 1-88 (1961). D11,420/61
- Monograph on the treatment of burns, with special sections on adrenal lesions in severely burned patients (187 refs.).
- Feller, I.: "A second look at adrenal cor-

tical function in burn stress." In: Artz, C. P., *Research in Burns*, pp. 163-170. Washington, D.C.: American Institute of Biological Sciences, 1962.

J11,913/62

Severe cutaneous burns may cause adrenal hemorrhage and necrosis in man.

Haynes, B. W. Jr., Lounds, E. A., Hume, D. M.: "Adrenocortical function in severe burns." *Sci. Progr. Am. Assoc. Surg. Trauma* p. 16 (1963).

J11,914/63

Following a transient period of increased corticoid and catecholamine secretion, severely burned patients may exhibit signs of adrenocortical insufficiency.

Foley, F. D., Pruitt, B. A. Jr., Moncrief, J. A.: "Adrenal hemorrhage and necrosis in seriously burned patients." *J. Trauma* 7: 863-870 (1967).

H3,644/67

Six cases of fatal adrenal hemorrhage and necrosis among 1,213 patients with cutaneous burns (21 refs.).

→**Hormones.** Talbot, N. B., Albright, F., Saltzman, A. H., Zygmuntowicz, A., Wixom, R.: "The excretion of 11-oxy corticosteroid-like substances by normal and abnormal subjects." *J. Clin. Endocrinol.* 7: 331-350 (1947).

98,831/47

In man, "non-specific trauma (Alarm Reaction) resulted in a rise of urinary 11-OHCS assays; thus, values of the order of magnitude found in Cushing's syndrome were obtained in three patients with severe burns, the excretion falling to normal in one of these patients, interestingly enough, about three days before a fatal issue."

Hume, D. M., Nelson, D. H., Miller, D. W.: "Blood and urinary 17-hydroxycorticosteroids in patients with severe burns." *Ann. Surg.* 143: 316-329 (1956).

C15,326/56

17-OHCS levels in the plasma and urine of severely burned patients were greatly increased, and continued examinations revealed no evidence of adrenal exhaustion. Indeed, the adrenal was capable of responding to exogenous ACTH during the postburn period (10 refs.).

Goodall, M., Stone, C., Haynes, B. W. Jr.: "Urinary output of adrenaline and noradrenaline in severe thermal burns." *Ann. Surg.* 145: 479-487 (1957).

C33,346/57

In patients who suffered severe burns, the urinary output of EP and NEP was greatly increased. In one group of burned patients,

all of whom died, there was an initial rise of NEP but only a moderate elevation of EP output (74 refs.).

Birke, G., Dunér, H., Liljedahl, S. O., Pernow, B., Plantin, L. O., Troell, L.: "Histamine, catechol amines and adrenocortical steroids in burns." *Acta Chir. Scand.* 114: 87-98 (1958).

J10,862/58

In severely burned patients, blood and urinary histamine, EP and NEP content, as well as the excretion of corticoids (17-KGS) were considerably increased during the first twenty-four hours, but the duration of the rise varied according to the substances examined. Their role in the genesis of burn shock is discussed.

Goodall, M., Haynes, B. W. Jr.: "Adrenal medullary insufficiency in severe thermal burn." *J. Clin. Invest.* 39: 1927-1932 (1960).

G98,084/60

Review of the literature and personal study of fourteen fatally burned patients show that approximately two-thirds of these have subnormal EP output and low EP content in the adrenals, suggesting an acute medullary insufficiency. "In some patients the inflow, or rate of resynthesis, is apparently inadequate to meet the heavy demands imposed by the severe 'stress' of burn and, consequently, the adrenals are emptied of their adrenaline storage" (47 refs.).

Egdahl, R. H.: "Adrenal cortical and medullary responses to trauma in dogs with isolated pituitaries." *Endocrinology* 66: 200-216 (1960).

J11,920/60

In dogs, urinary 17-OHCS levels were increased for about five days after removal of the brain above the inferior colliculus. Burns caused a further increase. The catecholamine levels were initially low, but rose after burns.

Timmer, R. F.: "Changes in corticosterone levels after severe stress in the rat." *Proc. Soc. Exp. Biol. Med.* 110: 694-697 (1962).

D32,903/62

In rats, severe burns raised the plasma corticosterone level. "Measurements of free corticosterone in 'burn tissue fluid' indicated that the maximum value occurred at three hours after stress."

Hulbanni, S. V., Desai, R. C., Vyas, B. K.: "The role of adrenal cortex in stress of burns." *Indian J. Med. Res.* 54: 1083-1086 (1966).

F77,680/66

In burned patients, urinary corticoid levels reach a maximum on the third day and are

roughly proportional to the severity of the injury. This is associated with eosinopenia whose intensity does not adversely affect prognosis. The changes are considered characteristic of the G.A.S.

Franzen, F., Friedrich, G., Gross, H.: "Normabweichendes Auftreten proteinogener Amine bei Verbrennungskranken" (Abnormal activities of proteinogenic amines in burned patients). *Z. Gesamte Inn. Med.* **22**: 401-404 (1967).

F87,778/67

In severely burned patients, the plasma and urinary concentrations of EP, NEP, 5-HT, histamine and other amines derived from protein decomposition are greatly increased. There is no evidence to suggest that these changes are due to stress rather than to the specific effect of burns.

Muzykant, L. I., Gordeev, V. F.: "On the system of hypothalamus-hypophysis-adrenal in burn disease." *Ekspl. Khir. Anesteziol.* **14** No. 4: 42-47 (1969).

H16,736/69

Review on the G.A.S. manifestations produced by burns. The reactions of the hypothalamus-pituitary-adrenal system are essentially the same as those elicited by other stressors.

Doleček, R., Závada, M., Beška, F., Buryšková, D.: "Plasma immunoreactive insulin and growth hormone levels in burned subjects." *Acta Chir. Plast.* **14**: 179-190 (1972).

H78,654/72

In patients with severe burns an increase in immunoreactive plasma, insulin and STH may persist for several weeks, but eventual exhaustion of the β -cells can cause "dangerous burn stress pseudodiabetes."

Wise, L., Margraf, H. W., Ballinger, W. F.: "Adrenal cortical function in severe burns." *Arch. Surg.* **105**: 213-220 (1972).

G92,241/72

"Severely burned patients have prolonged high levels of free plasma cortisol and a decrease in plasma corticosteroid binding globulin.... The sustained increase of 17-ketogenic steroids, as opposed to the rapid decrease of Porter-Silber chromogens, suggests that corticosteroids other than cortisol are secreted in larger than normal quantities, in response to the prolonged stress of severe burns" (22 refs.).

Doleček, R., Závada, M., Adámková, M., Leikep, K.: "Plasma renin-like activity (RLA) and angiotensin II levels after major

burns. A preliminary report." *Acta Chir. Plast.* **15**: 166-169 (1973). J9,675/73

In severely burned patients, plasma renin and angiotensin II levels were usually very high, and the rise persisted for days or weeks.

Wilmore, D. W., Long, J. M., Mason, A. D. Jr., Skreen, R. W., Pruitt, B. A. Jr.: "Catecholamines: mediator of the hypermetabolic response to thermal injury." *Ann. Surg.* **180**: 653-669 (1974) (56 refs.).

J18,526/74

Bane, J. W., McCaa, R. E., McCaa, C. S., Read, V. H., Turney, W. H., Turner, M. D.: "The pattern of aldosterone and cortisone blood levels in thermal burn patients." *J. Trauma* **14**: 605-611 (1974). J14,481/74

In severely burned patients, plasma aldosterone concentrations often rose considerably during the initial period and sometimes remained elevated for sixty days. Cortisol blood levels rose less markedly. In two patients, ACTH was administered after burns with "neither showing a rise in aldosterone or cortisol, whereas a large increase in both compounds occurred in a normal volunteer after ACTH" (28 refs.).

→ **Metabolites.** Neely, W. A., Petro, A. B., Holloman, G. H. Jr., Rushton, F. W. Jr., Turner, M. D., Hardy, J. D.: "Researches on the cause of burn hypermetabolism." *Ann. Surg.* **179**: 291-294 (1974). J10,979/74

The BMR rises in burned patients even if the temperature does not increase.

→ **Varia.** Haynes, B. W. Jr., DeBakey, M. E., Denman, F. R.: "Renal function studies of severely burned patients. A preliminary report." *Ann. Surg.* **134**: 617-625 (1951).

J8,722/51

The renal complications in severely burned patients are described, but the authors do not determine to what extent they depend upon stress.

Hamburg, D. A., Hamburg, B., deGoza, S.: "Adaptive problems and mechanisms in severely burned patients." *Psychiatry* **16**: 1-20 (1953). B28,101/53

Studies on severely burned patients concerning: "(1) emergency psychological defenses utilized under conditions of life-threatening stress; and (2) relations between pre-illness adaptive patterns and adaptation to injury."

Wase, A. W., Repplinger, E.: "The effect

of thermal burns on the thyroid activity of the rat." *Endocrinology* 53: 451-454 (1953).

B87,006/53

Review of earlier literature showing that under certain circumstances stressors may produce either hyper- or hypothyroidism. Skin burns reduce radioiodine uptake by the rat thyroid during the first four hours.

Sevitt, S.: "Adrenocortical function in burned patients with special reference to ACTH and adrenaline tests." *Br. Med. J.* March 6, 1954, pp. 541-546. B91,174/54

In severely burned patients, adrenocortical hyperactivity was established by their spontaneous eosinopenia and their strong response to ACTH and EP. Only in fatal or near fatal burns were these responses deficient.

Wilson, H., Lovelace, J. R., Hardy, J. D.: "The adrenocortical response to extensive burns in man." *Ann. Surg.* 141: 175-184 (1955). C16,145/55

As indicated by the rise in urinary corticoids and the eosinopenia, "the stress response in a severe burn is one of the most intense of which the body is capable."

Gelfand, D. W., Goldman, A. S., Law, E. J., MacMillan, B. G., Larson, D., Abston, S., Schreiber, J. T.: "Thymic hyperplasia in children recovering from thermal burns." *J. Trauma* 12: 813-817 (1972).

G94,744/72

In children recovering from burns, the thymus is often enlarged.

Eurenius, K., Rothenberg, J.: "Platelet aggregation after thermal injury." *J. Lab. Clin. Med.* 83: 355-363 (1974). J10,809/74

As indicated by ADP-induced platelet aggregation in rats, platelet function was markedly depressed during the first hours after scalds, concurrently with the transient appearance of a plasma inhibitor. These changes may contribute to the "hypercoagulability" frequently described in burned or traumatized patients (37 refs.).

Beathard, G. A., Granholm, N. A., Sakai, H. A., Ritzmann, S. E.: "Ultrastructural alterations in peripheral blood lymphocyte profiles following acute thermal burns." *Clin. Immunol. Immunopathol.* 2: 488-500 (1974). J15,203/74

In man, during the immediate postburn period "a marked defect in cellular immunity or T-cell function occurs simultaneously with a marked stimulation in humoral immunity

or B-cell function. The latter abnormality is reflected by the development of a polyclonal gammopathy and the development first of a marked B-lymphocytosis followed by a marked plasmacytosis" that coincides with a return to normal peripheral blood lymphocyte counts (39 refs.).

Goldman, A. S., Rudloff, H. B., McNamee, R., Loose, L. D., Luzio, N. R. di: "Deficiency of plasma humoral recognition factor activity following burn injury." *J. Reticuloendothel. Soc.* 15: 193-198 (1974). J12,833/74

"Plasma humoral recognition factor activity, which is essential for optimal phagocytosis, is significantly depleted in severely burned children, both in the presence or absence of bacteremia, as well as in burned rats." This may explain the increased susceptibility to infection following thermal injury (30 refs.).

Dressler, D. P., Skornik, W. A.: "Pulmonary bacterial susceptibility in the burned rat." *Ann. Surg.* 180: 221-227 (1974). J15,111/74

Exposure of burned and control rats to *P. aeruginosa* and *S. aureus* showed that susceptibility to pulmonary infection is greatly increased within twenty-four hours of thermal injury.

+Varia. Duncan, J. T. Jr.: "Adrenal insufficiency in thermal burn with septicemia. Successful replacement therapy." *Am. Surg.* 20: 57-59 (1954). J10,792/54

In a patient with adrenal insufficiency due to septicemia following a burn, cortisone was very efficacious as replacement therapy.

Caldwell, F. T. Jr.: "Metabolic response to thermal trauma: II. Nutritional studies with rats at two environmental temperatures." *Ann. Surg.* 155: 119-126 (1962). G48,655/62

At an environmental temperature of 30°C, rats with skin burns gained weight and maintained a positive nitrogen balance without mortality. At 20°C, animals with similar wounds lost weight rapidly, showed a negative nitrogen balance and had a 60 percent mortality rate although in both groups food intake was maintained at a preburn level. When the rats were allowed free access to food, the striking difference between those kept at 20°C and those kept at 30°C after burn was not seen. Normally, the burned rats consumed more food than the controls.

Langlois, P., Williams, H. B., Gurd, F. N.: "Effect of an elemental diet on mortality rates and gastrointestinal lesions in experimental burns." *J. Trauma* 12: 771-777 (1972). G94,742/72

Rats fed an "*elemental diet*" in which amino acids replaced all the protein showed

improved survival and diminished gastrointestinal lesions after burns.

Voorhis, C. C., Law, E. J., MacMillan, B. G.: "Operative treatment of Curling's ulcer in children: report of four cases with three survivors." *J. Trauma* 14: 175-180 (1974).

J10,330/74

Sound

The stressor effect of sound has been the subject of extensive investigations both in man and in experimental animals, especially because of the importance of "sound pollution" in modern cities, particularly in factories and around airports. For general orientation about the relevant literature (including the specific effects of sound upon the auditory apparatus), see the many reviews and monographs cited below. Attention should be called to the fact that a certain amount of sound (such as that generated by movements of coworkers in an office) is often beneficial through its arousal effect; and music is commonly employed in industry, especially for the relief of workers engaged in monotonous tasks. On the other hand, prolonged exposure to continuous and intense noise can definitely be conducive to typical diseases of adaptation.

→**Morphology.** Not unexpectedly, intense noise also produces all the morphologic changes characteristic of stress, both in experimental animals and in man. Thus, in mice, the adrenals are enlarged and show histologic signs of hyperactivity, and the eosinophil count drops rapidly, even before there is evidence of thymic lymphatic involution. In rats, repeated intense auditory stimulation induces ovarian, uterine and hepatic atrophy in combination with adrenal enlargement. Numerous other observations confirm that sound acts essentially as do other stressors. However, a few structural changes are worthy of special note.

Some investigators reported changes in the salivary and lacrimal glands of rats exposed to stress, although these claims could not be uniformly confirmed.

The audiovisual stress produced by various bells, buzzers and white noise generators may influence the atherogenic effect of thiouracil in rats on a high cholesterol diet, but here again, confirmatory data by other laboratories are lacking.

Both sound and electroshock allegedly increase the incidence of dental caries in rats and may cause "fluctuating dental asymmetry."

→**Hormones.** The hormonal changes produced in animals and man by exposure to intense sound are essentially the same as those elicited by other stressors. Particularly characteristic is the discharge of ACTH, glucocorticoids and catecholamines. The plasma STH level may also rise in persons exposed to intense noise in an industrial plant, as well as in squirrel monkeys in which this response is similarly elicited by a variety of other psychogenic stressors.

Intense auditory stimulation increases corticoid production and causes a fall in brain NEP. Furthermore, changes in the 5-HT content of the amygdala and temporal cor-

tex are considered in support of the hypothesis that 5-HT may inhibit the transmission of impulses through the auditory pathways.

Urinary VMA elimination was increased among workers exposed to industrial noise in factories. A rise in catecholamine excretion has also been noted in aircraft factory workers exposed to turbine noise.

In rhesus monkeys, plasma glucagon rose rapidly when they were startled by noise and this was not necessarily associated with any significant changes in plasma insulin. Similar effects were produced, even under light anesthesia, by drilling a burr hole in the skull, electroshock, rectal distention and other stressors.

→**Metabolites.** In rats, strong auditory stimulation allegedly reduced the glutathione level of the blood simultaneously with an actual increase in the ascorbic acid and cholesterol content of the adrenals.

In workers exposed to noise and vibration in a factory, serum aldolase and lactic dehydrogenase rose, supposedly as a nonspecific consequence of stress.

In guinea pigs, prolonged exposure to noise caused a variety of enzymologic changes ascribed to the alarm and resistance stages of the G.A.S.

In lambs, auditory stimulation was followed by a rise in plasma FFA, and the same was true in aircraft factory workers exposed to turbine noise.

Most of the other biochemical changes produced by noise in different species correspond to those elicited by other stressors, and do not deserve special mention.

→**Nervous System.** Continuous or interrupted strong auditory stimulation is generally known to cause psychogenic distress, usually accompanied by such objective indices of the G.A.S. as increased catecholamine and corticoid secretion. However, here again, our motto applies: "it is not so much what happens to you but the way you take it." Certain musical sounds are either relaxing or eustress-producing to most people, and there exist transitional situations such as are created by extremely strong music (for example, calypso) which is as pleasant to some as it is painful to others. Even the crying of a baby who wants milk or simply attention may be eustressful to the mother and distressful to others.

Most of the scientific work on the stressor effect of noise has been done in genetically predisposed mice or rats which develop epileptic-type convulsions under the influence of audiogenic stimulation—and many pertinent additional data will also be found in the section on Genetics. There is no convincing evidence, however, that the hereditary predisposition of these animals to convulsions is truly nonspecific and could be elicited by any other stressors.

→**Varia.** Among other manifestations of prolonged audiogenic stimulation, blood pressure instability usually resulting in hypertension has been reported in various susceptible species. In rats in which strong sound caused convulsive attacks, these were associated with an increased phagocytosis by leukocytes. In the absence of convulsions, the same sound produced an opposite effect. In various mammals, chronic exposure to intense sound disturbed the sexual cycle and fertility, presumably as a consequence of the "shift in hypophyseal hormone production."

In rats, intense sound decreased antithrombin and thromboplastin activity, but activated antithromboplastin. Thrombocyte adhesiveness after auditory stress may predispose to thrombosis in man.

+Genetics. Among the factors that influence responsiveness to sound, genetic predisposition is probably one of the most important. There are strains of mice and rats which develop intense and sometimes fatal audiogenic convulsions. These have been compared with epileptic seizures and are associated with eosinopenia, thymus involution and other characteristic manifestations of the alarm reaction. In man, EEG studies indicate that noise has comparatively little effect upon the sleep patterns of twenty-five-year-old subjects, but causes increasingly severe disturbances with progressing age.

Sound, like many other stressors, raises plasma cortisol in the carp.

Sound

(See also our earlier stress monographs, p. xiii)

Generalities. Day, E. D., Fletcher, D. C., Naimark, G. M., Mosher, W. A.: "Sonic radiation effects on rats." *J. Aviat. Med.* **22**: 316-318 (1951). B63,927/51

In rats, exposure to an intense sound imitating that of the engines of a turbojet caused death with typical manifestations of the G.A.S. The DNA content of hepatic and adrenal nuclei remained unchanged.

Greenberg, L. A., Lester, D.: "The effect of alcohol on audiogenic seizures of rats." *Q. J. Stud. Alcohol* **14**: 385-389 (1953).

J23,511/53

In rats, audiogenic seizures were largely inhibited by moderate ethanol intake.

Sackler, A. M., Weltman, A. S., Jurtschuk, P. Jr.: "Endocrine aspects of auditory stress." *Aerosp. Med.* **31**: 749-759 (1960).

C92,819/60

Review of the literature and personal observations on the stressor effect of sound, particularly in the rat (34 refs.).

Kivikoski, A., Grönroos, M., Näätänen, E.: "Effect of benzylimidazolin under audiogenic-visual stress conditions." *Ann. Med. Exp. Fenn.* **38**: 394-399 (1960).

D5,263/60

Broadbent, D. E.: "Non-auditory effects of noise." *Adv. Sci.* January 1961, pp. 406-409.

J16,322/61

Wilson, A.: *Noise: Final Report*, p. 41. Report of the Committee on the Problem of Noise. London: HMSO 22, 1963.

J2,653/63

Report to the British Parliament on the causes, biologic effects and distribution of noise in the United Kingdom, including chap-

ters on laws regulating noise, its development in towns, at work, in the home, hotels, schools, roads and so on.

Carpenter, A.: "How does noise affect the individual?" *Impulse* **24**: 23-25 (1964).

J16,325/64

Hruběš, V., Beneš, V.: "A study on the effect of repeated noise in rats." *Activ. Nerv. Sup.* (Praha) **7**: 165-167 (1965).

J23,487/65

Burns, W.: *Noise and Man*, p. 336. Philadelphia: J B Lippincott, 1968.

E8,840/68

Monograph on the effects of noise, sonic booms and vibration on man, with special reference to aerospace problems.

Welch, B. L., Welch, A. S. (eds.): *Physiological Effects of Noise*, p. 365. New York and London: Plenum Press, 1970.

E8,849/70

Extensive text on the pathogenic effect of noise upon animals and man with numerous references to the stressor action of sound, which can cause "diseases of adaptation." Rich source of pertinent literature.

Kryter, K. D.: *The Effects of Noise on Man*, p. 633. New York and London: Academic Press, 1970.

E8,839/70

Detailed technical monograph on the effects of noise upon the ears and the body as a whole, with a comparatively short section on "Stress and Health" (914 refs.).

Still, H.: *In Quest of Quiet*, p. 221. Harrisburg, Pa.: Stackpole Books, 1970.

E8,855/70

Popular description of the harm which can be inflicted by noise of the city, high-speed aircraft and industry. Based mainly on the author's empirical observations and many im-

pressive quotations from the daily press. Strictly scientific publications are cited only occasionally.

Bondarev, G. I., Sinitina, A. D., Efimov, I. N.: "Combined effect of low frequency vibration and noise on the adreno-cortical pituitary system." *Gig. Sanit.* 35 No. 5: 106-108 (1970) (Russian). J15,240/70

Anticaglia, J. R., Cohen, A.: "Extra-auditory effects of noise as a health hazard." *Am. Ind. Hyg. Assoc. J.* 31: 277-281 (1970). J22,894/70

Atherley, G. R. C., Gibbons, S. L., Powell, J. A.: "Moderate acoustic stimuli: the interrelation of subjective importance and certain physiological changes." *Ergonomics* 13: 536-545 (1970). J21,401/70

In man, "the noises of high subjective importance, the aircraft and the typewriter, both showed measurable physiological changes, whereas that of low subjective importance (white noise) showed no significant change compared with control levels. Estimations from four subjects showed a marked decrease in 24-hour urinary 17-ketosteroid and eosinophils, and an increase in total white cell count, lymphocytes and neutrophils."

Klosterkötter, W., Gono, F.: "Quellen und gesundheitliche Wirkung des Lärms" (Sources and health effects of noise.) *Zentralbl. Bakteriol. [Orig. B]* 155: 300-314 (1971). H75,581/71

Extensive statistical studies on the stressor effect of industrial, aircraft and traffic noise (17 refs.).

Glorig, A.: "Noise-exposure. Facts and myths." *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 75: 1254-1262 (1971).

J17,045/71

Rosen, S.: "Noise and health." *Mt. Sinai J. Med.* 38: 489-496 (1971) (10 refs.). J17,193/71

Krotky, H.: "Untersuchungen über akute Lärmschäden des Gehörs durch Einwirkung von Turbineschall hoher Frequenz in der zahnärztlichen Praxis" (Investigation of acute hearing defects caused by high frequency turbine sound in dental practice), p. 108. Doctoral thesis, University of Berlin, 1971. J15,035/71

Baron, R. A.: *The Tyranny of Noise*, p. 294. New York, Evanston, San Francisco and London: Harper & Row, 1971. E9,586/71

Very readable summary on the price you pay for the stressor effect of various types of noise characteristic of our civilization. Special attention is given to the noise of urban life, the abusive employment of technology, and aviation. Statistics on noise in terms of health and dollars. Technical means to avoid or minimize noise.

Wahi, P. N.: "Noise pollution and health." *Indian J. Med. Res.* 59: 1148-1153 (1971). G88,387/71

Inaugural address at a symposium on noise pollution in New Delhi. The importance of stress and the pathogenic actions of noise are discussed eloquently, but new facts or references are not given.

Selye, H.: "Report upon the damaging effects of noise in man and other mammals." Photocopied, 1971. G86,666/71

Extensive review of the literature on the effect of noise upon various organ systems of man and animals. [This unpublished manuscript of forty-six typed pages is composed in the "analytic-synthetic style" and available in photocopied form at cost by writing to the author (H. S.).]

Fisher, S.: "A 'distraction effect' of noise bursts." *Perception* 1: 223-236 (1972). H80,367/72

Selye, H.: "Stress and noise." *Can. Occup. Safety Mag.* 10: 4-5 (1972). G88,025/72

Brief summary of the stress concept in connection with "noise pollution."

Kryter, K. D.: "Non-auditory effects of environmental noise." *Am. J. Public Health* 62: 389-398 (1972) (25 refs.). J16,973/72

Bull, A. J., Burbage, S. E., Crandall, J. E., Fletcher, C. I., Lloyd, J. T., Ravneberg, R. L., Rockett, S. L.: "Effects of noise and intolerance of ambiguity upon attraction for similar and dissimilar others." *J. Soc. Psychol.* 88: 151-152 (1972). J16,972/72

Glass, D. C., Singer, J. E.: *Urban Stress: Experiments on Noise and Social Stressors*, p. 182. New York and London: Academic Press, 1972. E3,951/72

Monograph on the stressor effect of noise, mainly as a function of predictability and subject control. Despite the title, little is said about other stressors in urban life, but the book—which earned its authors the 1971 Socio-Psychological Prize of The American Association for the Advancement of Science—undoubtedly contains many valuable data

on human responses to psychosocial stressors (about 120 refs.).

Glass, D. C., Singer, J. E.: "Behavioral aftereffects of unpredictable and uncontrollable aversive events." *Am. Sci.* **60**: 457-465 (1972). J16,985/72

General discussion of sound as a stressor.

Lipscomb, D. M.: "Noise in the environment." *J. Tenn. Med. Assoc.* **66**: 707-729 (1973). J16,271/73

Review on the stressor effect of noise and its relation to premature aging.

Falk, S. A., Kryter, K. D., Chase, H. C.: "Environmental noise." *Am. J. Public Health* **63**: 833-837 (1973). J16,965/73

Carlestam, G., Karlsson, C. G., Levi, L.: "Stress and disease in response to exposure to noise. A review." *Proc. Int. Congr. on Noise Public Hlth. Problem*, pp. 479-486. Dubrovnik, Yugoslavia 1973.

J17,326/73

Gould, W. J., Sullivan, R. F.: "Noise." *Ann. N. Y. Acad. Sci.* **216**: 17-29 (1973). J16,964/73

Schiff, M.: "Nonauditory effects of noise." *Trans. Am. Acad. Ophthalmol. Otolaryngol.* **77**: ORL-384-ORL-398 (1973). J15,933/73

Lindvall, T., Radford, E. P.: "Measurement of annoyance due to exposure to environmental factors." *Environ. Res.* **6**: 1-36 (1973). J15,317/73

Review on various annoyance-producing environmental factors, especially sound, pollution, crowding and stressful interpersonal relations, as objective indicators of somatic stress (about 150 refs.).

Rosen, G.: "A backward glance at noise pollution." *Am. J. Public Health* **64**: 514-517 (1974) (22 refs.). J15,946/74

Chemin, P.: "Effets généraux du bruit sur l'organisme humain" (General effects of noise on the human organism). *Bordeaux Med.* **7**: 533-546 (1974) (30 refs.). H85,677/74

"Monkeys agree—noise is upsetting!" *Medical Times* (N.Y.) **102**: 71-76 (1974). J17,048/74

Review on the effect of noise (industrial, rock music, intermittent gunfire) upon rhesus monkeys. Blood cortisol levels show an initial rise followed by a drop during the third hour of exposure "despite behavioral indications that the animals continued to be

stressed." [Based on an earlier article of Watson (H.S.).]

Singer, J. E., Glass, D. C.: "Making your world more livable." In: Miller, E., *Stress. Blue Print for Health* **25** No. 1: 59-65 (1974). E10,820/74

"Other medical views and research on noise." *Medical Times* (N.Y.) **102**: 84-96 (1974). J17,049/74

→**Hormones.** Fortier, C.: "Studies on the adrenocorticotrophic effect of audiogenic stimulation." *Rev. Can. Biol.* **10**: 67 (1951). B49,477/51

Henkin, R. I., Knigge, K. M.: "The effects of sound on the hypothalamic-pituitary-adrenal axis." *Acta Endocrinol.* **51** Supp.: 39 (1960). C93,250/60

The discharge of corticosterone following exposure to sound is prevented if the reception of the stimulus by the auditory system is blocked. After twelve hours of continuous sound, hormone secretion diminishes.

Argüelles, A. E., Ibeas, D., Ottone, J. P., Chekherdemian, M.: "Pituitary-adrenal stimulation by sound of different frequencies." *J. Clin. Endocrinol. Metab.* **22**: 846-852 (1962). D28,851/62

In healthy young men, and even more markedly in anxious psychoneurotic patients, exposure to various pure sound frequencies for one-hour periods caused substantial elevations in 17-OHCS and 17-KGS excretion. "Adrenal cortical function in man may be remarkably sensitive to auditory stimulation, probably through the effect of ACTH released by intense sound."

Henkin, R. I., Knigge, K. M.: "Effect of sound on the hypothalamic-pituitary-adrenal axis." *Am. J. Physiol.* **204**: 710-714 (1963). D62,084/63

In rats, exposure to intense sound caused an initial increase with a subsequent depression of corticosterone secretion. Destruction of the middle ear abolished this response, but bilateral lesions in the posterior hypothalamus raised the resting level of corticosterone secretion and diminished the reaction to sound.

Argüelles, A. E.: "Endocrine response to auditory stress of normal and psychotic subjects." In: Bajusz, E., *An Introduction to Clinical Neuroendocrinology*, p. 121. Basel and New York: S Karger, 1967. E6,579/67

Review on the effect of audiogenic stress

upon corticoid production in animals and man.

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971). H37.353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound and aversive conditioning) increase plasma STH and cortisol levels but the two responses do not run parallel and are presumably regulated by diverse mechanisms. In the case of chair restraint, STH values fall to resting levels while cortisol continues to rise.

Favino, A., Scoz, R., Trecate, G.: "Effetti della stimolazione acustica sulla secrezione di ormone somatotropo umano" (Effect of acoustic stimulation on growth hormone secretion in man). *Boll. Soc. Ital. Biol. Sper.* **47**: 704-708 (1971). G89.995/71

In man, the intense noise of an industrial plant raised plasma STH levels. [No technical details are given (H.S.).]

Grisanti, G., Manzella, G., Martines, E., Adriano, M. P.: "Studio sperimentale sul comportamento delle catecolamine seriche umane in seguito ad intensa stimolazione acustica" (Experimental study of human catecholamine blood levels after intense acoustic stimulation). *Valsalva* **47**: 65-81 (1971). G85.995/71

Bloom, S. R., Daniel, P. M., Johnston, D. I., Ogawa, O., Pratt, O. E. "Changes in glucagon level associated with anxiety or stress." *Psychol. Med.* **2**: 426-427 (1972). G98.403/72

In monkeys [subspecies not mentioned (H.S.)], a sudden loud noise produced a large and rapid rise in plasma glucagon, even during ether anesthesia.

Anitesco, C., Contulesco, A.: "Etude de l'influence du bruit et des vibrations sur le comportement des catécholamines dans l'agression sonore vibratoire industrielle" (Studies on the influence of noise and vibration on the behavior of catecholamines in industrial vibratory acoustic stress). *Arch. Mal. Prof.* **33**: 365-372 (1972). G95.398/72

Slob, A., Wink, A., Radder, J. J.: "The effect of acute noise exposure on the excretion of corticosteroids, adrenalin and noradrenalin in man." *Int. Arch. Arbeitsmed.* **31**: 225-235 (1973). H93.238/73

EP and NEP excretion in control male students showed the anticipated drop on the second day of preparation for noise exposure, which was attributed to them "getting used" to the laboratory situation. No decrease was manifested, on the afternoon of the second day, by the group exposed to noise of 80 dB intensity at this time. Allegedly, this result was due to the "masking effect" of noise exposure upon both levels of excretion. Corticosteroid levels were not significantly affected at any time.

Calogero, B., Vetrano, G.: "Variations of the biogenic amines content in some different areas of the brain of rats subjected to physiological auditory stimulation and acoustic trauma." *Rev. Laryngol. Otol. Rhinol. (Bord.)* **94**: 429-443 (1973).

J9.516/73

In rats, intense sonic stimulation (120 decibels) produced adrenocortical activation and a fall in brain NEP. "Changes in 5-HT concentration in the amygdala and temporal cortex occurred under both moderate but prolonged (60 decibels) and intense (120 decibels) auditory stimulation. These data are in favour of a possible inhibitory role played by serotonin in the central auditory pathways." Plasma corticosterone levels were also raised. [It is not clear to what extent the brain catecholamine changes were due to stress or specifically to auditory stimulation (H.S.).]

Calogero, B.: "Variazioni del turnover delle amine biogene nel sistema nervoso centrale del ratto dopo stimolazione acustica" (Biogenic amine changes in the central nervous system following acoustic stimulation in the rat). *Minerva Otorinolaringol.* **23**: 55-60 (1973).

J4.054/73

Intense auditory stimulation causes significant changes in the catecholamine and 5-HT content of the temporal cortex, amygdala and hypothalamus of the rat. "Serotonin may inhibit the transmission of impulses through the auditory pathway under protracted stimulation."

Kajiwara, N., Kobayashi, Y., Murakami, A., Hashida, J., Uchiyama, T., Kita, T., Sato, M., Okumura, Y., Ono, M., Mikami, T., Oshima, K.: "The influence of stressful environmental stimuli on changes of catecholamines and blood pressure." *Jap. Heart J.* **14**: 170 (1973).

J11.352/73

Effect of sound and light upon adrenal weight, and upon catecholamines in the

adrenals, brain and heart. [This brief abstract does not lend itself to evaluation (H.S.).]

Anitesco, C., Bubuiaru, E., Contulesco, A.: "Interaction des catécholamines et des électrolytes dans le traumatisme sonore-vibratoire industriel" (Interaction of catecholamines and electrolytes in industrial sound-vibration trauma). *Arch. Mal. Prof.* **34**: 503-510 (1973). J8,774/73

"The sound-vibration stress in industry produces an impairment of the balance of the circulatory homeostasis." This is accompanied by an increase in the excretion of free and conjugated NEP and EP.

Bloom, S. R., Daniel, P. M., Johnston, D. I., Ogawa, O., Pratt, O. E.: "Release of glucagon, induced by stress." *Q. J. Exp. Psychol.* **58**: 99-108 (1973). G99,793/73

In both conscious and lightly anesthetized (pentobarbital) rhesus monkeys startled by noise, plasma glucagon rose rapidly, followed by an elevation of blood glucose but not of plasma insulin. Similar effects were produced in anesthetized animals by rectal distention, drilling a burr hole in the skull, or the passage of an electric current through the head. "These experiments show that glucagon is rapidly released in response to various types of stress."

Morelli, G., Bellotti, C., Perrella, F.: "'Stress' vibratorio nell'uomo: aspetti etiopatogenetici e lavorativi" (Vibrational stress in man: etiopathogenetic and working aspects). *Nuovo Arch. Ital. Otol.* **1**: 94-101 (1973). J7,745/73

In workers occupationally exposed to vibrations, a rise in blood cortisol and urinary VMA indicates a strong stress response. Industrial noise has similar effects.

Favino, A., Maugeri, U., Kauchtschischvili, G., Robustelli Della Cuna, G., Nappi, G.: "Radioimmunoassay measurements of serum cortisol, thyroxine, growth hormone and luteinizing hormone with simultaneous electroencephalographic changes during continuous noise in man." *J. Nucl. Biol. Med.* **17**: 119-122 (1973). J8,286/73

Ortiz, G. A., Argüelles, A. E., Crespin, H. A., Sposari, G., Villafañe, C. T.: "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium." *Horm. Res.* **5**: 57-64 (1974). H81,167/74

In aircraft factory workers exposed to turbine noise for three hours, there was gener-

ally a marked elevation of catecholamine excretion, blood cholesterol levels, FFA values, blood pressure, and pulse frequency. Unexpectedly, the plasma corticoid concentrations were slightly subnormal but this may have been due to circadian variations.

Collu, R., Jéquier, J. C., Chabot, C., Letarte, J., Leboeuf, G., Ducharme, J. R.: "Pituitary response to auditory stress: effect of treatment with α -methyl-p-tyrosine (α -MT)." *Endocrinology* (In press).

J18,335/

In rats, auditory stress increases plasma corticosterone through catecholaminergic, and decreases plasma STH through noncatecholaminergic, pathways, as judged by the effect of pretreatment with α -MT.

→**Morphology.** Miline, R., Kochak, O.: "L'influence du bruit et des vibrations sur les glandes surrénales" (Effects of noise and vibration on the adrenal glands). *C.R. Assoc. Anat. (Paris)* **70**: 692-703 (1952).

B56,901/52

In guinea pigs and rabbits exposed to strong sounds and vibrations for twenty-four hours in a boiler-making factory, the adrenal changes were quite characteristic of the G.A.S.

Anthony, A., Ackerman, E.: "Effects of noise on the blood eosinophil levels and adrenals of mice." *J. Acoust. Soc. Am.* **27**: 1144-1149 (1955). E80,678/55

In C57 male mice, daily exposure to noise resulted in temporary eosinopenia after about three hours and later in adrenocortical hypertrophy. "No evidence was obtained of permanent compensatory adrenal hypertrophy, of thymicolympathic involution or other tissue injury. On the basis of this, it is concluded that the eosinophil and adrenal changes are manifestations of a normal physiological response to a sensory stimulus rather than a response to sound as a severe stressor agent." [The fact that mild stress is a physiologic state has not been considered (H.S.).]

Sackler, A. M., Weltman, A. S., Bradshaw, M., Jurtshuk, P. Jr.: "Endocrine changes due to auditory stress." *Acta Endocrinol. (Kbh.)* **31**: 405-418 (1959). C71,159/59

In rats, repeated exposure to strong auditory stimulation causes adrenal enlargement, ovarian atrophy and diminution in the weight of the uterus and liver. Food consumption is also markedly reduced.

Jurtshuk, P. Jr., Weltman, A. S., Sackler, A. M.: "Biochemical responses of rats to auditory stress." *Science* **129**: 1424-1425 C68,703/59 (1959).

In rats, prolonged intense auditory stimulation reduced the glutathione level of blood, simultaneously increasing the weight, ascorbic acid and cholesterol content of their adrenals.

Jensen, M. M., Rasmussen, A. F.: "Stress and susceptibility to viral infection. I. Response of adrenals, liver, thymus, spleen and peripheral leukocyte counts to sound stress." *J. Immunol.* **90**: 17 (1963). D54,097/63

In mice, three hours of exposure to high intensity sound induced adrenal hypertrophy. "Peripheral leukocyte counts responded biphasically to this stressor, exhibiting a leukopenia during and a leukocytosis following the stress period on each day. Leukopenia was not seen in stressed-adrenalectomized animals."

Croce, G.: "Lo 'stress' uditivo e le sue riverberazioni extralabirintiche" (Auditory stress and its labyrinthine rebound). *Valsalva* **40**: 381-384 (1964). J10,965/64

No definite changes were noted in the extraorbital lacrimal gland of the rat upon exposure to the stress of noise.

Fiori-Ratti, L., Croce, G., Simoncelli, C.: "Esperienze sullo stress sensoriale acustico. 1. Nota introduttiva. 2. La ghiandola paraparotide di Loewenthal del ratto" (Experiments on sensory acoustic stress. 1. Introductory note. 2. The paraparotid gland of Loewenthal in the rat). *Valsalva* **40**: 272-279; 280-291 (1964). G22,184/64

In rats, exposure to strong "acoustic stress" produces changes in the paraparotid gland of Loewenthal that are ascribed to stress [although they may be specific to sound (H.S.)], in addition to the characteristic signs of the G.A.S.

Croce, G., Simoncelli, C.: "Esperienze sullo 'stress' sensoriale acustico. Nota III. Le ghiandole sottomascellari di ratto nello 'stress' audiogeno" (Research on sensory acoustic stress. Note III. The submaxillary gland in rats after audiogenic stress). *Valsalva* **40**: 323-328 (1964). J10,966/64

In contradiction to earlier investigators who used other stressors, the authors were unable to produce any significant changes in the salivary glands of rats exposed to intense sound. [Under the conditions of this experi-

ment, other manifestations indicative of the G.A.S. were not reported (H.S.).]

Raab, W., Chaplin, J. P., Bajusz, E.: "Myocardial necroses produced in domesticated rats and in wild rats by sensory and emotional stresses." *Proc. Soc. Expt. Biol. Med.* **116**: 665-669 (1964). F17,034/64

"Wild rats exposed after periods of isolation to frightening noises (tape recording of hissing cat and squealing rat) displayed myocardial necroses in nearly 70% of the experiments."

Campus, S., Pandolfo, G., Accatino, G., Rappelli, A.: "Effetto degli stimoli psichici isolati sulla pressione arteriosa ed il peso corporeo di ratti Sprague-Dawley" (Effect of isolated mental stimuli on arterial pressure and body weight in Sprague-Dawley rats). *Boll. Soc. Ital. Biol. Sper.* **41**: 1087-1089 (1965). J22,723/65

Thiébaut, L., Berthelot, J., Blaise, S.: "Influence d'agressions systémiques sur l'évolution d'une réaction inflammatoire expérimentale. I. Effets d'un stress auditif" (Influence of systemic stresses on the development of an experimental inflammatory reaction. I. Effects of an auditory stress). *J. Physiol. (Paris)* **57**: 708-709 (1965). G57,900/65

Geber, W. F., Anderson, T. A., Dyne, B. van: "Physiologic responses of the albino rat to chronic noise stress." *Arch. Environ. Health* **12**: 751-754 (1966). G39,248/66

In rats, exposure to a variety of sounds (gongs, horns, loudspeakers, bells, vibrators) caused roughly parallel decreases in blood eosinophils and ascorbic acid concentrations in the adrenal and other tissues. On the other hand, chronic audiogenic stress led to a subsequent increase in adrenal weight and ascorbic acid concentrations as well as in serum cholesterol.

Reyna, L. J., DiMascio, A., Berezin, N.: "Psychological stress and experimental caries." *Psychosomatics* **8**: 138-140 (1967). F85,046/67

In rats, psychogenic stressors (electroshock, sound) can increase the incidence of dental caries.

Osintseva, V. P., Pushkina, N. N., Bonashevskaia, T. T., Kaverina, V. F.: "Noise-induced changes in the adrenal glands." *Gig. Sanit.* **34** No. 10: 119-122 (1969) (Russian). J15,752/69

Histologic studies on adrenal changes produced in rats by exposure to excessive noise.

Lipscomb, D. M.: "Indicators of environmental noise." In: Thomas, W. A., *Indicators of Environmental Quality*, pp. 211-241. New York: Plenum Press, 1972.

G99,061/72

General review on the stressor effects of sound with personal experiments on rats that developed a classic stress triad after exposure to broad-band continuous white noise of 110 decibels for forty-eight hours (136 refs.).

Siegel, M. I., Smookler, H. H.: "Fluctuating dental asymmetry and audiogenic stress." *Growth* 37: 35-39 (1973).

J8,473/73

Dental asymmetry has previously been ascribed to environmental stress. In this study pregnant rats were exposed to intermittent audiogenic stress. "The degree of fluctuating asymmetry of mandibular molar width and length was determined for stressed litters and shown to be significantly greater than for controls reared under normal laboratory conditions."

Geber, W. J.: "Inhibition of fetal osteogenesis by maternal noise stress." *Fed. Proc.* 32: 2101-2104 (1973).

H78,365/73

Bennett, T. E., Farwell, R. W., Anthony, A.: "Spiral ganglion RNA changes in rats exposed to acute noise stress" (abstracted). *Physiologist* 17: 179 (1974).

H89,871/74

→Metabolites. Anthony, A., Babcock, S.: "Effects of intense noise on adrenal and plasma cholesterol of mice." *Experientia* 14: 104-105 (1958).

D78,677/58

Under the experimental conditions reported here, exposure to five minutes of noise daily caused no adrenal hypertrophy, thymus involution or changes in serum and adrenal cholesterol in mice. Apparently, "homeostatic adjustment mechanisms of animals are not taxed to dangerous limits by intense sound stimulation." [The possibility that the exposure was too short is not considered (H.S.).]

Jurtshuk, P. Jr., Weltman, A. S., Sackler, A. M.: "Biochemical responses of rats to auditory stress." *Science* 129: 1424-1425 (1959).

C68,703/59

In rats, prolonged intense auditory stimulation reduced the glutathione level of the blood, simultaneously increasing the weight, ascorbic acid and cholesterol content of their adrenals.

Gregorczyk, J., Lewandowska-Tokarz, A., Stanosek, J., Hepa, J.: "The effects of physi-

cal work and work under conditions of noise and vibration on the human body. I. Behavior of serum alkaline phosphatase, aldolase and lactic dehydrogenase activities." *Acta Physiol. Pol.* 16: 701-708 (1965) (Polish).

F59,655/65

In men working in an industrial establishment where they were exposed to considerable noise and vibration, increases in serum aldolase and lactic dehydrogenase were interpreted as manifestations of the stress syndrome. "It was assumed that the aforementioned stress factors produce changes in the sugar metabolism of the body."

Jonek, J., Stanosek, J., Krauze, M., Waclawczyk, H.: "Histochemische Untersuchungen über das Verhalten einiger Enzyme in Nebennieren bei Meerschweinchen nach chronischer Lärmeinwirkung" (Histochemical examinations of various enzymes in the adrenals of guinea pigs after chronic exposure to noise). *Z. Mikrosk. Anat. Forsch.* 73: 174-186 (1965).

G38,514/65

In guinea pigs, chronic exposure to noise (kind not clearly described) produced characteristic histochemical changes in various enzyme activities which gradually tended to disappear; the changes were ascribed to the alarm and resistance stages of the G.A.S.

Józkiewicz, S., Puchalik, M., Cygan, Z., Dróżdż, M., Gregorczyk, J., Grzesik, J., Krzoska, K., Lewandowska-Tokarz, A., Stanosek, J., Źak, T.: "Studies on the effect of acoustic and ultrasonic fields on biochemical processes. IX. Effect on some blood components in workingmen under noisy conditions." *Acta Physiol. Pol.* 16: 727-737 (1965) (Polish).

F59,658/65

Bost, J., Dorleac, E.: "Influence de trois types de stimulation sonore sur le taux plasmatique des acides gras non estérifiés (FFA) chez le Mouton" (Effects of three types of auditory stimulation on plasma levels of non-esterified fatty acids in lambs). *C.R. Soc. Biol. (Paris)* 160: 2340-2343 (1966).

F80,786/66

In lambs, various types of auditory stimulation greatly increased plasma FFA, although adaptation occurred eventually.

Friedman, M., Byers, S. O., Brown, A. E.: "Plasma lipid responses of rats and rabbits to an auditory stimulus." *Am. J. Physiol.* 212: 1174-1178 (1967).

F83,722/67

"Rats exposed to a continuous sound stimulus having an intensity of 102 db and an intermittent sound stimulus (200-cycle

square wave with a duration of about 1 sec and having an intensity of 114 db) exhibited marked elevation and prolongation of clearing of postprandial plasma *triglyceride* for a period of approximately 21 days.... Cholesterol-fed rabbits exposed to similar sound stimulus for 10 weeks exhibited a higher blood *cholesterol* and more intense atherosclerosis than similarly fed control animals."

Croce, G., Frenguelli, A., Campora, E. de: "Esperienze sullo 'stress' sensoriale acustico. V. Il comportamento del sodio e del potassio nella ghiandola sottomascellare di ratto nello 'stress' audiogeno" (Experiments with acoustic sensory stress. V. Behavior of sodium and potassium in the rat submandibular gland in audiogenic stress). *Boll. Mal. Orecch.* **87**: 300-306 (1969). G74,773/69

The marked changes in salivary *potassium* and *sodium* in the submandibular glands of rats exposed to the stressor effect of sound indicate that the salivary glands are important "organs of stress."

Ortiz, G. A., Argüelles, A. E., Cresco, H. A., Sposari, G., Villaflaño, C. T.: "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium." *Horm. Res.* **5**: 57-64 (1974). H81,167/74

In aircraft factory workers exposed to turbine noise for three hours, there was generally a marked elevation of catecholamine excretion, blood *cholesterol* levels, *FFA* values, blood pressure, and pulse frequency. Unexpectedly, the plasma corticoid concentrations were slightly subnormal but this may have been due to circadian variations.

→**Nervous System.** Korobow, N.: "Reactions to stress: a reflection of personality trait organization." *J. Abnorm. Soc. Psychol.* **51**: 464-468 (1955). J13,194/55

When speech is tape-recorded for immediate reproduction after a short time-lag, the subject, upon hearing his recorded speech while still talking, experiences "audiogenic stress" (AS) which leads to a breakdown in speech organization. The speech becomes halting with variations in speed, volume and integration, occasional repetition of words and phrases and addition of superfluous words. "Speech errors made under stress were analyzed to establish the degree of relationship with perception of the stress and personality traits."

Jerison, H. J.: "Effects of noise on human

performance." *J. Appl. Psychol.* **43**: 96-101 (1959). D54,809/59

Changes of performance in various environments "are discussed in terms of noise as a source of psychological stress."

Broadbent, D. E.: "The effects of noise on behaviour." In: Harris, C. M., *Handbook of Noise Control*. New York: McGraw-Hill. 1957. J12,863/57

Anthony, A., Marks, B.: "Noise induced convulsions in mice." *Experientia* **15**: 320-321 (1959). E80,668/59

Certain strains of mice are considered to be "seizure-resistant," but actually, among mongrel mice of the Swiss albino type, very intense noise with low frequency caused convulsions in virtually all individuals.

Nitschkoff, S., Kriwitzkaja, G. N., Gnüchtel, Ü.: "Über neurovegetative Schäden und histomorphologische Veränderungen im Gehirn der Ratte bei Einwirkung akustischer Reize" (Neurovegetative disturbances and histomorphologic changes in the rat brain after acoustic stress). *Acta Biol. Med. Ger.* **19**: 33-45 (1967). F88,672/67

Angeleri, F., Faleg, G., Granati, A., Lenzi, R.: "Aspects expérimentaux des effets du bruit sur le système nerveux central" (Experimental aspects of the effects of noise on the central nervous system). *Acta Otorhinolaryngol. Belg.* **25**: 221-232 (1971). J18,252/71

Pelnar, P. V.: "L'influence des aspects physico-chimiques du lieu de travail sur l'équilibre mental du travailleur" (The influence of the physical and chemical aspects of place of employment upon the mental equilibrium of the worker). *Un. Méd. Can.* **100**: 1985-1989 (1971). H46,885/71

Tokarenko, I. I.: "Nervous mechanisms of acoustic stress-reaction." *Fiziol. Zh.* **18**: 529-534 (1972) (40 refs., Ukrainian). J19,874/72

Harcum, E. R., Monti, P. M.: "Cognitions and 'placebos' in behavioral research on ambient noise." *Percept. Mot. Skills* **37**: 75-99 (1973). J17,475/73

Busnel, R. G., Lehmann, A.: "Effets synergiques de stimulations acoustiques et d'une situation 'stressante' sur des comportements globaux objectivables" (Synergistic effects of acoustic stimulation and of a "stressful" situation on total objectively-verifiable be-

havior). *C.R. Acad. Sci. (Paris)* **279**: 583-585 (1974). J17,619/74

Frankenhaeuser, M., Lundberg, U.: "Immediate and delayed effects of noise on performance and arousal." *Biol. Psychol.* **2**: 127-133 (1974). J19,036/74

Hartley, L. R., Adams, R. G.: "Effect of noise on the Stroop test." *J. Exp. Psychol.* **102**: 62-66 (1974). J17,211/74

In the Stroop color interference test, "color names written in inks of different hues, excluding ink of the hue the name indicates, are presented to Ss who are required to name the hue of the ink and not the color name." Brief exposure to noise is beneficial, whereas prolonged exposure to intense noise damages performance, in that elimination of the irrelevant interfering feature (color name) is more difficult during stress.

Brierley, H., Jamieson, R.: "Anomalous stress reactions in patients suffering from depression and anxiety." *J. Neurol. Neurosurg. Psychiatry* **37**: 455-462 (1974).

J13,469/74

The forearm muscle blood flow changes caused by the stressor effect of noise revealed that "depressive patients show something akin to a freeze response to stress, while patients with anxiety states show an arousal response."

→Varia. Medoff, H. S., Bongiovanni, A. M.: "Blood pressure in rats subjected to audiogenic stimulation." *Am. J. Physiol.* **143**: 300-305 (1945). 91,713/45

In old rats, unlike in young ones, daily audiogenic stimulation produces *hypertension*. The authors "believe this to be objective evidence for neurogenic influences in the etiology of hypertension."

McCann, S. M., Rothballer, A. B., Yeakel, E. H., Shenkin, H. A.: "Adrenalectomy and blood pressure of rats subjected to auditory stimulation." *Am. J. Physiol.* **155**: 128-131 (1948). A51,784/48

In rats, prolonged auditory stimulation produced *hypertension* that was favorably influenced by adrenalectomy. "It is suggested that the adrenal cortex mediated the elevation of blood pressure occurring during prolonged auditory stimulation."

Zondek, B., Tamari, I.: "Effect of audiogenic stimulation on genital function and reproduction." *Am. J. Obstet. Gynecol.* **80**: 1041-1048 (1960). D4,871/60

"Exposure to stimulation of the auditory organs in mature rats stimulates the anterior pituitary gonadotropic function, manifested by prolonged or persistent estrus, enlargement of the ovaries, and increase of the corpora lutea in number and size." In rabbits, enlargement of the ovaries and follicle hematomas with corpus luteum formation and sometimes galactorrhea are noted. The stimulating effect of auditory stimuli on female *genital function* is in contrast to the inhibitory action on fertility. The stressor effect of sound can also interrupt pregnancy.

Shatalov, N. N., Saitanov, A. O., Glotova, K. V.: "On the state of the cardiovascular system under conditions of exposure to continuous noise." *Gig. Tr. Prof. Zabol.* **6**: 10-14 (1962). J6,200/62

"In persons exposed to the effect of continuous industrial medium-frequency and high-frequency noise of intensity 85 to 120 db, functional disturbances of the *cardiovascular* system were frequently observed. Very often the subjects exhibited an instability of the arterial blood pressure. The electrocardiographic data showed bradycardia with a tendency to retardation of the intravesicular conductivity, plus a depression of the T-wave that was most frequently observed after physical stress and at the end of the work-period."

Rosecrans, J. A., Watzman, N., Buckley, J. P.: "The production of hypertension in male albino rats subjected to experimental stress." *Biochem. Pharmacol.* **15**: 1707-1718 (1966). G42,049/66

In rats subjected to "a chronic variable stress program consisting of flashing lights, audiogenic stimulation, and oscillation" *hypertension* developed after several months. This was associated with an increase in catecholamine excretion which disappeared after several weeks, and a rise in plasma corticosterone which tended to persist. "These results suggest that the adrenal glands had become more efficient in the rate of synthesis and release of steroids after chronic exposure to the stressors."

Ter-Markarian, N. G.: "Participation of adrenal glands and adrenocorticotrophic hormone of the hypophysis in changes of the phagocytic activity of blood leukocytes of rats in the action of a strong sound stimulus." *Probl. Endokrinol. Gormonoter.* **12** No. 5: 81-84 (1966) (Russian). F72,472/66

In rats, convulsive attacks induced by a

strong sound ("bell epilepsy") increased *phagocytosis* by leukocytes. In the absence of convulsions the same sound caused an opposite result in the rats. The effect of adrenalectomy and ACTH upon this phenomenon is also discussed. [The published results are difficult to evaluate (H.S.).]

Singh, K. B., Rao, P. S.: "Studies on the polycystic ovaries of rats under continuous auditory stress." *Am. J. Obstet. Gynecol.* **108**: 557-564 (1970). G78,701/70

In rats, continuous auditory stress can produce polycystic ovaries with inhibition of corpus luteum formation, thereby interfering with *reproduction*.

Jatho, K., Hellmann, H.: "Zur Frage des Lärm- und Klangtraumas des Orchester-musikers" (The problem of acoustic trauma in orchestra musicians). *H.N.O. (Berlin)* **20**: 21-29 (1972). J17,046/72

Effect of audiogenic stress upon professional musicians.

Byshevsky, A. S., Babich, V. P., Danilchenko, E. V.: "The mechanism of increase of blood coagulation at the early periods following sonic action." *Patol. Fiziol. Eksp. Ter.* **16** No. 6: 73-74 (1972) (Russian).

H79,323/72

In rats, exposure to intense sound decreased *antithrombin* activity within five minutes and thromboplastin activity much later and to a lesser extent. Activation of antithromboplastin was also of short duration.

Singh, K. B.: "Effects of sound on the female reproductive system." *Am. J. Obstet. Gynecol.* **112**: 981-991 (1972).

G89,061/72

Review on the effect of prolonged and intense sound upon the female *reproductive system* of various mammals. In accordance with the "hypophyseal-shift" theory, this stressor tends to diminish fertility through decreased gonadotropin production, resulting in ovarian atrophy. Pregnancy may also be disturbed.

Maass, B., Jacobi, E., Esser, G.: "Thrombozytenadhäsivität unter Lärmeinwirkung" (Thrombocyte adhesiveness during noise). *Dtsch. Med. Wochenschr.* **98**, 2153-2155 (1973). H78,870/73

Various forms of auditory stress increase *thrombocyte adhesiveness* and may thereby predispose to thrombosis in man (27 refs.).

Bell, R. W., Nitschke, W., Bell, N. J., Zachman, T. A.: "Early experience, ultra-

sonic vocalizations, and maternal responsiveness in rats." *Dev. Psychobiol.* **7**: 235-242 (1974).

J12,730/74

Exposure to cold and several other stressors induces ultrasonic *vocalization* in neonatal rats and consequent agitation in their mothers. "If the pup is mildly stressed he displays a pattern of ultrasonic signaling which elicits adaptive maternal responsiveness. If the pup is too severely stressed he displays persistent signaling which agitates the mother, preventing an adaptive pattern of behavior, and resulting in a prolonged response to stress in the pup."

+Genetics. Bevan, W.: "Sound-precipitated convulsions: 1947 to 1954." *Psychol. Bull.* **52**: 473-504 (1955). D78,855/55

Review on genetic and stress factors causing audiogenic convulsions. It is deplored that "despite general preference for a physiological model, nothing has been done to assay systematically physiological differences among susceptible and nonsusceptible animals. Although electroshock convulsions have been discussed within the framework of Selye's adaptation syndrome hypothesis, and although audiogenic seizures have been regarded as a stress phenomenon by both physiologically and psychologically biased investigators, no vigorous attempt to exploit Selye's logic has been made for the latter phenomenon" (145 refs.).

Anthony, A.: "Effects of noise on eosinophil levels of audiogenic-seizure-susceptible and seizure-resistant mice." *J. Acoust. Soc. Am.* **27**: 1150-1153 (1955). E80,679/55

"A prolonged eosinopenia occurs with several successive noise bursts—at a moderately low level (*ca* 250 eosinophils/cu mm blood) in seizure-resistant mice and at lower levels (*ca* 100 eosinophils/cu mm blood) in mice which experience convulsions during treatment. It was concluded that noise stimulation acts as a mild stress stimulus and is harmful only when it results in the production of fatal convulsions."

Anthony, A.: "Changes in adrenals and other organs following exposure of hairless mice to intense sound." *J. Acoust. Soc. Am.* **28**: 270-274 (1956). E82,034/56

On the basis of observations in hairless mice, it was concluded that both immobilization and intense sound vibrations on the skin surface can act as stressors. When the sound is very intense, the systemic response is similar to that seen after skin burns. Here, heat

and not sound is considered to be the responsible stressor.

Weltman, A. S., Sackler, A. M.: "Timidity and metabolic elimination patterns in audiogenic-seizure susceptible and resistant female rats." *Experientia* **22**: 627-629 (1966).

G16,051/66

There is a positive relationship between timidity and seizure susceptibility in rats exposed to "auditory stress." The rats also demonstrate an increase in diuresis and the quantity of feces.

Weltman, A. S., Sackler, A. M., Owens, H.: "Effects of levels of audiogenic-seizure susceptibility on endocrine function of rats." *Physiol. Behav.* **3**: 281-284 (1968).

H5,154/68

Rats susceptible to audiogenic seizures developed adrenal hypertrophy and thymus involution upon exposure to the stressor effect of an alarm bell.

Roth, T., Kramer, M., Trinder, J.: "The effect of noise during sleep on the sleep patterns of different age groups." *Can. Psychiatr. Assoc. J.* **17**: SS197-SS201 (1972).

H79,724/72

EEG, electromyographic and electrooculographic recordings indicate that noise of moderate intensity has little effect upon the sleep patterns of twenty-five-year-old subjects but causes increasingly more disturbance with progressing age.

Poirel, C., Bouten, F., Hengartner, O.: "Analyse chronobiologique des rythmes circadiens de la crise audiogène chez la souris Swiss/Albinos (Rb)" (Chronobiologic analysis of the circadian rhythms of audiogenic seizure in the Swiss/Albinos [Rb] mouse). *Ann. ACFAS* **40**: 128 (1973).

H87,899/73

In mice genetically predisposed to audiogenic seizures, the mathematical relationship of the seizures to the circadian rhythm has been analyzed.

Hallbäck, M., Folkow, B.: "Cardiovascular responses to acute mental 'stress' in spontaneously hypertensive rats." *Acta Physiol. Scand.* **90**: 684-698 (1974).

J13,405/74

Genetically hypertensive rats showed more pronounced cardiovascular responses to the stressor effect of sound than normotensive controls or renal hypertensive rats of a normal strain. Hence, the hyperreactivity is genetically conditioned.

Redgate, E. S.: "Neural control of pituitary adrenal activity in cyprinus carpio." *Gen. Comp. Endocrinol.* **22**: 35-41 (1974).

H81,914/74

"The prompt responses of plasma cortisol concentration to stimuli, such as sound, hypothalamic stimulation, the photoperiod, and restraint, indicate that the pituitary adrenal system of the carp is controlled by neural pathways in the brain of this teleost."

+Varia. Lazovik, A. D., Patton, R. A.: "The relative effectiveness of auditory stimulation and *motivational stress* in precipitating convulsions associated with magnesium deficiency." *J. Comp. Physiol. Psychol.* **40**: 191-202 (1947).

B26,573/47

Józkiewicz, S., Stanosek, J., Gregorczyk, J., Krzoska, K., Lewandowska-Tokarz, A.: "Über den Einfluss der chronischen Einwirkung von Lärm und Vibrationen niedriger Frequenzen auf die Zusammensetzung des Blutes, das relative Gewicht einiger Organe sowie den Gehalt der Askorbinsäure in den Nebennieren bei Meerschweinchen" (The influence of the chronic effects of noise and low frequency vibrations on the blood composition and the relative weight of several organs, as well as the ascorbic acid content of the adrenals in the guinea pig). *Acta Biol. Med. Ger.* **13**: 331-335 (1964).

F25,307/64

In guinea pigs, noise and *vibration* caused adrenal ascorbic acid depletion, especially when applied in combination. The change is ascribed to the G.A.S.

Anderson, T. A., Geber, W. F.: "Combined effects of chronic audio-visual stress and thiouracil administration on the cholesterol-fed rat." *J. Cell. Comp. Physiol.* **66**: 141-146 (1965).

G35,191/65

In rats, audiovisual stress can be produced by various bells, buzzers and white noise generators in addition to interrupted intense *illumination*. This may influence the atherogenic effect of thiouracil and high cholesterol diets.

Constanta, A., Contulesco, A., Ionesco, G., Miclesco-Groholsky, S.: "Recherches sur l'activité des transaminases et de la phosphatase acide dans l'agression sonore et vibratoire industrielle" (The activity of transaminases and acid phosphatase in the stress of industrial noise and vibration). *Arch. Mal. Prof.* **32**: 647-652 (1971).

G98,066/71

An increase in serum phosphatase and transaminase occurred in workers of a metal-

lurgical plant exposed to considerable noise and vibration. This increase is claimed to be characteristic of stress.

Sommer, H. C., Harris, C. S.: "Combined effects of noise and vibration on mental performance as a function of time of day." *Aerospace Med.* **43**: 479-482 (1972).

J16,970/72

Bergamaschi, M., Caravaggi, A. M., Mandelli, V., Shanks, R. G.: "The role of beta adrenoceptors in the coronary and systemic hemodynamic responses to emotional stress in conscious dogs." *Am. Heart J.* **86**: 216-226 (1973). H72,433/73

In dogs, "emotional stress produced by firing a gun increased heart rate, cardiac output, and left ventricular work." The responses were reduced by propranolol and practolol, and abolished by alprenolol.

Hadjiolova, I.: "Veränderungen des Plasma- und Nebennierenrindencorticosterons bei Ratten während Hypokinesie und zusätzlicher Stress-Einwirkungen" (Influence of hypokinesia and subsequent stress upon the rat plasma and adrenal corticosterone level). *Int. Arch. Arbeitsmed.* **33**: 59-70 (1974). J17,473/74

Studies on plasma and adrenal corticosterone in rats exposed to different stressors

(heat, restraint, noise) alone or in combination. "A moderate increase in the levels of both plasma and adrenal corticosterone was observed after 24 hrs of hypokinesia. In a subsequent period of 60 days the corticosterone levels did not differ significantly from the levels found in the control animals. However, a marked decrease in adrenal weight and a slighter response to additional thermal stress were demonstrated after 60 days of hypokinesia. Differences between the restrained and the control animals were also found in the adaptation to chronic auditory stress."

Poulton, E. C., Edwards, R. S.: "Interactions and range effects in experiments on pairs of stresses: mild heat and low-frequency noise." *J. Exp. Psychol.* **102**: 621-628 (1974). J17,212/74

Review of the literature on the interaction between the stressor effects of heat and noise in man.

Wells, A., Jones, A., Williams, M., Geist, C. R.: "Noise, vitamin A deficiency, and emotional behavior in rats." *Percept. Mot. Skills* **38**: 392-394 (1974). J17,474/74

In rats, aversive stimulation (noise) appears to have a greater effect during food deprivation or vitamin A deficiency than otherwise.

Ultrasound, Sonic Booms

(See also Aerospace in the section on Occupations)

In guinea pigs exposed to ultrasound, morphologic changes typical of the G.A.S. develop quite readily.

In people exposed to repeated simulated sonic booms, stress manifestations have been surprisingly inconspicuous under the experimental conditions employed up to now.

Occasional exposure to sonic booms had no remarkable effect upon either the reproduction of minks or the ability of chicken eggs to be hatched.

Ultrasound, Sonic Booms

(See also our earlier stress monographs, p. xiii)

Introna, F.: "Ricerche sperimentali sulla patologia da ultrasuoni" (Experimental research on the pathology of ultrasound). *Med.-Leg. Assicur.* **1**: 13-42 (1953).

C4,806/53

In guinea pigs exposed to ultrasound, morphologic changes occur in various tissues, and particularly in mesenchymal tissue, similar to those "described by Selye in the condition of stress." In view of the occupational

exposure of various people to ultrasound, these findings have legal as well as medical significance.

Debijadji, R., Perovic, L., Varagic, V.: "Evaluation of the sympatho-adrenals activity in pilots by determination of urinary catecholamines during supersonic flight." *Aerosp. Med.* **41**: 677-679 (1970).

J21,924/70

Observations on supersonic pilots "indicate that stress reactions to flight conform to the General Adaptation Syndrome pattern."

Filcescu, V.: "Aspecte de fiziologie și fizioterapie ale zborului supersonic" (Aspects of physiology and physiopathology of supersonic flight). *Fiziol. Norm. și Pat.* **17**: 143-150 (1971) (Roumanian). J20,646/71

Thackray, R. I., Touchstone, R. M., Jones, K. N.: *The Effects of Simulated Sonic Booms on Tracking Performance and Autonomic Responses*, p. 15. Washington, D.C.: Federal Aviation Administration pamphlet, 1971. G85,874/71

In subjects exposed to four simulated indoor sonic booms over approximately thirty minutes, no evidence of performance impairment was found in two-dimensional compensatory tracking tasks. "Rather, performance improved significantly following boom stimulation along with heart-rate deceleration and skin conductance increase. The obtained pattern suggests that the simulated booms may have elicited more of an orienting or alerting response than a startle reflex."

Smith, R. C., Hutto, G. L.: *Sonic Booms and Sleep: Affect Change as a Function of Age*, p. 11. Washington, D.C.: Federal

Aviation Administration pamphlet, 1972.

G98,578/72

Subjects aged twenty-one to seventy-two years spent twenty-one consecutive nights in a sleeping room where they were exposed hourly to simulated sonic booms of moderate intensity. The noise had no significant effect as judged by answers to a composite mood adjective questionnaire.

Collins, W. E., Iampietro, P. F.: *Simulated Sonic Booms and Sleep: Effects of Repeated Booms of 1.0 PSF*, p. 27. Washington, D.C.: Federal Aviation Administration pamphlet, 1972. J4,892/72

Males aged twenty-one to seventy-two years were exposed hourly to simulated sonic booms during 21 consecutive nights. As judged by various physiologic indicators (EEG, muscle tone, REM sleep) "the changes in sleep appear roughly comparable to what might occur in response to the noise of a passing truck at 40-45 dBA" (32 refs.).

Thackray, R. I., Touchstone, R. M., Bailey, J. P.: "Behavioral, autonomic, and subjective reactions to low- and moderate-level simulated sonic booms: a report of two experiments and a general evaluation of sonic boom startle effects." Federal Aviation Administration, Aviation Med. pamphlet, pp. 1-14. Washington, D.C., 1974. J19,035/74

Brewer, W. E.: "Effects of noise pollution on animal behavior." *Clin. Toxicol.* **7**: 179-189 (1974). J13,847/74

Under the conditions of these experiments, occasional exposure to sonic booms had no severe effect upon either reproduction in minks or the ability of chicken eggs to be hatched.

Ionizing Rays

Observations on various species suggest that the radiation syndrome is very similar to the alarm reaction of the G.A.S. However, the thymic lymphatic involution is particularly pronounced, and the characteristic symptoms of x-ray injury (especially the bone marrow damage) are much more prominent than those resulting from exposure to other stressors. In view of the severe malfunctioning of the hemopoietic apparatus, the typical stress-induced polymorphonuclear leukocytosis is not only lacking but is replaced by leukopenia.

A very characteristic effect of x-irradiation is a phenomenon strikingly similar to premature aging. This model has been successfully used for many studies on the mechanism of aging, although it is still debatable whether the manifestations of x-irradiation are strictly comparable to those of natural aging.

+Varia. The effect of ionizing rays upon the action of various other agents has been the subject of innumerable studies, especially in relation to aerospace medicine, where cosmic radiation in space is always a danger and may affect hypoxia, changes in gravity, and other factors that confront the astronaut. The voluminous literature on the effect of exposure to cold or artificial hibernation upon x-ray resistance is quite contradictory and virtually impossible to evaluate.

"Electroshock stress" before x-irradiation does not significantly affect the survival of rats, but if applied afterwards, actually decreases resistance to this as well as to other stressors.

The adrenocortical changes of the alarm reaction produced by infection with *Salmonella*, and those of x-irradiation, are additive if the two stressors are applied concurrently. However, it has also been claimed that under certain conditions stressors can increase x-ray resistance.

Ionizing Rays

(See also our earlier stress monographs, p. xiii)

Generalities. Dougherty, T. F., White, A.: "Pituitary-adrenal cortical control of lymphocyte structure and function as revealed by experimental X-radiation." *Endocrinology* **39**: 370-385 (1946).

95,612/46

"CBA mice, 60 to 80 days old, received total body X-radiation. A large dose of X-rays, 200 r, produced within 3 hours a lymphopenia, tissue lymphocyte degeneration, and total serum protein and gamma globulin increases. These changes also occurred in 1 day postoperative adrenalectomized mice receiving 200 r. This dose gave an anamnestic response in previously immunized mice in the absence of the adrenals." Smaller x-ray doses were effective in intact but not in adrenalectomized mice, presumably because the action is partially mediated through the pituitary-adrenal axis.

Kohn, H. I.: "Changes in blood plasma of guinea-pig during acute radiation syndrome." *Am. J. Physiol.* **162**: 703-708 (1950).

B49,916/50

Observations on guinea pigs suggest that the radiation syndrome is similar to the alarm reaction of the G.A.S., yet certain differences show that the two conditions are not identical.

Mole, R. H.: "Whole body irradiation and the idea of stress." *Br. J. Exp. Pathol.* **37**: 528-531 (1956).

C26,307/56

Summary of personal observations and published data suggesting that certain

phenomena that were formerly thought to be due to nonspecific stress are "physiological consequences of cell death, a specific effect of irradiation . . . as soon as mechanisms are investigated in detail it would appear that the nonspecific response is really the sum of specific responses. Somatic stress is compounded of specific responses to starvation, dehydration, cell death and so on, just as shock is compounded of specific responses to blood and fluid loss, infection, pain and psychic disturbance. Some of these specific responses may share final common paths, and one of these may be adrenal activity, but when the specific responses are abstracted there may be nothing left of a general syndrome which needs explanation in nonspecific terms."

Gorizontov, P. D., Grafov, A. A., Shakhodyrov, V. V.: "The question of the role of the pituitary-adrenal system in the development of some manifestations in experimental radiation disease." *Vestn. Akad. Med. Nauk SSSR* **13**: 12-21 (1958) (Russian).

D2,825/58

Extensive review on ionizing radiation as a stressor agent.

Scholz, H.: "Die Behandlung des Bestrahlungssyndrom mit Prednisolon" (Treatment of the radiation syndrome with prednisolone). *Zentralbl. Gynäk.* **81**: 1065-1075 (1959).

C78,296/59

Review of the literature and personal observations suggest that the radiation syndrome is essentially related to the G.A.S. and associated with adrenocortical deficiency. Prednisolone allegedly exerts a therapeutic

effect both on the generalized radiation syndrome and on local x-ray damage.

Fridrich, R.: "Beitrag zur zentral-nervösen Beeinflussung des Strahlensyndroms" (Contribution on central nervous system mediation in the radiation syndrome). *Radiol. Clin. Biol.* **34**: 78-82 (1965). J23,648/65

Pospíšil, M., Šikulová, J.: "Individual differences in the radiation mortality of mice as predicted from the pre-irradiation stress responses." *Int. J. Radiat. Biol.* **9**: 597-600 (1965). J23,230/65

Bertók, L., Kocsár, L. T.: "Die Rolle des Endotoxins beim intestinalen Syndrom der Strahlenkrankheit" (The role of endotoxins in the intestinal syndrome of radiation disease). *Wiss. Z. Karl-Marx Univ. Leipzig, Math.-Naturwiss. R.* **23**: 65-66 (1974). J15,372/74

In rats sensitized with lead acetate, minute doses of bacterial endotoxin sufficed to cause death. With this technique it could be demonstrated that after x-irradiation endotoxin is absorbed into the blood. Hence, endotoxemia probably plays an important role in the irradiation syndrome.

→Varia. Berliner, D. L., Stevens, W., Berliner, M. L.: "The effects of ionizing radiation on the biosynthesis and biotransformation of corticosteroids." *Proc. Int. Symp. Effects Ionizing Radiat. Reprod. Syst., Colorado 1962*, pp. 433-449 (1963). G11,813/63

X-radiation increases blood *corticoids*, as do other stressors. The literature on this subject, and particularly on the effect of ionizing rays upon the biosynthesis and metabolism of corticoids, is reviewed (55 refs.).

Tobias, P. R.: "The effects of radiation on integrated behavior." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 395-417. Glencoe, Ill.: Free Press, 1963. E10,434/63

Review on the effects of various intensities of x-irradiation upon the *behavior* of animals and men, with special reference to aerospace medicine.

Parin, V. V., Antipov, V. V., Raushenbakh, M. O., Saksonov, P. P., Shashkov, V. S., Chernov, G. A.: "Changes in blood serotonin level in animals exposed to ionizing radiation and dynamic factors of space flight." *Fed. Proc.* **25**: T103-T106 (1966). F60,935/66

In various species of animals traveling on

satellite spaceships, exposure to x-rays, acceleration and vibration considerably diminished the blood 5-HT content.

Lucas, D. R., Peakman, E. M.: "Ultrastructural changes in lymphocytes in lymph nodes, spleen and thymus after sublethal and supralethal doses of X-rays." *J. Pathol.* **99**: 163-169 (1969). G72,305/69

The EM changes induced by ionizing irradiation in the *lymphocytes* of various lymphatic organs are described and well illustrated.

Polis, B. D., Polis, E., DeCani, J., Schwarz, H. P., Dreisbach, L.: "Effect of physical and psychic stress on phosphatidyl glycerol and related phospholipids." *Biochem. Med.* **2**: 286-312 (1969). G65,013/69

In rats exposed to ionizing radiation or "acceleration stress," the plasma concentration of *phosphatidylglycerol* was consistently increased. "Extension of the studies to humans stressed by acceleration to grayout, sleep deprivation, schizophrenia, combat, etc., revealed that all stresses were accompanied by significant increments in plasma phosphatidyl glycerol." In rats, hypophsectomy prevented the increase in phosphatidylglycerol induced by acceleration stress, but a rise in the brain level of this compound remained even in the absence of the pituitary.

Lundin, P., Järplid, B.: "Effects of corticosteroid and radiation on lymphoid tissue in mice. Comparisons and mutual interactions." *Lymphology* **6**: 158-166 (1973).

J7,450/73

In mice, similar degrees of *thymus involution* were produced by x-rays and prednisolone. "After steroid treatment the lymphocytolysis in the lymph nodes, spleen and the Peyer's patches was most marked in the germinal centres whereas the so-called thymic dependent areas were mainly preserved. After irradiation compared to steroid-treatment the cytology was definitely more pronounced in all parts of these lymphoid tissues, including the white pulp of the spleen, the whole follicles and the subcapsular parts of the lymph node cortex and the follicles and partially the interfollicular areas of the Peyer's patches. From the time of the first regeneration of the thymic cortex after irradiation, steroid sensitive cells could be found in all lymphoid tissues, indicating that the pool of these cells regenerates rapidly after irradiation." These changes are related

to the classic lymphocytolysis and thymic involution of the alarm reaction.

Lancranjan, I., Popescu, H. I.: "The eliminations of 17 hydroxycorticosteroids and total neutral 17-ketosteroids in subjects long-term occupationally exposed to ionizing radiations." *Health Phys.* **26**: 575-577 (1974) (15 refs.). J13,621/74

Kobayashi, S.: "Role of histamine and corticosterone on the depletion of tissue histamine in the irradiated rats." *Proc. Soc. Exp. Biol. Med.* **146**: 25-29 (1974). H87,165/74

+Varia. Taylor, J. W.: *X-irradiation and Acceleration Stress*. Aviation Medicine Acceleration Lab. Report No. NADC-MA-6003 (1960). J11,875/60

Newton, G., Heimstra, N.: "Effects of early experience on the response to whole-body X-irradiation." *Can. J. Psychol.* **14**: 111-120 (1960). D84,835/60

Weanling rats which have been previously handled lose less weight following x-irradiation than do controls.

Kinsell, L. W.: "Physiologic aging and radiologic life-shortening." *Fed. Proc.* **20**: 14-21 (1961). D12,597/61

Critical review of the literature on the induction of artificial aging by ionizing radiations and its relation to natural aging. "There would appear to be no question that radiation, in common with many other physical agents, if used in sufficient amount, can produce in any cell, tissue, or organ a state in which catabolism goes on at a greater rate than anabolism." It remains to be seen, however, whether such changes are comparable to physiologic aging. "The stress of a life in which the threat of sudden death is ever present must certainly influence the aging process" (99 refs.).

Forssberg, A., Tribukait, B., Vikterlöf, K.-J.: "Early blood leucocyte changes in mice and guinea pigs following X-irradiation and stress caused by operative manipulations." *Acta Physiol. Scand.* **52**: 1-7 (1961). D7,253/61

Hall, C. E., Schneider, M., Hall, O.: "Increased sensitivity to X-irradiation exhibited by stressed rats." *Radiat. Res.* **17**: 118-126 (1962). D30,291/62

"Electroshock stress" applied before x-irradiation does not affect the survival rate of rats but decreases the survival rate if

applied afterwards. The same is true of the stress of being shipped to the laboratory.

Gambino, J. J., Bennett, L. R., Billings, M. S., Lamson, B. G.: "Biological effect of stress following ionizing radiation." *Aerosp. Med.* **35**: 220-224 (1964). G9,697/64

Review of the literature on the effect of hypothermia upon x-ray resistance. Rats given a single dose of 500 rads (total body irradiation) showed "reduced longevity; retarded growth; cataracts; accelerated onset of skin ulcers, greying, enlarged mammary glands and palpable tumors; and increased incidence of palpable tumors." Repeated exposure to brief periods of cold did not significantly influence these changes, with the possible exception of tumorigenesis (41 refs.).

Musacchia, X. J., Barr, R. E.: "Helium-cold induced hypothermia in the hamster and radio-resistance." *Physiologist* **10**: 257 (1967). F86,700/67

In hamsters rendered hypothermic by being placed in an 80 percent helium-20 percent oxygen atmosphere at low temperatures, resistance to cobalt irradiation is increased.

Reinhardt, K.: "Bestrahlung, insbesondere Lokal- und fraktionierte Bestrahlung in Hypothermie bei der Ratte" (Irradiation, especially local and fractionated irradiation, during hypothermia in rats). *Strahlentherapie* **132**: 274-283 (1967). G45,682/67

In rats, induced hypothermia protects against local and whole body x-irradiation.

Phillips, R. D., Kimeldorf, D. J.: "Effect of x-irradiation on the resistance of rats to low temperature." *Fed. Proc.* **27**: 508 (1968). H565/68

In rats exposed to cold after whole body x-irradiation, survival time was diminished.

Phillips, R. D., Kimeldorf, D. J.: "An immediate irradiation effect on resistance of rats to low temperature." *J. Appl. Physiol.* **24**: 768-772 (1968). G58,748/68

X-irradiation has a detrimental effect on the survival of rats upon exposure to cold.

Vácha, J., Pospíšil, M.: "Individual differences in the stress response of mice and their relationship to the differences in radiation tolerance." *Med. Exp. (Basel)* **19**: 58-63 (1969). H17,170/69

In mice, pretreatment with various stressors (*starvation, isolation*) increases x-ray tolerance, but only if the stress produced is of moderate intensity.

Kurasz, S., Musiatowicz, B., Borzuchowska, A., Swiderska, K.: "Histologische und histochemische Veränderungen in der Nebennierenrinde des Kaninchens nach experimenteller Infektion mit *Salmonella typhimurium* und Bestrahlung" (Histologic and histochemical changes in the adrenal cortex of rabbits after experimental infection with *Salmonella typhimurium*, and irradiation). *Zentralbl. Bakter. [Orig. A]* **224**: 463-471 (1973).

J11,180/73

In rabbits, *infection* with *Salmonella typhimurium* plus x-irradiation produces adrenocortical changes characteristic of the alarm reaction. These are more intense following exposure to both agents than after application of either of them alone.

Warren, S., Chute, R. N., Porter, M. W.: "The effect of *parabiosis* on life-span of rats stressed by radiation." *J. Gerontol.* **30**: 15-21 (1975).

J19,637/75

Light Rays

The circadian rhythm differs in various species. Thus, the eosinophil count reaches a maximum in man and a minimum in mice at about 03:00. The reverse is true between 14:00 and 17:00. Yet, in both species, intense light causes eosinopenia at all times; this has been ascribed to the alarm reaction.

In rats exposed to constant strong light, polycystic ovaries and continuous vaginal estrus may develop concurrently with the typical adrenal hypertrophy of the stress response. In mice, the blood corticosterone levels reach a peak in the winter with a nadir in the spring and summer. Differences in lighting have been alleged to play a role in this circannual rhythm.

In women, strong light raises urinary catecholamine excretion, presumably as a result of stress.

Light Rays

(See also our earlier stress monographs, p. xiii)

Lamb, J. H., Shelmire, B., Cooper, Z., Morgan, R. J., Keaty, C.: "Solar dermatitis." *Arch. Derm. Syph.* **62**: 1-25 (1950).

B54,900/50

Solar dermatitis may be associated with certain hormonal derangements characteristic of the G.A.S.

Kivikoski, A., Grönroos, M., Näätänen, E.: "Effect of benzylimidazolin under audiogenic-visual stress conditions." *Ann. Med. Exp. Fenn.* **38**: 394-399 (1960).

D5,263/60

Critchlow, V.: "The role of light in the neuroendocrine system." In: Nalbandov, A. V., *Advances in Neuroendocrinology*, pp. 377-402. Urbana, Ill.: University of Illinois Press (1963) (163 refs.).

J12,265/63

Hollwich, F., Tilgner, S.: "Reaktionen der

Eosinophilen-Zahl auf okulare Lichtreize." (Changes in blood eosinophil count after ocular light stimulation). *Dtsch. Med. Wochenschr.* **89**: 1430-1436 (1964).

F17,971/64

The blood eosinophil count reaches a maximum in man and a minimum in mice at about 03:00. The reverse is true between 14:00 and 17:00. In both species, intense light causes eosinopenia at all times; this is ascribed to the stressor effect and the resulting alarm reaction.

Anderson, T. A., Geber, W. F.: "Combined effects of chronic audio-visual stress and thiouracil administration on the cholesterol-fed rat." *J. Cell. Comp. Physiol.* **66**: 141-146 (1965).

G35,191/65

In rats, audiovisual stress can be produced by various bells, buzzers and white noise generators in addition to interrupted intense illumination. This may influence the atherogenic effect of thiouracil on high-cholesterol diets.

Singh, K. B.: "Induction of polycystic ovarian disease in rats by continuous light. I. The reproductive cycle, organ weights, and histology of the ovaries." *Am. J. Obstet. Gynecol.* **103**: 1078-1083 (1969).

G65,765/69

In rats exposed to constant light, persistent vaginal estrus and atrophic polycystic ovaries developed in combination with adrenal hypertrophy. These changes were ascribed to stress [although a specific effect was not eliminated (H.S.).]

Kamchatnov, V. P.: "Effect of working in red light on development of fatigue." *Ind. Med. Surg.* **38**: 445-447 (1969).

J15,917/69

"Persons working in red light show a sharp decrease in working ability compared with persons working in normal lighting, and this may evidently explain their greater proneness to fatigue."

Haus, E., Halberg, F.: "Circannual rhythm in level and timing of serum corticosterone in standardized inbred mature C-mice." *Environ. Res.* **3**: 81-106 (1970).

G73,872/70

In mice, blood corticosterone levels are highest during winter and lowest during

spring and summer. The circadian rhythm likewise varies during the phases of the circannual cycle. Lighting plays an important role in these changes, although the mechanism of its effect is not yet clear (95 refs.).

Meduri, R., Puddu, P., Descovich, G. C., Rimondi, S.: "Variazioni delle catecolamine urinarie dopo stimolazioni luminose policromatiche e di grande lunghezza d'onda (Nota Prima)" (Urinary catecholamine variations after stimulation with polychromatic light of long wavelength [First Note]). *Ann. Ottal.* **97**: 635-649 (1971). J1,616/71

In women exposed to strong polychromatic light urinary catecholamine excretion was increased, presumably as a result of stress.

Mos, L., Vriend, J., Poley, W.: "Effects of light environment on emotionality and the endocrine system of inbred mice." *Physiol. Behav.* **12**: 981-989 (1974). J13,743/74

Mice of different strains were reared in either a dark or a light environment. "Strain and sex affected all organ weights, light rearing affected adrenal, spleen and ovary weight, and emotionality testing affected pituitary and adrenal weight. The results were interpreted that light rearing affects maturation of the hypothalamic-pituitary-adrenal axis and response to stress."

Ultraviolet Rays

Very little work has been done on the stressor effect of ultraviolet rays, but allegedly, they can enhance the development of restraint-induced ulcers in the rat.

Ultraviolet Rays

(See also our earlier stress monographs, p. xiii)

Dumas, J., Péres, G.: "Action du rayonnement ultraviolet sur la formation de l'ulcère de contrainte chez le rat blanc" (Action

of ultraviolet irradiation on the formation of restraint ulcer in the white rat). *C.R. Acad. Sci. (Paris)* **163**: 863-865 (1969).

H19,005/69

Ultraviolet irradiation accelerates the development of stress ulcers by restraint in the rat.

Vibration

Exposure to strong vibrations can act as a powerful stressor. This effect has been studied especially in connection with problems of aerospace medicine and industrial work.

→**Hormones.** In monkeys, simulated "space stressor conditions," such as vibration, centrifugation and isolation with restraint, caused a rise in catecholamine and a fall in

17-KS excretion, with a diminution of diuresis. On the other hand, in rats, "vibratory stress" allegedly increased urinary 17-KS and corticoid elimination; this was accompanied by thymus atrophy. As we have pointed out before, 17-KS excretion is difficult to interpret because it may indicate corticoid or testoid elimination, a rise in the former and a fall in the latter being characteristic of stress. Increased catecholamine elimination and thymus atrophy are indubitably stress indicators. Yet, in man, certain types of sinusoidal vibration have been claimed to diminish plasma and urinary corticoid levels, while causing clinically manifest signs of stress and intense discomfort. These observations are difficult to interpret.

In dogs, even under light pentobarbital anesthesia, whole body vibration does raise the 17-OHCS plasma level, although not as much as in unanesthetized animals. Evidently, emotional factors are important, but not indispensable, for this response. In dogs, horizontal whole body vibration increased 17-OHCS and EP, but not 5-HT and NEP concentrations in plasma. In man, after repeated exposure to mechanical vibration of low frequency, the initial rise in plasma catecholamine and blood sugar content tends to diminish, whereas an increase in plasma cortisol levels usually persists without any evidence of adaptation.

In workers occupationally exposed to strong vibrations, blood cortisol and urinary VMA elimination "indicates a strong stress response."

→**Varia.** Among other changes possibly related to vibration, special attention was given to the atrophy of the thymicolymphatic apparatus, adrenal hypertrophy with a fall in its ascorbic acid content, rises in serum aldolase and lactic dehydrogenase, as well as psychoneurologic alterations.

+**Varia.** Several publications have attempted (with moderate success) to distinguish between the stressor effect of vibration and that of other concurrent stimuli common in space, industry and so on. Apparently, male rats are more sensitive than females to the typical adrenal enlargement, thymicolymphatic and gonadal atrophy, as well as the loss of weight caused by vibration.

Vibration

(See also our earlier stress monographs, p. xiii)

Generalities. Huddleston, H. F.: "Vertical sinusoidal vibration as a psychological stress." *Nature* (Lond.) **211**: 324-325 (1966). J22,633/66

Burns, W.: *Noise and Man*, p. 336. Philadelphia: J B Lippincott, 1968. E8,840/68

Monograph on the effects of noise, sonic booms and vibration on man, with special reference to aerospace problems.

Stewart, A. M., Goda, D. F.: "Vibration syndrome." *Br. J. Ind. Med.* **27**: 19-27 (1970). J14,819/70

Bjerker, N., Kylin, B., Lidström, I. M.: "Changes in the vibratory sensation thresh-

old after exposure to powerful vibration." *Ergonomics* **15**: 399-406 (1972).

H81,609/72

→**Hormones.** Winters, W. D.: "Various hormone changes during simulated space stresses in the monkey." *J. Appl. Physiol.* **18**: 1167-1170 (1963). E35,060/63

In *Macaca nemestrina* monkeys, urinary excretion of 17-KGS and catecholamines as well as diuresis were examined under simulated space stressor conditions, namely centrifugation, vibration and isolation with restraint. The results varied with the type of stressor used, but a reduction in urine volume was obvious in all instances. "A fall in steroid and slight elevation in catecholamine excretion were observed following vibration and centrifugation. The centrifugation ap-

peared to be slightly more stressful. Isolation with restraint appears to be a severe stress to the animals as demonstrated by a marked elevation of amine and a marked reduction in both urine output and steroid excretion."

Weltman, A. S., Sackler, A. M., Owens, H., Bernstein, M.: "Effects of vibration on the endocrine system of male rats." *Am. Zoolgist* **3**: 526 (1963). E59,922/63

In rats, "vibratory stress" caused an increase in urinary 17-KS and corticoids, as well as thymus atrophy.

Litta-Modignani, R., Blivaiss, B. B., Magid, E. B., Priede, I.: "Effects of whole-body vibration of humans on plasma and urinary corticosteroid levels." *Aerospace Med.* **35**: 662-667 (1964). G18,097/64

Exposure of men to sinusoidal vibration by means of a Western Gear Mechanical Shake Table in a modified jet aircraft seat produced—contrary to expectations—a decrease in plasma and urinary corticoids. "The vibration gave a rather dramatic general discomfort associated frequently with dyspnea, chest pain, abdominal pain, and in some cases, the experiment had to be interrupted for this reason. Such a combination of symptoms is characteristic of stress response which is usually associated with an increase in plasma 17-OH-CS" (43 refs.).

Korukaev, I. S.: "Plasma 17-hydroxycorticosteroids in patients with vibration sickness." *Gig. Tr. Prof. Zabol.* **8** No. 3: 7-10 (1964). Transl. Sup.: *Fed. Proc.* **24**: 253-254 (1965) (English translation; Russian original). F33,746/65

Industrial workers exposed to chronic vibration developed a typical stress syndrome with increased blood 17-OHCS.

Blivaiss, B. B., Litta-Modignani, R., Galansino, G., Foa, P. P.: "Endocrine and metabolic response of dogs to whole body vibration." *Aerospace Med.* **36**: 1138-1144 (1965). F75,989/65

In dogs, horizontal whole body vibration produced an increase of 17-OHCS and EP but not of 5-HT or NEP in plasma. This response persisted but was less severe under pentobarbital anesthesia.

Litta-Modignani, R., Magid, E. B., Blivaiss, B. B.: "Effects of whole body vibrations of humans on plasmatic and urinary corticosteroid levels." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp.

517-525. New York and London: Academic Press, 1965. E5,496/65

In man, vibrations of a sinusoidal nature performed by a mechanical shake table that attempts to imitate conditions in a jet aircraft seat did not cause any increase in plasma 17-OHCS but rather a small decrease. A slight diminution was also found in urinary blue-tetrazolium-reducing steroids (BTS) and 17-KGS. Under these moderate conditions of vibration, "a mild inhibition of the hypothalamic-hypophysis-adrenal axis could have occurred."

Blivaiss, B. B., Litta-Modignani, R., Priede, I.: "Plasma 17-hydroxycorticosteroids in dogs after whole body vibration." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 511-516. New York and London: Academic Press, 1965.

E5,495/65

In dogs anesthetized with pentobarbital, whole body vibration still causes a "stress-like response" in that it increases plasma 17-OHCS; this reaction is more pronounced in nonanesthetized animals. Evidently, emotional factors are important but consciousness is not indispensable for typical adrenal stress reactions.

Parin, V. V., Antipov, V. V., Raushenbakh, M. O., Saksonov, P. P., Shashkov, V. S., Chernov, G. A.: "Changes in blood serotonin level in animals exposed to ionizing radiation and dynamic factors of space flight." *Fed. Proc.* **25**: T103-T106 (1966).

F60,935/66

In various species of animals traveling on satellite spaceships, exposure to x-rays, acceleration and vibration considerably diminished the blood 5-HT content.

Starlinger, H., Hawel, W., Rutenfranz, J.: "Untersuchungen zur Frage der Catecholaminausscheidung im Harn als Kriterium für emotionalen Stress unter verschiedenen Umgebungsbedingungen. Vibrationsbelastung, Filmdarbietungen und Prüfungssituierung" (Studies on the question of urinary catecholamine excretion as criterion of emotional stress under various environmental conditions. Vibration load, presentation of motion pictures and examination periods). *Int. Z. Angew. Physiol.* **27**: 1-14 (1969).

G65,048/69

Dolkas, C. B., Leon, H. A., Chackerian, M.: "Short term response of insulin, glucose, growth hormone and corticosterone to acute

vibration in rats." *Aerosp. Med.* **42**: 723-726 (1971). J10,866/71

In rats, exposure to lateral vibration causes a transient decrease in plasma insulin and an increase in plasma glucose with only minor variations in the corticosterone and STH concentration of the blood (25 refs.).

Mesolella, C., Pezzarossa, G., Testa, B.: "Aspetti patogenetici dello 'stress' vibratorio nell'uomo: ricerche su sordomuti" (Pathogenetic aspects of vibrational "stress" in man: investigations of deaf-mutes). *Boll. Mal. Orecch.* **90**: 27-37 (1972).

J11,757/72

In certain industries vibration acts as a potent stressor, eliciting typical G.A.S. manifestations including increases in urinary corticoid and VMA elimination.

Pesquies, P., Boucher, D., Demange, J., Thieblot, L.: "Action des vibrations mécaniques de basse fréquence sur la fonction corticosurrénalienne chez l'homme" (Effects of mechanical vibrations of low frequency on adrenocortical function in man). *C.R. Soc. Biol. (Paris)* **166**: 874-878 (1972).

H64,970/72

In man, exposure to mechanical vibration of low frequency initially induces hyperglycemia and increases the plasma catecholamine concentration as a consequence of stress. However, after repeated exposure, these responses diminish, whereas elevated plasma cortisol levels persist without evidence of adaptation.

Nagano, C., Sugawara, N.: "Stimulation of synthesis of corticosterone by mechanical vibration." *Folia Endocrinol. Jap.* **48**: 604-611 (1972) (Japanese). J20,200/72

Increase in corticoid production due to the stressor effect of vibration in the rat (33 refs.).

Anitesco, C., Contulesco, A.: "Etude de l'influence du bruit et des vibrations sur le comportement des catécholamines dans l'agression sonore vibratoire industrielle" (Studies on the influence of noise and vibration on the behavior of catecholamines in industrial vibratory acoustic stress). *Arch. Mal. Prof.* **33**: 365-372 (1972).

G95,398/72

In an autobus construction factory, the appearance of a significantly increased amount of VMA in the urine of a group of eighty subjects after four hours of exposure to noise and industrial vibrations "is interpreted as the expression of the impairment

of the neuroendocrine-humoral ratio, by inciting the descendant activating system." The depression of the adrenal function by the diminution of VMA and the 17-KS values during night rest, compared to the controls of the investigation, show an insufficiency of endocrine supply.

Gołabek, W.: Effect of vibration on the catecholamine content in the brain, adrenals and spleen. *Acta Physiol. Pol.* **23**: 1011-1019 (1972) (31 refs.). H91,916/72

Sugawara, N., Nagano, C., Terui, K., Okada, A.: "The effect of vibration on corticosterone and nicotinamide-adenine-dinucleotide-phosphate level in the rat adrenal and serum." *Jap. J. Hyg.* **27**: 347-352 (1972) (Japanese). H81,438/72

In rats, whole body vibration significantly increased the serum and adrenal level of corticosterone but failed to influence adrenal NADPH. Low frequency vibration was most effective.

Morelli, G., Bellotti, C., Perrella, F.: "Stress' vibratorio nell'uomo: aspetti etiopatogenetici e lavorativi" (Vibrational stress in man: etiopathogenic and working aspects). *Nuovo Arch. Ital. Otol.* **1**: 94-101 (1973). J7,745/73

In workers occupationally exposed to vibrations, a rise in blood cortisol and urinary VMA indicates a strong stress response. Industrial noise has similar effects.

→Varia. Miline, R., Kochak, O.: "L'influence du bruit et des vibrations sur les glandes surrénales" (Influence of noise and vibration on the adrenal glands). *C.R. Assoc. Anat. (No. 70)*: 692-703 (1952).

B56,901/52

In guinea pigs and rabbits exposed to strong sounds and vibrations for twenty-four hours in a boilermaking factory there were adrenal changes quite typical of the G.A.S.

Marsh, J. T., Rasmussen, A. F. Jr.: "Response of adrenals, thymus, spleen and leucocytes to shuttle box and confinement stress." *Proc. Soc. Exp. Biol. Med.* **104**: 180-183 (1960). C89,538/60

"Changes in organ weights and leucocytes following daily exposure to emotionally disturbing shuttle box or confinement stress were consistently observed. Adrenal hypertrophy and drops in circulating leucocytes were relatively rapid with significant changes observed following 3 to 7 days of stress. Involution of thymus and spleen occurred more

slowly, with differences becoming maximum following 14 to 28 days of stress. Differences between experimental and control values returned to non-significant levels in 21 days following termination of stress."

Pushkina, N.: "Some biochemical blood indices in subjects exposed to vibration." *Gig. Tr. Prof. Zabol.* **2**: 29 (1961) (Russian).

J15,358/61

Pramatarov, A., Balev, L.: "Menstrual anomalies and the influence of motor vehicle vibrations on conductors from the city transport." *Akush. Ginekol. (Mosk.)* **8**: 31 (1969) (Russian).

J15,928/69

Tarnawski, A.: "The influence of vibration on adrenocortical function." *Patol. Pol.* **21**: 193-195 (1970) (Polish). H51,720/70

Prolonged exposure of guinea pigs to vibration allegedly exhausts the *adrenal cortex* and causes insufficiency with irresponsiveness to ACTH. The Polish literature on the stressor effect of vibration is reviewed (8 refs.).

Koźmińska, A., Różański, J., Langner, B.: "Studies on the effect of vibration on the peripheral blood vessels." *Przegl. Dermatol.* **57** No. 1: 31-39 (1970). J15,224/70

Borsukowski, W., Kwarecki, K.: "Changes in the morphology of adenohypophysis under the effect of vibration." *Pol. Med. J.* **10**: 110-113 (1971). G84,034/71

In guinea pigs, "vibration disease" is associated with characteristic morphologic changes in the *adenohypophysis*.

Mesolella, C., Pezzarossa, G., Morelli, G.: "Stress' vibratorio, ghiandole salivari e pancreas: studio sperimentale nel ratto" (Vibrational "stress," salivary glands and pancreas: experimental study of rats). *Boll. Mal. Orecch.* **90**: 18-26 (1972). J11,756/72

In rats, characteristic histologic changes occurred in the *salivary glands* and *pancreas* during an alarm reaction produced by vibration.

Doneshka, P.: "Etudes encéphalographiques sur les stades du sommeil qui suivent la vibration" (Encephalographic study of the sleep stages following vibration). *Iugosl. Physiol. Pharmacol. Acta* **8**: 61-66 (1972). H79,379/72

In cats, the duration of paradoxical *sleep* increases considerably after exposure to vibration, whereas slow sleep remains unaffected.

Floyd, W. N., Broderson, A. B., Goodno, J. F.: "Effect of whole-body vibration on peripheral *nerve conduction* time in the rhesus monkey." *Aerosp. Med.* **44**: 281-285 (1973). H80,348/73

+Varia. Nadel, A. B.: "Vibration." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 379-394. Glencoe, Ill.: Free Press, 1963.

E10,433/63

Review on the psychologic and somatic effects of vibration, especially in relation to aerospace medicine.

Józkiewicz, S., Stanosek, J., Gregorczyk, J., Krzoska, K., Lewandowska-Tokarz, A.: "Über den Einfluss der chronischen Einwirkung von Lärm und Vibrationen niedriger Frequenzen auf die Zusammensetzung des Blutes, das relative Gewicht einiger Organe sowie den Gehalt der Askorbinsäure in den Nebennieren bei Meerschweinchen" (The influence of the chronic effects of noise and low frequency vibrations on the blood composition and the relative weight of several organs, as well as the ascorbic acid content of the adrenals in the guinea pig.) *Acta Biol. Med. Ger.* **13**: 331-335 (1964).

F25,307/64

In guinea pigs, *noise* and vibration caused adrenal ascorbic acid depletion, especially when they were applied in combination. The change is ascribed to the G.A.S.

Gregorczyk, J., Lewandowska-Tokarz, A., Stanosek, J., Hepa, J.: "The effects of physical work and work under conditions of noise and vibration on the human body. I. Behavior of serum alkaline phosphatase, aldolase and lactic dehydrogenase activities." *Acta Physiol. Pol.* **16**: 701-708 (1965).

F59,655/65

In men working in an industrial establishment where they were exposed to considerable *noise* and vibration, increases in serum aldolase and lactic dehydrogenase were interpreted as manifestations of the stress syndrome. "It was assumed that the aforementioned stress factors produce changes in the sugar metabolism of the body."

Sackler, A. M., Weltman, A. S.: "Effects of vibration on the endocrine system of male and female rats." *Aerosp. Med.* **37**: 158-166 (1966). G36,884/66

Comparatively low-gravity vibration in a reciprocating Kahn shaker for thirty minutes daily caused more pronounced stress effects

(adrenal enlargement, thymic lymphatic or gonadal atrophy, loss of body weight, and so on) in *male* than in *female* rats (40 refs.).

Bondarev, G. I., Sinitina, A. D., Efimov, I. N.: "Combined effect of low frequency vibration and *noise* on the adreno cortical-pituitary system." *Gig. Sanit.* **35** No. 5: 106-108 (1970) (Russian). J15,240/70

Armstrong, R. C., McCann, J. P., Vorbeck, D. W., Short, L. L., Purdy, C. H.: "Effect of *environmental pressure* on biological stress from vibration." *Aerosp. Med.* **41**: 885-890 (1970). J21,335/70

Constanta, A., Contulesco, A., Ionesco, G., Miclesco-Groholsky, S.: "Recherches sur

l'activité des transaminases et de la phosphatase acide dans l'agression sonore et vibratoire industrielle" (The activity of transaminases and acid phosphatase in the stress of industrial noise and vibration). *Arch. Mal. Prof.* **32**: 647-652 (1971). G98,066/71

An increase in serum phosphatase and transaminase is claimed to be characteristic of stress, and occurred in workers of a metallurgic plant exposed to considerable *noise* and vibration.

Sommer, H. C., Harris, C. S.: Combined effects of *noise* and vibration on mental performance as a function of *time of day*." *Aerosp. Med.* **43**: 479-482 (1972).

J16,970/72

Air Blasts

Rats exposed to intermittent air blasts developed morphologic and biochemical changes characteristic of stress. These were blocked by lesions in various parts of the limbic system and hypothalamus, suggesting that different mechanisms may be involved in their production.

Air Blasts

(See also our earlier stress monographs, p. xiii)

Hahn, E. W., Hays, R. L.: "Modification of the incidence of mating in rats by stimulation with a short air blast." *Psychol. Rep.* **16**: 862-864 (1965). J23,030/65

Usher, D. R., Kasper, P., Birmingham, M. K.: "Comparison of pituitary-adrenal function in rats lesioned in different areas of

the limbic system and hypothalamus." *Neuroendocrinology* **2**: 157-174 (1967).

F88,389/67

Rats exposed to intermittent air blasts developed thymus involution and a pronounced increase in plasma corticosterone and pituitary ACTH levels. Lesions in various locations of the limbic system and hypothalamus blocked these effects independently of each other, indicating that different mechanisms are involved in their production.

Compression, Decompression

The stressor effect of compression and decompression is of special clinical interest in connection with diving and orbital flights. Several observations confirm that these agents can produce clearcut manifestations of stress, as might have been expected.

Compression, Decompression

(See also our earlier stress monographs, p. xiii)

Smith, D. C., Brown, F. C.: "Effects of acute decompression stress upon some blood components, especially leucocytes, in intact

and splenectomized cats." *Am. J. Physiol.* **164**: 752-765 (1951). B56,267/51

In normal and splenectomized cats, "decompression stress" produced an initial increase in blood lymphocytes followed by a decrease to subnormal levels. The number of neutrophils rose in both intact and splenec-

tomized cats submitted to this stressor. Changes in eosinophil counts were difficult to interpret because of great individual variations.

Edholm, O. G., Bacharach, A. L. (eds.): *The Physiology of Human Survival*, p. 581. London and New York: Academic Press, 1965. E6,283/65

A monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal and muscular exercise. Each chapter is written by a specialist in the corresponding field, and numerous references indicate the difference between specific defense mechanisms and the stressor effects of the agents used.

Bertelli, A., Cerrati, A., Rossano, M. A., Schiantarelli, P.: "Aumento della resistenza all'ipobarismo di ratti trattati con 3'-5'-AMP ciclico" (Increased resistance to hypobarism in rats treated with cyclic 3'-5'-AMP). *Atti Accad. Med. Lomb.* **21**: 597-600 (1966).

F93,526/66

Hale, H. B., Williams, E. W.: "Nitrogen and helium as factors affecting decompression stress severity." *Aerosp. Med.* **39**: 1178-1181 (1968). G75,914/68

Schaefer, K. E., Bond, G. F., Mazzzone, W. F., Carey, C. R., Dougherty, J. H. Jr.: "Carbon dioxide retention and metabolic changes during prolonged exposure to high pressure environment." *Aerosp. Med.* **39**: 1206-1215 (1968). J22,414/68

Hale, H. B., Ellis, J. P., Williams, E. W.: "Decompression stress in simulated orbital flight." *Aerosp. Med.* **39**: 1171-1174 (1968). H22,179/68

Hale, H. B., Williams, E. W.: "Endocrine-metabolic response to sequential decompression during simulated orbital flight." *Aerosp. Med.* **39**: 1175-1177 (1968). H22,180/68

In men exposed to sequential decompression during simulated orbital flights, "nonspecific stress was evident, as there were decompression-induced elevations (which were

progressive with time) in creatinine, urine volume, sodium, norepinephrine, and urea. Epinephrine was also elevated, but the peak effect came at an early time. As a late effect, 17-OHCS excretion became elevated."

Jacey, M. J., Madden, R. O., Tappan, D. V.: "Hemostatic alterations following severe dysbaric stress." *Aerosp. Med.* **45**: 1062-1066 (1974). J16,190/74

In rats, "acute decompression stress produced a transient decrease in clotting time. Circulating platelet population was unchanged during the early phase of recovery from severe decompression but had declined significantly by 2 d post-surfacing and then returned to control levels by the end of the observation period. Associated with the thrombocytopenic episode was a tendency toward platelet aggregation." A significant hyperfibrinogenemia had developed on the day after the "dysbaric stress" with subsequent normalization. Alterations in prothrombin time or partial thromboplastin time were not found (24 refs.).

Wolthuis, R. A., Bergman, S. A., Nicogossian, A. E.: "Physiological effects of locally applied reduced pressure in man." *Physiol. Rev.* **54**: 566-595 (1974). H89,398/74

Suction, when applied to various regions of the body under reduced atmospheric pressure, can act as a stressor by shifting blood to certain areas. Negative pressure applied to the lower part of the body is of particular interest in connection with gravity (as for example, in the launching of space ships) (95 refs.).

Powell, M. R., Doebbler, G. F., Hamilton, R. W. Jr.: "Serum enzyme level changes in pigs following decompression trauma." *Aerosp. Med.* **45**: 519-524 (1974). J13,389/74

Studies on the serum levels of creatine phosphokinase and lactate dehydrogenase in pigs as indicators of stress caused by decompression.

Jacey, M. J., Tappan, D. V., Ritzler, K. R.: "Hematologic responses to severe decompression stress." *Aerosp. Med.* **45**: 417-421 (1974) (26 refs.). J11,927/74

Gravity

The so-called gravitational stress has been studied in experimental animals and man, especially in relation to actual or simulated space flights and centrifugation. Weightlessness as such does not appear to be a strong stressor, but intense acceleration or

deceleration does produce typical somatic manifestations of the stress syndrome. It is difficult, however, to distinguish clearly between the effects of changes in gravity as such and associated phenomena such as vibration, emotional excitement and several environmental factors. Under various conditions of acceleration, deceleration, impact and centrifugation, the blood sugar, lactate, FFA and catecholamine levels do not always parallel each other.

Gravity

(See also our earlier stress monographs, p. xiii)

Generalities. Tepperman, J., Tepperman, H. M., Patton, B. W., Nims, L. F.: "Effects of low barometric pressure on the chemical composition of the adrenal glands and blood of rats." *Endocrinology* **41**: 356-363 (1947).

B4,674/47

In rats, five hours of anoxia produces a decrease in the cholesterol ester and ascorbic acid content of the adrenals as well as characteristic changes in plasma cholesterol, plasma amino acid, nitrogen, blood lactate and blood glucose.

Gauer, O. H., Zuidema, G. D. (eds.): *Gravitational Stress in Aerospace Medicine*, [Foreword by J. P. Stapp, Colonel, USAF (MC)], p. 278. Boston: Little, Brown, 1961.

E3,700/61

Symposium sponsored by the Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio. Fourteen experts (mostly members of the USAF) discussed the psychic and somatic results of exposure to stress in aircraft and spaceships, with primary emphasis upon acceleration, deceleration and weightlessness.

Goswami, S. L., Trivedi, C. P., Gupta, R. K.: "A preliminary study of motion induced stress in rats." *Arch. Int. Pharmacodyn. Ther.* **134**: 1-9 (1961).

D15,576/61

Chambers, R. M.: "Operator performance in acceleration environments." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 193-319. Glencoe, Ill.: Free Press, 1963.

E10,430/63

Brief review on performance in acceleration environments with special reference to space flights.

Little, V. Z., Leverett, S. D., Hartman, B. O.: "Psychomotor and physiologic changes during accelerations of 5, 7, and 9 + G_x." *Aerosp. Med.* **39**: 1190-1197 (1968) (24 refs.).

J22,413/68

Burton, R. R., Smith, A. H.: "Criteria for physiological stress produced by increased chronic acceleration." *Proc. Soc. Exp. Biol. Med.* **128**: 608-611 (1968). H2,172/68

"Physiological fitness relative to exercise capacity, sexual development, and survival of an individual with respect to a stressful environment, increased chronic acceleration, may be quantitatively determined in the chicken by hematological methods."

Parkhurst, M. J., Leverett, S. D. Jr., Shubrooks, S. J. Jr.: "Human tolerance to high, sustained +G_x acceleration." *Aerosp. Med.* **43**: 708-712 (1972).

H79,716/72

Rolf, I. P.: "Structural integration. A contribution to the understanding of stress." *Conf. Psychiatr.* **16**: 69-79 (1973).

J7,128/73

Speculations on the effect of gravitation upon the structural integration of the body, and the importance of lying down to remove the stressor action of gravity during or after other stressful activities.

→**Hormones and Hormone-like Substances.** Zuidema, G. D., Silverman, A. J., Cohen, S. I., Goodall, M.: "Catecholamine and psychologic correlates of vascular responses." *N. Engl. J. Med.* **256**: 976-979 (1957).

J15,625/57

Studies on the catecholamine output of men exposed to centrifugation.

Goodall, McC., Berman, M. L.: "Urinary output of adrenaline, noradrenaline, and 3-methoxy-4-hydroxymandelic acid following centrifugation and anticipation of centrifugation." *J. Clin. Invest.* **39**: 1533-1538 (1960).

C92,945/60

Urinary excretion of catecholamines was accelerated in young men exposed to the "gravitational stress" of centrifugation. Catecholamine excretion was accelerated to a somewhat lesser extent by the mere anticipation of centrifugation. "Under high gravitational stress, increased adrenaline release seems to be largely related to the emotions,

while the noradrenaline release seems more closely related to the physical changes (hemodynamics and so forth) produced by centrifugation. Following the increased release of either or both adrenaline and noradrenaline, there is a commensurate rise in the urinary output of their common metabolic product, 3-methoxy-4-hydroxymandelic acid" (34 refs.).

Frankenhaeuser, M., Sterky, K., Jaerpe, G.: "Psychophysiological relations in habituation to gravitational stress." *Percept. Mot. Skills* **15**: 63-72 (1962). D46,292/62

In male medical students, gravitational stress (centrifugation) increased EP excretion without causing any pronounced change in NEP elimination or heart rate. After repeated centrifugation, adaptation occurred.

Goodall, M.: "Sympathoadrenal response to gravitational stress." *J. Clin. Invest.* **41**: 197-202 (1962). E41,813/62

EP excretion was increased in subjects before, during and immediately after centrifugation, presumably because of anxiety associated with the procedure. NEP output was elevated only during centrifugation and immediately afterwards. These changes "appeared to be dependent upon the physical stress imposed by centrifugation and had no direct relationship to the G tolerance of the subject."

Winters, W. D.: "Various hormone changes during simulated space stresses in the monkey." *J. Appl. Physiol.* **18**: 1167-1170 (1963). E35,060/63

In *Macacca nemestrina* monkeys, diuresis and urinary excretion of 17-KGS and catecholamines were examined under simulated space stressor conditions, namely centrifugation, vibration and isolation with restraint. The results varied with the type of stressor used, but reduction in urine volume was obvious in all instances. "A fall in steroid and slight elevation in catecholamine excretion was observed following vibration and centrifugation. The centrifugation appeared to be slightly more stressful. Isolation with restraint appears to be a severe stress to the animals as demonstrated by a marked elevation of amine and a marked reduction in both urine output and steroid excretion."

Bowman, R. E., Wolf, R. C.: "Plasma 17-OHCS response of the infant rhesus monkey to a noninjurious, noxious stimulus." *Proc. Soc. Exp. Biol. Med.* **119**: 133-135 (1965). F42,116/65

In two-day-old rhesus monkeys, centrifugation caused elevations in the nonconjugated 17-OHCS content of the plasma, but this effect was not as marked as that obtained with ACTH, "suggesting either that the restraint and rotation was not sufficiently stressful or that the infant CNS-hypophyseal axis was not sufficiently developed to stimulate fully the adrenal cortex."

Parin, V. V., Antipov, V. V., Raushenbakh, M. O., Saksonov, P. P., Shashkov, V. S., Chernov, G. A.: "Changes in blood serotonin level in animals exposed to ionizing radiation and dynamic factors of space flight." *Fed. Proc.* **25**: T103-T106 (1966).

F60,935/66

In various species of animals traveling on satellite spaceships, exposure to x-rays, acceleration and vibration considerably diminished the blood 5-HT content.

Foster, P., Sonntag, R. W. Jr.: "Urinary excretion of catecholamines and 17-hydroxycorticosteroids following +G_x impact in humans." *Aerospace Med.* **40**: 18-23 (1969).

H24,229/69

In humans, prior to both real and threatened impact in a decelerator, urinary NEP, EP, and 17-OHCS increased significantly. After impact, there was no change in NEP but EP levels rose fivefold over the controls, and 17-OHCS showed gradual but significant increases. There were no significant differences between the excretion rates in true and sham impacts with reference to 17-OHCS and NEP, but EP elimination was significantly higher following true impact. "Comparison of sham impact and actual impact data reveal that epinephrine is probably the mediator of the increased sympathetic activity associated with impact and that the threatened or actual exposure of a human to impact is more of a psychological than a physical stress."

Fluck, D. C., Salter, C.: "Effect of tilting on plasma catecholamine levels in man." *Cardiovasc. Res.* **7**: 823-826 (1973).

J8,857/73

In man, tilting of the body from a horizontal to a 30° position caused a significant rise in plasma EP and NEP, but both catecholamines approached the resting level after twenty-five minutes of tilting. Neither the pulse rate nor the blood pressure was affected. The change was ascribed to stress.

Arslan, M., D'Amelio, G., Marchiori, C.: "Clinical and endocrinological effects of cori-

olis accelerations and their behavior under drug treatment." *Acta Otolaryngol.* (Stockh.) **77:** 155-158 (1974). J12,116/74

Coriolis accelerations occur in subjects who make head movements during a body rotation at constant angular speed by provoking a flow of endolymph in the semicircular canals. This is associated with nausea, dizziness, pallor, sweat, vomiting, variations in pulse rate and arterial pressure, and a considerable rise in urinary catecholamine, 17-KS and 17-OHCS elimination. The authors conclude that "for normal subjects, exposure to Coriolis accelerations represents a stress which affects the adrenergic but not the hypophysial-cortical system. This stress is consistently related to the emotional tension originated by the test itself. The possibility of preventing the adrenergic hyperactivity of emotional origin by diazepam is discussed."

Mueller, R. A., Millward, D. K., Woods, J. W.: "Circulating catecholamines, plasma renin and dopamine-beta-hydroxylase activity with postural stress." *Pharmacol. Biochem. Behav.* **2:** 757-761 (1974).

J19,468/74

Oyama, J.: "Drug alteration of brain biogenic amines and effect of acceleration stress-induced hypothermia." *Fed. Proc.* **33:** 287 (1974).

H84,041/74

→**Metabolites.** Neuman, W. F.: *Possible Effects of Weightlessness on Calcium Metabolism in Man*, p. 12. University of Rochester Atomic Energy Project pamphlet, 1963.

G29,450/63

In astronauts, a two-week period of weightlessness and immobilization can cause loss of skeletal calcium, hypercalcemia, hypercalciuria, and possibly a tendency toward the formation of kidney stones.

Feller, D. D., Neville, E. D.: "Blood glucose and corticosterone changes accompanying altered lipid metabolism induced by exposure to acceleration stress." *Proc. Soc. Exp. Biol. Med.* **121:** 223-227 (1966).

F61,364/66

Oyama, J., Daligcon, B. C.: "Liver glycogenesis, glycogen synthetase and adrenal responsiveness of rats exposed to acceleration stress." *Endocrinology* **80:** 707-713 (1967).

F81,569/67

As judged by changes observed after centrifugation, "increased liver glycogenesis in stressed rats was always preceded by an in-

crease in total synthetase activity due to an increase in the G-6-P independent form of the enzyme. No increase in liver glycogenesis or synthetase activity occurred in 14-day-old rats, in rats treated with actinomycin D or Metopirone, or in adrenalectomized rats."

Polis, B. D., Polis, E., DeCanis, J., Schwarz, H. P., Dreisbach, L.: "Effect of physical and psychic stress on phosphatidyl glycerol and related phospholipids." *Biochem. Med.* **2:** 286-312 (1969).

G65,013/69

In rats exposed to ionizing radiation or "acceleration stress," the plasma concentration of *phosphatidylglycerol* was consistently increased. "Extension of the studies to humans stressed by acceleration to grayout, sleep deprivation, schizophrenia, combat, etc., revealed that all stresses were accompanied by significant increments in plasma phosphatidyl glycerol." In rats, hypophrectomy prevented the increase in phosphatidylglycerol induced by acceleration stress, but a rise in the brain level of this compound persisted even in the absence of the pituitary.

Harrison, M. H.: "Adrenergic beta-receptor blockade and metabolic response to centrifugation stress." *J. Appl. Physiol.* **35:** 793-797 (1973).

J9,353/73

In men exposed to centrifugation stress, the β-adrenergic blocking agent oxprenolol curtailed the increase in FFA and tachycardia but had little effect on the raised glycerol levels. "It is concluded that increased norepinephrine secretion is responsible for the observed metabolic effects of centrifugation and that centrifugation-induced tachycardia is not a purely beta response."

Oyama, J., Chan, L.: "Oxygen consumption and carbon dioxide production in rats during acute centrifugation stress and after adaptation to chronic centrifugation." *Fed. Proc.* **32:** 392 (1973).

H67,544/73

In rats, continuous centrifugation causes a pronounced hypothermia and a decrease in the BMR. However, upon prolonged exposure to the stressor, when adaptation occurs, the BMR rises above normal. The authors conclude that "the principal factor responsible for the centrifugation stress-induced hypothermia in rats is a decrease in their rate of heat production."

Harrison, M. H.: "Comparison of the metabolic effects of centrifugation and heat stress in man." *Aerosp. Med.* **44:** 299-303 (1973).

H80,109/73

In fasted men, the stress of centrifugation or exposure to heat increased blood lactate, glucose, FFA, glycerol and catecholamine levels, but these changes did not always parallel each other (30 refs.).

→**Cardiovascular System.** Beckman, E. L.: "Protection afforded the cerebrovascular system by the cerebrospinal fluid under the stress of negative G." *J. Aviat. Med.* **20** Sect. 2, Supp.: 430-438; 442 (1949).
B27.423/49

In goats submitted to negative gravity forces, the cerebrospinal fluid protects the brain vessels against damage.

Henry, J. P., Gauer, O. H., Kety, S. S., Kramer, K.: "Factors maintaining cerebral circulation during gravitational stress." *J. Clin. Invest.* **30**: 292-300 (1951) (36 refs.).
B57.309/51

Beckman, E. L., Duane, T. D., Ziegler, J. E., Hunter, H. N.: "Some observations on human tolerance to accelerative stress. Phase IV. Human tolerance to high positive G applied at a rate of 5 to 10 G per second." *J. Aviat. Med.* **25** Sect. 2, Supp.: 50-66 (1954).
J12.416/54

Studies on ECG changes in men exposed to accelerative stress.

Green, J. F., Miller, N. C.: "A model describing the response of the circulatory system to acceleration stress." *Ann. Biomed. Eng.* **1**: 455-467 (1973).
J10.890/73

Klinger, K. P., Brilling, G., Strasser, H.: "Pulsreaktionen bei kurzzeitiger Beschleunigung während einer Achterbahnfahrt. Erfahrungen mit dem Einsatz eines mobilen EKG-Speichergeräts" (Pulse reactions in short bursts of acceleration during a switchback ride). *Münch. Med. Wochenschr.* **116**: 1653-1656 (1974).
H95.276/74

Kunitsch, G., Marées, H. de, Barbey, K.: "Untersuchung über Kreislaufregulationen während der orthostatischen Anpassungsphase. 2. Mitteilung: Verhalten von Herzvolumen und anderen Kreislaufgrößen während akuter orthostatischer Belastung" (Investigation of circulatory regulation during the orthostatic adaptation phase. Part 2. Heart volume and other circulatory parameters during acute orthostatic stress). *Basic Res. Cardiol.* **69**: 278-288 (1974).
J21.709/74

Nunneley, S. A., Shindell, D. S.: "Cardiopulmonary effects of combined exercise and +G_x acceleration" (abstracted). *Physiologist* **17**: 298 (1974).
H89.933/74

Forgacs, P.: "Gravitational stress in lung disease." *Br. J. Dis. Chest* **68**: 1-10 (1974).
J10.403/74

Description of various pulmonary manifestations in man, particularly respiratory difficulties and asthma, resulting from exposure to "gravitational stress" (about 50 refs.).

→**Varia.** Loftus, J. P. Jr., Hammer, L. R.: "Weightlessness." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 353-377. Glencoe, Ill.: Free Press, 1963.
E10.432/63

Review of the literature on space travel suggests that man can *function* effectively in a weightless environment.

Burton, R. R., Sluka, S. J., Besch, E. L., Smith, A. H.: "Hematological criteria of chronic acceleration stress and adaptation." *Aerospace Med.* **38**: 1240-1243 (1967).
G63.027/67

Oyama, J., Platt, W. T., Holland, V. B.: "Deep-body temperature changes in rats exposed to chronic centrifugation." *Am. J. Physiol.* **221**: 1271-1277 (1971).
J19.653/71

In rats, the stressor effect of centrifugation causes a rapid fall in *deep-body temperature* monitored continuously by implant biotelemetry.

Hase, T., Scarborough, E. S.: "Development of stress ulcer in rats and guinea pigs by mechanical rotation." *J. Appl. Physiol.* **30**: 580-582 (1971).
G84.313/71

In guinea pigs and rats, stress *ulcers of the stomach* can be produced by mechanical rotation in a specially-designed chamber.

→**Varia.** Mitchell, H. H., Edman, M.: *Nutrition and Climatic Stress*, p. 235. Springfield, Ill.: Charles C Thomas, 1951.
B65.5070/51

Technical discussion of observations on stress caused by cold, heat, high altitude and acceleration in relation to the *nutrition* of man (more than 750 refs.).

Silverman, A. J., Cohen, S. I., Zuidema, G. D.: "Psychophysiological investigations in cardiovascular stress." *Am. J. Psychiatry* **113**: 691-693 (1957).
C29.216/57

Personal aggressiveness was seen to be a significant factor in the gravity tolerance of men subjected to centrifugal stress, those individuals with outgoing and aggressive personalities proving definitely more resistant to centrifuge-induced blackout and loss of sight. Even among such better adapted individuals G tolerance varied according to the immediate psychologic state, so that they experienced "highest black-out levels just after they had expressed some anger, or were relatively free from anxiety. Lowest black-out levels were obtained when they were worried, depressed, anxious."

Taylor, J. W.: *X-irradiation and Acceleration Stress*. Aviation Medicine Acceleration Lab. Report No. NADC-MA-6003 (1960).

J11,875/60

Taliaferro, E. H., Wempen, R. R., White, W. J.: "The effects of minimal dehydration upon human tolerance to positive acceleration." *Aerospace Med.* **36**: 922-926 (1965).

G34,349/65

In man, "heat stress" decreases tolerance to positive acceleration as a result of minimal dehydration.

Oyama, J., Medina, R., Platt, W. T.: "Influence of age on liver glycogenesis in rats exposed to acceleration stress." *Endocrinology* **78**: 556-560 (1966).

F62,885/66

"Significant increases in liver glycogen deposition occurred in centrifuged rats 18 days or older but not in younger rats. The unresponsiveness of the younger rats was attributed to their limited ability to elaborate

increased amounts of adrenal corticosterone during centrifugation."

Atherton, R. W., Ramm, G. M.: "General observations, erythrocyte counts and hemoglobin concentration in chick embryos subjected to centrifugal stress." *Aerospace Med.* **40**: 389-391 (1969). J22,401/69

Allan, J. R., Crossley, R. J.: "Effect of controlled elevation of body temperature on human tolerance to +G_x acceleration." *J. Appl. Physiol.* **33**: 418-420 (1972).

J19,375/72

"Fully acclimatized subjects may show a smaller adverse effect of thermal stress on G tolerance, attributable to the cardiovascular changes which characterize this adaptive response."

Tillman, F. R., Miller, J. A. Jr.: "Hypothermia and resistance of mice to lethal exposures to high gravitational forces." *Aerospace Med.* **43**: 860-866 (1972). H79,348/72

Bjurstedt, H., Rosenhamer, G., Tydén, G.: "Acceleration stress and effects of propranolol on cardiovascular responses." *Acta Physiol. Scand.* **90**: 491-500 (1974).

J12,120/74

In man, "after propranolol, the heart rate response to increased G at rest averaged 38% of that observed without blockade, indicating that G-induced cardioacceleration is predominantly due to sympathetic stimulation." However, subjective G tolerance was well preserved; hence, sympathetic chronotropic stimulation of the heart is not essential for the circulatory defense against gravitational stress.

Electricity, Electroschok

→**Hormones.** The production by electroschok of typical stress manifestations with adrenocortical activation has been amply demonstrated on the many patients who received this therapy for mental illness. The results have also been confirmed in experimental animals, showing that the hormonal response to electroschok is essentially the same as that produced by other acute stressors. However, in rats, electroschok (like starvation, hypoxia, surgical interventions and adrenalectomy) allegedly failed to produce a depletion of brain 5-HT and NEP, such as would be induced by swimming to exhaustion in cold water. These negative findings require confirmation, especially since in guinea pigs brain EP and NEP do drop considerably after electroschok. This effect is long-lasting and can be inhibited but not completely abolished by phenobarbital sedation. Electroschoks (like several other stressors) diminish insulin secretion in the rat. This has been ascribed to endogenous EP.

→**Varia.** In rats, repeated electroshocks caused considerable enlargement of the adrenals with an increase in their ascorbic acid and cholesterol content, gastric ulcer formation, and raised plasma FFA. Single shocks resulted in a drop in adrenal ascorbic acid and cholesterol.

Among the other effects described as characteristic of electroshock in rats are induced fighting behavior, a high incidence of dental caries, and myocardial damage.

+**Varia.** As previously stated, the stressor action of electroshock can be diminished, though rarely abolished, by various sedatives and tranquilizers. In schizophrenics, electroconvulsive therapy raises the plasma 17-OHCS level even when epileptic seizures are blocked by diphenylhydantoin.

On high-fat, high-cholesterol diets, periodic electroshocks caused marked hypercholesterolemia, hyperlipemia and a predisposition for coronary atherosclerosis in the rat. During the early neonatal period, electroshock fails to produce the usual ascorbic acid depletion and increase in adrenal corticosterone content in the rat, presumably because of an immaturity of the hypothalamic centers. However, these observations have not been confirmed by subsequent investigators, who were able to elicit obvious stress reactions in rats during the first five days of life. The production of gastric lesions by electroshock and cold is facilitated if the stressors are administered simultaneously.

Electroshock applied before x-irradiation does not affect the survival rate of rats but does shorten it if applied afterwards.

The genetically determined mouse-killing activity of certain strains of rats is blocked by chronic electroconvulsive shock therapy, and at the same time, brain NEP rises. Hunger and thirst did not affect the fighting behavior elicited by electroshock in rats. Handling during infancy caused only minor variations in the aggressiveness of rats exposed to electric footshock in adulthood.

Electricity, Electroshock

(See also our earlier stress monographs, p. xiii, and Neuropsychiatric Diseases of Adaptation)

Generalities. Sager, O., Badenschi, G., Cotăescu, E., Roth, R. R.: "Actiunea electroșocului asupra glandelor cu secreție internă" (Effects of electroshock on endocrine gland secretion). *Bull. Sci. Acad. R.P.R. Roumanie, Sci. Méd.* 2: 651-659 (1950). (Roumanian).

G99,776/50

In man, electroshocks produce increased ACTH secretion, eosinopenia and lymphopenia, reaching a maximum within about four hours. Repeated electroshocks may also cause menstrual disturbances in women and impotence in men. All these effects are ascribed to the G.A.S.

Hall, C. E., Hall, O., Adams, A. R.: "An electromechanical apparatus for stressing

small animals." *J. Appl. Physiol.* 14: 869-870 (1959). E42,437/59

→**Hormones.** Cleghorn, R. A., Goodman, A. J., Graham, B. F., Jones, M. H., Rublee, N. K.: "Activation of the adrenal cortex in human subjects following electroconvulsive therapy (E.C.T.) and psychomotor stress. Program Thirtieth Meet. Assoc. for the Study of Internal Secretions, Chicago, 1948, p. 40. *J. Clin. Endocrinol.* 8: 608 (1948). B19,125/48

Reiss, M.: "Investigations of hormone equilibria during depression." In: Hoch, P. H. and Zubin, J., *Depression*. New York: Grune and Stratton, 1954.

J12,862/54

Electroshock administered to depressive patients increases corticoid production, presumably through stimulation of the hypothalamo-pituitary system.

Bliss, E. L., Migeon, C. J., Branch, C. H. H., Samuels, L. T.: "Reaction of the adrenal cortex to emotional stress." *Psychosom. Med.* **18**: 56-76 (1956).

C13,032/56

In normal people and psychiatric patients emotional stress (subjectively estimated by manifestations of anxiety and tension) whether occurring spontaneously or elicited experimentally, caused consistent but very modest increases in blood and urinary 17-OHCS. These changes were always much less pronounced than those produced by ACTH, Piromen, insulin, electroshock or moderate physical exercise.

Fortier, C., Groot, J. de, Hartfield, J. E.: "Plasma free corticosteroid response to faradic stimulation in the rat." *Acta Endocrinol. (Kbh.)* **30**: 219-221 (1959).

C63,267/59

Kellio, I. V. I., Tala, E. O. J.: "Changes in the free 17-hydroxycorticosteroid levels in plasma after electroshock therapy." *Acta Endocrinol. (Kbh.)* **30**: 99-108 (1959).

J11,258/59

Levine, S.: "Plasma-free corticosteroid response to electric shock in rats stimulated in infancy." *Science* **135**: 795-796 (1962).

D20,781/62

In rats manipulated during infancy, electric shocks caused significant increases of plasma corticoids within fifteen seconds, whereas nonmanipulated subjects did not show this response until after about five minutes. Furthermore, blood corticosteroid elevations were considerably higher in manipulated than in nonmanipulated animals.

Barchas, J. D., Freedman, D. X.: "Brain amines: response to physiological stress." *Biochem. Pharmacol.* **12**: 1232-1238 (1963).

E29,915/63

In rats, swimming to exhaustion especially in cold water caused depletion of brain 5-HT and NEP. Similar changes could not be obtained by having them run in a revolving cage, for under the conditions of the experiment the rats soon gave up and just allowed themselves to be dragged. On the other hand, immersion in cold water did reproduce the catecholamine depletion, whereas several other stressors (electroshock, starvation, hypoxia, surgery, adrenalectomy) were ineffective in this respect. The response is not dependent upon the pituitary-adrenocortical system, since active stressors deplete brain catecholamines even after hypophysectomy,

as does LSD. It is noteworthy that drugs that induce a similar change in brain amines produce a unique pattern of central excitation, acting on brain mechanisms concerned with metabolic and physiologic temperature regulation. "If the stressors have such a central action, a role for the biogenic amines in central as well as in peripheral aspects of temperature regulation should be sought."

Paulsen, E. C., Hess, S. M.: "The rate of synthesis of catecholamines following depletion in guinea pig brain and heart." *J. Neurochem.* **10**: 453-459 (1963).

D69,702/63

In guinea pigs, brain EP was restored about four hours after "electroshock stress." This relatively slow rate suggests that the animals sustained an aftereffect from the treatment. Data on the literature also indicate that electroshock decreases NEP in the brain of guinea pigs after prolonged swimming in cold water, whereas "insulin stress" allegedly causes no change in the catecholamine content of the brain.

Ferguson, H. C., Bartram, A. C. G., Fowlie, H. C., Cathro, D. M., Birchall, K., Mitchell, F. L.: "A preliminary investigation of steroid excretion in depressed patients before and after electro-convulsive therapy." *Acta Endocrinol. (Kbh.)* **47**: 58-68 (1964).

F19,672/64

In five women with depressive illness, electroshock therapy resulted in increased corticoid excretion with a diminution of 11-deoxy-17-oxosteroids. The changes were ascribed to stress.

Levi, R., Maynert, E. W.: "The subcellular localization of brain-stem norepinephrine and 5-hydroxytryptamine in stressed rats." *Biochem. Pharmacol.* **13**: 615-621 (1964).

G11,756/64

Electroshock decreased the total amount of brain stem NEP in normal but not in phenobarbital-sedated rats; it rose above normal in both shocked and unshocked rats treated with 1-phenyl-2-hydrazinopropane (Catron). The 5-HT concentration was altered only after treatment with Catron. Differential, gradient-density centrifugation of brain stem homogenates showed that NEP and 5-HT have approximately the same localization, about 25 percent being found in the fraction composed almost entirely of nerve ending particles. "It is suggested that in animals treated with sedatives or monoamine oxidase inhibitors the brain-stem NE,

ordinarily released by stress, fails to leave the nerve endings."

Wright, P. H., Malaisse, W. J.: "Effects of epinephrine, stress, and exercise on insulin secretion by the rat." *Am. J. Physiol.* **214**: 1031-1034 (1968). F97,956/68

In rats, various stressors (EP, swimming, electroshock) diminish insulin secretion. "It is suggested that endogenous epinephrine released during stress or exercise is sufficient to suppress insulin secretion even under conditions of hyperglycemia" (29 refs.).

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971). H37,353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound and aversive conditioning) increase plasma STH and cortisol levels but the two responses do not run parallel and presumably are regulated by diverse mechanisms. In the case of chair restraint, STH values fall to resting levels whereas cortisol continues to rise.

Madden, J., Rollins, J., Anderson, D. C., Conner, R. L., Levine, S.: "Preshock-produced intensification of passive avoidance responding and of elevation in corticosteroid level." *Physiol. Behav.* **7**: 733-736 (1971). G90,607/71

In rats exposed to inescapable intense electroshock, corticosterone secretion was greater in preshocked animals (mild shock) than in nonpreshocked controls. Passive avoidance behavior was facilitated in preshocked rats.

Samorajski, T., Rolsten, C., Ordy, J. M.: "Changes in behavior, brain, and neuroendocrine chemistry with age and stress in C57-BL/10 male mice." *J. Gerontol.* **26**: 168-175 (1971). G83,474/71

Extensive studies on the histologic and biochemical changes induced by repeated electroshocks, with special reference to the acetylcholinesterase, 5-HT and NEP content of the brain and the histology of the brain, pituitary and adrenals.

Singh, A. K., Singh, R. K., Wahi, R. S., Tandon, A. K., Chansouria, J. P. N., Udupa, K. N.: "Endocrine and metabolic response to electric shock in rabbits: Part II. Changes in cortisone and insulin treated rabbits." *Indian J. Exp. Biol.* **10**: 412-414 (1972). J20,223/72

Allen, J. P., Denney, D., Kendall, J. W., Blachly, P. H.: "Corticotropin release during ECT in man." *Am. J. Psychiatry* **131**: 1225-1228 (1974). J18,141/74

Observations on psychiatric patients receiving electroshock treatment "suggest that the pituitary of man contains a readily dischargeable pool of ACTH that can be secreted promptly in response to a stressful stimulus. Furthermore, the pituitary has the capacity to respond to multiple successive seizures by maintaining elevated plasma ACTH concentrations as new but smaller boluses of ACTH are secreted following the first stimulus."

Pina-Cabral, J. M., Rodrigues, C.: "Blood catecholamine levels, factor VIII and fibrinolysis after therapeutic electroshock." *Br. J. Haematol.* **28**: 371-380 (1974). J18,676/74

Observations on patients undergoing therapeutic electroshock "suggest that while catecholamines are probably not responsible for plasminogen activator release during stress, adrenergic mediation of the concomitant increase in factor VIII is highly probable."

Swanson, D. W., Hanson, N. P., Rosenbaum, A. H., Swenson, W. M.: "Correlation of psychiatric factors and pituitary responsiveness: a negative report." *J. Nerv. Ment. Dis.* **158**: 100-103 (1974). J10,817/74

In both normal and schizophrenic patients, electroshock often caused a rapid increase in plasma FSH and LH, but this was inconstant and apparently not influenced by the mental disease.

Leenen, F. H., Shapiro, A. P.: "Effect of intermittent electric shock on plasma renin activity in rats." *Proc. Soc. Exp. Biol. Med.* **146**: 534-538 (1974). H87,670/74

In rats, repeated electroshocks caused a marked increase in both the renin and corticosterone concentration of plasma. Hypophysectomy did not inhibit the rise in plasma renin activity, which was blocked by dexamethasone and propranolol but potentiated by phentolamine. Presumably, "stress-induced release of renin is mediated via β -adrenergic receptors and... endogenous corticosteroids modify this response."

Bassett, J. R., Cairncross, K. D.: "Time course for plasma 11-hydroxycorticosteroid elevation in rats during stress." *Pharmacol. Biochem. Behav.* **3**: 139-142 (1975). J21,787/75

The time course of plasma 11-OHCS elevation "was studied in two stress situations: regular unsignalled foot shock which produces an intermediate steroid elevation and irregular signalled foot shock with the possibility of escape, which produces an extreme steroid elevation. The initial time course for steroid elevation followed a similar pattern for both treatment groups with the exception that in the irregular signalled group the plasma steroid elevation was more pronounced and there was an indication of biphasic response."

→Varia. O'Connor, W. J., Verney, E. B.: "The effect of increased activity of the sympathetic system in the inhibition of waterdiuresis by emotional stress." *Q. J. Exp. Physiol.* **33**: 77-90 (1945). 95,009/45

Altschule, M. D., Parkhurst, B. H., Tillotson, K. J.: "Decreases in blood eosinophilic leukocytes after electrically induced convulsions in man." *J. Clin. Endocrinol. Metab.* **9**: 440-445 (1949). B26,656/49

In psychiatric patients in whom approximately equal degrees of *eosinopenia* were produced by electroconvulsive therapy or ACTH, only the former caused clinical remission. Presumably, increased ACTH secretion is not the decisive factor responsible for improvement under these conditions.

Taylor, R. H., Gross, M., Ruby, I. J.: "Nonconvulsive electrostimulation and the pituitary-adrenocortical system." *J. Nerv. Ment. Dis.* **114**: 377-383 (1951).

J8,693/51

Both convulsive and nonconvulsive electrostimulation produced marked *eosinopenia* even in schizophrenic patients although earlier investigators claimed that these usually failed to show such a response. Pentothal anesthesia did not prevent this *eosinopenia* which was therefore not attributed to stress but to a direct action of electric current on the hypothalamus. The literature on the effect of electroshock upon blood eosinophils is reviewed (17 refs.).

Royce, J. R., Rosvold, H. E.: "Electroshock and the rat adrenal cortex." *Arch. Neurol. Psychiatry* **70**: 516-527 (1953).

B98,318/53

In rats, repeated electroshocks caused a considerable increase in the weight of the *adrenals*. A single shock sufficed to induce depletion of adrenal ascorbic acid and cholesterol whereas repeated shocks were followed

by a rise of these values above normal, suggesting functional hypertrophy (about 100 refs.).

Lazarus, R. S., Deese, J., Hamilton, R.: "Anxiety and stress in learning: the role of intraserial duplication." *J. Exp. Psychol.* **47**: 111-114 (1954). J13,308/54

Friedman, M., Uhley, H. N.: "Role of the adrenal in hastening blood coagulation after exposure to stress." *Am. J. Physiol.* **197**: 205-206 (1959). C71,261/59

In rats, repeated electroshocks caused depletion of *adrenal cholesterol* and acceleration of *blood clotting* time. The latter was not affected by adrenalectomy.

Sines, J. O.: "The effects of electroconvulsive shock on *emotionality* and autonomic response to subsequent stress in the rat." *J. Gen. Psychol.* **99**: 261-267 (1961).

J23,522/61

Paré, W. P.: "The effect of chronic environmental stress on *stomach ulceration*, *adrenal function*, and *consummatory behavior* in the rat." *J. Psychol.* **57**: 143-151 (1964) (21 refs.). J21,903/64

Khan, A. U., Forney, R. B., Hughes, F. W.: "Plasma free fatty acids in rats after shock as modified by centrally active drugs." *Arch. Int. Pharmacodyn. Ther.* **151**: 466-474 (1964). F26,605/64

Repeated intermittent electric shocks elevated the plasma *FFA* in rats. This was prevented by tranquilizers (pentobarbital and ethanol) in doses that by themselves cause no change in plasma *FFA*.

Reyna, L. J., DiMascio, A., Berezin, N.: "Psychological stress and experimental caries." *Psychosomatics* **8**: 138-140 (1967). F85,046/67

In rats, psychogenic stressors (electroshock, sound) can increase the incidence of *dental caries*.

Conner, R. L., Levine, S., Vernikos-Danellis, J.: "Shock-induced fighting and pituitary-adrenal activity." *Proc. 78th Convention, APA*. 1970, pp. 201-202.

J12,864/70

Observations on *fighting* behavior induced by electroshock in the rat.

Dropp, J. J., Sodetz, F. J.: "Autoradiographic study of *neurons* and *neuroglia* in autonomic ganglia of behaviorally stressed rats." *Brain Res.* **33**: 419-430 (1971).

J20,190/71

Knutson, J. F.: "The effects of shocking one member of a pair of rats." *Psychom. Sci.* **22**: 265-266 (1971). J11,343/71

When one member of a pair of rats was insulated from electric foot-shock, the frequency of *aggression* between them was greatly lowered. Also, the shocked rats developed relatively frequent, stereotyped, successful avoidance responses. Apparently, "avoidance or escape responses to shock will take priority over attack responses to shock."

Lauria, P., Sharma, V. N., Vanjani, S.: "Effect of prolonged stress of repeated electric shock on rat *myocardium*." *Indian J. Physiol. Pharmacol.* **16**: 315-318 (1972).

H80,120/72

Wald, E. D., Mackinnon, J. R., Desiderato, O.: "Production of gastric ulcers in the unrestrained rat." *Physiol. Behav.* **10**: 825-827 (1973). J3,751/73

In unrestrained rats, *gastrointestinal ulcers* developed following six hours of exposure to intermittent electroshocks.

+Varia. Covian, M. R.: "Role of emotional stress in the survival of adrenalectomized rats given replacement therapy." *J. Clin. Endocrinol.* **9**: 678 (1949).

B48,388/49

Unlike domesticated rats, wild Norway rats cannot be indefinitely maintained on sodium chloride after *adrenalectomy* and are particularly sensitive to the fatal effects of electroshock, "indicating that the emotional state of *captive wild rats* is such that therapy sufficient to offset the loss of adrenals in laboratory rats is insufficient to keep the wild rats alive."

Bliss, E. L., Migeon, C. J., Nelson, D. H., Samuels, L. T., Branch, C. H. H.: "Influence of E.C.T. and insulin coma on level of adrenocortical steroids in peripheral circulation." *Arch. Neurol. Psychiatry* **72**: 352-361 (1954). C1,997/54

In schizophrenics, electroconvulsive therapy as well as insulin coma increased the plasma level of 17-OHCS. When *diphenylhydantoin* was used to eliminate cyanosis, apnea and violent muscular movements, seizures still resulted in a rise in corticoids but of shortened duration.

Uhley, H. N., Friedman, M.: "Blood lipids, clotting and coronary atherosclerosis in rats exposed to a particular form of stress." *Am. J. Physiol.* **197**: 396-398 (1959). C73,763/59

In rats kept on a high-fat, high-cholesterol diet in a cage that periodically delivered electric shocks, unusually pronounced hypercholesterolemia, hyperlipemia and coronary atherosclerosis developed at the end of ten months.

Hall, C. E., Schneider, M., Hall, O.: "Increased sensitivity to x-irradiation exhibited by stressed rats." *Radiat. Res.* **17**: 118-126 (1962). D30,291/62

"Electroshock stress" applied before *x-irradiation* does not affect the survival rate of rats, but decreases it if applied afterwards. The same is true of the stress of being shipped to the laboratory.

Schapiro, S., Geller, E., Eiduson, S.: "Neonatal adrenal cortical response to stress and vasopressin." *Proc. Soc. Exp. Biol. Med.* **109**: 937-941 (1962). D24,932/62

In rats, electroshock (unlike natural or synthetic vasopressin) fails to elicit the usual ascorbic acid depletion and increase the corticosterone concentration of the adrenal cortex during the first eight days of life. This "stress-non-responsive period" (SNR period) is ascribed to the "immaturity of the hypothalamic osmoreceptor mechanism which underlies adjustments in vasopressin secretion."

Haltmeyer, G. C., Denenberg, V. H., Thatcher, J., Zarrow, M. X.: "Response of the neonatal rat after subjection to stress." *Nature* **212**: 1371-1373 (1966).

F74,906/66

In the rat, the stress of heat or electric shock during the first five days of life raises the adrenal and plasma concentration of corticosterone. Manifestly, the *neonatal* rat adrenal can respond normally to stressors by both an increased synthesis and release of corticoids. These data contradict earlier reports of a "stress-non-responsive period" (SNR) in this species. When adrenal ascorbic acid depletion is used as an indicator, the situation appears to be different, and reactivity also depends upon the stressor (20 refs.).

Rosenberg, A.: "Production of gastric lesions in rats by combined cold and electrostress." *Am. J. Dig. Dis.* **12**: 1140-1148 (1967). G51,611/67

In rats, combined exposure to *cold* and electrostress was much more effective in producing gastric lesions than either of these stressors alone. "The cold-electrostress-induced gastric lesions were prevented by atropine sulfate, atropine methyl nitrate and

propantheline." Several other central depressants were less effective or ineffective.

Doteuchi, M.: "Studies on the experimental gastrointestinal ulcers produced by reserpine and stress. I. Relationship between production of ulcers and changes in tissue monoamines." *Jap. J. Pharmacol.* **17**: 638-647 (1967). F96,238/67

Ader, R., Friedman, S. B., Grotta, L. J., Schaefer, A.: "Attenuation of the plasma corticosterone response to handling and electric shock stimulation in the infant rat." *Physiol. Behav.* **3**: 327-331 (1968).

H5,148/68

In eight-, fifteen- and twenty-one-day-old rats, stress-induced elevations of plasma corticosterone were first seen at fifteen days, at which time the response to handling and electric shock was similar. Twenty-one-day-old unmanipulated rats showed a greater reaction to electric shock than to handling. Previously shocked animals displayed little adaptation, whereas repeated handling diminished the plasma corticosterone response.

Treiman, D. M., Fulker, D. W., Levine, S.: "Interaction of genotype and environment as determinants of corticosteroid response to stress." *Dev. Psychobiol.* **3**: 131-140 (1970).

G82,877/70

In very young rats, "highly significant and opposing genetic and maternal effects inter-

acted to limit extreme plasma corticosterone concentrations following stress" (electroshock).

Creer, T. L.: "Hunger and thirst in shock-induced aggression." *Behav. Biol.* **8**: 433-437 (1973). H80,353/73

Hunger and thirst did not affect the mean of fighting among rats who initially showed considerable combativeness after electric shocks to the feet. Fasting likewise failed to alter the frequency of fighting in low-aggression rats but water deprivation increased it.

Vogel, J. R., Haubrich, D. R.: "Chronic administration of electroconvulsive shock effects on mouse-killing activity and brain monoamines in rats." *Physiol. Behav.* **11**: 725-728 (1973). J7,248/73

In rats, *mouse killing* tendencies are blocked by chronic electroconvulsive shocks as well as by antidepressant drugs. At the same time, brain NEP concentrations rise (23 refs.).

Thor, D. H., Ghiselli, W. B., Ward, T. B.: "Infantile handling and sex differences in shock-elicited aggressive responding of hooded rats." *Dev. Psychobiol.* **7**: 273-279 (1974). J12,750/74

Handling during infancy caused only minor changes in the aggressive response of male and female rats exposed to electric footshock in adulthood.

Magnetism

Several investigators reported data showing that mice, as well as squirrel monkeys and men, when placed in an electromagnetic field, develop manifestations of stress, particularly increased adrenocortical activity.

Magnetism

(See also our earlier stress monographs, p. xiii)

Barron, C. I., Dreher, J. J.: "Effects of electric fields and negative ion concentrations on test pilots." *Aerosp. Med.* **35**: 20-23 (1964). G37,107/64

The results of a study on pilots exposed to ionic or electric fields "neither support nor negate the hypothesis that negative ions or ions plus electric fields may be beneficial in ameliorating the effects of fatigue or stress."

Friedman, H., Becker, R. O., Bachman, C. H.: "Effect of magnetic fields on reaction time performance." *Nature* **213**: 949-950 (1967). E79,913/67

Observations on man "indicate that experimentally produced modulated magnetic fields can significantly affect reaction time performance." [The relationship of this finding to stress is not specifically discussed (H.S.).]

Barnothy, M. F., Sümegi, I.: "Abnormalities in organs of mice induced by a magnetic field." *Nature* **221**: 270-271 (1969).

H7,197/69

In a magnetic field, various organ changes occurred—especially in the adrenal cortex—that were suggestive of stress produced by other means.

Negoescu, I., Constantinesco, A., Don, M., Helteanu, C.: "Le stress et le transport des hormones thyroïdiennes" (Stress and transport of thyroid hormones). *Rev. Roum. Endocrinol.* **6**: 215-220 (1969).

J15,906/69

In rats subjected to the stressor effect of repeated exposure to a magnetic field, the free thyroxine content of the blood was raised whereas the albumin bound fraction was diminished. PBI was not significantly altered (22 refs.).

Barnothy, M. F., Sümegi, I.: "Effects of the magnetic field on internal organs and the endocrine system of mice." In: Barnothy, M. F., *Biological Effects of Magnetic Fields*, pp. 103-126. New York and London: Plenum Press, 1969.

E8,191/69

In this monograph on the biologic effects of magnetic fields, a chapter deals with the endocrine system. It is assumed that many organ changes (particularly those in the adrenals) that develop in mice living in a homogeneous magnetic field are manifestations of the G.A.S.

Krueger, W. F., Giarola, A. J., Bradley, J. W., Daruvalla, S. R.: "Influence of low-

level electric and magnetic fields on the growth of young chickens." *Biomed. Sci. Instrum.* **9**: 183-186 (1972). H79,363/72

In chickens, continuous exposure to electromagnetic radiation depressed growth and food consumption. [Earlier literature on the stressor effect of magnetic fields is not described (H.S.).]

Friedman, H., Carey, R. J.: "Biomagnetic stressor effects in primates." *Physiol. Behav.* **9**: 171-173 (1972).

G97,850/72

Urinary corticoid excretion rose in squirrel monkeys exposed to a magnetic field. "This was the result of an initial transient elevation of the stress product early in the experimental period which subsided with continued magnetic field exposure."

Romero-Sierra, C., Tanner, J. A.: "Biological effects of nonionizing radiation: an outline of fundamental laws." *Ann. N. Y. Acad. Sci.* **238**: 263-272 (1974).

H95,268/74

Davis, A. R., Rawls, W. C. Jr.: *Magnetism and its Effects on the Living System*, p. 132. Hicksville, N.Y.: Exposition Press, 1974.

E10,705/74

Bassett, C. A. L., Pawluk, R. J., Pilla, A. A.: "Acceleration of fracture repair by electromagnetic fields. A surgically noninvasive method." *Ann. N. Y. Acad. Sci.* **238**: 242-262 (1974).

H95,267/74

Osmotic Pressure

Intense osmotic changes have been proven to act as highly potent stressors in various species.

Osmotic Pressure

(See also our earlier stress monographs, p. xiii and the section on Electrolytes in the subdivision, Drugs, under Stressors and Conditioning Agents.)

McBean, R. L., Goldstein, L.: "Accelerated synthesis of urea in *Xenopus laevis* during osmotic stress." *Am. J. Physiol.* **219**: 1124-1130 (1970).

J21,501/70

Haider, S., Sathyanesan, A. G.: "Osmotic

stress induced histochemical changes in the ependyma and the preoptic neurons of the teleost fish *Rita rita* (Ham.) with a note on the periventricular vascularization." *Z. Mikrosk. Anat. Forsch.* **87**: 549-560 (1973).

J9,414/73

Narasimham, C., Parvatheswarao, V.: "Adaptations to osmotic stress in a freshwater euryhaline teleost, *Tilapia mossambica*. X. Role of mucopolysaccharides." *Acta Histochem. (Jena)* **51**: 37-49 (1974).

J21,845/74

Microorganisms and Their Toxins

Infections are particularly powerful stressors, and the adaptive hormones produced during systemic stress can considerably influence resistance to microbes and their toxins.

In certain species such as the guinea pig, bacterial endotoxins frequently produce hemorrhagic necrosis of the adrenals, which can be prevented by hypophysectomy, but up to now it has not been possible to block it by destruction of hypothalamic nuclei except those situated near the stalk. This selective adrenal necrosis, often combined with the Waterhouse-Friderichsen syndrome, is so characteristic of certain bacterial toxins that it could hardly be a consequence of nonspecific stress alone. Probably, some special conditioning circumstances are involved in its pathogenesis, although these have not yet been clearly identified.

Polymorphonuclear leukocytosis is likewise so predominant during infection that its development must be facilitated by some specific conditioning circumstances; yet to a lesser degree, it also occurs (in combination with eosinopenia) following exposure to stressors other than microorganisms.

Numerous publications describe the typical stress-induced hormonal changes elicited by microorganisms and their toxins, particularly the rises in ACTH and glucocorticoid production. Certain bacterial polysaccharide preparations (for example, Piromen) are frequently used as standard stressors in clinical medicine, either to test the functional efficiency of the pituitary-adrenocortical system or as nonspecific therapeutic agents.

In man, bacterial pyrogens also augment plasma STH levels.

Among the factors which can particularly predispose to bacterial stressors are starvation, x-irradiation, artificial hibernation, and a rise in ambient temperature. On the other hand, a certain amount of crowding allegedly protects cockerels against *E. coli* infection, owing to cross-resistance. Furthermore, immune reactions to various antigens are strongly depressed by certain bacterial toxins. It remains to be shown whether this immunosuppressive effect is mediated exclusively by an increase in endogenous glucocorticoid production or by other factors as well.

Microorganisms and Their Toxins

(See also our earlier stress monographs, p. xiii)

Generalities. Schmid, R., Gonzalo, L., Blobel, R., Muschke, E., Tonutti, E.: "Über die hypothalamische Steuerung der ACTH-Abgabe der Hypophyse bei Diphtherie-Toxin-Vergiftung" (The hypothalamic regulation of ACTH secretion from the hypophysis in diphtheria toxin poisoning). *Endokrinologie* 34: 65-91 (1957).

D74,892/57

In guinea pigs, selective destruction of anterior or posterior hypothalamic nuclei could not prevent the hemorrhagic necrosis of the adrenals normally produced by bacterial endotoxin. Lesions situated closer to the pitu-

itary stalk did offer protection against this effect.

Schayer, R. W.: "Relationship of induced histidine decarboxylase activity and histamine synthesis to shock from stress and from endotoxin." *Am. J. Physiol.* 198: 1187-1192 (1960). C90,163/60

Dalmau-Ciria, M.: "Pirógenos y reacción de alarma" (Pyrogens and the alarm reaction). *Med. Clin. (Barcelona)* 40: 366-369 (1963). E31,173/63

Pyrogens are described as "alarmogens" in that they elicit the acute phase of the G.A.S.

Yuwiler, A., Geller, E., Schapiro, S., Guze, L. B.: "Absence of adrenocortical stress re-

sponses in experimental pyelonephritis." *Proc. Soc. Exp. Biol. Med.* **122**: 465-468 (1966). F67,285/66

In rats, pyelonephritis caused by intravenous *Streptococcus faecalis* produces no obvious evidence of general illness or any change in adrenocortical activity, characteristic of stress. Hence, "it seems most likely that experimental pyelonephritis simply does not elicit a stress response."

Gorizontov, P. D.: "Infection and corticosteroid hormones." *Klin. Med.* **44** No. 6: 5-12 (1966) (Russian). G43,190/66

Discussion of the relationships between infection and the G.A.S., with major emphasis, on the one hand, upon microbes and their toxins as stressors and, on the other, upon stress hormones as modifiers of infectious disease.

Berry, L. J., Agarwal, M. K., Snyder, I. S.: "Comparative effect of endotoxin and reticuloendothelial 'blocking' colloids on selected inducible liver enzymes." In: Luzio, N. R. di and Paoletti, R., *The Reticuloendothelial System and Atherosclerosis*, pp. 266-274. New York: Plenum Press, 1967. E7,069/67

In mice, stress induced by endotoxin lowers the activity of tryptophan pyrolase and increases that of tyrosine- α -ketoglutarate transaminase in the liver. Presumably, such enzyme responses are characteristic of stress.

Rosoff, C. B., Goldman, H.: "Effect of the intestinal bacterial flora on acute gastric stress ulceration." *Gastroenterology* **55**: 212-222 (1968). G60,200/68

In rats, polymyxin B offers significant protection against acute stress ulcers elicited by restraint, probably because this nonabsorbable antibiotic reduces the coliform bacteria in the intestine. "This change in the flora results in a decrease in the motor tone of the stomach and cecum, and in the volume and concentration of gastric acid produced in response to the stress of immobilization. The protection offered by the coliform-poor state is eliminated when endotoxin is given to antibiotic-treated animals." Conversely, systemic administration of endotoxin increases both gastric acid and stress ulcers. "It is suggested that, under the conditions induced by stress, detoxification mechanisms suffer and permit absorbed bacterial products to reach the systemic circulation and stimulate the hypothalamus."

Richardson, R. S., Norton, L. W., Sales,

J. E. L., Eiseman, B.: "Gastric blood flow in endotoxin-induced stress ulcer." *Arch. Surg.* **106**: 191-195 (1973). G99,516/73

In pigs, endotoxin shock invariably caused stress ulcers of the stomach, with changes in the gastric circulation.

Huldt, G., Gard, S., Olovson, S. G.: "Effect of toxoplasma gondii on the thymus." *Nature* **244**: 301-303 (1973).

H78,384/73

In adult mice infected with *Toxoplasma gondii*, thymus weight and immune responses were severely depressed. "A direct thymocytolytic effect of the toxoplasms can probably be ruled out, as they were never found in thymic lymphocytes and experiments on cultured lymphocytes have failed to indicate any direct or indirect lytic effect of the parasite. The possibility of some kind of interference with the differentiation and migration of thymocytes should be considered."

Terragna, A., Rossolini, A., Bianchini, A. M., Cellesi, C., Mattei, C.: "Alterazioni metaboliche nello shock da batteri Gram negativi. Ricerche sperimentali" (Metabolic changes in shock produced by Gram negative bacteria. Experimental studies). *G. Mal. Infett.* **25**: 529-557 (1973). J11,411/73

Small monograph on the metabolic, histochemical and EM alterations characteristic of endotoxin shock in the rabbit (almost 100 refs.).

Goodenough, S., Simmons, G., Mullane, J., Feldman, N., Huber, G.: "Impairment of pulmonary antibacterial defenses by experimental stress" (abstracted). *Clin. Res.* **22**: 442A (1974).

H90,289/74

In rats, the stress of restraint reduced resistance to infection, especially in the lungs. "Alveolar lining material from stressed animals had diminished alveolar macrophage bactericidal stimulating activity, implying that the effect of the stress-induced impairment is mediated through this acellular alveolar lining component of the host defense system rather than on the cellular alveolar macrophage component."

Greenberg, L., Himal, H. S.: "Hydrochloric acid clearance and endotoxin induced duodenal erosions in dogs." *Surg. Gynecol. Obstet.* **139**: 561-565 (1974).

H92,596/74

In dogs, intravenous endotoxin inhibited transmucosal hydrogen ion passage, bile flow and pancreatic juice flow, all of which normally cleared instilled hydrochloric acid.

When the bile and pancreatic ducts were ligated and acid given, the high concentration of hydrochloric acid remaining in the pouches led to acute duodenal erosions. When no acid was instilled, endotoxin markedly stimulated fluid and electrolyte flow into the lumen, and this was associated with hemorrhagic necrosis of the duodenal mucosa. The authors conclude that duodenal damage caused by endotoxin may vary from acute focal erosions to hemorrhagic necrosis, depending upon the ability of the duodenum to clear hydrochloric acid.

Leise, E. M., LeSane, F., Gray, I.: "Lymphocyte and polymorphonuclear enzymes in stress. IV. Changes associated with an acute bacterial infection with *Diplococcus pneumoniae*." *Biochem. Med.* 9: 206-213 (1974). J11,685/74

Leise, E. M., LeSane, F., Gray, I.: "V. Changes associated with a viral infection: herpes simplex." *Biochem. Med.* 9: 214-224 (1974). J11,686/74

Holtzman, S., Schuler, J. J., Earnest, W., Erve, P. R., Schumer, W.: "Carbohydrate metabolism in endotoxemia." *Circ. Shock.* 1: 99-105 (1974). J14,353/74

In rats, dexamethasone, even after endotoxin, reduced the magnitude of changes in carbohydrate metabolism. Presumably, one of the beneficial effects of glucocorticoids "may be to confer protection in endotoxemia by stimulating gluconeogenesis" (27 refs.).

Bertók, L., Kocsár, L. T.: "Die Rolle des Endotoxins beim intestinalen Syndrom der Strahlenkrankheit" (The role of endotoxin in the intestinal syndrome of radiation disease). *Wiss. Z. Karl-Marx Univ. Leipzig, Math.-Naturwiss. R.* 23: 65-66 (1974). J15,372/74

In rats sensitized with lead acetate, minute doses of bacterial endotoxin sufficed to cause death. By the use of this technique it could be demonstrated that following x-irradiation, endotoxin is absorbed into the blood. Hence, endotoxinemia probably plays an important role in the irradiation syndrome.

Bailenger, J., Carcenac, F.: "Répercussions du parasitisme par *Strongyloides ratti* sur la sécrétion des gluco-cortico-stéroïdes chez le rat." (Repercussions of parasitism by *Strongyloides ratti* on the secretion of glucocorticoids in the rat). *Int. J. Parasitol.* 4: 307-310 (1974). J16,045/74

In rats, infestation with *Strongyloides ratti* leads to increased glucocorticoid secretion during the alarm reaction, with a hypofunc-

tion of the adrenals allegedly related to the phase of resistance of the G.A.S.

→**Hormones.** Altschule, M. D., Parkhurst, B. H., Promisel, E.: "Effects of intravenous injection of typhoid vaccine on blood leukocytes and adrenal cortex." *Arch. Intern. Med.* 86: 505-518 (1950). B26,082/50

In patients given typhoid vaccine intravenously for the treatment of psychoses, there was lymphopenia, eosinopenia and fever. The ratio of urinary uric acid to creatinine varied inversely with the fever. 17-KS excretion followed a pattern typical with other stressors.

Bliss, E. L., Migeon, C. J., Branch, C. H., Samuels, L. T.: "Reaction of the adrenal cortex to emotional stress." *Psychosom. Med.* 18: 56-76 (1956). C13,032/56

In normal people and in psychiatric patients emotional stress (subjectively estimated by manifestations of anxiety and tension), whether occurring spontaneously or elicited experimentally, caused consistent but very modest increases in blood and urinary 17-OHCS. These changes were always much less pronounced than those produced by ACTH, Piromen, insulin, electroshock or moderate physical exercise.

Wexler, B. C., Faehnrich, J. L., Weiss, M. E., Grace, O. D.: "The use of bacterial polysaccharide (Piromen) as a pituitary-adrenal stimulant in dogs." *Am. J. Vet. Res.* 18: 642-647 (1957) (26 refs.).

C51,233/57

Wexler, B. C., Dolgin, A. E., Zaroslinski, J. F., Tryczynski, E. W.: "Effects of a bacterial polysaccharide (Piromen) on the pituitary adrenal axis: cortisone blockade of Piromen-induced release of ACTH." *Endocrinology* 63: 201-204 (1958).

C56,640/58

In rats, ACTH release by bacterial polysaccharide (Piromen) is blocked by cortisone but not by DOC.

Frommel, E., Fleury, C., Ledebur, I. von, Beguin, M.: "On the differential mobilisation of adrenalin and cortisone in the progress of stress under hypothermic conditions of external cause and of vaccine fever." *Med. Exp. (Basel)* 6: 261-264 (1962). D27,769/62

In guinea pigs, hypothermia "due to refrigeration, mobilizes adrenalin with an ephemeral action and brief duration, whereas vaccine fever stimulates the hormones of the adrenal cortex, possessing a slower and more lasting effect."

Fukui, S.: "The influence of stress upon the excretion of adrenocortical hormone in pulmonary tuberculosis. II." *Kekkaku* **37**: 125-129 (1962) (Japanese). J23,475/62

Greenwood, F. C., Landon, J.: "Growth hormone secretion in response to stress in man." *Nature* **210**: 540-541 (1966).

F65,986/66

In man, anxiety causing emotional stress or injection of pyrogen (kind not specified) increased plasma STH levels.

Frohman, L. A., Horton, E. S., Lebovitz, H. E.: "Growth hormone releasing action of a pseudomonas endotoxin (Piromen)." *Metabolism* **16**: 57-67 (1967). F75,314/67

In man, *Pseudomonas* endotoxin given intravenously elevates both the ACTH and the STH levels of the plasma.

Jenkins, J. S.: "The pituitary-adrenal response to pyrogen." In: James, V. H. T. and Landon, J., *Memoirs of the Society for Endocrinology*. No. 17, pp. 205-212. Cambridge: Cambridge University Press, 1968.

E7,508/68

In man, the stressor effect of bacterial pyrogens provides a useful test of pituitary-adrenal reactivity as indicated by the resulting increase in plasma cortisol. "If our present views on the pituitary site of its action are correct, the pyrogen test would seem to be complementary to such procedures as the vasopressin test, where the site of action seems to lie in the hypothalamus."

Matsui, N., Ishihara, I., Ukai, M., Miyakawa, M.: "Germfree environment and adrenocortical function in the rat." *A.R. Res. Inst. Env. Med. Nagoya Univ.* **19**: 51-60 (1972).

H80,428/72

Circadian variations in plasma and adrenal 11-OHCS were somewhat smaller in adult germfree rats than in conventional rats, although the plasma 11-OHCS levels were slightly higher. The stress of handling caused the usual increase in both plasma and adrenal 11-OHCS.

Zeitoun, M. M., Hassan, A. I., Hussein, Z. M., Fahmy, M. S., Ragab, M., Hussein, M.: "Adrenal glucocorticoid function in acute viral infections in children." *Acta Paediatr. Scand.* **62**: 608-614 (1973).

J9,160/73

In Egyptian children, plasma 17-OHCS levels rose under the influence of all viral infections studied (measles, chickenpox, mumps, poliomyelitis). ACTH and metyra-

pone tests revealed normal pituitary-adrenal function (25 refs.).

Spackman, D., Riley, V.: "Increased corticosterone, a factor in LDH-virus induced alterations of immunological responses in mice" (abstracted). *Proc. Am. Assoc. Cancer Res.* **15**: 143 (1974). H83,767/74

In mice, LDH-virus increases blood corticosterone levels and causes thymus involution with lymphocytopenia, that is, it causes a stress reaction. It is possible that LDH-virus modifies neoplastic diseases by inhibiting immune responses through its stressor effects.

Rayfield, E. J., George, D. T., Beisel, W. R.: "Altered growth hormone homeostasis during acute bacterial sepsis in the rhesus monkey." *J. Clin. Endocrinol. Metab.* **38**: 746-754 (1974). H86,214/74

Studies on monkeys suggest that chlorpromazine can suppress the exaggerated STH response following an intravenous glucose load during the stress of acute infection.

+Varia. Malmros, H.: "The relation of nutrition to health. A statistical study of the effect of the war-time on arteriosclerosis, cardiosclerosis, tuberculosis and diabetes." *Acta Med. Scand.* **138**: 137-153 (1950).

B60,638/50

During the postwar years in Germany *starvation* increased the incidence of tuberculosis.

Egdahl, R. H.: "The differential response of the adrenal cortex and medulla to bacterial endotoxin." *J. Clin. Invest.* **38**: 1120-1125 (1959).

G33,275/59

In dogs, *spinal cord transection* at C-7 abolishes adrenal medullary discharge by large doses of bacterial endotoxin but leaves febrile, hypotensive and adrenal cortical responses intact. "Epinephrine release is not necessary for the febrile and adrenocortical stimulating effects of endotoxin."

Vaškú, J.: "Die Beeinflussung der experimentellen diphtherischen Intoxikation durch den künstlichen Winterschlaf" (The influence of artificial hibernation on experimental diphtheria intoxication). *Z. Gesamte Inn. Med.* **16**: 885-894 (1961). D80,395/61

Hibernation did not protect guinea pigs against the adrenal changes elicited by diphtheria toxins, but it did increase their sensitivity as indicated by a rise in mortality. The "artificial hibernation" (drugs plus cold) used in these experiments acted as a stressor.

Noble, G. A.: "Stress and parasitism. I. A preliminary investigation of the effects of stress on ground squirrels and their parasites." *Exp. Parasitol.* **11**: 63-67 (1961).

G38,126/61

In ground squirrels (*Citellus armatus*), exposure to various stressors increased susceptibility to infection with protozoa, mostly Trichomonas.

Siegel, H. S., Gross, W. B.: "Social grouping, stress and resistance to coliform infection in cockerels." *Poult. Sci.* **44**: 1530-1536 (1965).

G37,829/65

In cockerels subjected to various types of social grouping, "evidences of mild stress such as lower total leucocytes, increased adrenal weight, reduced bursa weight and/or reduced adrenal cholesterol concentrations were discernible." *E. coli* infection caused more severe leukopenia and plasma corticosterone levels rose, but under certain conditions there was "cross" or 'nonspecific' resistance as suggested by Selye."

Gross, W. B., Siegel, H. S.: "The effect of social stress on resistance to infection with *Escherichia coli* or *Mycoplasma gallisepticum*." *Poult. Sci.* **44**: 998-1001 (1965).

J11,921/65

"Social stress" was produced in chickens by moving males into cages with other birds according to a schedule that kept contact with previously encountered birds to a minimum. After two weeks their resistance to *E. coli* inoculation was increased but their sensitivity to *Mycoplasma gallisepticum* remained unchanged.

Osborne, J. C., Meredith, J. H.: "The influence of environmental and surgical stressors on susceptibility to bacterial endotoxin." *Exp. Med. Surg.* **28**: 39-44 (1970).

H39,299/70

In young piglets, "stress associated with transport, weaning, sunburn and a new environment appeared to be responsible for a state of decreased susceptibility to bacterial endotoxin."

Hamilton, P. B., Harris, J. R.: "Interaction of aflatoxicosis with *Candida albicans* infections and other stresses in chickens." *Poultry Sci.* **50**: 906-912 (1971).

J21,253/71

Kurasz, S., Musiatowicz, B., Borzuchowska, A., Swiderska, K.: "Histologische und histochemische Veränderungen in der Nebennierenrinde des Kaninchens nach experimenteller Infektion mit *Salmonella typhi murium* und Bestrahlung" (Histologic and histochem-

ical changes of the adrenal cortex of rabbits after experimental infection with *Salmonella typhimurium* and irradiation). *Zentralbl. Bakteriol. [Orig. A]* **224**: 463-471 (1973).

J11,180/73

In rabbits, infection with *Salmonella typhimurium* plus *x-irradiation* produces adrenocortical changes characteristic of the alarm reaction. These are more intense following exposure to both agents than after application of either of them alone.

Wessenberg, H.: "The pathogenicity of entamoeba histolytica: is heat stress a factor?" *Perspect. Biol. Med.* **17**: 250-266 (1974).

H81,930/74

Review of the literature and personal observations suggest that heat stress, especially in combination with physical exertion and solar radiation, predisposes to infection with *Entamoeba invadens* and *histolytica*. In military epidemics, the emotional factor of anxiety also plays an important role. "Whether or not heat stress is the directly antecedent cause of tissue invasion, the lesson seems clear regarding the danger of heat stress to carriers of the amoebae or to those exposed to infection" (66 refs.).

Melby, J. C.: "Systemic corticosteroid therapy: pharmacology and endocrinologic considerations." *Ann. Intern. Med.* **81**: 505-512 (1974).

J16,876/74

In patients with rheumatoid arthritis, pyrogen therapy was often superior to treatment with glucocorticoids. "High-dose corticosteroid therapy abolished the hypothalamic-pituitary-adrenal response to pyrogen stress, whereas low doses of steroids produced only insignificant alterations to the response to pyrogen stress. Other studies involving testing of the negative feedback response (metyrapone test) may be abnormal even at rather modest doses of corticosteroids."

Gross, W. B.: "Stressor effects of initial bacterial exposure of chickens as determined by subsequent challenge exposures." *Am. J. Vet. Res.* **35**: 1225-1228 (1974).

J23,893/74

Chickens bred for a low concentration of plasma corticosterone "inoculated initially with live or killed *Escherichia coli* had increased resistance to *E. coli*, lessened resistance to *Mycoplasma gallisepticum*, and reduced capability to produce antibody." Chickens selected for a high corticosterone concentration were less responsive to the initial inoculation. Metyrapone blocked the resistance induced by the exposure to *E. coli*.

Immunity

As expected, any intense immune reaction, particularly serum sickness or severe allergy, can act as a powerful stressor. In guinea pigs sensitized with heterologous protein, repeated injections of the antigen have been said to produce the typical three stages of the G.A.S.

In rabbits, repeated inoculation with foreign proteins causing a protracted state of hypersensitivity can bring on cardiovascular and renal lesions similar to those elicited by other stressors.

Immunity

(See also our earlier stress monographs, p. xiii)

Cutuly, E., Cutuly, E. C.: "Inhibition of gonadotropic activity by sex hormones in parabiotic rats." *Endocrinology* **22**: 568-578 (1938). 72,076/38

Rats united by parabiosis go through a critical period during the first or second week after the operation. "In this stage the animals may present one or all of the symptoms described by Selye under the term 'alarm reaction.'"

Dougherty, T. F., White, A.: "Pituitary-adrenal cortical control of lymphocyte structure and function as revealed by experimental X-radiation." *Endocrinology* **39**: 370-385 (1946). 95,612/46

"CBA mice, 60 to 80 days old, received total body X-radiation. A large dose of X-rays, 200 r, produced within 3 hours a lymphopenia, tissue lymphocyte degeneration, and total serum protein and gamma globulin increases. These changes also occurred in 1 day postoperative adrenalectomized mice receiving 200 r. This dose gave an anamnestic response in previously immunized mice in the absence of the adrenals." Smaller x-ray doses were effective in intact but not in adrenalectomized mice, presumably because the action is partially mediated through the pituitary-adrenal axis.

Thompson, R. M., Arnold, A. C., Mitchell, R. B.: "Effects of stresses associated with flying on the cardiovascular-renal lesions produced by hypersensitive reactions. I. Effects of acute altitude exposure on the cardiovascular-renal lesions in hypersensitive animals." *Tex. Rep. Biol. Med.* **9**: 834-853 (1951). B75,765/51

Hypersensitivity to foreign proteins and/or hypoxia was induced in rabbits. "The degree of heart and kidney damage was much

greater with a combination of the protracted hypersensitive state and exposure to simulated high altitude than in the animals prepared with either the hypersensitive state alone or the altitude stress alone."

Gupta, S., Kumar, S.: "Studies in anaemia of infection. Part VI. Relation of plasma iron with stress and adreno-cortical function." *Indian. J. Med. Res.* **48**: 140-145 (1960). C99,744/60

Since various divergent stimuli, including infections, produce a common state of distress in rabbits and man, "it is postulated that 'stress' caused by these stimuli may be concerned in some way with the production of hypoferraemia."

Marsh, J. T., Lavender, J. F., Chang, S. S., Rasmussen, A. F.: "Poliomyelitis in monkeys: decreased susceptibility after avoidance stress." *Science* **140**: 1414-1415 (1963). D69,198/63

In cynomolgus monkeys, "avoidance stress" prior to inoculation with Type I polio-virus protected against the fatal effect of the infection. The circulating lymphocytes decreased significantly during stress. These findings contrasted sharply with earlier observations in which stressors diminished the resistance of mice to virus infection. However, a factor of different timing may be important (10 refs.).

Johnsson, T., Lavender, J. F., Hultin, E., Rasmussen, A. F. Jr.: "The influence of avoidance-learning stress on resistance to Coxsackie B virus in mice." *J. Immunol.* **91**: 569-575 (1963). G37,497/63

Mice became particularly susceptible to infection with Coxsackie virus B1 during avoidance learning stress. Furthermore, "a significantly higher virus titer could be demonstrated in the pancreas, liver, heart and muscle of stressed mice as compared to unstressed mice."

Fortak, W.: "Morphologic and histochemical investigations of the adrenal gland in guinea pigs during sensitization with heterologous protein." *Endokrinol. Pol.* **16**: 457-473 (1965) (Polish). F72,853/65

In guinea pigs sensitized with heterologous protein, the adrenals "show typical, three-phasic changes, indicating hypersecretion of the hormones during the early period of sensitization, and relative stability of hormone secretion during the unstable period of sensitization but hormonal exhaustion during the late period of sensitization. In the late period of sensitization the guinea pigs showed the highest sensitivity after the second application of protein antigen. From the results obtained the author concludes that the pathogenesis of the changes in the adrenal glands can be explained on the basis of Selye's General Adaptation Syndrome."

Johnsson, T., Rasmussen, A. F.: "Emotional stress and susceptibility to poliomyelitis virus infection in mice." *Arch. Gesamte Virusforsch.* **17**: 392-397 (1965).

G36,032/65

In mice, the stress induced by avoidance learning increased susceptibility to poliomyelitis virus.

Friedman, S. B., Ader, R., Glasgow, L. A.: "Effects of psychological stress in adult mice

inoculated with Coxsackie B viruses." *Psychosom. Med.* **27**: 361-368 (1965).

J15,626/65

In mice exposed to various environmental stressors, susceptibility to infection with Coxsackie virus B2 was greatly increased.

Anderlik, P., Bános, Z., Szeri, I., Koltay, M., Virág, I.: "Response to stressors of mice undergoing graft-versus-host reaction." *Experientia* **26**: 94-95 (1970).

H21,168/70

In mice, intravenous injection of homologous splenic cells causes lymphopenia with body weight loss. Following such treatment, these animals no longer respond to a second stressor with further lymphopenia.

Huldt, G., Gard, S., Olovson, S. G.: "Effect of toxoplasma gondii on the thymus." *Nature* **244**: 301-303 (1973).

H78,384/73

In adult mice infected with *Toxoplasma gondii*, thymus weight and immune responses were severely depressed. "A direct thymocytolytic effect of the toxoplasms can probably be ruled out, as they were never found in thymic lymphocytes and experiments on cultured lymphocytes have failed to indicate any direct or indirect lytic effect of the parasite. The possibility of some kind of interference with the differentiation and migration of thymocytes should be considered."

Hypoxia, Decreased Barometric Pressure and Hyperbaric Oxygenation

The stressor effects of hypoxia and decreased barometric pressure have been examined mainly in connection with aerospace medicine, diving, mountaineering and populations normally living at very high altitudes. As expected, lack of oxygen can produce typical stress manifestations such as a discharge of ACTH, glucocorticoids and catecholamines, eosinopenia, lymphopenia and decreased performance in various classic stress tests. At the same time, there is adrenal enlargement with loss of cholesterol and lipids, and thymus atrophy with a variety of nonspecific metabolic changes.

As with so many other stressors encountered in daily life, hypoxia rarely affects man unaccompanied by conditioning factors whose effects are difficult, if not impossible, to separate from those of a lack of oxygen in itself. Among these, the most important are an increase in carbon dioxide or—in the case of mountaineering, diving or parachute jumping—emotional excitement, cold and muscular fatigue.

Upon prolonged exposure to high altitudes or other agents associated with comparative oxygen deficiency, a considerable degree of adaptation can occur.

In rats under reduced oxygen tension, the body temperature drops but returns to normal after three or four days. This acquired adaptation is not dependent on the

presence of the adrenals since it persists after adrenalectomy if the animals are maintained on corticoids.

Interestingly, rats subjected to oxygen under pressure develop an adrenal enlargement with lipid depletion not unlike that caused by hypoxia. Here again, an elevation of tissue carbon dioxide may be a complicating factor.

Adrenalectomy allegedly increases survival after exposure to high oxygen pressure; this protection is said to be counteracted both by adrenocortical extract and EP.

Up to now, only a few investigators have reported any changes in blood insulin, glucagon, renin, or urinary aldosterone levels as a result of exposure to high altitudes.

In fasted rats exposed to reduced oxygen pressure, hepatic glycogen stores accumulate considerably, but this may be due to a loss of carbon dioxide caused by hyper-ventilation rather than to hypoxia per se.

Increased lactic acid excretion (similar to that produced by EP) has been regarded as an indicator of the severity of hypoxic stress.

Stimulation of splenic erythropoiesis is undoubtedly a specific adaptive response to lack of oxygen. It remains to be seen, however, whether the malformations occasionally observed in the young of mice exposed to hypoxia in pregnancy are true stress manifestations although malformations have been noted in the offspring of animals and women exposed to other stressors during pregnancy.

Among the factors that can significantly affect the stress response to hypoxia, temperature variations, muscular work and malnutrition have received special attention.

Hypoxia, Decreased Barometric Pressure including Hyperbaric Oxygenation

(See also our earlier stress monographs, p. xiii)

Generalities. Giragossintz, G., Sundstroem, E. S.: "Cortico-adrenal insufficiency in rats under reduced pressure." *Proc. Soc. Exp. Biol. Med.* **36**: 432-434 (1937).

A6,932/37

In rats kept at reduced oxygen pressure, "intestinal hemorrhages" and "histological evidence for adrenal damage" were obtained. In adrenalectomized rats exposed to low oxygen pressure, cortical extract offered some protection.

Sundstroem, E. S., Michaels, G.: "The adrenal cortex in adaptation to altitude, climate, and cancer." *Mem. University of California* **12**: 1-410 (1942).

B23,079/42

Liere, E. J. van: *Anoxia, Its Effect on the Body*, p. 269. Chicago: University of Chicago Press, 1942.

B26,199/42

Monograph on the somatic effects of hypoxia without direct reference to the G.A.S. (178 refs.).

Mitchell, H. H., Edman, M.: *Nutrition and Climatic Stress*, p. 235. Springfield, Ill.: Charles C Thomas, 1951.

B65,070/51

Technical discussion of observations on stress caused by cold, heat, high altitude and acceleration in relation to the nutrition of man (more than 750 refs.).

Flückiger, E., Verzar, F.: "Überdauern der Adaptation an niedrigen atmosphärischen Druck, nachgewiesen an der Wärmeregulation" (Body temperature regulation indicating retained adaptation under reduced oxygen tension). *Helv. Physiol. Pharmacol. Acta* **11**: 67-72 (1953).

B92,392/53

In rats exposed to reduced oxygen tension the body temperature drops, but it returns to normal after three to four days. "This 'retained adaptation' is not dependent on the presence of the adrenals. The phenomenon can also be seen in adrenalectomized rats kept alive with corticoids."

Marbarger, J. P., Wechsberg, P. H., Pestel, C. V., Vawter, G. F., Franzblau, S. A.: "Altitude stress in subjects with impaired cardiorespiratory function. A comparison of the responses of normal subjects, patients with angina pectoris, and patients with anemia to hypoxia" *J. Aviat. Med.* **24** Sect. 2, Supp.: 263-300 (1953).

H63,339/53

Haymaker, W., Strughold, H.: "Atmospheric hypoxidosis." In: Lubarsch, O., Henke, F., Rössle, R., *Handbuch der Spe-*

ziellen Pathologischen Anatomie und Histologie: Nervensystem (Handbook of specialized pathology and anatomy: the nervous system), pp. 1673-1711. Berlin, Göttingen and Heidelberg: Springer Verlag, 1957.

D36,513/57

Very extensive review on the effect of atmospheric hypoxia upon various organ changes and the possibilities of adaptation to lack of oxygen. The G.A.S. is not specifically discussed (several hundred refs.).

Bruner, H., Jovy, D., Klein, K. E.: "Hypoxia as a stressor." *Aerosp. Med.* **32**: 1009-1018 (1961). D14,766/61

Brüner, H., Jovy, D., Klein, K. E., Ruff, S.: "Zur Beurteilung der biologischen Leistungreserve eines Piloten" (Examination of the energy reserve of pilots). *Jarbuch W.G.L.R.* pp. 576-581 (1962). G23,490/62

Description of a hypoxia resistance test which allegedly measures the energy reserve of a pilot exposed to repeated demands simulating flight conditions. "This method is a simple and time-saving one, and is very suitable for the selection and routine examinations of the flying personnel."

Stickney, J. C., Liere, E. J. van: *Hypoxia*. Chicago: University of Chicago Press, 1963. E10,620/63

Edholm, O. G., Bacharach, A. L. (eds.): *The Physiology of Human Survival*, p. 581. New York and London: Academic Press, 1965. E6,283/65

A monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal, and muscular exercise. Each chapter is written by a specialist in the corresponding field, and numerous references indicate the difference between specific defense mechanisms and the stressor effect of the agents used.

Barron, C. I., Schwichtenberg, A. H., Secrest, R. R.: "Medical evaluation of airmen exposed to altitudes in excess of 50,000 feet." *Aerosp. Med.* **36**: 665-668 (1965).

F69,910/65

Sciarli, R.: "La plongée libre et ses dangers" (Free diving and its dangers). *Arch. Med. Gen. Trop.* **42**: 297-316 (1965).

G37,313/65

Review on diving as a stressor agent capable of eliciting the G.A.S. as judged by its

metabolic and hormonal consequences. Probably, one important factor is hypoxia.

Morrison, P.: "Responses of mountaineers to multiple stressors. A program in human ecology." *Arch. Environ. Health* **17**: 599-602 (1968). G61,522/68

Mountaineers ascending Mount MacKinley (20,320 ft.) and exposed to the multiple stressors of altitude, cold, nutritional deficiency, dehydration, wind, confinement and isolation were tested for urinary and plasma cortisol, plasma catecholamines, proteins, lactic dehydrogenase, creatine phosphokinase, as well as EEG and neurophysiologic activity. The results of these tests are not described in detail although they were repeated later under laboratory conditions in an altitude chamber. It was clear, however, that extreme lassitude and somnolence affected those who reached the summit and memory was badly impaired as indicated by their capacity to repeat random numbers forward and backward. The digit recall ability was reduced even after return to sea level.

McFarland, R. A.: "The effects of altitude on pilot performance" (abstracted). *Aerosp. Med.* **40**: 350 (1970). J15,324/70

Abati, A. L., McGrath, J. J.: "Physiological responses to acute hypoxia in altitude-acclimatized chickens." *J. Appl. Physiol.* **34**: 804-808 (1973) (32 refs.). H81,614/73

Hunter, C., Clegg, E. J.: "Changes in body weight of the growing and adult mouse in response to hypoxic stress." *J. Anat. (Lond.)* **114**: 185-199 (1973). J2,541/73

→**Morphology.** Thorn, G. W., Jones, B. F., Lewis, R. A., Mitchell, E. R., Koepf, G. F.: "The role of the adrenal cortex in anoxia: the effect of repeated daily exposures to reduced oxygen pressure." *Am. J. Physiol.* **137**: 606-619 (1942). A57,759/42

In rats, rabbits and dogs exposed to decreased barometric pressure, the adrenals enlarge and show signs of hyperactivity. Adrenalectomy greatly reduces resistance to hypoxia.

Dalton, A. J., Mitchell, E. R., Jones, B. F., Peters, V. B.: "Changes in the adrenal glands of rats following exposure to lowered oxygen tension." *J. Natl. Cancer Inst.* **4**: 527-536 (1944). 84,981/44

In rats exposed to decreased oxygen tension there was an immediate loss of adrenocortical lipids which could be prevented by

adrenocortical extract. After the rats' repeated exposure to hypoxia, the adrenal enlargement was associated with an increase of its lipid granules, often above the initial level.

Hailman, H. F.: "The effect of preventing acapnia on adrenal cortical hypertrophy under conditions of decreased barometric pressure." *Endocrinology* **34**: 187-190 (1944).

A69,734/44

In rats, an excess of CO₂ inhibits the adrenal hypertrophy caused by lack of oxygen at a given low barometric pressure. "It is suggested that the adrenal cortex is stimulated by either a relative or absolute increase in basic cations or acidic anions. In the former case the adrenal cortex secretes a hormone increasing the excretion of sodium in the urine and in the latter case a hormone preventing the excretion of sodium in the urine."

Nichols, J.: "Quantitative histochemical changes in the adrenal following exposure to anoxia." *J. Aviat. Med.* **19**: 171-178 (1948).

B26,390/48

In rats, anoxia depletes the adrenal cholesterol esters before the free cholesterol, and the other lipid fractions disappear even more slowly. Conversely, cholesterol esters recover last upon interruption of anoxia. The changes are ascribed to the G.A.S. (29 refs.).

Bean, J. W., Johnson, P. C.: "Adrenocortical response to single and repeated exposure to oxygen at high pressure." *Am. J. Physiol.* **179**: 410-414 (1954). C1,583/54

In rats exposed to oxygen under pressure, adrenal enlargement with lipid depletion occurs either because of a direct stressor effect exerted by the stimulus or through an elevation of tissue CO₂ and the enzyme poisoning caused by it.

Markoe, A. M., Okunewick, J. P., Schiffer, L. M.: "Kinetic analysis of splenic erythropoiesis in mice under prolonged hypoxic stress." *Exp. Hematol.* **1**: 340-349 (1973).

J11,982/73

Hunter, C., Clegg, E. J.: "Changes in skeletal proportions of the rat in response to hypoxic stress." *J. Anat. (Lond.)* **114**: 201-219 (1973). J2,542/73

Krasnovskaia, I. A.: "Changes in hypothalamo-hypophyseal neurosecretory system of rats under conditions of prolonged hypoxia." *Probl. Endokr.* **20** No. 2: 53-57 (1974) (Russian). H92,515/74

In rats exposed to hypoxia, histologic evidence of decreased neurosecretion was noted in the paraventricular nucleus of the hypothalamus, presumably as a consequence of "training".

→Hormones. Pincus, G., Hoagland, H: "Steroid excretion and the stress of flying." *J. Aviat. Med.* **14**: 173-193 (1943).

84,492/43

In subjects found fatigued on the Steven's serial coordination meter or the Hoagland-Werthessen pursuit meter, and in pilots on test flights or instruction flights, there was increased urinary 17-KS excretion that caused diuresis. Poor response on the Hoagland-Werthessen pursuit meter was associated with poorer performance with increasing "altitude" owing to reduced oxygen tension. Presumably, "the simulated and actual stress of flying studied induces adrenal steroid hormone hypersecretion that is reflected in the 17-ketosteroid output; this hypersecretion either causes or is accompanied by diuresis."

Burrill, M. W., Ivy, A. C.: "Excretion of neutral 17-ketosteroids in human subjects repeatedly exposed to hypoxia under conditions of simulated high altitude." *J. Appl. Physiol.* **2**: 437-445 (1950). B48,847/50

In man, intermittent exposure to simulated altitudes of 18,000 ft. causes an initial decrease followed by an increase in 17-KS excretion but as exposure continues this change gradually disappears. Hyperventilation tends to enhance KS elimination. "The results show that some alteration in ketosteroid excretion occurs in the response of the human subject to conditions of simulated altitude. These results alone, however, cannot be considered proof that the adrenal cortex is functionally involved in this response."

Koller, F., Schwarz, E., Marti, M.: "Ueber die Reaktion der Nebennierenrinde beim Aufstieg ins Hochgebirge" (The reaction of the adrenal cortex during passive ascent to high altitudes). *Acta Endocrinol. (Kbh.)* **16**: 118-140 (1954). B96,680/54

In normal people, a sudden ascent of 2,650 m. by rail from Lauterbrunnen to Jungfraujoch causes an increase in thrombocytes and total leukocyte count, a decrease in eosinophils and antithrombin, and an increase in excretion of 17-KS and of reducing-corticoids. It is concluded that passive ascent to high altitudes produces a typical "unspecific stress reaction, the origin of which, however, is not yet clearly understood." Hypoxia alone

cannot be responsible for it since exposure to a comparable drop in oxygen tension within a low pressure chamber is not equally effective.

Timiras, P. S., Pace, N., Hwang, C. A.: "Plasma and urine 17-ketosteroid levels in man during acclimatization to high altitude." *Fed. Proc.* **16**: 340 (1957). C33,237/57

Barchas, J. D., Freedman, D. X.: "Brain amines: response to physiological stress." *Biochem. Pharmacol.* **12**: 1232-1238 (1963). E29,915/63

In rats, swimming to exhaustion especially in cold water caused depletion of brain 5-HT and NEP. Similar changes could not be obtained by having them run in a revolving cage, for under the conditions of the experiment the rats soon gave up and just allowed themselves to be dragged. On the other hand, immersion in cold water did reproduce the catecholamine depletion, whereas several other stressors (electroshock, starvation, hypoxia, surgery, adrenalectomy) were ineffective in this respect. The response is not dependent upon the pituitary-adrenocortical system since active stressors deplete brain catecholamines even after hypophysectomy, as does LSD. It is noteworthy that drugs that induce a similar change in brain amines produce a unique pattern of central excitation acting on brain mechanisms concerned with metabolic and physiologic temperature regulation. "If the stressors have such a central action, a role for the biogenic amines in central as well as in peripheral aspects of temperature regulation should be sought."

Mazeaud, M.: "Influence de divers facteurs sur l'adrénalinémie et la noradrénalinémie de la carpe" (The influence of different factors on blood adrenaline and noradrenaline in the carp). *C. R. Soc. Biol.* (Paris) **158**: 2018-2021 (1964). F36,962/64

In the carp, muscular activity and hypoxia cause a slight increase in the EP and a marked rise in the NEP content of the blood. The latter values also rise considerably after hemorrhage and trauma.

Doležal, V., Luxa, J., Svačinka, J., Rybák, R., Zemanova, Z., Samek, L., Čermak, K.: "The influence of 6 days sojourn in mountains on human efficiency." *Riv. Med. Aero-naut. Spaz.* **29**: 383-401 (1966). F75,919/66

In eight young men who spent six days at a 1,500 m. altitude in the High Tatra mountains, a gradual disappearance of signs con-

sidered to be characteristic of stress suggested a particularly rapid development of adaptation. Although there were changes in corticoid and catecholamine excretion, these were variable and unaccompanied by esinopenia. Besides, it would have been impossible to distinguish clearly between the results of hypoxia, physical stress and emotional excitement.

Ulvedal, F., Roberts, J. J.: "Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. VI. Excretion of steroids and catecholamines." *Aerosp. Med.* **37**: 572-578 (1966). F93,442/66

Men kept in a double-walled space cabin simulator in an oxygen-helium atmosphere showed no significant disturbance in glucocorticoid or catecholamine elimination. A reversal of the corticoid excretion rhythm was noted in subjects who slept during the day and worked at night (22 refs.).

Mefferd, R. B. Jr., Wieland, B. A.: "Comparison of responses to anticipated stress and stress." *Psychosom. Med.* **28**: 795-807 (1966). G42,966/66

Young airmen were exposed to actual or anticipated severe hypoxia. Catecholamine and corticoid secretion as well as other metabolic changes were used as objective indicators of stress. There were great individual variations in the response to anticipated stress: "some reacted hardly at all, while others had an alarm reaction. Upon actual exposure to hypoxia (except for those compensatory adaptations specific to hypoxia) these general responses simply increased in magnitude in all subjects, i.e., they maintained their rank-order positions during the stress."

Richtarik, A., Hift, H., Valdivia, E.: "Catecholamines in tissue of guinea pigs subjected to hypoxia." *Arch. Int. Pharmacodyn. Ther.* **159**: 44-47 (1966). F62,068/66

Schaefer, K. E., McCabe, N., Withers, J.: "Stress response in chronic hypercapnia." *Am. J. Physiol.* **214**: 543-548 (1968).

F96,116/68

In guinea pigs, the prolonged respiratory acidosis produced by exposure to 15 percent carbon dioxide in 21 percent oxygen caused a rise in blood corticoids and plasma FFA, with a depletion of adrenal cholesterol and a reduction of lymphopenia.

Sutton, J., Young, J. D., Lazarus, L., Hickie, J. B., Garmendia, F., Velasquez, T.:

"Hormonal response to altitude." *Lancet* December 5, 1970, p. 1194. H32,885/70

In Morococha Peruvian Indians who live at an altitude of 4,540 m. the fasting basal blood STH level is high but does not increase much during physical exercise. By contrast, in normal Australian males performing similar exercise at a simulated altitude of 4,550 m., a striking and sustained increment in serum STH was noted. No change occurred in plasma glucose, insulin or glucagon, but there was a rise in plasma cortisol. After three months of adaptation to high altitude, the hormonal response to exercise was the same as at sea level.

Myles, W. S.: "The excretion of 11-hydroxycorticosteroids by rats during exposure to altitude." *Int. J. Biometeorol.* **16**: 367-374 (1972). H78,664/72

In rats, at 7,300 m. the excretion of 11-OHCS and catecholamines continued at elevated levels throughout the exposure period.

Hale, H. B., Williams, E. W., Ellis, J. P. Jr.: "Human endocrine-metabolic responses to graded oxygen pressures." *Aerosp. Med.* **44**: 33-36 (1973). G99,503/73

In soldiers, EP and NEP output varied inversely with different oxygen pressures.

Hogan, R. P., Kotchen, T. A., Boyd, A. E., Hartley, L. H.: "Effect of altitude on renin-aldosterone system and metabolism of water and electrolytes." *J. Appl. Physiol.* **35**: 385-390 (1973). J5,657/73

In healthy young males, exposure to a simulated altitude of 12,000 ft. decreased plasma renin activity and urinary aldosterone excretion in proportion to the symptoms of acute mountain sickness that were manifested. It remains to be proved whether these changes are due to stress or to the specific effects of anoxia (45 refs.).

Molteni, A., Zakheim, R. M., Mullis, K. B., Mattioli, L.: "The effect of chronic alveolar hypoxia on lung and serum angiotensin I converting enzyme activity." *Proc. Soc. Exp. Biol. Med.* **147**: 263-265 (1974). H95,543/74

In mice, hypoxia caused elevations in serum and lung angiotensin I converting enzyme, closely related to renal renin granules. "The significance of the stimulation of the renin angiotensin aldosterone system in the response to hypoxia remains unknown. It may be an adjustment to the stress of hypoxia or be necessary to the erythropoietic response."

Koob, G. F., Annau, Z.: "Behavioral and neurochemical alterations induced by hypoxia in rats." *Am. J. Physiol.* **227**: 73-78 (1974). H89,535/74

In rats, hypoxia caused a decrease in the NEP content, but no change in the 5-HT concentration of the forebrain. When electrodes were implanted into the lateral hypothalamus, "self-stimulation rates increased while food and water intake decreased during the first 12 h and subsequently returned toward control levels... The results suggest a time-related activation of central adrenergic neuronal systems during exposure to hypoxia." The observation of a differential effect of hypoxia on NEP and 5-HT agrees with several earlier studies using other stressors (36 refs.).

→ Enzymes and Other Metabolites.
Langley, L. L., Nims, L. F., Clarke, R. W.: "Role of CO₂ in the stress reaction to hypoxia." *Am. J. Physiol.* **161**: 331-335 (1950).

B59,437/50

In fasted rats, exposure to a simulated altitude of 20,000 ft. causes accumulation of liver glycogen which is more likely due to loss of CO₂ as a result of hyperventilation than to hypoxia *per se*. "This mechanism may prove beneficial to the animal under stress conditions of hypoxia."

Wegmann, H. M., Brüner, H., Jovy, D., Klein, K. E.: "Änderung von Enzymaktivitäten im Serum als Ausdruck unspezifischer Anpassung" (Plasma enzyme changes as a result of nonspecific adaptation). *Dtsch. Versuchsanstalt für Luft- und Raumfahrt* September, 1965, pp. 11-17. F61,311/65

Brief report on plasma enzyme changes under the influence of hypoxia and other stressors.

Russell, J. A., Crook, L.: "Comparison of metabolic responses of rats to hypoxic stress produced by two methods." *Am. J. Physiol.* **214**: 1113-1116 (1968). F97,961/68

Klain, G. J.: "Acute high altitude stress and enzyme activities in the rat adrenal medulla." *Endocrinology* **91**: 1447-1449 (1972). H62,369/72

Chatterjee, A. K., Dighe, S. K., Naithani, R. C., Sachan, A. S., Krishna, B.: "The role of DL-dihydroxy phenyl alanine (DOPA) on plasma transaminase level under altitude stress." *Jap. J. Pharmacol.* **23**: 269-271 (1973). H85,774/73

A rise in plasma and tissue *transaminase* is considered to be characteristic of stress in the rat. As judged by these observations, DOPA is not a particularly effective "antistress drug."

Das, H. K., Ghosh, N. C.: "Blood sugar levels in rats exposed to varying altitude stress for different periods of time." *Aerosp. Med.* **45**: 716-720 (1974). J20,928/74

Chiodi, H., Whitmore, S.: "Lipid metabolism in suckling rats with fatty liver induced by hypoxia." *Experientia* **30**: 463-465 (1974). H87,847/74

In newborn rats, the hypoxia induced by decreased barometric pressure causes considerable *lipid* accumulation in the liver associated with characteristic enzymatic changes.

Myles, W. S., Radomski, M. W.: "Excretion of lactic acid by rats exposed to simulated high altitude." *Aerosp. Med.* **45**: 422-424 (1974). J12,121/74

Hypoxia (like EP injections) increased the urinary *lactate* level in rats and this may furnish us with "an indicator of the severity of hypoxic stress at altitude."

Penney, D. G.: "Lactate dehydrogenase subunit and activity changes in hypertrophied heart of the hypoxically exposed rat." *Biochim. Biophys. Acta* **358**: 21-24 (1974). J14,758/74

→**Nervous Changes.** McFarland, R. A.: "The psycho-physiological effects of high altitude." *16th Int. Physiol. Kongr.*, Zürich, 1938, p. 42. 73,068/38

Hoagland, H., Pincus, G., Elmadjian, F.: "Stressful psychomotor performance and adrenal cortical function in man." *Fed. Proc.* **5**: 48 (1946). A95,861/46

In man breathing air low in oxygen, performance (as scored in the Hoagland pursuit meter) shows a decline roughly parallel to the degree of lymphopenia and the rise in urinary 17-KS.

Nair, C. S., Malhotra, M. S., Gopinath, P. M.: "Effect of altitude acclimatization and simultaneous acclimatization to altitude and cold on critical flicker frequency at 11,000 ft. altitude in man." *Aerosp. Med.* **43**: 1097-1100 (1972). H81,634/72

In healthy men acclimatization to high altitude did not significantly affect critical flicker frequency whereas "cold stress produced a profound deterioration."

→**Varia.** Walton, A., Uruski, W.: "The effects of low atmospheric pressure on the fertility of male rabbits." *J. Exp. Biol.* **23**: 71-75 (1946). B40,070/46

Ingalls, T. H.: "Causes and prevention of developmental defects." *J.A.M.A.* **161**: 1047-1051 (1956). C27,896/56

In mice, hypoxia applied as a standard stressor during pregnancy leads to a variety of *malformations* in the offspring. There is evidence that a similar process occurs in women.

Mefferd, R. B. Jr., Hale, H. B., Shannon, I. L., Prigmore, J. R., Ellis, J. P. Jr.: "Stress responses as criteria for personnel selection: baseline study." *Aerosp. Med.* **42**: 42-51 (1971). G99,772/71

Exploratory studies on the feasibility of using a battery of tests for the selection of *stress-resistant personnel* for Air Force duty. Moderate hypoxia was employed as a stressor, and various psychologic and metabolic changes were used as indicators. A number of potentially useful indices are listed, but no definite combination of these is recommended as an overall stress resistance test.

Blatteis, C. M., Filkins, J. P., Fuste, F. J., Morris, H. P.: "Depressed growth of Morris hepatomas and altered lysosomal hydrolases during altitudinal hypoxia." *Proc. Soc. Exp. Biol. Med.* **146**: 786-794 (1974).

H89,018/74

The growth of Morris *hepatomas* in rats was impaired by exposure to low barometric pressure. This effect, which involved alterations in the activities of lysosomal enzymes in both hepatomas and host livers, was ascribed to stress.

+**Varia.** Gerschman, R., Gilbert, D. L., Nye, S. W., Nadig, P. W., Fenn, W. O.: "Role of adrenalectomy and adrenal-cortical hormones in oxygen poisoning." *Am. J. Physiol.* **178**: 346-350 (1954). B97,929/54

In rats, *adrenalectomy* increases survival time after exposure to high oxygen pressure. This effect is counteracted by both adrenocortical extract and EP. Evidently, not all stressors are efficiently combatted by adrenal hormones.

Nair, C. S., Malhotra, M. S., Gopinath, P. M.: "Effect of altitude and cold acclimatization on the basal metabolism in man." *Aerosp. Med.* **42**: 1056-1059 (1971). H75,566/71

In man, *cold* and hypoxia exert an additive effect in raising the BMR.

Hartzell, W. G., Newberry, P. D.: "Effect of fasting on tolerance to moderate hypoxia." *Aerosp. Med.* **43**: 821-826 (1972).

H80,194/72

In man, "acute *fasting*" significantly increases the orthostatic, hypotensive response to moderate hypoxia. This synergistic effect was sufficient to induce a syncopal attack in one normal individual during stress by moderate hypoxia while fasting, and this subject's recovery was delayed for more than 20 minutes after return to breathing room air."

Hale, H. B., Williams, E. W., Ellis, J. P. Jr.: "Cross-adaptation in military trainees in a hot climate." *Aerosp. Med.* **43**: 978-983 (1972).

J2,006/72

Young men were exposed to hyperoxia, *heat* or both agents combined. "Differences in the metabolic response patterns of the trainees studied in summer and winter strongly suggest that heat adaptation led to positive cross-adaptation."

Mullane, J. F., Smith, J. C., Wilfong, R.

G.: "Hypoxia and stress ulcer formation in the rat." *Surgery* **74**: 326-332 (1973).

G98,010/73

In rats, hypoxia increased the incidence of gastric ulcers produced by *restraint* or *EP* injections.

Nagasaki, T.: "Thermal and metabolic responses to cold and norepinephrine in cold- and hypoxia-acclimated rabbits" *Jap. J. Physiol.* **23**: 575-585 (1973). J10,543/73

In rabbits, adaptation to hypoxia increases tolerance to *cold*; this represents an example of cross resistance.

Gold, A. J., Costello, L. C.: "Effects of altitude and semistarvation on heart mitochondrial function." *Am. J. Physiol.* **227**: 1336-1339 (1974). H97,949/74

Various enzymologic tests suggest that hypoxia, especially when combined with *starvation*, decreases mitochondrial function in the rat heart.

McManus, B. M., Horvath, S. M., Bolduan, N., Miller, J. C.: "Metabolic and cardiorespiratory responses to long-term work under hypoxic conditions." *J. Appl. Physiol.* **36**: 177-182 (1974) (31 refs.).

J10,301/74

Hemorrhage

In man as in other mammals, hemorrhage produces the usual manifestations of stress, with a rise in ACTH, corticoid and catecholamine discharge.

Allegedly, in the carp, hemorrhage causes a more pronounced increase in the NEP than in the EP content of the blood. In the Pacific salmon, it elicits a rise in plasma 17-OHCS levels. Hence, fish apparently respond very much like mammals to this stressor.

Hemorrhage can also elicit stress ulcers in various species. In pigs, these are inhibited by cholestyramine (which binds bile acids) as well as by 5-HT antagonists and glucocorticoids, but only under certain circumstances which have not yet been clearly identified.

α -Ethyltryptamine prevents the rise in ACTH secretion produced by hemorrhage in the dog; this is ascribed to the pressor property of the compound.

Hemorrhage

(See also our earlier stress monographs, p. xiii)

Post, R. S., Visscher, P. H., Wiggers, C. J.: "Sequential changes in oxygen consumption during oligemic and normovolemic shock, and their meaning." *Am. J. Physiol.* **153**: 71-80 (1948).

B25,993/48

Studies on dogs in normovolemic and oligemic shock produced by hemorrhage, with or without restoration of the withdrawn heparinized blood, show that reduction of oxygen consumption is not a necessary concomitant of the irreversible shock picture. "Even when body temperature is kept constant oxygen consumption is not a

measure of basal metabolic rate during shock. This is due to the fact that oxygen uptake is predominately affected by reduction in oxygen transport capacity, excessive respiratory effort, and varying degrees of acidosis with accumulation of oxygen debt."

Hume, D. M., Nelson, D. H.: "Adrenal cortical function in surgical shock." *Surg. Forum* **5**: 568-575 (1954). E40,942/54

In the dog, surgical trauma markedly increases the 17-OHCS content of adrenal venous blood over that of convalescent animals in which ACTH secretion drops considerably and shows intermittent variations. The cortex maintains high corticoid levels in severe shock despite substantially reduced blood flow, but when the blood pressure drops below 35 mm. Hg adrenal blood flow becomes so low that corticoid output is significantly diminished unless blood transfusions overcome the hypotension. Hemorrhage can increase corticoid output even above the level seen in surgical shock.

Mazeaud, M.: "Influence de divers facteurs sur l'adrénalinémie et la noradrénnalénémie de la carpe" (The influence of different factors on blood adrenaline and noradrenaline in the carp). *C.R. Soc. Biol. (Paris)* **158**: 2018-2021 (1964).

F36,962/64

In the carp, muscular activity and hypoxia cause a slight increase in the EP and a marked rise in the NEP content of the blood. The latter values also rise considerably after hemorrhage and trauma.

Hane, S., Robertson, O. H., Wexler, B. C., Krupp, M. A.: "Adrenocortical response to stress and ACTH in Pacific salmon (*Oncorhynchus tshawytscha*) and steelhead trout (*Salmo gairdnerii*) at successive stages in the sexual cycle." *Endocrinology* **78**: 791-800 (1966).

F63,818/66

In the Pacific salmon (*Oncorhynchus tshawytscha*), plasma 17-OHCS concentrations rose at various phases of migration upstream during the spawning season as well as after bleeding, confinement in a tank or treatment with ACTH. Spawning steelhead trout (*Salmo gairdnerii*) showed an even greater increase in plasma corticoids than did spawning salmon after ACTH injection.

Ganong, W. F., Boryczka, A. T., Lorenzen, L. C., Egge, A. S.: "Lack of effect of α -ethyltryptamine on ACTH secretion when blood pressure is held constant." *Proc. Soc.*

Exp. Biol. Med. **124**: 558-559 (1967).

F77,622/67

In dogs, the increased ACTH secretion produced by hemorrhage is prevented by α -ethyltryptamine in doses which restore the blood pressure. Presumably, it is the pressor effect of α -ethyltryptamine that causes the inhibition of ACTH secretion.

Kies, C., Fox, H. M., Williams, E. R.: "Time, stress, quality, and quantity as factors in the nonspecific nitrogen supplementation of corn protein for adult men." *J. Nutr.* **93**: 377-385 (1967).

H6,953/67

In man, nitrogen retention after the stress of hemorrhage can be improved by a nitrogen-supplemented corn diet, but a similarly supplemented milk diet is even more effective.

Carey, L. C., Sapira, J. D., Curtin, R. A.: "Hemorrhage as a stimulus to adrenal epinephrine secretion." *Bull. Soc. Int. Chir.* **31**: 393-401 (1972).

H78,459/72

Dottke, R. B.: "Intrapartaler Blutverlust und Stress Syndrom" (Hemorrhage during delivery and the stress-syndrome), p. 63. Thesis, University of Berlin, 1972.

J16,430/72

A detailed description of the G.A.S. and personal observations on the increase in glucocorticoid elimination following delivery, especially when associated with severe hemorrhage (149 refs.).

Beard, J. D., Knott, D. H., Simpson, J. R., Sargent, W. Q.: "Cardiovascular response to hemorrhage in dogs after alcohol." *Q. J. Stud. Alcohol* **34**: 1303-1314 (1973).

J9,037/73

In dogs, mortality owing to repeated hemorrhage was considerably higher after daily gavages of ethanol solution than following treatment with isocaloric glucose solution. This decrease in resistance may be due to depletion of cardiac reserve caused by stress, but other stressors have not yet been examined under similar circumstances.

Menguy, R., Desbaillets, L., Masters, Y. F.: "Mechanism of stress ulcer: influence of hypovolemic shock on energy metabolism in the gastric mucosa." *Gastroenterology* **66**: 46-55 (1974).

J9,756/74

Experiments on the production of stress ulcers by hemorrhage in rabbits "suggest that the extraordinary vulnerability of gastric mucosal energy metabolism to shock-induced ischemia results from this tissue's

lack of glycogen (not described previously) and its relative inability to utilize anaerobic glycolysis as an alternate source of energy. We propose that a profound decrease in energy metabolism in the gastric mucosa is the cause of the rapid cellular necrosis occurring in this tissue during hypovolemic shock."

Leise, E. M., LeSane, F., Gray, I.: "Lymphocyte and polymorphonuclear enzymes in stress. III. Variations resulting from multiple bleedings and source of New Zealand white rabbits." *Biochem. Med.* **9**: 193-205 (1974).

J11,684/74

Norton, L., Mathews, D., Avrum, L., Eisenman, B.: "Pharmacological protection against swine stress ulcer." *Gastroenterology* **66**: 503-508 (1974). J12,432/74

In pigs, hemorrhagic shock induces stress ulcers in the stomach that can be prevented by cholestyramine (which binds bile acids), methysergide (a 5-HT antagonist) and methylprednisolone, but only under certain conditions of dosage and timing so that the clinical usefulness of this approach is still problematic.

Menguy, R., Masters, Y. F.: "Mechanism of stress ulcer. IV. Influence of fasting on the tolerance of gastric mucosal energy metabolism to ischemia and on the incidence of stress ulceration." *Gastroenterology* **66**: 1177-1186 (1974). J13,618/74

Fasting greatly sensitized the gastric mucosa of the rabbit to the induction of stress ulcers by hemorrhage. These and many other observations suggest that "stress ulceration complicating hemorrhagic shock results from a gastric mucosal energy deficit due to shock-induced mucosal ischemia."

Alexander, D. P., Britton, H. G., Forsling, M. L., Nixon, D. A., Ratcliffe, J. G.: "Pituitary and plasma concentrations of adrenocorticotrophin, growth hormone, vasopressin and oxytocin in fetal and maternal sheep during the latter half of gestation and the response to haemorrhage." *Biol. Neonate* **24**: 206-219 (1974). J14,326/74

By the ninetieth day, the fetal pituitary of sheep can synthesize and store several hormones. Hemorrhage is a potent stimulus for the release of ACTH and arginine vasopressin.

Muscular Exercise

The stressor effect of muscular work has been the subject of particularly careful study for various reasons. It was one of the first agents used to produce a typical stress syndrome, relatively free of any side effects, whose possible specificity could not be easily demonstrated. Furthermore, muscular exercise is associated with numerous activities of daily life such as physical labor, athletics, and even forced restraint (a classic stressor in experimental animals) which inescapably provokes struggle for freedom. Finally, muscular work is one of the most natural and widely applied nonspecific therapeutic measures for the maintenance or rehabilitation of fitness, and resistance to muscular exercise (for example, on a treadmill or a bicycle ergometer) gives us a convenient indicator of stress tolerance.

Physical exercise of sufficient intensity and duration elicits all the characteristic manifestations of the G.A.S. These need not be recapitulated here, since they have been described at length in the various monographs, reviews and original articles abstracted in the following pages.

It may be worth pointing out, however, that the rise in plasma glucose and FFA is not specifically connected with muscular work as such, since it occurs also after the application of other stressors, whereas the strong cardiovascular and respiratory reactions are preponderantly specific adaptive responses to muscular contraction.

The ability of muscular work to produce a discharge of catecholamines, ACTH and glucocorticoids, as well as the metabolic consequences of these hormonal responses, have been extensively described. It is of some historical interest that probably the

first demonstration of corticoid excretion during stress was based on corticoid determinations in the urine of horses before and after a race.

In rats, swimming to exhaustion depletes brain 5-HT and NEP. This appears to be related to stress but is not reproduced by all stressors tested. Both exercise and EP diminish insulin secretion.

In man, plasma STH often rose during physical exercise whereas insulin levels remained unchanged or decreased. EP did not cause a similar release of STH. The failure of plasma insulin levels to rise in response to exercise-induced hyperglycemia is consistent with the finding that EP impairs insulin release. Hard work on a bicycle ergometer increased plasma NEP, FFA and lactate levels, but there was no strict correlation between these variables.

Although a relatively "pure" stressor, muscular exercise is also always modified in its effects by conditioning factors. Those factors inherent in muscle work (for example, energy metabolism, cardiovascular and respiratory adjustments) are readily identified, whereas others can be recognized only by special investigations.

Genetic factors can greatly influence susceptibility to the stressor effect of muscular work, as shown by the striking differences among various species of animals and even different individuals within the same species. In the carp, muscular activity causes only a slight increase in the EP but a pronounced rise in the NEP level of the blood. Contrary to expectations, wild and domesticated mice withstood forced swimming about equally well. The plasma cortisol rise produced by exercise in the horse does not strictly parallel the degree of eosinopenia, but essentially, adrenocortical function in this species is similar to that in other mammals.

The ambient temperature also has a marked effect, especially in that work in very cold or very hot places is particularly stressful. For example, in mine workers, a standard exercise which normally caused no significant change in blood cortisol elicited a pronounced rise in hot surroundings.

Limitation of food intake greatly sensitizes the rat to the induction of gastric ulcers by forced muscular work. Hence, this combination of agents is often used for the standard production of stress ulcers.

In men over forty-five years of age, a standardized bicycle ergometer test causes more pronounced platelet aggregation than in controls of less than twenty-two years. This fact may play a part in the well known age-dependence of predisposition to thromboembolic processes.

Muscular Exercise

(See also our earlier stress monographs, p. xiii)

Generalities. Andersen, D. H.: "The effect of food and of exhaustion on the pituitary, thyroid, adrenal and thymus glands of the rat." *J. Physiol. (Lond.)* 85: 162-167 (1935). 32,606/35

In rats, forced exercise causes adrenal enlargement and thymus atrophy. The latter "suggests accidental involution, but characteristic histological changes are not found." [The functional relationship between these alterations has not yet been suspected but

they are compared with other corresponding changes seen during estrus (H.S.).]

Holmes, T. H., Wolff, H. G.: "Life situations, emotions and backache." In: Wolff, H. G., Wolf, S. G., et al., *Life Stress and Bodily Disease*, pp. 750-772. Baltimore: Williams & Wilkins, 1950. B51,943/50

Increased generalized skeletal muscle hyperfunction along with electric activity was "part of an individual's reaction to a threatening life situation engendering conflict, anxiety and other strong emotions and was often provocative of pain in the back, neck, and extremities."

Edholm, O. G., Bacharach, A. L. (eds.): *The Physiology of Human Survival*, p. 581. New York and London: Academic Press, 1965. E6,283/65

A monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal and muscular exercise. Each chapter is written by a specialist in the corresponding field, and numerous references indicate the difference between specific defense mechanisms and the stressor effect of the agents used.

Levitt, R. A., Webb, W. B.: "Effect of infantile treadmill experience on body-weight and resistance to exhaustion in the rat." *Nature* **208**: 1128-1129 (1965).

F58,465/65

Rats forced to run in a treadmill during the first few weeks of life initially lost weight but then grew better than the controls and became much more resistant to exhaustion. "It appears that the treadmill acted as a stressor and that this 'acute stress' during infancy was responsible for the increased growth of muscle and other tissue. It is not known whether the improved treadmill performance is indicative of a general increased resistance to stress or is a specific effect of the early treadmill experience."

Frenkl, R., Csalay, L., Csakvary, G.: "A study of the stress reaction elicited by muscular exertion in trained and untrained man and rats." *Acta Physiol. Acad. Sci. Hung.* **36**: 365-370 (1969).

G76,181/69

Weingarten, G., Alexander, J. F.: "Effects of physical exertion on mental performance of college males of different physical fitness level." *Percept. Mot. Skills* **31**: 371-378 (1970).

J21,334/70

Elliott, S. E., Miller, C. W., Armstrong, W. T. Jr., Osborn, J. J.: "The use of the digital computer in the study of patients during exercise-induced stress." *Am. Heart J.* **79**: 215-222 (1970).

H20,844/70

A computer analysis technique for monitoring cardiovascular and respiratory responses to exercise in man. [There is no evidence showing that the changes are due to stress rather than to the specific effects of exercise (H.S.).]

Kolanowski, J., Hausman, A., Crabbe, J.: "Répercussions hydro électrolytiques et hormonales de l'effort physique selon la

température ambiante" (Hydro-electrolyte and hormonal effects of physical effort at different ambient temperatures). *Rev. Inst. Hyg. Mines Hasselt* **26**: 159-180 (1971).

H78,606/71

In mine workers submitted to a standard exercise, cortisolemia remained uninfluenced at normal but was greatly increased at high ambient temperatures.

Kypke, W., Höllge, J., Scriba, B.: "Augeninnendruck während und nach körperlicher Belastung. Eine systematische Untersuchung unter reproduzierbaren Arbeitsbedingungen. I. Kreislaufparameter" (Intraocular pressure under physical stress. A methodical investigation under reproducible conditions. I. Circulatory parameters). *Albrecht. v. Graefes Arch. Klin. Exp. Ophthal.* **186**: 91-104 (1973).

H92,275/73

In young people of both sexes, the stress of muscular exercise on a bicycle ergometer caused a decrease in intraocular pressure. This correlated well with pulse frequency and blood pressure.

Ferguson, E. W., Guest, M. M.: "Exercise, physical conditioning, blood coagulation and fibrinolysis." *Thromb. Diath. Haemorrh.* **31**: 63-71 (1974).

H87,867/74

In healthy young men "immediately after exercise, a marked increase in fibrinolytic activity and an acceleration of most clotting assays were observed. After physical conditioning, there was a decrease in the level of fibrinolytic activity at rest and after exercise, but the reactivity of the fibrinolytic system, i.e., the percent increase in fibrinolytic activity in response to exercise, was unaltered. Following physical conditioning, the clotting times of certain assays were less accelerated."

Hawkey, C. M., Britton, B. J., Wood, W. G., Peele, M., Irving, M. H.: "Changes in blood catecholamine levels and blood coagulation and fibrinolytic activity in response to graded exercise in man." *Br. J. Haematol.* **29**: 377-384 (1975).

J23,871/75

→Hormones. Wada, M., Seo, M., Abe, K.: "Effect of muscular exercise upon the epinephrine secretion from the suprarenal gland." *Tohoku J. Exp. Med.* **27**: 65-86 (1935).

34,821/35

Selye, H., Dosne, C.: "Treatment of wound shock with corticosterone." *Lancet* July 20, 1940, pp. 70-71.

A33,299/40

In horses, muscular exercise caused in-

creased glucocorticoid excretion (cold test). [This was probably the first demonstration of corticoid elimination during stress (H.S.).]

Nichols, J., Miller, A. T. Jr.: "Excretion of adrenal corticoids in the sweat." *Proc. Soc. Exp. Biol. Med.* **69**: 448-449 (1948).

B28,608/48

In man, exposure to heat and intense muscular exercise increase the rate of corticoid excretion in sweat more than in urine. Hence "it is a reasonable assumption that it indicates an activation of the adrenal cortex in response to the stresses of heat and strenuous exertion. Our results also emphasize the fact that in stresses associated with sweating, a significant fraction of the total corticoid excretion is accounted for in the sweat."

Bliss, E. L., Migeon, C. J., Branch, C. H. H., Samuels, L. T.: "Reaction of the adrenal cortex to emotional stress." *Psychosom. Med.* **18**: 56-76 (1956). C13,032/56

In normal people and psychiatric patients, emotional stress (subjectively estimated by manifestations of anxiety and tension), whether occurring spontaneously or elicited experimentally, caused consistent but very modest increases in blood and urinary 17-OHCS. The changes were always much less pronounced than those produced by ACTH, Piromen, insulin, electroshock or moderate physical exercise.

Kärki, N. T.: "The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it." *Acta Physiol. Scand.* **39** Supp. 132: 1-96 (1956). C26,120/56

Monograph on catecholamine excretion in man as influenced by circadian variations, age, muscular work, emotional stress and sex (160 refs.).

Gray, I., Beetham, W. P. Jr.: "Changes in plasma concentration of epinephrine and nor-epinephrine with muscular work." *Proc. Soc. Exp. Biol. Med.* **96**: 636-638 (1957).

C45,827/57

Connell, A. M., Cooper, J., Redfearn, J. W.: "The contrasting effects of emotional tension and physical exercise on the excretion of 17-ketogenic steroids and 17-ketosteroids." *Acta Endocrinol. (Kh.)* **27**: 179-194 (1958). C47,363/58

In a group of medical students, the psychogenic stress of an important examination significantly increased 17-KGS and slightly raised 17-KS excretion. Muscular activity (treadmill exercise, route march) elicited a

moderate decrease in 17-KS and no marked change in 17-KGS elimination. "It is suggested that emotional stress causes an increase in the formation of adrenal cortical hormones; this formation is in preparation for the physical stress and effort which, under 'natural' conditions, could be expected to follow on the initial emotional strain."

Hasselman, M., Schaff, G., Metz, B.: "Influences respectives du travail, de la température ambiante et de la privation de sommeil sur l'excrétion urinaire de catécholamines chez l'homme normal" (Influence of work, ambient temperature and sleep deprivation on urinary catecholamine secretion in normal men). *C.R. Soc. Biol. (Paris)* **154**: 197 (1960). C88,413/60

In people performing multiple choice psychomotor muscular work, catecholamine excretion rose; this effect was particularly pronounced following periods of sleep deprivation.

Frenkl, R., Csalay, L.: "Effect of regular muscular activity on adrenocortical function in rats." *J. Sports Med. Phys. Fitness* **2**: 207-211 (1962). J12,182/62

Barchas, J. D., Freedman, D. X.: "Brain amines: response to physiological stress." *Biochem. Pharmacol.* **12**: 1232-1238 (1963). E29,915/63

In rats, swimming to exhaustion especially in cold water caused depletion of brain 5-HT and NEP. Similar changes could not be obtained by having them run in a revolving cage, for under the conditions of the experiment the rats soon gave up and just allowed themselves to be dragged. On the other hand, immersion in cold water did reproduce the catecholamine depletion, whereas several other stressors (electroshock, starvation, hypoxia, surgery, adrenalectomy) were ineffective in this respect. The response is not dependent upon the pituitary-adrenocortical system since active stressors deplete brain catecholamines even after hypophysectomy, as does LSD. It is noteworthy that drugs that induce a similar change in brain amines produce a unique pattern of central excitation, acting on brain mechanisms concerned with metabolic and physiologic temperature regulation. "If the stressors have such a central action, a role for the biogenic amines in central as well as in peripheral aspects of temperature regulation should be sought."

Mazeaud, M.: "Influence de divers facteurs sur l'adrénalénémie et la noradrénalénémie de la carpe" (The influence of dif-

ferent factors on blood adrenaline and noradrenaline in the carp). *C.R. Soc. Biol. (Paris)* **158**: 2018-2021 (1964).

F36,962/64

In the carp, muscular activity and hypoxia cause a slight increase in the EP and a marked rise in the NEP content of the blood. The latter values also rise considerably after hemorrhage and trauma.

Schalch, D. S.: "The influence of physical stress and exercise on growth hormone and insulin secretion in man." *J. Lab. Clin. Med.* **69**: 256-269 (1967). G44,274/67

Human plasma STH often rose during periods of physical stress or exercise while insulin values remained unchanged or were decreased. EP did not reproduce the release of STH. The failure of plasma insulin levels to rise in response to stress-induced hyperglycemia is consistent with the finding that EP infusion impairs insulin discharge. Plasma glucose and FFA levels rose as expected during physical exercise. Presumably, certain stressors are diabetogenic not only because of EP and corticoid release but also because of a discharge of STH on the one hand, and an EP-induced suppression of insulin secretion on the other.

Wright, P. H., Malaisse, W. J.: "Effects of epinephrine, stress, and exercise on insulin secretion by the rat." *Am. J. Physiol.* **214**: 1031-1034 (1968). F97,956/68

In rats, various stressors (EP, swimming, electroshock) diminish insulin secretion. "It is suggested that endogenous epinephrine released during stress or exercise is sufficient to suppress insulin secretion even under conditions of hyperglycemia" (29 refs.).

Bellet, S., Roman, L., Barham, F.: "Effect of physical exercise on adrenocortical excretion." *Metabolism* **18**: 484-487 (1969).

H13,622/69

After a brief review of the literature on increased corticoid excretion under the influence of psychogenic stressors, personal observations are reported showing that, in healthy young students, even moderate exercise on a treadmill suffices to raise urinary 11-OHCS elimination.

Stone, E. A.: "Swim-stress induced inactivity: relation to body temperature and brain norepinephrine, and effects of d-amphetamine." *Psychosom. Med.* **32**: 51-59 (1970). G72,775/70

Kozłowski, S., Brzezińska, Z., Nazar, K., Kowalski, W.: "Activation of adrenergic sys-

tem during exercise in men: relation to work load and physical working capacity." *Bull. Acad. Pol. Sci. Cl. 2 No. 20*: 897-901 (1972). H80,315/72

In man, hard work on a bicycle ergometer increased plasma NEP, FFA and lactate levels, but there was no strict correlation among these changes.

Jobin, M., Dulac, S.: "Effets aigus et chroniques de l'exercice sur l'activité hypophyso-thyroiđosurrénaliennes" (Acute and chronic effects of exercise on hypophysis-thyroid-adrenal activity). *Ann. ACFAS* **40**: 128 (1973). H87,896/73

In rats, chronic forced exercise caused adrenal enlargement in association with an increase in plasma TTH. In man, after ten weeks of muscular training plasma T4 was diminished without any significant change in plasma T3 although the latter exhibited an initial rise. These and other observations suggest an acceleration of T4 metabolism followed by an increment in its secretion.

Davies, C. T. M., Few, J. D.: "Effects of exercise on adrenocortical function." *J. Appl. Physiol.* **35**: 887-891 (1973). J9,355/73

Exact quantitative studies on the increase of cortisol production induced in man by exercise on a treadmill.

Viru, A., Kõrge, P.: *Hormonal Homeostatic Mechanisms During Muscular Activity*, pp. 155-165. Estonian Contr. Int. Biol. Program, Rep. No. 4. Tartu, 1973.

H86,934/73

Sarviharju, P. J.: "Effect of physical exercise on the urinary excretion of catecholamines and 17-hydroxycorticosteroids in young healthy men." *J. Sports Med. Phys. Fitness* **13**: 171-176 (1973). J11,169/73

Mason, J. W., Hartley, L. H., Kotchen, T. A., Mougey, E. H., Ricketts, P. T., Jones, L. G.: "Plasma cortisol and norepinephrine responses in anticipation of muscular exercise." *Psychosom. Med.* **35**: 406-414 (1973). J7,263/73

Tharp, G. D., Buuck, R. J.: "Adrenal adaptation to chronic exercise." *J. Appl. Physiol.* **37**: 720-722 (1974). J18,803/74

Observations on rats chronically forced to exercise led the authors to the conclusion that "part of the diminished in vivo corticosterone release occurring with training is due to adaptation of the adrenal gland to ACTH stimulation."

DeLacerda, F. G., Steben, R. E.: "The effect of an endurance type exercise program

on the circadian rhythm of urinary 17-ketosteroids." *Med. Sci. Sports* **6**: 126-128 (1974). J16,584/74

Effect of bicycle ergometer exercise upon the circadian rhythm of urinary 17-KS in man.

Kato, M., Ogino, T., Suzuki, T.: "Cardiac rhythm and urinary excretion of catecholamine under mental work and physical exercise." *Tohoku J. Exp. Med.* **112**: 111-118 (1974). H86,189/74

Bray, G. A., Whipp, B. J., Koyal, S. N., Wasserman, K.: "Effects of acute exercise on arterial insulin and glucose concentration in obese and normal men." *Program Amer. Soc. Clin. Invest., 66th Ann. Meet., Atlantic City, N. J.* (1974) p. 10a. H88,711/74

In obese as well as in lean subjects, arterial insulin and glucose decreased during exercise.

Few, J. D.: "Effect of exercise on the secretion and metabolism of cortisol in man." *J. Endocrinol.* **62**: 341-353 (1974).

H92,214/74

Davies, C. T. M., Few, J., Foster, K. G., Sargeant, A. J.: "Plasma catecholamine concentration during dynamic exercise involving different muscle groups." *Eur. J. Appl. Physiol.* **32**: 195-206 (1974). J12,781/74

Observations in man suggest that the plasma catecholamine concentration "in exercise may be closely related to circulatory stress and may reflect the degree of vasoconstriction present in 'non-active' tissues and efficacy of the body's ability to maintain the integrity of systemic blood pressure in the face of increased demands of the exercising muscles for blood and the transport of oxygen" (28 refs.).

Follenius, M., Brandenberger, G.: "Influence de l'exercice musculaire sur l'évolution de la cortisolémie et de la glycémie chez l'homme" (Effect of muscular exercise on diurnal variations of plasma cortisol and glucose in normal men). *Eur. J. Appl. Physiol.* **33**: 23-33 (1974). J16,058/74

In man, exercise on a bicycle ergometer raises plasma cortisol within ten minutes. Blood glucose decreases at first but is elevated to the initial level twenty minutes after cessation of work.

Cronan, T. L., Howley, E. T.: "The effect of training on epinephrine and norepineph-

rine excretion." *Med. Sci. Sports* **6**: 122-125 (1974). J16,583/74

Hawkey, C. M., Britton, B. J., Wood, W. G., Peele, M., Irving, M. H.: "Changes in blood catecholamine levels and blood coagulation and fibrinolytic activity in response to graded exercise in man." *Br. J. Haematol.* **29**: 377-384 (1975). J23,871/75

→Enzymes and Other Metabolites. Schalch, D. S.: "The influence of physical stress and exercise on growth hormone and insulin secretion in man." *J. Lab. Clin. Med.* **69**: 256-269 (1967). G44,274/67

In man, plasma STH often rose during periods of physical stress or exercise while insulin values remained unchanged or were decreased. EP did not reproduce the release of STH. The failure of plasma insulin levels to rise in response to stress-induced hyperglycemia is consistent with the finding that EP infusion impairs insulin discharge. Plasma glucose and FFA levels rose as expected during physical exercise. Presumably, certain stressors are diabetogenic not only because of EP and corticoid release but also because of a discharge of STH on the one hand, and an EP-induced suppression of insulin secretion on the other.

Körge, P., Masso, R., Roosson, S.: "The effect of physical conditioning on cardiac response to acute exertion." *Can. J. Physiol. Pharmacol.* **52**: 745-752 (1974).

H87,465/74

In rats "an attempt was made to evaluate the possible role of *Na-K-ATPase* in the mechanism of depression of potassium transport against its electrochemical gradient after chronic physical overload. In comparison with normal response of the heart, both morphological and biochemical changes were diminished in both the trained and, to a smaller extent, the overtrained heart during acute extreme exertion. It is concluded that potassium accumulation in myocardial cells is an essential adaptive reaction to physical exertion and the extent of potassium uptake depends on the functional state of the heart."

Lopez-S., A., Vial, R., Balart, L., Arroyave, G.: "Effect of exercise and physical fitness on serum lipids and lipoproteins." *Atherosclerosis* **20**: 1-9 (1974). H87,491/74

During physical training there was a decrease in serum triglycerides, pre-β-proteins and α-lipid proteins in healthy young students. The serum cholesterol levels showed comparatively little change.

Struck, P. J., Tipton, C. M.: "Effect of acute exercise on glycogen levels in adrenalectomized rats." *Endocrinology* **95**: 1385-1391 (1974). H94,156/74

+Varia. Foss, C. R., Horvath, S. M.: "Reactions of wild and albino mice in response to forced swimming." *Proc. Soc. Exp. Biol. Med.* **120**: 588-592 (1965).

F59,402/65

The ability of wild and domestic albino mice to swim until exhaustion was much shorter in water at 20° C than at 37° C. The drop in colonic temperature was an excellent indication of exhaustion in temperatures of 28° C or less but remained normal or even rose at higher temperatures. There was no significant difference either in colonic temperature or in endurance between the two strains.

James, V. H. T., Horner, M. W., Moss, M. S., Rippon, A. E.: "Adrenocortical function in the horse." *J. Endocrinol.* **48**: 319-335 (1970). H32,502/70

In the horse, *surgical trauma* or *hypoglycemia* increases plasma cortisol levels, whereas exercise is much less effective in this respect. The cortisol variations are not necessarily associated with changes in the eosinophil count. "It is concluded that the mechanisms of control of adrenocortical function in the horse are not dissimilar to those described for other mammalian species."

Wyndham, C. H.: "The physiology of exercise under heat stress." *Annu. Rev. Physiol.* **35**: 193-220 (1973). H67,021/73

A review on the physiology of muscular exercise "under heat stress," with special reference to metabolic and vascular reactions. Very little attention is given to stress in general or to adaptive hormones (122 refs.).

Scheele, K., Müller, K. M., Böhm, B., Westphal, G.: "Morphologische Funktionsstudien an Thrombozyten während und nach dosierter Ergometerbelastung in verschiedenen Altersstufen" (Morphologic studies on thrombocyte function during and after standardized bicycle ergometer tests in different age groups). *Dtsch. Med. Wochenschr.* **99**: 252-255 (1974). H82,593/74

When subjected to a standardized bicycle ergometer test, older men (forty-five years) had a greater tendency toward platelet aggregation than did younger men (22 years).

Lasting platelet aggregation after such "physical stress" was demonstrable only in the older age group. It is concluded that "regular physical activity is indicated in order to avoid thromboembolic episodes during or after sudden physical stress in persons of the older age groups." The authors emphasize that such platelet aggregation may be due to a discharge of EP which would raise ADP, a substance that plays a prominent role in platelet aggregation. The phenomenon appears to be characteristic of the alarm reaction, but it is impossible to ascertain whether psychic stimulation or the muscular activity is of primary causal significance.

Pintar, K., Schulte, W. J., Barboriak, J. J.: "Histologic study of gastric lesions in food-restricted rats." *Proc. Soc. Exp. Biol. Med.* **145**: 1353-1358 (1974). H86,412/74

"Rats limited to food intake of one hour a day and allowed to run in an activity wheel developed gastric lesions which on histologic examination resembled human stress ulcers."

McManus, B. M., Horvath, S. M., Bolduan, N., Miller, J. C.: "Metabolic and cardiorespiratory responses to long-term work under hypoxic conditions." *J. Appl. Physiol.* **36**: 177-182 (1974) (31 refs.).

J10,301/74

Gisolfi, C. V., Coping, J. R.: "Thermal effects of prolonged treadmill exercise in the heat." *Med. Sci. Sports* **6**: 108-113 (1974).

J16,280/74

Johnson, T. H., Tharp, G. D.: "The effect of chronic exercise on reserpine-induced gastric ulceration in rats." *Med. Sci. Sports* **6**: 188-190 (1974). J16,755/74

A study on cross-resistance in rats, using reserpine-induced gastric ulcers as an indicator of stress, and having them run in a treadmill or swim as a second stressor. "The degree of ulceration of the glandular portion of the stomach produced by administration of reserpine was significantly lower in treadmill runners than in their controls, however, the degree of ulceration for the swimmers was not significantly different from that of their controls.... It might be that the swimmers were still in Selye's 'stage of resistance' and not quite in the 'trained state.' Thus, the corticosterone level may have still been higher than normal and may have contributed to the increased ulceration in the swimmers" (19 refs.).

Restraint

Physical restraint has been one of the most popular stressors in experimental medicine. The very first investigations of the alarm reaction were performed on rats immobilized in a way that denied them free motion by use of shackles of soft tape to prevent them from incurring self-inflicted injury from struggling. In addition, their heads were fixed in a position which made it impossible for them to chew away their fetters and incidentally traumatize their limbs. In this manner, we hoped to produce the purest stress of frustration by depriving the animals of their liberty to move about. Actually, further investigations showed that even this stressor is complex. The immobilization is accompanied by strong struggling which means muscular exercise, and at the same time thermoregulation is impeded by stretching out the animals and preventing them from huddling together.

Various modifications of the apparatus used for confinement have been designed, for example, tubular enclosures and wire cages for small rodents, or restraint chairs for primates.

Restraint proved to be very effective in eliciting typical nonspecific stress manifestations, such as: thymicolympathic and splenic atrophy, polymorphonuclear leukocytosis, eosinopenia, lymphopenia, gastroduodenal ulcers, and both morphologic and functional signs of adrenocortical hyperactivity with a discharge of medullary catecholamines. If prolonged, the stress of constraint also causes a drop in body temperature and loss of weight of all organs except the adrenal cortex.

Repeated restraint produced degranulation of the pancreatic β -cells in the rat and atrophy of the excretory parenchyma with the exception of small "halos" around the Langerhans islets. The mechanism of this latter change has still not been clarified, although it was among the first morphologic signs of the alarm reaction to be described.

The so-called restraint ulcers have been the subject of particularly intense investigations because of the great clinical importance of stress-induced gastric erosions. They will be reconsidered at length in the section on Experimental Diseases of Adaptation.

The fact that immobilization causes hemorrhagic mucosa ulcerations in the stomach, the duodenum, and sometimes even in the upper small intestine was one of the first observations made in establishing "the classical triad of the alarm reaction," consisting of these ulcers in combination with thymicolympathic involution and adrenocortical hyperactivity. Ever since that time these changes have received considerable attention as readily determined and very reliable indicators of stress, especially during the acute phase of the alarm reaction.

It was also one of our first findings that immobilization (like other stressors) produced no thymicolympathic involution or other manifestations of increased ACTH and glucocorticoid secretion after adrenalectomy; however, the restraint ulcers were in fact more than normally severe in animals deprived of their adrenals. In this respect, glucocorticoid substitution therapy, at maintenance dose levels, actually exerted a protective effect. On the other hand, a heavy overdose of glucocorticoids predisposes to peptic ulceration and delays healing even in intact animals. However, it is difficult to explain why, under certain circumstances, prednisolone may offer some protection against restraint ulcers in the rat.

These early findings have been described at length in our monographs on stress (see Reviews) and will not be included in the annotated bibliography at the end of this section. There, we shall limit ourselves to more recent confirmatory data showing that

restraint ulcers can also be produced in various species other than the rat, including the rabbit, mouse, guinea pig, hamster, monkey and even fish.

It is especially noteworthy that these ulcerations are markedly aggravated by a cold surrounding temperature as well as by drugs (for example, reserpine) which decrease the body temperature in the rat. The combination of immobilization plus cold has therefore developed into one of the most commonly employed models for the production of stress ulcers.

Young rats are more sensitive to restraint ulcers than are old animals.

The data on the possible protective effect of bilateral vagotomy are somewhat contradictory.

In rats, EP, like atropine and other anticholinergic drugs, inhibited the development of restraint ulcers, as did chlorpromazine, benactyzine, and pentobarbital; acetazolamide was inactive in this respect.

α -Methyldopa, bretylium, phenoxybenzamine, and phentolamine also reduced the incidence of restraint ulcers in the rat. From these observations it was concluded that an increased turnover of NEP may be causally related to the development of ulcerations.

Nicotinic acid prevents restraint ulcers in fasted rats even more effectively than does chlorpromazine.

According to some investigators, diazepam pretreatment or vagotomy inhibits restraint ulcers to some extent in the rat, but combined application of these agents offers the best protection. The effects of diazepam are ascribed to its action on the vegetative centers in the hypothalamic and limbic systems, leading to a partial inhibition of vagally controlled hydrochloric acid and pepsin secretion.

According to one report, restraint ulcers in the rat are often associated with hydrothorax; overnight fasting prevents the hydrothorax but reduces gastric ulceration, in contradiction to most other observations. Some protection was also obtained by crowding of the animals and a rise in ambient temperature. In fact, crowding may have increased the body temperatures of the animals.

If rats are immobilized during the active period of the circadian cycle, stress ulcers develop more easily than during the inactive period.

Food deprivation is a particularly powerful sensitizer for the production of restraint ulcers. Hence, all experiments with agents which depress appetite must be carefully examined to establish whether these stimuli are effective as such or merely diminish caloric intake. For further discussion of specific factors affecting restraint ulcers by their direct pharmacologic effect upon the gastric mucosa and its secretions, the reader is referred to the original articles quoted at the end of this section.

In constrained rats, unpredictable electric shocks produced a higher incidence of gastric ulcers than did predictable shocks.

Supine exercise during prolonged bedrest was tested for its effect upon urinary cortisol and catecholamine excretion in a small group of healthy young men. The results suggested that "exercise could decrease the severity of deconditioning" under these circumstances, but the number of observations is insufficient to draw any definite conclusions.

The effect of confinement is conditioned by numerous agents. Many of them have already been discussed in relation to conditioning for "restraint ulcer" formation, which has been the topic of the most intensive investigations. Exposure to cold is particularly damaging to immobilized animals (as shown especially in rats and rabbits), perhaps

because restraint, in itself, tends to lower body temperature, and exogenous cooling has an additive effect.

Possibly, reserpine, which likewise causes hypothermia, sensitizes the rat to the stressor action of constraint for the same reason. The muscle-relaxing effect of zoxazolamine is enhanced by the stress of physical limitation, especially in cold environments.

In guinea pigs, overheating reduced the adrenal cortical response to the stress of restraint without altering reactivity to exogenous ACTH.

The tumorigenic action of murine sarcoma virus is allegedly increased by immobilization of the rat, perhaps by interference with immunologic defense as a consequence of the stress-induced thymus involution.

Genetic predisposition may alter sensitivity to restraint, and this stressor has been found to be effective in various species of mammals, and even in fish, as shown by the rise in plasma cortisol produced by constraint in the carp.

In rabbits, immobilization causes a rapid rise in blood pressure, and the same is true in other species.

EEG studies suggest that homeostatic mechanisms mediated by the mesencephalic reticular formation and gray matter are the principal regulators of blood pressure and renin release under these circumstances.

Understandably, the greatest emphasis was placed upon changes in adaptive hormone production as a consequence of restraint, but these deserve no special consideration since they are essentially the same as those elicited by other stressors.

Restraint

(See also our earlier stress monographs, p. xiii)

Generalities. Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* 17: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction" characterized by adrenocortical enlargement with acute loss of lipids, thymicolumphantic atrophy and decreased body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and to a lesser extent hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug" but greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Renaud, S.: "Improved restraint-technique for producing stress and cardiac necrosis in

rats." *J. Appl. Physiol.* 14: 868-869 (1959). C62,636/59

Pfeiffer, C. J.: "The physiologic effects of restricted activity in the rat: stress effects of chronic restraint." *Exp. Med. Surg.* 25: 201-217 (1967). H1,775/67

Dost, F. N., Johnson, D. E., Wang, C. H.: "A restraint system for squirrel monkeys." *Lab. Anim. Sci.* 22: 893-897 (1972). H79,351/72

Description of a chair for the restraint of squirrel monkeys, which permits comfortable confinement for periods of several days.

→**Hormones.** Kvetňansky, R., Mikulaj, L.: "Adrenal and urinary catecholamines in rats during adaptation to repeated immobilization stress." *Endocrinology* 87: 738-743 (1970). H30,286/70

In rats subjected to repeated restraint, the gradual diminution of urinary catecholamine excretion after each stress experience is attributed to "an enhanced ability to replace the released catecholamine rather than to a diminished catecholamine release after repetition of this stress."

Perhach, J. L. Jr., Barry, H.: "Stress responses of rats to acute body or neck re-

straint." *Physiol. Behav.* **5**: 443-448 (1970).
G77,139/70

In rats, blood corticoid increases were noted after various types of restraint.

Kvetňanský, R., Weise, V. K., Gewirtz, G. P., Kopin, I. J.: "Synthesis of adrenal catecholamines in rats during and after immobilization stress." *Endocrinology* **89**: 46-49 (1971). H43,006/71

Immobilization is known to augment tyrosine hydroxylase in rat adrenals. It could now be shown that "the increased levels of enzymes result in enhanced synthesis of epinephrine-¹⁴C from tyrosine-¹⁴C but not from dopa-³H. During immobilization, conversion of tyrosine-¹⁴C to catecholamines is further increased and may exceed the capacity of even the elevated levels of dopamine- β -hydroxylase to convert dopamine to norepinephrine."

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971). H37,353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound, and aversive conditioning) increase plasma STH and cortisol levels, but the two responses do not run parallel and are presumably regulated by different mechanisms. In the case of chair restraint, STH values fall to resting levels whereas cortisol continues to rise.

Euker, J., Meites, J., Riegle, G.: "Serum LH and prolactin following restraint stress in the rat." *Physiologist* **16**: 307 (1973). H73,456/73

In rats, restraint increased serum LTH levels, whereas the proestrus surge of LH was blocked by this stressor.

Leach, C. S., Hulley, S. B., Rambaut, P. C., Dietlein, L. F.: "The effect of bedrest on adrenal function." *Space Life Sci.* **4**: 415-423 (1973). J9,311/73

In a very small group of healthy young men, the stressor effect of prolonged bedrest, with or without supine exercise, was tested using urinary cortisol and catecholamines as indicators. The "data suggest that exercise could decrease the severity of deconditioning caused by bedrest." [The number of subjects is too small for statistical evaluation (H.S.).]

Riegle, G. D.: "Chronic stress effects on adrenocortical responsiveness in young and aged rats." *Neuroendocrinology* (Basel) **11**: 1-10 (1973). H67,112/73

Young and old rats were subjected to repeated restraint for twenty days. The decrease in stress responsiveness was greater in the former than in the latter groups.

Yanase, M.: "A study on the role of brain for the establishment of adaptation to the repeated immobilization stress. II. A role of the limbic-midbrain system in the repeated immobilization stress." *J. Physiol. Soc. Jap.* **35**: 171-178 (1973) (Japanese). J17,716/73

In rabbits, ACTH release following repeated restraint diminished as a consequence of adaptation. This was not found after sectioning of the fornix. "Therefore, hippocampal inhibition of ACTH release is considered to correlate with the inhibition of ACTH release under the repeated stress, and hippocampus may play an important role in the establishment of adaptation to the stress."

Zachariasen, R. D., Newcomer, W. S.: "Phenylethanolamine-N-methyl transferase activity in the avian adrenal following immobilization or adrenocorticotropin." *Gen. Comp. Endocrinol.* **23**: 193-198 (1974). H88,608/74

In cockerels, ACTH or immobilization resulted in an increase in plasma EP and NEP with an accompanying decrease in the adrenal levels of these catecholamines; plasma corticosterone also rose as did the phenylethanolamine-N-methyl transferase (PNMT) content of the adrenals without affecting adrenal corticosterone. "It is suggested that the rapid increase in PNMT activity, occurring with the acute application of stressors in chickens, may provide a means of sustaining an increased outflow of EP in times of 'stress.'" Corticosterone may play a role in the elevation of PNMT during the avian stress response.

→Enzymes and Other Metabolites.
Bartlett, R. G. Jr., Miller, M. A.: "The adrenal cortex in restraint hypothermia and in adaptation to the stress of restraint." *J. Endocrinol.* **14**: 181-187 (1956). C25,043/56

In rats, mild restraint for one week increased the ascorbic acid and to a lesser extent the cholesterol content of the adrenals. Restraint, sufficiently severe to reduce body temperature, produced inverse changes. Loss of adrenal cholesterol and ascorbic acid from the adrenals was particularly severe in animals restrained while exposed to cold.

Buchel, L., Liblau, L., Murawsky, M., Prioux-Guyonneau, M.: "Influence de sub-

stances psychotropes sur les variations du taux plasmatique des acides gras libres chez le rat constraint" (Influence of psychotropic substances on variations of total plasma free fatty acids in restrained rats). *Arch. Sci. Physiol.* **23**: 407-414 (1969). G68,704/69

In rats, restraint severe enough to cause gastric ulcers diminishes the FFA content of the plasma, contrary to most other stressors.

Kvetnansky, R., Weise, V. K., Kopin, I. J.: "Elevation of adrenal tyrosine hydroxylase and phenylethanolamine-N-methyl transferase by repeated immobilization of rats." *Endocrinology* **87**: 744-749 (1970).

H30,287/70

Sobocińska, J.: "The effect of prolonged immobilization on diuresis and water intake in rats." *Space Life Sci.* **4**: 200-203 (1973).

H79,375/73

In rats immobilized in their natural position for many weeks, there was an increase in diuresis but no changes in sodium or potassium excretion.

Zachariasen, R. D., Newcomer, W. S.: "Phenylethanolamine-N-methyl transferase activity in the avian adrenal following immobilization or adrenocorticotropin." *Gen. Comp. Endocrinol.* **23**: 193-198 (1974).

H88,608/74

In cockerels, ACTH or immobilization resulted in an increase in plasma EP and NEP with an accompanying decrease in the adrenal levels of these catecholamines; plasma corticosterone also rose as did the phenylethanolamine-N-methyl transferase (PNMT) content of the adrenals without affecting adrenal corticosterone. "It is suggested that the rapid increase in PNMT activity, occurring with the acute application of stressors in chickens, may provide a means of sustaining an increased outflow of EP in times of 'stress.'" Corticosterone may play a role in the elevation of PNMT during the avian stress response.

→Varia. Elmadjian, F., Pincus, G.: "The adrenal cortex and the lymphocytopenia of stress." *Endocrinology* **37**: 47-49 (1945).

B366/45

In mice, both restraint and cold produce a typical stress lymphocytopenia.

Marsh, J. T., Rasmussen, A. F. Jr.: "Response of adrenals, thymus, spleen and leucocytes to shuttle box and confinement stress." *Proc. Soc. Exp. Biol. Med.* **104**: 180-183 (1960).

C89,538/60

"Changes in organ weights and leucocytes following daily exposure to emotionally disturbing shuttle box or confinement stress were consistently observed. Adrenal hypertrophy and drops in circulating leucocytes were relatively rapid with significant changes observed following 3 to 7 days of stress. Involution of thymus and spleen occurred more slowly, with differences becoming maximum following 14 to 28 days of stress. Differences between experimental and control values returned to non-significant levels in 21 days following termination of stress."

Portugalov, V. V., Kaplanskii, A. S., Durnova, G. N.: "The condition of immunocompetent organs in the presence of hypokinesia." *Vestn. Akad. Med. Nauk SSR* **26** No. 10: 29-34 (1971) (Russian). [Eng. transl.: *Vestn. USSR Acad. Med. Sci.* **26**: 40-46 (1971).] J20,535/71

The thymicolympathic and splenic involution associated with stress (restraint) is accompanied by a decrease in the production of immunocompetent cells, but this paradoxically fails to diminish the antibody content of the blood.

Whittaker, D. K., Wilson, T. R.: "The effect of age and strain differences on the incidence of restraint-induced oral and gastric ulcers in three strains of rats." *J. Dent. Res.* **51**: 619-625 (1972). J19,863/72

In different strains of rats, the stress of restraint may cause predominantly *gastric* or *oral ulcers*. The clinical literature suggesting that ulcerative gingivitis, chronic periodontitis, and herpes labialis may also be related to stress in man is reviewed.

Tsukiyama, H., Otsuka, K., Kyuno, S., Fujishima, S., Kijima, F.: "Influence of immobilization stress on blood pressure, plasma renin activity and biosynthesis of adrenocorticoid." *Jap. Circ. J.* **37**: 1265-1270 (1973). H81,677/73

In rabbits, "shortly after the beginning of immobilization stress a remarkable elevation in the *arterial pressure*, a significant increase in plasma renin levels and plasma corticosterone concentrations were observed." However the changes in plasma renin and corticosterone did not run parallel, and hence there appear to be different mechanisms activating the renin-angiotensin and pituitary-adrenocortical systems. EEG studies suggest that the homeostatic mechanisms mediated by the mesencephalic reticular formation and grey matter regulate blood

pressure and renin release while the hippocampus, amygdala and anterior hypothalamic area are less effective in this respect. Findings from selective electric stimulation of various brain areas are in accordance with this interpretation.

Moritz, V., Baumann, R., Hecht, K., Poppei, M., Treptow, K.: "Relationen zwischen neurotisch induzierter Blutdruckdysregulation und Granulagehalt der Pankreas-B-Zellen bei der Albinoratte" (Relation between neurosis-induced blood pressure dysfunction and granule content in the pancreatic β -cells of the albino rat). *Acta Biol. Med. Ger.* **30**: 231-240 (1973).

J7,756/73

Under certain circumstances, repeated restraint can cause degranulation of pancreatic β -cells in the rat. This change is ascribed to stress.

Metz, G., Classen, H. G., Vogel, W., Mittermayer, C.: "Sympathico-adrenerge Stimulation und Lungenveränderungen" (Sympathico-adrenergic stimulation and pulmonary changes) (abstracted). *5th Europ. Congr. Anaesthesiology*, p. 202. Madrid, 1974.

J18,264/74

In rats, the stress of restraint causes edema and disseminated hemorrhages in the lungs which can be prevented by certain α -adrenergic blocking agents and analgesics.

+Varia. Lange, K., Gold, M. M. A., Weiner, D., Kramer, M.: "Factors influencing resistance to cold environments." *Bull. U.S. Army* **8**: 849-859 (1948).

B23,962/48

The survival time of restrained rabbits is greatly diminished at -20°C and their body temperature drops precipitously.

Frankel, H. M.: "Effects of restraint on rats exposed to high temperature." *J. Appl. Physiol.* **14**: 997-999 (1959).

J11,919/59

Restraint diminished the resistance of rats to high temperatures, although the final rectal temperatures were not greatly different.

Taylor, R. E. Jr., Fregly, M. J.: "Effect of reserpine on body temperature regulation of the rat." *J. Pharmacol. Exp. Ther.* **138**: 200-207 (1962).

D41,319/62

In rats, reserpine given intraperitoneally diminishes body temperature much more at low than at high environmental temperatures. It acts by decreasing heat production rather than by increasing heat loss. Restraint aug-

ments the reserpine-induced drop in body temperature.

Brodie, D. A., Valitski, L. S.: "Production of gastric hemorrhage in rats by multiple stresses." *Proc. Soc. Exp. Biol. Med.* **113**: 998-1001 (1963).

E28,039/63

"Gastric hemorrhage was produced in 93% of rats subjected to cold + restraint stress for 60 minutes." This combination of stressors also elicited a marked depression of body temperature lasting three hours after the stress. "Anticholinergics, ganglionic blocking agents, certain central nervous system depressants and epinephrine reduced the incidence of hemorrhage."

Ader, R.: "Gastric erosions in the rat: effects of immobilization at different points in the activity cycle." *Science* **145**: 406-407 (1964).

F16,095/64

Ader, R.: "Behavioral and physiological rhythms and the development of gastric erosions in the rat." *Psychosom. Med.* **29**: 345-353 (1967).

H62,749/67

In rats, stress ulcers of the stomach develop much more readily if they are immobilized during the active period (18:00 to 03:00) than during the inactive period of their circadian cycle.

Mikhail, A. A.: "Relationship of conditioned anxiety to stomach ulceration and acidity in rats." *J. Comp. Physiol. Psychol.* **68**: 623-626 (1969).

G68,624/69

In rats, conditioned anxiety did not aggravate the production of stress ulcers by restraint.

Martin, M. S., André, C., Martin, F., Lambert, R.: "Rôle du froid dans l'ulcère de contrainte chez le Rat" (Effects of cold on restraint ulcers in rats). *C. R. Soc. Biol. (Paris)* **163**: 158-161 (1969).

H14,537/69

In rats, restraint at 5°C is highly effective in producing gastric ulcers within three hours and a concurrent drop in rectal temperature.

Noel, W. K., Kilmore, M. A.: "Effect of stress and restricted food intake on corticosteroid-induced ulcers." *J. Am. Osteopath. Assoc.* **69**: 1051-1052 (1970).

J23,510/70

In rats, moderate amounts of cortisol increased the severity of restraint ulcers.

Blaszkowski, T. P., DeFeo, J. J., Guarino, A. M.: "Central vs. peripheral catecholamines in rats during adaptation to chronic restraint stress." *Pharmacology (Basel)* **4**: 321-333 (1970).

H36,516/70

Reserpine pretreatment increases the mortality of rats exposed to the stress of restraint, presumably because of its central rather than peripheral NEP-depleting action.

Prioux-Guyonneau, M.: "Répercussions de la contrainte sur la régulation thermique du rat blanc maintenu à différentes températures ambiantes" (Repercussions of restraint on thermal regulation of white rats kept at different environmental temperatures). *C.R. Soc. Biol. (Paris)* **164**: 72-75 (1970).

J21,917/70

Ritchie, W. P. Jr., Roth, R. R., Fischer, R. P.: "Studies on the pathogenesis of 'stress ulcer': effect of hemorrhage, transfusion, and vagotomy in the restrained rat." *Surgery* **71**: 445-451 (1972).

G89,104/72

"Restraint-induced ulcers in the rat resemble posttraumatic 'stress ulcers' in man in that they are acute and multiple, occur mainly in the stomach, are confined to the oxytic cell area, and are not associated with gastric acid hypersecretion." The production of these ulcers is enhanced by *hemorrhage* and greatly diminished by *vagotomy*.

Buchel, L., Prioux-Guyonneau, M., Liblau, L., Murawsky, M.: "Influence de la contrainte du rat blanc sur l'activité, la pénétration et le métabolisme de l'hexobarbital et du barbital" (Influence of restraint on the activity, penetration and metabolism of hexobarbital and barbital in white rats). *Thérapie* **27**: 609-625 (1972).

G92,849/72

"The potentiation of the hypnotic effects, increase of the sleeping time with *hexobarbital*, shortening of the latent period with *barbital*, in relation with short or long lasting restraint in rats, are attributable to two different mechanisms: inhibition of hexobarbital metabolism; increase of barbital penetration into the brain."

Ivanova, G. N., Altukhova, V. I., Kenig, E. E., Skebelskaia, I. B.: "Functional condition of the adrenal cortex of guinea pigs under conditions of prolonged and continuous overheating." *Probl. Endokrinol. (Mosk.)* **18** No. 5: 98-103 (1972).

H60,926/72

In guinea pigs, *overheating* at 35°C from five hours up to twenty-one days reduced the adrenocortical response to the stress of restraint but did not alter blood 17-OHCS levels or reactivity to exogenous ACTH. "A conclusion could be drawn that reduced response to stress in these animals was as-

cociated with a lesser excretion of endogenous ACTH."

Seifter, E., Rettura, G., Zisblatt, M., Levenson, S. M., Levine, N., Davidson, A., Seifter, J.: "Enhancement of tumor development in physically-stressed mice inoculated with an oncogenic virus." *Experientia* **29**: 1379-1382 (1973).

H80,975/73

In mice, restraint by a partial body cast produced the typical manifestations of systemic stress and at the same time increased susceptibility to the tumorigenic action of murine *sarcoma virus*. In the immobilized animals "there appeared to be a smaller number of small lymphocytes due to stress and a proliferation of epithelioid elements. Hassal bodies were also involved in agreement with earlier findings of Selye. If stress or cortisone treatment result in impaired function of these structures, then the endocrine function of the thymus gland as well as its role in providing circulating cells would be disturbed." In any event, the response of the thymus during stress is assumed to increase susceptibility to the virus through interference with immune reactions.

Yano, S., Harada, M.: "A method for the production of stress erosion in the mouse stomach and related pharmacological studies." *Jap. J. Pharmacol.* **23**: 57-64 (1973).

H85,804/73

In mice, stress ulcers of the stomach can be produced most reliably by immersing them in water of 25°C for eighteen hours while they are enclosed in a restraint cage of special design. The technique is said to be particularly useful in the assay of drugs inhibiting such erosions. Curiously, immersion at lower or higher temperatures causes less severe gastric ulcers.

Buchel, L., Murawsky, M.: "Métabolisme et activité de la zoxazolamine chez le rat blanc au cours de l'immobilisation forcée accompagnée ou non d'hypothermie" (Zoxazolamine metabolism and activity in white rats during restraint with or without hypothermia). *Arch. Sci. Physiol.* **27**: 37-53 (1973).

J7,077/73

In rats, the muscle-relaxing effect of *zoxazolamine* is considerably enhanced by the stress of restraint, especially in cold surroundings. This is ascribed mainly to increased sensitivity of the nervous system and to a lesser extent to impaired zoxazolamine metabolism during stress.

Lindenbaum, E. S., Diamond, B., Yaryura-Tobías, J. A.: "Nicotinic acid and restraint induced ulcers." *Acta Physiol. Lat.-Amer.* **23**: 288-292 (1973). J9,059/73

In rats, the gastric ulcers produced by restraint coupled with food and water deprivation are more effectively inhibited by *nicotinic acid* than by *chlorpromazine*.

Sibilly, A., Krivošić, I., Foucher, G., Fresnel, P. L., Boutelier, P.: "Prévention locale de l'ulcère gastrique expérimental. (Etude préliminaire)" (Topical prevention of experimental gastric ulcer. [Preliminary study]). *J. Chir. (Paris)* **106**: 521-534 (1973). J10,151/73

In rats, the stress ulcers produced by restraint are aggravated by *fasting* and prevented by oral administration of *glucose* or *aluminum gel*. Neutralization of the gastric acid does not seem to be decisive since aluminum gel protects less than hypertonic glucose; perhaps the latter helps to maintain cell metabolism and the gastric barrier.

Redgate, E. S.: "Neural control of pituitary adrenal activity in *Cyprinus carpio*." *Gen. Comp. Endocrinol.* **22**: 35-41 (1974).

H81,914/74

"The prompt responses of plasma cortisol concentration to stimuli, such as sound, hypothalamic stimulation, the photoperiod, and

restraint, indicate that the pituitary adrenal system of the *carp* is controlled by neural pathways in the brain of this teleost."

Tran, T. A., Gregg, R. V.: "Hypothermia in restraint-induced gastric ulcers in *parabiotic* rats." *Gastroenterology* **67**: 271-275 (1974). J15,225/74

Hadjiolova, I.: "Veränderungen des Plasma- und Nebennierenrindencorticosterone bei Ratten während Hypokinesie und zusätzlicher Stress-Einwirkungen (Influence of hypokinesia and subsequent stress upon the rat plasma and adrenal corticosterone level)." *Int. Arch. Arbeitsmed.* **33**: 59-70 (1974). J17,473/74

Studies on plasma and adrenal corticosterone in rats exposed to different stressors (*heat, restraint, noise*) alone or in combination. "A moderate increase in the levels of both plasma and adrenal corticosterone was observed after 24 hrs of hypokinesia. In a subsequent period of 60 days the corticosterone levels did not differ significantly from the levels found in the control animals. However, a marked decrease in adrenal weight and a slighter response to additional thermal stress were demonstrated after 60 days of hypokinesia. Differences between the restrained and the control animals were also found in the adaptation to chronic auditory stress."

Athletics

For the sake of convenience, we have separated the literature on athletics from that on muscular exercise in general, but from a medical point of view this is justified only in that the two are usually associated with different sets of conditioning factors. For example, the psychologic accompaniments of forced labor and the environmental stimuli of work in factories or mines (noise, vibration, air pollution, extremes of temperature) frequently differ from those of athletic activities, usually performed in healthy surroundings. Yet, here also, hypoxia in mountain climbing, compression and decompression in diving and so on, may add to the stressor effect of muscular work itself.

Perhaps the most important conditioning agents in the stress response during competitive athletic performances are emotional factors. Interestingly, observations on Harvard-Yale boat racing crews showed marked eosinopenia even in the coxswain, who shared only the excitement, not the muscular work, of his teammates.

In athletes, uropepsin excretion is increased during the alarm reaction stage after various types of effort.

In young athletes, swimming to exhaustion may cause renal malfunction with abundant urinary casts and proteinuria.

Of course, most publications on the stressor effect of athletic exercise emphasize its therapeutic action in helping patients keep fit, or in rehabilitation, as after cardiac accidents or damage to the locomotor system.

The most typical stressor actions of athletic exercises are changes in adaptive hormone production. In high school boys, running and other athletic activities increase EP and NEP excretion to approximately the same extent. Many further observations confirm that catecholamine (EP, NEP, VMA) elimination rises after basketball, soccer, skiing, rowing and other types of physical exertion. Allegedly, aggressive emotional displays tend to favor NEP excretion, whereas anxious but passive activities are more likely to augment EP elimination. Aldosterone excretion rose, particularly in certain anxiety states associated with athletics, while glucocorticoid production, as indicated by blood levels, urinary excretion products or eosinopenia, depended more upon the intensity than the type of activity or the emotional attitude toward it.

Bicycle riding tends to decrease plasma insulin levels, while STH, cortisol and EP values rise. However, these observations require confirmation as they have been based on a relatively small number of subjects. Exercise on the bicycle ergometer raised the cortisol level not only in blood and urine but also in saliva; yet, with training, most of the hormonal changes tend to diminish as a consequence of adaptation.

The combination of athletic exercise with various conditioning agents has not yet been adequately studied using reliable indicators of stress. Of course, the effects of "doping," tranquilizers, alcohol, and other psychoactive drugs upon performance are well known, but this is not strictly relevant to the subject of our treatise.

In ski jumpers, emotional stressors are predominantly mediated through adrenergic β -receptors, and accordingly, the associated tachycardia is diminished by β -receptor-blocking agents, for example, oxprenolol.

In rats forced to swim in cold water, the brain NEP stores are greatly diminished but this change can be prevented by rewarming or swimming in warm water. Here, apparently, temperature is an important conditioning factor.

Athletics

(See also our earlier stress monographs, p. xiii)

Generalities. Selye, H.: "Die Algemene Aanpassingsindroom en die Aanpassingsiektes" (The general adaptation syndrome and the diseases of adaptation). *Manpower Volkskrante* 5: 8-124 (1946) (Afrikaans).

B1,207/46

Translation of the first detailed review on the concepts of the general adaptation syndrome and the diseases of adaptation, with an editorial foreword on their applicability to athletics (698 refs.).

Selye, H.: "Le syndrome général d'adaptation" (The general adaptation syndrome). 9e

Congr. Féd. Int. Médico-Sportive, pp. 7-15
Paris, 1952.
B69,346/52

Review on the G.A.S. in the form of a lecture adapted to the interests of athletes.

Steingass, G., Falkenhahn, A. H., Kenter, H.: "Muskeltraining und Stresseffekt auf den Elektrolythaushalt bei Ratten" (Muscle training and stress effect on electrolyte metabolism in rats). *Z. Gesamte Inn. Med.* 18: 292-298 (1963).
D66,673/63

Review of the G.A.S. in relation to athletic activity.

Schlüssel, H.: "Sport und Arteriosklerose" (Sports and arteriosclerosis). *Med. Welt (Stuttg.)* 28: 1563-1569 (1965).
F46,438/65

Review of animal experiments and observations on man suggesting that muscular work diminishes the severity and intensity of arteriosclerosis.

Bach, G., Wuschech, H., Hofer, E.: "Verhalten des Fibrins unter starker körperlicher Belastung" (Behavior of fibrin under severe physical stress). *Dtsch. Gesundheitsw.* **21**: 1112-1114 (1966).

J23,669/66

Eigelsreiter, H.: "Zur Uropepsin-Ausscheidung nach sportlichen Anstrengungen" (Uropepsin excretion after athletic exertion).

Forsch. Forscher Tiroler Ärzteschule **6**: 163-184 (1966).

G63,751/66

In athletes, uropepsin excretion is increased during the alarm reaction and decreased in the stage of exhaustion of the G.A.S.

Shephard, R. J.: "The heart and circulation under stress of Olympic conditions." *J.A.M.A.* **205**: 775-779 (1968).

H2,199/68

Blatter, K., Imhof, P.: "Die Rolle der adrenergen Beta-Rezeptoren bei der emotionalen Tachykardie; radiotelemetrische Untersuchungen an Skispringern" (The role of adrenergic beta-receptors in emotional tachycardia; radiotelemetric studies on ski jumpers)." *Schweiz. Z. Sportmed.* **17**: 131-149 (1969) (35 refs.).

J21,848/69

Imhof, P. R., Blatter, K., Fuccella, L. M., Turri, M.: "Beta-blockade and emotional tachycardia; radiotelemetric investigations in ski jumpers." *J. Appl. Physiol.* **27**: 366-369 (1969).

G79,995/69

In ski jumpers, emotional stresses are predominantly mediated through adrenergic β -receptors, as indicated by the fact that the associated tachycardia can be diminished by oxprenolol, a β -receptor-blocking agent.

Viru, A., Körge, P.: "Metabolic processes and adrenocortical activity during marathon races." *Int. Z. Angew. Physiol.* **29**: 173-183 (1971).

G84,664/71

Among fourteen first-class marathon runners, all except the two best showed lowering of blood cortisol levels during the race. Urinary sodium decreased and potassium increased. In most cases, glutamic-pyruvic transaminase activity and nonprotein nitrogen rose in plasma, and excretion of nitrogen and creatinine was reduced. "It was suggested that before the end of the marathon

race the protein catabolism is diminished due to a decrease of the glucocorticoid function of the adrenal gland."

Schmidt, P.: "Entstehungsmöglichkeiten psychopathologischer Komplikationen im Spitzensport" (The possibility of psychopathologic complications in high-calibre sports). *Schweiz. Z. Sportmed.* **19**: 203-207 (1971).

J21,831/71

Buskirk, E. R.: "Stress limits in the young athlete." *Maryland Med. J.* **20**: 35-37 (1971).

J20,175/71

Krahenbuhl, G. S.: "Stress reactivity in tennis players." *Res. Q. Am. Assoc. Health Phys. Educ.* **42**: 42-46 (1971).

J22,358/71

Karpman, V. L., Sinjakow, A. F., Ljubina, B. G., Gudkow, I. A.: "Der Blutkreislauf bei gesteuerter Tachykardie bei Sportlern" (The circulation of athletes during programmed tachycardia). *Med. Sport (Berl.)* **12**: 374-379 (1972).

H92,279/72

Knobloch, J., Behrmann, H., Bauer, W.: "Eine psychophysiologische Untersuchung zur Stressanfälligkeit" (Psychophysiological study on stress susceptibility). *Z. Exp. Angew. Psychol.* **20**: 591-613 (1973).

J21,670/73

Studies on the stress susceptibility of top-ranking cyclists as judged by questionnaires and responses to films.

Fernandez, A. E., Miatello, V. R., Zanetti, N. L., Olego, O., Carbalal, J.: "Manifestaciones renales consecutivas al esfuerzo físico" (Renal effects of physical effort). *Prensa Méd. Argent.* **60**: 1006-1008 (1973).

H81,565/73

Among perfectly healthy boys thirteen to fifteen years of age in whom careful examination showed no renal anomalies, the considerable physical effort of a swimming race led to the appearance of abundant urinary casts and proteinuria. "These urinary patterns are similar to those found in severe glomerulopathies."

Bugard, P.: *Stress, Fatigue et Dépression. (L'homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue and depression. Man and the aggression of everyday life). Vol. 1, p. 294; Vol. 2, p. 302. Paris: Doin Edit., 1974.

E10,487/74

There is a section on athletics, especially in

relation to fatigue, within this monograph on stress.

Eliot, R. S.: *Stress and the Heart*, Vol. 1, p. 415. Contemporary Problems of Cardiology. Mount Kisco, N.Y.: Futura, 1974.

E10,556/74

Monograph containing many articles by numerous experts on the role of stress in the production of cardiovascular disease with special reference to hypertension and myocardial infarction. Individual chapters deal with the role of occupation, homeostasis, environmental influences, sex, athletics, emotion, stress tests, and the therapeutic value of various techniques for relaxation, including Transcendental Meditation, Yoga, Zen, sencit cycles, hypnosis, and related practices.

Opie, L. H.: "Sudden death and sport." *Lancet* February 1, 1975, pp. 263-266.

H98,865/75

"Of 21 sudden deaths in sportsmen, 18 were thought to be caused by heart-attacks either during or after sport." Psychologic factors were considered to be important in eight cases.

→**Hormones.** Renold, A. E., Quigley, T. B., Kennard, H. E., Thorn, G. W.: "Reaction of the adrenal cortex to physical and emotional stress in college oarsmen." *N. Engl. J. Med.* **244:** 754-757 (1951). B65,108/51

Harvard-Yale boat race crews showed a marked eosinopenia which was interpreted as a sign of stress-induced corticoid secretion. Muscular effort was not the only stressor, for the coxswain likewise responded with pronounced eosinopenia although he was almost exclusively under emotional stress.

Euler, U. S. von, Hellner, S.: "Excretion of noradrenaline and adrenaline in muscular work." *Acta Physiol. Scand.* **26:** 183-191 (1952). B89,579/52

In male high school students, muscular work (running, general athletics) increased EP and NEP excretion approximately to the same extent. The authors conclude that there appears to be a correlation between the degree of stress involved in work and the output of catecholamines.

Hill, S. R. Jr., Goetz, F. C., Fox, H. M., Murawski, B. J., Krakauer, L. J., Reifenstein, R. W., Gray, S. J., Reddy, W. J., Hedberg, S. E., St. Marc, J. R., Thorn, G. W.: "Studies on adrenocortical and psychological

response to stress in man." *Arch. Intern. Med.* **97:** 269-298 (1956). C35,720/56

The intense muscular and psychogenic stressor effect of crew racing caused eosinopenia with increased urinary elimination of 17-OHCS, 17-KS, and uropepsin, but signs of adrenal hyperactivity were obvious during the prerace tension as well. Earlier studies found that eosinopenia developed likewise in the coxswain and coach during the race; hence "the physical exertion of rowing was not the only stress involved capable of inducing a marked eosinopenia."

Pugh, L. G. C. E.: "The adrenal cortex and winter sports. With a note on other exercise." *Br. Med. J.* February 7, 1959, pp. 342-344. C64,349/59

During winter sports, eosinopenia may become very severe, but it tends to diminish after the third week in association with improved physical conditions. "In Channel swimming virtual disappearance of the eosinophils and an eightfold rise in urinary 17-hydroxysteroids, reported elsewhere, suggest an adrenal cortical response comparable with that found in major surgery."

Elmadjian, F.: "Epinephrine, norepinephrine, and aldosterone: release and excretion." In: Schaefer, K. E. (ed.), *Man's Dependence on the Earthly Atmosphere*, pp. 100-116. New York: Macmillan, 1962. D30,946/62

Studies of EP and NEP secretion in normal people and psychiatric patients during stressful life situations "support the hypothesis that active, aggressive, emotional displays are related to increased excretion of norepinephrine, whereas tense, anxious, but passive emotional displays are related to increased excretion of epinephrine." Aldosterone elimination was elevated during certain anxiety states without demonstrable increases in catecholamine excretion. The stressors examined were manipulation of the Hoagland-Werthessen pursuit meter, hockey, boxing, basketball, baseball and anxiety-inducing interviews.

Schmid, E., Schmerwitz, K.: "Untersuchungen über die Aktivierung des sympathikoadrenalen Systems bei Basketballspielern an Hand der Vanillinmandelsäure-Bestimmung im Harn" (Studies on the activation of the sympathetic adrenal system in basketball players, as shown by urinary vanillylmandelic acid excretion). *Sportarzt und Sportmed.* No. 12: 399-402 (1964). G26,892/64

In basketball players, urinary VMA excretion rises in proportion to the effort exerted (30 refs.).

Simpson, H. W.: "Field studies of human stress in polar regions." *Br. Med. J.* March 4, 1967, pp. 530-533. F78,155/67

In men at a British Antarctic sledging base, eosinopenia was especially marked in the evening after a full day of travel. Similarly, in a party skiing 400 miles across Greenland, 17-OHCS excretion was high during the forty days of crossing from coast to coast. No adaptation to stress occurred.

Nowacki, P., Schmid, E.: "Über die sympathico-adrenale Reaktion im Training und Wettkampf bei verschiedenen Sportarten" (Sympathetic adrenal activation by various athletic activities during training and competition). *Med. Welt* 21: 1682-1688 (1970).

H30,897/70

Comparative study on the increase in plasma and urinary catecholamines elicited by different athletic activities such as basketball, skiing, handball and rowing. There is good evidence that what counts in such activities is not only the muscular but also the psychic stressor component.

Rose, L. I., Friedman, H. S., Beering, S. C., Cooper, K. H.: "Plasma cortisol changes following a mile run in conditioned subjects." *J. Clin. Endocrinol. Metab.* 31: 339-341 (1970).

H30,088/70

Viru, A., Körge, P.: "Metabolic processes and adrenocortical activity during marathon races." *Int. Z. Angew. Physiol.* 29: 173-183 (1971).

G84,664/71

Among fourteen first-class marathon runners, all except the two best showed lowering of blood cortisol levels during the race. Urinary sodium decreased and potassium increased. In most cases, glutamic-pyruvic transaminase activity and nonprotein nitrogen rose in plasma, and excretion of nitrogen and creatinine was reduced. "It was suggested that before the end of the marathon race the protein catabolism is diminished due to a decrease of the glucocorticoid function of the adrenal gland."

MacInnes, C., Rothwell, R. I., Jacobs, H. S., Nabarro, J. D. N.: "Plasma-11-hydroxy-corticosteroid and growth-hormone levels in climbers." *Lancet* January 9, 1971, pp. 49-51.

H34,116/71

In mountain climbers plasma 17-OHCS

levels were increased on days of considerable physical exertion. However, in two of five exhausted mountain climbers, unexpectedly low concentrations of plasma 11-OHCS were found.

Metze, R., Linke, P. G.: "Adrenalin- und Noradrenalinausscheidung bei Fussballspielern" (Adrenaline and noradrenaline excretion in football players). *Med. Sport* 11: 23-27 (1971).

H57,011/71

In football players, EP and NEP elimination is increased during training and even more during competition owing to the associated physical and psychic stress.

Hartley, L. H., Mason, J. W., Hogan, R. P., Jones, L. G., Kotchen, T. A., Mougey, E. H., Wherry, F. E., Pennington, L. L., Ricketts, P. T.: "Multiple hormonal responses to graded exercise in relation to physical training." *J. Appl. Physiol.* 33: 602-606 (1972).

H79,757/72

In man, the stress of heavy bicycle exercise increased plasma STH, cortisol and EP values but decreased insulin concentration.

Linke, P. G., Metze, R.: "Die Katecholaminausscheidung trainierter und untrainierter Jugendlicher bei physischer Belastung" (Catecholamine excretion in trained and untrained adolescents during physical load). *Ärztl. Jugendk.* 63: 177-189 (1972).

H80,366/72

Comparative studies on EP and NEP excretion in trained and untrained, twelve- to thirteen-year-old boys performing different types of physically exhausting athletic exercises (58 refs.).

Sarviharju, P. J., Vihko, V.: "Plasma FFA during psychophysical loading and endurance training." *J. Sports Med. Phys. Fitness* 12: 250-257 (1972).

H81,647/72

Stress produced in male students by intense work on a bicycle ergometer and a difficult mental choice situation caused greatly increased catecholamine excretion. Plasma FFA elevations were noted only after physical work.

Okada, A., Miyake, H., Takizawa, A., Minami, M.: "A study on the excreted catecholamines in the urine of Bobsleigh-tobogganing contestants." *J. Sport Med. (Torino)* 12: 71-75 (1972).

J19,089/72

Hoffmann, H. D., Fiedler, H., Görtler, H., Kibittel, W.: "Der Einfluss von Fahrrader-

gometerarbeit, Sparring und Wettkampf auf die Plasmainsulinkonzentration und den Blutzuckerspiegel bei Boxern" (The influence of muscular exercise [bicycle ergometer], sparring, and competition on the plasma insulin concentration and blood sugar level in boxers). *Med. Sport (Berl.)* **12**: 119-123 (1972). H90,857/72

Viru, A. A., Korge, P. K., Viru, E. A.: "Interrelations between the suprarenal glucocorticoid activity, the cardiovascular system, and the electrolyte metabolism during exhausting work." *Fiziol. Zh. SSSR* **59** No. 1: 105-110 (1973) (Russian). H79,331/73

In sportsmen, exercise on a bicycle ergometer raised the cortisol level in blood, saliva and urine. With further work, glucocorticoid activity decreased. These changes were roughly proportional to the characteristic blood pressure variations.

Neacșu, C.: "L'expression endocrino-métabolique du stress dans l'effort sportif" (Endocrine and metabolic effects of physical efforts). *Rev. Roum. Physiol.* **10**: 397-405 (1973). J8,137/73

Brief, mainly speculative résumé on the endocrine and metabolic consequences of the stress associated with athletic activities.

O'Boyle, A., Gannon, D., Hingerty, D.: "Sympatho-adrenal response to stress." *J. Ir. Med. Assoc.* **66**: 699-704 (1973).

J10,153/73

Review on the sympathoadrenal participation in stress, with personal observations "on cardiac infarct patients, normal and toxæmic pregnant subjects, and on subjects undergoing various forms of athletic stress."

Euler, U. S. von: "Sympatho-adrenal activity in physical exercise." *Med. Sci. Sports* **6**: 165-173 (1974) (47 refs.).

J16,754/74

Rennie, M. J., Johnson, R. H.: "Alteration of metabolic and hormonal responses to ex-

ercise by physical training." *Eur. J. Appl. Physiol.* **33**: 215-226 (1974). J20,051/74

Liesen, H., Hollmann, W., Budinger, H.: "Biochemical changes after long lasting exercise on 9-13 year old girl field hockey players." *Acta Paediatr. Belg.* **28** Suppl.: 287-296 (1974) (39 refs.). J21,518/74

Sutton, J. R., Casey, J. H.: "The adrenocortical response to competitive athletics in veteran athletes." *J. Clin. Endocrinol. Metab.* **40**: 135-138 (1975). H97,318/75

+Varia. Stone, E. A.: "Behavioral and neurochemical effects of acute swim stress are due to hypothermia." *Life Sci. [I]* **9**: 877-888 (1970). G77,276/70

In rats, forced swimming at 15°C causes hypothermia, inactivity and reduction of brain NEP. These changes can be prevented by rapid rewarming or by swimming in 37°C water.

Shigalevskii, V. V.: "On the development of 'chronic overexertion' in young sportsmen." *Kardiologiya* **14** No. 4: 117-124 (1974) (Russian). J22,432/74

Among young athletes, ECG changes and evidence of chronic fatigue are most commonly due to a "combination of excessive physical overload with marked mental stress."

Polis, B. D., Polis, E., Schwarz, H. P., Dreisbach, L.: "The effect of cold on the composition of the phospholipids of the blood plasma of healthy athletes." *Proc. Soc. Exp. Biol. Med.* **145**: 70-73 (1974).

J21,416/74

In athletes, the phosphatidyl glycerol content of plasma was very significantly elevated immediately after and seven minutes following exposure to cold.

Rennie, M. J., Johnson, R. H.: "Effects of an exercise-diet program on metabolic changes with exercise in runners." *J. Appl. Physiol.* **37**: 821-825 (1974) (33 refs.).

J20,086/74

Neuropsychologic Stimuli

(See also Physical Agents—sound, vibration, electroshock; Occupations—aerospace, military; Treatment—Transcendental Meditation, Zen, Yoga, hypnosis, psychoanalysis; Mechanisms—selective stimulation or lesion of certain nervous centers; Stress Tests—media, inter-

views; and various other sections of this treatise where agents which affect the nervous system are discussed)

Those neuropsychologic stressors which have one predominant characteristic (pain, anxiety, public speaking, fighting, sensory or sleep deprivation, motivation, cognition, and so on) are discussed in separate sections to facilitate retrieval of data on particular subjects. However, the various manifestations of psychogenic stress are arbitrarily discussed conjointly in the section, Anxiety, Anticipation, Fear, Arousal (p. 203), since all nervous stimuli in this category overlap. Here, we shall also find key references on combined treatment with neuropsychologic stressors and other agents.

Generalities

Neuropsychologic stimuli are of paramount importance, especially in higher mammals because of their complex CNS. This is particularly true of man, for whom cognitive and emotional stimuli play a predominant rôle in his interpersonal relationships within his family, workplace, social life and in the manifold activities necessary for preserving harmonious homeostasis among individuals, groups and nations. Furthermore, with increasing phylogenetic development, CNS regulation has assumed greater importance, controlling biochemical defenses, even against physical aggressors, both directly (for example, through logical analysis of responses and autonomic nervous reactions) and indirectly (for example, through the hypothalamic centers directing the defensive activities of the endocrine system). It is for this reason that laymen, and even some physicians, are still tempted to equate stress, and, particularly distress, with nonspecific arousal, mental exhaustion or frustration. Such a restriction of the concept is perfectly satisfactory for the great majority of stress situations encountered by man in his daily life. However, this would greatly limit the scope of the stress concept by excluding from it the nonspecific defenses that persist after decerebration or during deep anesthesia, when conscious feelings of arousal or frustration are eliminated, as well as the nonspecific stress reactions of all comparatively primitive living beings, such as plants and unicellular organisms, that have no nervous system.

A general overview of this subject can be obtained by consulting some of the many books and review articles on neuropsychiatric agents that will be cited. More specific information on individual stimuli, especially those important for man, will be considered in separate sections. However, at the outset, attention must be called to the difficulty of categorizing neuropsychologic stimuli, because as we have said, they almost always overlap, owing to the many connections between the parts of the nervous system, which tend to generalize the impulses wherever they happen to arise. If this is kept in mind, some categorization will still be of practical use in leading the reader rapidly to information specifically concerned with pain, anxiety, arousal, fight, leisure, sensory deprivation, sleep deprivation, motivation, cognition, or whatever. Depending upon the degree of his interest, he may then also look up other more or less closely related subjects but will have immediate access to what we have considered the most instructive key references dealing with one of these stimuli in particular.

Generalities

(See also our earlier stress monographs, p. xiii)

Darrow, C. W., Henry, C. E.: "Psychophysiology of stress." In: Committee on Undersea Warfare (eds.), *Human Factors in Undersea Warfare*, pp. 417-439. Washington, D.C.: National Research Council, 1949.

B47,919/49

Review on the relationship between psychologic factors and organic manifestations of the G.A.S. Special attention is given to undersea warfare (102 refs.).

Romano, J. (ed.): *Adaptation*, p. 113. Ithaca, N.Y.: Cornell University Press, 1949.

B90,996/49

Anthology of papers on adaptation to various environmental factors, with main emphasis upon emotional, intellectual and neurotic reactions. The G.A.S. is not mentioned.

Selye, H.: "The general-adaptation-syndrome in its relationships to neurology, psychology, and psychopathology." In: Weider, A., *Contributions Toward Medical Psychology. Theory and Psychodiagnostic Methods*, Vol. 1, pp. 234-274. New York: Ronald Press, 1953 (247 refs.).

B76,657/53

Hinkle, L. E. Jr., Wolff, H. G.: "Stress, emotions, and cardiovascular disease." *Mod. Med.* **23**: 151-160 (1955).

J13,310/55

Funkenstein, D. H., King, S. H., Drolette, M. E.: *Mastery of Stress*, p. 329. Cambridge, Mass.: Harvard University Press, 1957.

C49,747/57

Observations on stress-producing situations and their prevention in both man and experimental animals. Main emphasis is laid upon psychologic factors, but the somatic aspects of the G.A.S. are also considered.

Tong, J. E., Murphy, I. C.: "A review of stress reactivity research in relation to psychopathology and psychopathic behaviour disorders." *J. Ment. Sci.* **106**: 1273-1295 (1960) (212 refs.).

J10,963/60

Bovard, E. W.: "A note on the threshold for emotional stress." *Psychol. Rev.* **68**: 216-218 (1961).

D15,112/61

A review on the nervous centers regulating psychogenic stress as manifested by the response of the pituitary-adrenocortical axis.

Kollar, E. J.: "Psychological stress: a re-evaluation." *J. Nerv. Ment. Dis.* **132**: 382-396 (1961).

D7,763/61

On the basis of the literature and personal observations, the author states that "the concept of stress has been extended to include inhibitory-conservatory shifts as well as excitatory shifts in homeostasis. These shifts may be either adaptive or maladaptive. If the response is prolonged in duration or inappropriate to the stress, pathophysiological and tissue changes may result."

Dohrenwend, B. P.: "The social psychological nature of stress: a framework for causal inquiry." *J. Abnorm. Soc. Psychol.* **62**: 294-302 (1961).

D15,127/61

General review on the relationships between the G.A.S. and psychosocial stressors.

Menninger, K., Mayman, M., Pruyser, P.: *The Vital Balance. The Life Process in Mental Health and Illness*, p. 531. New York: Viking Press, 1963.

E6,393/63

Well-documented treatise with an extensive bibliography on psychosomatic medicine. Special emphasis is placed upon coping devices in everyday life, aggression, neurotic behavior and the importance of a personal relationship between physician and patient.

Torrance, E. P.: *Constructive Behavior: Stress, Personality and Mental Health*, p. 432. Belmont, Cal.: Wadsworth, 1965.

E10,436/65

Monograph on the psychologic implications of the G.A.S., with particular reference to performance and the development of a healthy personality. There are chapters examining how groups and individuals cope with stress, how constructive responses to stress can be developed, and what personality resources support such responses (350 refs.).

Müller, K. E.: *Einführung in die Allgemeine Psychologie* (Introduction to general psychology), p. 257. Stuttgart: Ferdinand Enke Verlag, 1965.

E4,995/65

Textbook on psychology with a penetrating analysis of psychosomatic interrelations, especially with regard to the stress syndrome.

Appley, M. H.: "Some issues in psychological stress research." *McGill University Psychology Colloquium pamphlet*, p. 29. Montreal: McGill University, 1965.

G41,364/65

Lecture summarizing the psychologic implications of stress research.

Appley, M. H., Trumbull, R.: "On the concept of psychological stress." In: Appley, M. H. and Trumbull, R., *Psychological Stress*.

- Issues in Research*, pp. 1-13. New York: Appleton-Century-Crofts, 1967. E10,407/67
 Introductory remarks on the G.A.S. in relation to psychic stressors are included in the proceedings of a large congress at which numerous authors discussed various aspects of stress.
- Teichner, W. H.: "Interaction of behavioral and physiological stress reactions." *Psychol. Rev.* **75**: 271-291 (1968) (54 refs.). J22,708/68
 "Experimental study on individual differences in reaction to psychological stress." *Jap. J. Psychol.* **39**: 308-313 (1969). J23,082/69
- Pressey, A. W., Zubek, J. P.: *Readings in General Psychology: Canadian Contributions*, p. 403. Toronto: McClelland and Stewart, 1970. E8,856/70
 An anthology of articles on psychology for university students, consisting mainly of papers previously published elsewhere. One chapter deals with the G.A.S.
- McGrath, J. E.: *Social and Psychological Factors in Stress*, p. 352. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,312/70
 A collection of papers on stress in man, based mainly on a conference on social and psychologic stressors which took place in 1967 under the auspices of the Air Force Office of Scientific Research. The book includes contributions from twelve conference participants.
- Wrench, D. F.: *Readings in Psychology: Foundations and Applications*, p. 456. New York and St. Louis: McGraw-Hill, 1971. E8,929/71
 An anthology of articles about psychology by various authors. It deals particularly with attention and perception, learning, motivation, emotion, individuality and psychosociology, and contains a special section on "The Stress of Life."
- Klepping, J., Escousse, A., Didier, J. P.: "Système adrénnergique et stress" (The adrenergic system and stress). *Sem. Hôp. Paris* **47**: 116-132 (1971). G81,581/71
 Extensive review on the G.A.S. with special emphasis upon the sympathetic system and adrenergic responses to various stressors (46 refs.).
- Weiss, J. M.: "Psychological factors in stress and disease." *Sci. Am.* **226**: 104-113 (1972). G90,892/72
 A review on psychogenic stress reactions with special reference to the induction of gastric ulcers in rats.
- Houston, B. K.: "Control over stress, locus of control, and response to stress." *J. Pers. Soc. Psychol.* **21**: 249-255 (1972). J12,693/72
 Levi, L., Kagan, A.: "A synopsis of ecology and psychiatry: some theoretical psychosomatic considerations, review of some studies and discussion of preventive aspects." Proc. 5th World Congr. of Psychiatry, Mexico, D. F. (1971), *Int. Congr. Series No. 274*, pp. 369-379 (1973). J16,708/73
- Dohrenwend, B. S., Dohrenwend, B. P. (eds.): *Stressful Life Events: Their Nature and Effects*, p. 340. New York, London and Sydney: John Wiley & Sons, 1974. E10,778/74
 Antonovsky, A.: "Conceptual and methodological problems in the study of resistance resources and stressful life events." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 245-258. New York, London and Sydney: John Wiley & Sons, 1974. E10,793/74
 Dohrenwend, B. S., Dohrenwend, B. P.: "A brief historical introduction to research on stressful life events." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 1-5. New York, London and Sydney: John Wiley & Sons, 1974. E10,779/74
 Dohrenwend, B. S., Dohrenwend, B. P.: "Overview and prospects for research on stressful life events." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 313-331. New York, London and Sydney: John Wiley & Sons, 1974. E10,796/74
 Cobb, S.: "A model for life events and their consequences." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 151-156. New York, London and Sydney: John Wiley & Sons, 1974. E10,787/74
 Kahn, R. L.: "Conflict, ambiguity, and overload: three elements in job stress." In: McLean, A., *Occupational Stress*, pp. 47-61. Springfield, Ill.: Charles C Thomas, 1974. E10,887/74

Arthur, R. J.: "Extreme stress in adult life and its psychic and psychophysiological consequences." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 195-207. Springfield, Ill.: Charles C Thomas, 1974. E10,691/74
pp. 227-241. Springfield, Ill.: Charles C Thomas, 1974 (36 refs.). E10,693/74

Kurtsin, I. T.: "Emotional stress and corticovisceral resonance." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 26-30. Baku, USSR, 1974 (Russian, with extensive English summary). J17,529/74

Review on psychologic stimulation as a cause or consequence of stress (41 refs.).

Rubin, R. T.: "Biochemical and neuroendocrine responses to severe psychological stress: 1. U.S. Navy aviator study. 2. Some general observations." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*,

Levi, L.: "Emotional stress and visceral functions." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 71-76. Baku, USSR, 1974 (Russian, with extensive English summary). J17,543/74

Pain and Grief

(See also Climate, Environment—social, cultural, isolation, captivity, concentration camps, relocation, catastrophe; and various other agents which can cause pain)

It will be recalled that pain, hunger, fear and rage were the stimuli that Cannon used in his classic studies on emotional factors capable of stimulating sympathetic activity and EP secretion. Ever since then, somatic pain and mental pain (grief) have been the subject of intensive investigations, not only with regard to this special response but as paradigms of stressors of considerable importance, particularly in man and other higher mammals.

A number of more or less accurate dolorimeters have been devised to produce a standard degree of pain (by heat, electric stimulation and so on), as a basis for objective measurements of its mental and somatic consequences. Undoubtedly these represent an important step toward quantification, but unfortunately they are still subject to many imperfections, because the same degree of stimulation may cause different intensities of pain depending upon a variety of conditioning factors which determine somatic pain sensitivity. Furthermore, such instruments do not help in the quantitative assessment of the indices that can be considered as truly nonspecific and hence as stress effects. All these criticisms apply even more to mental pain, such as grief and sorrow.

Still, it has been clearly established that physical pain increases plasma cortisol levels and interferes with its normal circadian rhythm. Even psychoneurotics respond to standardized heat (applied to the forehead) with lymphopenia, increased GSR, and EEG changes characteristic of stress; hence, such tests are appropriate even for mentally deranged patients.

In rabbits, painful electroshock applied to the earlobes causes an increase in plasma corticoid and FFA levels as well as polymorphonuclear leukocytosis. The literature contains a distressingly large number of reports on both physical and mental torture, sometimes using the most ingenious techniques of cruelty.

Somewhat unexpectedly, in mice, painful stimuli accelerated morphine-induced analgesia, but photic and auditory stimuli did not.

The sorrow of parents whose children suffered from neoplastic disease led to an increase in 17-OHCS excretion, which depended largely upon the individual's coping

behavior. As might have been expected, the response was greatest when the parents were first informed of the bad prognosis; later, adaptation progressed at varying rates but rarely became complete. Similarly, a study on army recruits who had recently lost a parent, revealed increases in 17-OHCS excretion that roughly paralleled the psychologic manifestations of their grief. In mothers of spina bifida children, responses to the MPI questionnaire were thought to be fairly accurate criteria of their subjective grief.

A multivariate analysis of stress effects (GSR, respiration rate, muscle tension, heart rate, digit span, tracking performance, and so on) showed that it is possible to discriminate patterns of response to pain from those elicited by other stressors. This was considered to be surprising "in that theories of response to aversive stimuli such as Cannon's and Selye's predict essentially similar response patterns to any strong emotion whether pain, fear, or threat." Such misunderstandings of the stress theory are so common that they deserve careful consideration. An investigation on stress can be meaningful only if it is realized that stress is the nonspecific response of the body to any demand, and hence by definition must be uniform whatever the eliciting agent. However, its manifestations cannot be the same in all cases because of the diverse conditioning agents which always influence it. As explained in the General Outline of the stress theory (in the introductory section of this treatise), the most important among these are the specific effects of the particular stressor employed, as well as the numerous endogenous and exogenous conditioning factors which invariably modify the standard response to stress. In the last-mentioned series of investigations, the most striking fact was that so many parameters of the multivariate analysis were similarly affected. It would, however, be inconceivable for them always to have been precisely the same in all respects, regardless of the particular stressor used and of individual variations in responsiveness.

Pain and Grief

(See also our earlier stress monographs, p. xiii)

Lindemann, E.: "Symptomatology and management of acute grief." *Am. J. Psychiatry* **101**: 141-148 (1944). B26,743/44

Malmo, R. B., Shagass, C., Davis, J. F., Cleghorn, R. A., Graham, B. F., Goodman, A. J.: "Standardized pain stimulation as controlled stress in physiological studies of psychoneurosis." *Science* **108**: 509-511 (1948). B47,043/48

In psychoneurotics, heat applied to the forehead caused stress manifested by lymphopenia, as well as GSR and EEG changes. It is concluded that pain tests "may profitably be employed in more extensive analyses of disturbances in mental patients undergoing stress."

Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear and Rage*, p. 404. Boston: Charles T Branford, 1953. A19,828/53

Excellent summary of the author's classic observations on the somatic manifestations of acute emotions, particularly with regard to the effect of fear, rage, hunger and thirst upon the sympathetic nervous system and EP secretion.

Grad, B., Kral, V. A.: "Adrenal cortical stress effects in senility. II. The response to heat stimulation produced by the Hardy-Wolff-Goodell dolorimeter." *Can. Psychiatr. Assoc. J.* **6**: 66-74 (1961). J10,361/61

Friedman, S. B., Mason, J. W., Hamburg, D. A.: "Urinary 17-hydroxycorticosteroid levels in parents of children with neoplastic disease. A study of chronic psychological stress." *Psychosom. Med.* **25**: 364-376 (1963). E23,527/63

Parents of children who suffered from neoplastic diseases were tested for 17-OHCS excretion and ranked according to its intensity. "Adrenal cortical activity was hypothesized to be related to the effectiveness of the individual's coping behavior. The group data

showed slight, but statistically significant, elevations at the time the parents were first admitted to the ward and when psychological stress was judged to be maximal."

Shenkin, H. A.: "The effect of pain on the diurnal pattern of plasma corticoid levels." *Neurology* (Minneap.) **14**: 1112-1117 (1964). C23,146/64

In patients with pain of somatic origin, plasma cortisol levels were usually increased, whereas in subjects without objective evidence of the cause of pain, these values and their diurnal variations were frequently normal.

Chodoff, P., Friedman, S. B., Hamburg, D. A.: "Stress, defenses and coping behavior: observations in parents of children with malignant disease." *Am. J. Psychiatr.* **120**: 743-749 (1964). G9,191/64

Tecce, J. J., Friedman, S. B., Mason, J. W.: "Anxiety, defensiveness and 17-hydroxycorticosteroid excretion." *J. Nerv. Ment. Dis.* **141**: 549-554 (1966). G37,624/66

Data on the stressor effect of grief upon parents of children with leukemia.

Winnik, H. Z.: "Second thoughts about 'psychic trauma'?" *Isr. Ann. Psychiatry* **7**: 82-95 (1969). J23,437/69

Discussion of the relationship between psychic trauma and the G.A.S.

Poe, R. O., Rose, R. M., Mason, J. W.: "Multiple determinants of 17-hydroxycorticosteroid excretion in recruits during basic training." *Psychosom. Med.* **32**: 369-378 (1970). G77,861/70

In recruits during basic training, psychologic ratings and weight were correlated with, and together predicted, 17-OHCS levels more accurately than did either alone. In twelve of fourteen men who lost a parent, the 17-OHCS values were extremely high. The results "suggested that an individual's 17-OHCS level is influenced by psychologic, biologic, historic and environmental variables" (27 refs.).

Kakizaki, T.: "Stress response during mental task. 1. Biochemical response of rabbits subjected to an electrical stimulation." *Ind. Health* **9**: 99-104 (1971). J10,262/71

Stress was produced in rabbits by painful electric stimulation of the ear lobes. Among the many possible indicators, the serum 11-OHCS and FFA levels were consistently increased and blood leukocytes decreased. Blood

lactic acid, serum phospholipids, and LDH activity were less significantly elevated.

Hare, E. H., Payne, H., Laurence, K. M., Rawnsley, K.: "Effect of severe stress on the Maudsley personality inventory score in normal subjects." *Br. J. Soc. Clin. Psychol.* **11**: 353-358 (1972). G97,218/72

In mothers of spina bifida children, the MPI score is considerably influenced by the stress of grief.

Hofer, M. A., Wolff, C. T., Friedman, S. B., Mason, J. W.: "A psychoendocrine study of bereavement. Part I. 17-Hydroxycorticosteroid excretion rates of parents following death of their children from leukemia." *Psychosom. Med.* **34**: 481-491 (1972). G97,602/72

Hofer, M. A., Wolff, C. T., Friedman, S. B., Mason, J. W.: "A psychoendocrine study of bereavement. Part II. Observations on the process of mourning in relation to adrenocortical function." *Psychosom. Med.* **34**: 492-504 (1972). G97,603/72

Urinary 17-OHCS excretion rates in parents of children who died of leukemia show rather variable results from which few conclusions can be drawn.

Vaudry, H., Dupont, W.: Action des stress douloureux sur la pression artérielle du rat. Essai d'interprétation par l'anastomose surrénaло-jugulaire" (Effect of painful stress on arterial pressure in rats. Attempt at interpretation by means of adrenalo-jugular anastomosis). *C. R. Soc. Biol. (Paris)* **166**: 24-28 (1972). H60,773/72

Anokhin, A. P. K., Shumilina, A. I., Mamedov, A. M.: "Statistical characteristics of tension-rhythm parameters in the EEG of cerebral cortex and subcortical structures during painful stress." *Dokl. Akad. Nauk SSSR, Otd. Biol.* **209** No. 1: 249-252 (1973) (Russian). [Engl. transl.: *Proc. Acad. Sci. U.S.S.R., Biol. Sci.* **208** No. 1: 156-158 (1973).] J19,679/73

"Medical aspects of torture." *Lancet* October 20, 1973, pp. 900-901. H77,363/73

Brief report of a group that met in London under the auspices of Amnesty International to study the medical aspects of physical and mental torture methods which cause severe stress. A short list of pertinent publications is attached.

Stevens, M. W., Domer, F. R.: "Alterations in morphine-induced analgesia in mice

exposed to pain, light or sound." *Arch. Int. Pharmacodyn. Ther.* **206**: 66-75 (1973).

H82,603/73

In mice, pain stimuli significantly increased both the onset and intensity of morphine analgesia. This was not the case in animals exposed to photic or auditory stimuli.

Davidson, P. O., Neufeld, R. W. J.: "Response to pain and stress: a multivariate analysis." *J. Psychosom. Res.* **18**: 25-32 (1974).
J12,477/74

In man, "it is possible, using multiple measures and appropriate statistical analyses, to discriminate patterns of response to pain

from other types of stressors. These results are encouraging and somewhat surprising in that theories of response to aversive stimuli such as Cannon's and Selye's predict essentially similar response patterns to any strong emotion, whether pain, fear, or threat." The measures used were GSR, respiration rate, muscle tension, heart rate, anxiety differential, digit span, tracking performance and so on (47 refs.). [Many of these parameters were similarly affected, but differences were to be expected because the specific actions of each stressor influence the stereotyped pattern through conditioning (H.S.).]

Anxiety, Anticipation, Fear, Arousal

(See also Climate and Environment—captivity, concentration camps, relocation, catastrophe; Occupations—aerospace, military, industry; Manic-depressive illness—suicide; and various other sections of this treatise in which agents that cause anxiety, anticipation, arousal or fear are discussed)

As we said at the outset of this chapter, neuropsychologic stressors that have one predominant characteristic (pain, anxiety, fighting, sensory or sleep deprivation, motivation, cognition, and so on) are treated in separate sections to facilitate retrieval of data on particular subjects. However, the various manifestations of psychogenic stress are arbitrarily discussed conjointly in this section on anxiety, anticipation, fear and arousal, since all these nervous stimuli overlap. Here, we shall also find key references on the combined effect of neuropsychologic stressors and other agents, except those used for therapy. (For these see Treatment.)

Most of the experimental work on the stressor effect of anxiety, anticipation, fear and arousal was concerned with reactions to such experiences as problem solving, academic examinations, anticipation of surgery, social problems and real or simulated panic situations. In the majority of these investigations, only psychologic indicators of stress were employed, and with these it is always difficult if not impossible to ascertain that they really reflect nonspecific biologic stress as presently defined.

Still—as was expected—these studies made it clear that anxiety does cause distress and interferes with performance in various tests. For example, students who were praised (irrespective of their actual success) after a first examination usually did better during a second test than those who were sharply criticized. But even here conditioning factors play a decisive role, as shown by personality inventories which can predict coping behavior to a considerable extent. Some people are stimulated by failure to ever greater efforts, while others are discouraged.

The term *arousal* is used rather loosely and is difficult to define. Certainly, it applies to any state of vigilance, but also to fighting, aggression, hate and anxiety; hence, it is somewhat arbitrary whether a particular psychologic stress situation is mentioned in one or the other of these categories. For example, the stressor effect of

Public Speaking has been listed separately after Anxiety, to facilitate retrieval. In any event, arousal is not synonymous with stress, but every type of arousal can produce typical stress manifestations.

A study of the general literature discussed in this section is more likely to help by offering practical tips on coping with anxiety than by elucidating stress mechanisms.

We may facilitate orientation in this somewhat complicated chapter by enumerating the subheadings that refer to separate sections on the effects of anxiety, anticipation, fear and arousal.

- Generalities
- Catecholamines
- ACTH and Corticoids
- STH
- TTH and Thyroid Hormones
- Other Hormones and Hormone-like Substances
- Metabolites
- Morphology
- Nervous System (including performance in general)
- Accident Proneness
- Suicide
- Cardiovascular System
- Varia
- +Genetics
- +Restraint
- +Electroshock
- +Drugs, Hormones
- +Varia

→**Hormones.** The most objective and quantifiable indicators of stress elicited by anxiety, anticipation, fear and arousal are hormonal changes. Most of the early studies were concerned with the increase in *glucocorticoid* production. This was virtually uniformly confirmed, in both man and experimental animals as for example, in patients anticipating surgery, in students undergoing academic examinations, in psychiatric patients in whom anxiety occurred spontaneously or was evoked by discussion of stressful subjects, in hypnotically-induced anxiety, in experimental situations causing feelings of shame or threat.

Increased urinary 17-OHCS excretion and elevated blood cortisol levels were observed repeatedly in patients who attempted, and sometimes subsequently committed, suicide. Also, the highest cholesterol concentrations were found in the adrenals of patients who committed suicide or died of hypertensive disease.

Even the anxiety caused by blood drawing, in subjects unfamiliar with this procedure, may raise blood corticoid levels. This is of special importance in studies in which the first sample is taken for control purposes.

Cortisol given intravenously disappears from the plasma more rapidly in anxious than in normal subjects, despite greater corticoid excretion. This would suggest that corticoid metabolism is accelerated during anxiety-induced fear.

In most of these studies, the increased glucocorticoid production correlated fairly well with psychologic indicators of emotional excitation, and as always depended upon personality factors and other conditioning agents.

In rhesus monkeys, conditioned anxiety and avoidance similarly induced marked elevations of plasma 17-OHCS, quite comparable in magnitude to those elicited by a maximally effective dose of intravenous ACTH. Monkeys brought to an experimental cage for the first time also exhibited a substantial rise in plasma corticoids; this is why the first sample should not be used to determine the normal control value. Relocation to a new cage is a well-known, commonly used stressor in various animal species.

Much less is known about *mineralocorticoid* production during fear and anxiety. In healthy people undergoing stressful experiences, such as examinations or the presentation of papers at public meetings, aldosterone excretion was frequently elevated. This rise roughly paralleled the degree of anxiety and was associated with an increase in 17-OHCS elimination.

The *ACTH* blood levels are likewise greatly elevated in students during oral examinations, as well as in preoperative patients. Although few publications deal with this fact, it is of course indirectly implied by the amply documented rise in glucocorticoid production.

Probably the earliest experiment on increased *catecholamine* production during fear was a demonstration by Cannon (1911) that "cats frightened by the proximity of a barking dog showed indirect evidence of enhanced adrenal secretion" which indicated EP release from the adrenal medulla, since at that time NEP and the importance of its discharge from sympathetic nerve endings were not yet known.

Many more recent investigators examined the same problem with modern techniques and found that during oral examinations increased glucocorticoid elimination is associated with a rise in the urinary excretion of both EP and NEP. Allegedly, in various stressful life situations, including anxiety-inducing interviews, active aggressive emotional displays are associated with a rise in NEP excretion, whereas tense, anxious, but passive behavior results in a predominant elevation of EP elimination. In students, feelings of anticipation, uncertainty and helplessness raised EP output three-fold and NEP secretion to a somewhat lesser extent in comparison with values in controls reading magazines while comfortably relaxing. In another study in which students were asked to accomplish choice-reaction tasks and received electric shocks as punishment for poor performance, both EP and NEP excretion rose. By increasing the subject's control over the situation, it was possible to counteract the rise in EP but not in NEP, in comparison with controls who received the punishment at random, irrespective of performance. In general, subjects with the highest rates of EP and NEP excretion were most efficient in their performance.

In rhesus monkeys, conditioned emotional disturbances augment NEP concentrations in plasma, roughly in proportion to the rise in plasma 17-OHCS.

The increased secretion of catecholamines during anxiety may lead to a cycle since it has also been demonstrated that in man continuous intravenous infusions of EP in turn produce moderate anxiety reactions (in addition to the classic stress effects of sweating, tachycardia, hypertension and cutaneous pallor).

Little is known about other hormonal responses to anxiety, but in wild rabbits fear can cause an acute discharge of *TTH*, often associated with an actual inhibition of ACTH secretion. The resulting, sometimes fatal, stress thyrotoxicosis may have a parallel in clinical medicine, and the fact that here increased TTH production is accompanied by diminished ACTH secretion would appear to support the "hypophyseal shift" theory. As expected, hypophysectomy prevents the fear-induced TTH discharge in these rabbits.

In students, the stress of an examination significantly raised 17-KGS and slightly increased 17-KS excretion. It remains to be seen whether this indicates a rise in testoid or corticoid hormones.

In man, anxiety-inducing emotional stress (like the injection of pyrogen) increases plasma STH levels. A similar rise in plasma STH (concurrently with an elevation of plasma cortisol) was seen in anxious but not in relaxed patients undergoing cardiac catheterization.

In rhesus monkeys, conditioned avoidance raises plasma STH levels.

→**Metabolites.** Among other biochemical changes elicited by anxiety in man, emotional *hyperglycemia* and even temporary *glycosuria* were the first to be observed. In rats, psychogenic stress increases blood sugar, as well as *insulin hypoglycemia*.

More recently, special attention has been given to alterations in *lipid* metabolism. For example, in students undergoing examinations, the blood cholesterol content may rise very significantly, often in combination with an increase in plasma lipoproteins of low density. These and other anxiety-inducing experiences, such as stressful interviews, criticism and frustration, have been shown to augment plasma *triglycerides* and *FFA*. Comparable findings have been made in animals.

In patients showing obvious severe anxiety before surgery, the blood *pyruvic acid* level rises and *hippuric acid* synthesis decreases.

Blood *uric acid* remained approximately unchanged in medical students who, during examinations, exhibited a marked rise in blood *cholesterol*.

The augmented corticoid secretion during academic examinations may or may not be associated with changes in *diuresis* and *creatinine* excretion. In dogs, emotional excitement inhibits diuresis, presumably as a consequence of enhanced vasopressin secretion. On the other hand, in patients, the discussion of stressful subjects raised diuresis and increased 17-OHCS, *nitrogen*, *sodium* and *potassium* elimination.

The effects of emotional stress upon *blood clotting* mechanisms differ in normotensive and hypertensive individuals. There is general agreement that emotional stress raises plasma FFA, often with a concurrent increase in blood pressure and corticoid secretion.

→**Morphology.** One of the most striking morphologic manifestations of stress induced by fear was the great increase in the incidence of often perforating *stress ulcers* during air raids in London.

In students, before and throughout examinations, *eosinopenia* was quite consistently observed. This effect of anxious anticipation also occurred (in combination with other typical manifestations of stress) in the coxswain and coach during crew racing. Eosinopenia could even be elicited in subjects induced to believe that they accidentally caused injury to a companion through misuse of explosives. In rats, anticipation of an electroshock produces the same effect.

In hares kept in captivity, the constant presence of a hunting dog causes *testicular* atrophy, and in rats exposed to fear by keeping them in front of a dog's cage, the histologic and biochemical changes of *thyrotoxicosis* were associated with a decrease in serum cholesterol and body weight. Apparently, the genetic factors that condition thyroid reactions to stress also influence thyroid-mediated alterations in serum cholesterol.

→**Nervous System.** Of course, the greatest attention was given to the *psychologic* consequences of anxiety and fear, such as the impairment of the most diverse types of problem solving and performance, learning ability, coping behavior, accident and suicide proneness and so on. In these studies, the techniques used for inducing fear or anxiety, anticipation of pleasant or unpleasant events, and the criteria for the determination of psychologic reactions, were so different and complex that the pertinent literature does not lend itself to meaningful condensation and must be consulted in the abstracts of the original publications.

The effects of various psychogenic stressors upon problem solving and perception vary according to conditioning factors. Psychologic stress appears to result in a special intolerance of ambiguity and incongruity in the expected performance.

A very common and characteristic manifestation of stress induced by anxiety is the rise in the GSR with increased *sweating*.

Anxiety, like so many other psychogenic stressors, produced *cardiovascular* changes such as an increase in blood pressure and pulse rate associated with flushing or pallor of the skin, and rather characteristic ECG alterations.

→**Varia.** One of the most dramatic effects of acute anxiety is the so-called *Voodoo death* induced by spells, sorcery or "black magic" among primitive natives in various parts of the world. Although its mechanism has never been clearly established, it may be caused by sudden arrhythmias or ventricular fibrillation.

+**Varia.** (see also Treatment) *Genetic* predisposition certainly plays a very important role in determining stress resistance. Certain strains of wild rabbits can be literally frightened to death. These fear responses are associated with thyroid hypertrophy, increased TTH production and a diminution of ACTH secretion, which contrasts sharply with the rise in ACTH production characteristic of stress in other strains. In students undergoing academic examinations, augmentation of plasma cortisol is also largely dependent upon constitutional factors.

Nitrous oxide, in amounts just sufficient to cause euphoria, impairs problem-solving activity, as does exposure to various stressors, but combining nitrous oxide and stress allegedly results in a cancellation of this blocking effect.

In rats, mouse-killing activity is blocked by chronic electroconvulsive shocks or *antidepressant drugs*.

In rats, conditioned anxiety and unpredictable electric shocks aggravated the production of stress ulcers by *restraint*; subdiaphragmatic vagotomy did not significantly reduce their incidence.

In *schizophrenic* patients, convulsive and nonconvulsive electrostimulation produced marked eosinopenia.

In persons with *vestibular defects* who accompanied experienced pilots on acrobatic flights, the usual increase in urinary catecholamine and corticoid excretion was largely suppressed, presumably because their inner ear anomalies prevented them from fully experiencing the stressor effects of the flights.

Anxiety, Anticipation, Fear, Arousal

(See also our earlier stress monographs, p. xiii)

Generalities. Brown, C. H., Gelder, D.

van: "Emotional reactions before examinations: I. Physiological changes." *J. Psychol.* 5: 1-9 (1938). B26,249/38

In emotionally aroused students, the blood

pressure, pulse rate and respiratory rate may be increased, and hyperglycemia with glycosuria may develop before examinations. [Chemical indices of stress have not been determined (H.S.).]

Beier, E. G.: "The effect of induced anxiety on flexibility of intellectual functioning." *Psychol. Monogr.* **65**: 1-26 (1951).

D92,619/51

"For the purpose of this study 'stress' is defined as the perception of threat with resulting anxiety."

Deese, J., Lazarus, R. S., Keenan, J.: "Anxiety, anxiety reduction, and stress in learning." *J. Exp. Psychol.* **46**: 55-60 (1953).
E62,140/53

Basowitz, H., Persky, H., Korchin, S. J., Grinker, R. R.: *Anxiety and Stress*, p. 320. New York, Toronto and London: McGraw-Hill, 1954.
C6,957/54

Well-documented monograph on anxiety, especially in relation to stress and the G.A.S.

Eriksen, C. W.: "Some personality correlates of stimulus generalization under stress." *J. Abnorm. Soc. Psychol.* **49**: 561-565 (1954).
E60,917/54

Jacobs, A., Leventer, S.: "Response to personality inventories with situational stress." *J. Abnorm. Soc. Psychol.* **51**: 449-451 (1955).
J13,192/55

Studies on "the effects of situational stresses induced by academic examinations and threats of failure upon scores achieved on standard personality inventories."

Janis, I. L.: *Psychological Stress*, p. 439. New York: John Wiley & Sons, 1958.
E5,435/58

Psychoanalytic and behavioral studies on surgical patients with reports of interviews before and after operations and an evaluation of the practical lessons to be drawn from them.

Coleman, J. C.: *Personality Dynamics and Effective Behavior*, p. 566. Chicago: Scott, Foresman, 1960.
C92,253/60

A monograph on human behavior with several sections on the psychologic effects of stress and the stressor actions of anxiety. An annotated bibliography deals with such problems as the stress of college life, marriage and the family, and aging.

Hawkins, D. R., Monroe, J. T., Sandifer, M. G., Vernon, C. R.: "Psychological and physiological responses to continuous epi-

nephrine infusion. An approach to the study of the affect, anxiety." *Psychiatr. Res. Rep. APA* **12**: 40-52 (1960).
J11,148/60

In man, continuous intravenous infusions of EP produced a moderate anxiety reaction in addition to the well-known somatic effects (sweating, tachycardia, hypertension, skin pallor).

Saltz, E.: "The effect of induced stress on free associations." *J. Abnorm. Soc. Psychol.* **62**: 161-164 (1961).
J4,045/61

Walters, G. C.: "Frequency and intensity of pre-shock experiences as determinants of fearfulness in an approach-avoidance conflict." *Can. J. Psychol.* **17**: 412-419 (1963).
J23,401/63

Mayhew, P. W.: "Stresses of school examinations." *Roy. Soc. Health J.* **84**: 38-41 (1964).
J23,949/64

Kelley, H. H., Condry, J. C. Jr., Dahlke, A. E., Hill, A. H.: "Collective behavior in a simulated panic situation." *J. Exp. Soc. Psychol.* **1**: 20-54 (1965).
J10,618/65

Psychologic analysis of collective behavior of a group attempting to escape one at a time from a simulated panic situation. [Relationships to the somatic aspects of the G.A.S. are not discussed (H.S.).]

Spielberger, C. D.: *Anxiety and Behavior*, p. 414. New York and London: Academic Press, 1966.
E10,532/66

Monograph on anxiety with extensive sections on its relationship to psychogenic stress. Little attention is given to the hypothalamus-pituitary-adrenal system.

Hermann, M. G.: "Testing a model of psychological stress." *J. Pers.* **34**: 381-396 (1966).
J23,350/66

Orr, D. B.: "The development and tryout of a laboratory procedure for inducing physical threat stress." *J. Psychol.* **65**: 183-194 (1967).
J23,608/67

Knott, J. R., Irwin, D. A.: "Anxiety, stress and the contingent negative variation (CNV)." *Electroencephalogr. Clin. Neurophysiol.* **24**: 286-287 (1968).
J22,592/68

Shephard, D. A. E.: "The anxious surgical patient and anaesthesia." *N. S. Med. Bull.* **47**: 107-111 (1968).
G58,805/68

Practical hints on ways to avoid the stressor effect of anesthesia in anxious patients.

Mason, J. W.: "A re-evaluation of the

concept of 'nonspecificity' in stress theory." *J. Psychiatr. Res.* **8**: 323-333 (1971).

G86,484/71

Brief but excellent analysis of evidence contradicting Selye's definition of stress. The author states that stress "may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole."

Fishman, D. B., Schneider, C. J.: "Predicting emotional adjustment in home dialysis patients and their relatives." *J. Chron. Dis.* **25**: 99-109 (1972).

J20,341/72

"Home dialysis does involve a uniquely stressful family situation in which one family member treats another in a life-saving, but potentially lethal way. This may explain why many clinical reports claim that greater psychological stresses for patient and relative occur on home dialysis than on in-center dialysis" (23 refs.).

Skelton, M., Dominian, J.: "Psychological stress in wives of patients with myocardial infarction." *Br. Med. J.* April 14, 1973, pp. 101-103.

H68,778/73

→**Catecholamines.** Cannon, W. B., de la Paz, D.: "Emotional stimulation of adrenal secretion." *Am. J. Physiol.* **28**: 64-70 (1911).

34,664/11

In cats frightened by the proximity of a barking dog, indirect physiologic evidence of EP secretion was apparent.

Funkenstein, D. H.: "The physiology of fear and anger." *Sci. Am.* **192**: 74-80 (1955).

D84,417/55

A review on observations in man which suggest that anger directed outward increases NEP, while depression and anxiety are associated with excessive EP secretion.

Mason, J. W., Mangan, G. Jr., Brady, J. V., Conrad, D., Rioch, D. M.: "Concurrent plasma epinephrine, norepinephrine and 17-hydroxycorticosteroid levels during conditioned emotional disturbances in monkeys." *Psychosom. Med.* **23**: 344-353 (1961).

D10,040/61

In rhesus monkeys, various conditioned emotional disturbances augment 17-OHCS and NEP concentrations in plasma. "It is suggested that the element of uncertainty or unpredictability, in combination with such factors as the threat of a noxious stimulus and the anticipation of coping activity, may

be a particularly critical factor in the determination of epinephrine release during emotional disturbances."

Pekkarinen, A., Castrén, O., Iisalo, E., Koivusalo, M., Laihinens, A., Simola, P. E., Thomasson, B.: "The emotional effect of matriculation examinations on the excretion of adrenaline, noradrenaline, 17-hydroxycorticosteroids into the urine and the content of 17-hydroxycorticosteroids in the plasma." In: *Biochemistry, Pharmacology and Physiology*, pp. 117-137. London: Pergamon Press, 1961.

E85,207/61

"While an operation often clearly increases both the excretion of adrenaline and noradrenaline and total 17-OHCS in the plasma, the psychic tension of student examination clearly increases the excretion of adrenaline only. The eosinopenia caused by examination therefore seems to be chiefly due to the increased excretion of adrenaline." The free 17-OHCS in plasma immediately after examination and urinary elimination of these compounds before and during the tests are less consistently increased, and the conjugated 17-OHCS levels remain normal.

Elmadjian, F.: "Epinephrine, norepinephrine, and aldosterone: release and excretion." In: Schaefer, K. E., *Man's Dependence on the Earthly Atmosphere*, pp. 100-116. New York: Macmillan, 1962.

D30,946/62

Studies on EP and NEP secretion during stressful life situations in normal people and psychiatric patients "support the hypothesis that active, aggressive, emotional displays are related to increased excretion of norepinephrine, whereas tense, anxious, but passive emotional displays are related to increased excretion of epinephrine." Aldosterone elimination was elevated in certain anxiety states without demonstrable increases in catecholamine excretion. The stressors examined were manipulation of the Hoagland-Werthessen pursuit meter, hockey, boxing, basketball, baseball and anxiety-inducing interviews.

Levi, L.: "The urinary output of adrenalin and noradrenalin during experimentally induced emotional stress in clinically different groups. A preliminary report." *Acta Psychother.* **11**: 218-227 (1963).

E37,966/63

Healthy young soldiers were exposed to "industrial stress" simulating actual working conditions in a factory or workshop, or to "film stress" (viewing scenes of cruelty, vio-

lence and military surgery). Both stressors caused increased catecholamine excretion.

Euler, U. S. von: "Quantitation of stress by catecholamine analysis." *Clin. Pharmacol. Ther.* **5**: 398-404 (1964). G18,238/64

Review of the literature and personal observations on man suggest that "gravitational stress and exposure to cold are mainly associated with an increase in the norepinephrine excretion, indicating the importance of this hormone in circulatory and temperature controlling homeostatic mechanisms. Mental stress involving exhilarating or aggressive reactions is also associated with an increase in the norepinephrine excretion. The types of emotional stress which are mainly characterized by apprehension, anxiety, pain, or general discomfort are regularly accompanied by an increase in the epinephrine excretion." Special sections are devoted to catecholamine excretion associated with flying, mental work and exposure to cold.

Pátkai, P., Frankenhaeuser, M., Rissler, A., Bjorkvall, C.: "Catecholamine excretion, performance, and subjective stress." *Scand. J. Psychol.* **8**: 113-122 (1967). G75,474/67

In students undergoing moderately stressful psychologic tests, performance was better among subjects with high than among those with low EP excretion. No consistent relationship could be demonstrated between NEP elimination and psychologic variables.

Pinter, E. J., Peterfy, G., Cleghorn, J. M., Pattee, C. J.: "The influence of emotional stress on fat mobilization; the role of endogenous catecholamines and the β adrenergic receptors." *Am. J. Med. Sci.* **254**: 634-651 (1967). G52,170/67

Anxiety-inducing hypnotic suggestion increases catecholamine secretion and blood FFA. Pretreatment with β -adrenergic blocking agents inhibits the adipokinetic response.

Carlson, L. A., Levi, L., Orö, L.: "Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid." *J. Clin. Invest.* **47**: 1795-1805 (1968). H1,440/68

In male volunteers, emotional stressors (dazzling light, standardized criticism, sorting steel balls of different sizes) caused a rise in plasma FFA and triglycerides as well as increased catecholamine excretion. Concurrent treatment with nicotinic acid prevented the elevation in FAA and triglycerides, but not the stressor-induced increase in catechol-

amine elimination or the associated rise in heart rate and blood pressure.

Starlinger, H., Hawel, W., Rutenfranz, J.: "Untersuchungen zur Frage der Catecholaminausscheidung im Harn als Kriterium für emotionalen Stress unter verschiedenen Umgebungsbedingungen. Vibrationsbelastung, Filmdarbietungen und Prüfungssituation" (Studies on the question of urinary catecholamine excretion as a criterion of emotional stress under various environmental conditions. Vibration load, presentation of motion pictures and examination periods). *Int. Z. Angew. Physiol.* **27**: 1-14 (1969).

G65,048/69

Frankenhaeuser, M., Rissler, A.: "Catecholamine output during relaxation and anticipation." *Percept. Mot. Skills* **30**: 745-746 (1970).

G82,215/70

Mere anticipation, uncertainty and a feeling of helplessness evoked heightened catecholamine excretion in students who, while completely inactive, knew that they would occasionally receive relatively mild electric shocks. In comparison with a control group of students reading magazines while comfortably relaxing, those anticipating the harmless shocks had an increased excretion of EP and, to a lesser extent, of NEP. Thus, anticipation of unpleasant though harmless events which the subject cannot influence brings about a nearly threefold increase in EP output.

Frankenhaeuser, M., Rissler, A.: "Effects of punishment on catecholamine release and efficiency of performance." *Psychopharmacologia* **17**: 378-390 (1970). G77,863/70

Male university students were asked to accomplish a choice-reaction task and received electric shocks either at random or as punishment for slow performance. Others were not punished, irrespective of performance. "Punishment produced a rise in both adrenaline and noradrenaline release. By increasing the subject's control over the situation it was possible to counteract the adrenaline increase, while noradrenaline release appeared unaffected. On the whole, subjects with high as compared with low rates of adrenaline and noradrenaline excretion were more efficient in terms of both speed and accuracy of performance."

Webster, A. W.: "Beta-adrenergic stimulants and 'exam nerves.'" *Lancet* September 9, 1972, p. 542.

J20,194/72

Johansson, G., Frankenhaeuser, M., Magnusson, D.: "Catecholamine output in school

children as related to performance and adjustment." *Scand. J. Psychol.* **14**: 20-28 (1973). H80,791/73

In school boys, mean EP excretion increased significantly during performance of an arithmetic test as compared to viewing a neutral film. Among children of both sexes, those with enhanced EP output were better than the others at solving arithmetic problems.

O'Hanlon, J. F., Horvath, S. M.: "Interrelationships among performance, circulating concentrations of adrenaline, noradrenaline, glucose, and the free fatty acids in men performing a monitoring task." *Psychophysiology* **10**: 251-259 (1973). J3,116/73

In young men performing an exacting vigilance test, basal blood EP and NEP were inversely related to glucose. EP initially increased during the test but later returned to its basal level in proportion to performance. NEP was not related to performance. Glucose and FAA were elevated during the task and throughout a control period (watching slide projections).

→**ACTH and Corticoids.** Mirsky, I. A., Miller, R., Stein, M.: "Relation of adrenocortical activity and adaptive behavior." *Psychosom. Med.* **15**: 574-584 (1953) (54 refs.). B89,518/53

Franksson, C., Gemzell, C. A.: "Adrenocortical activity in the preoperative period." *J. Clin. Endocrinol. Metab.* **15**: 1069-1072 (1955). D95,673/55

A great majority of patients examined showed an increase in plasma 17-OHCS during the preoperative period, presumably owing to the stress of anxiety.

Hetzell, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man." *J. Clin. Endocrinol. Metab.* **15**: 1057-1068 (1955). C8,424/55

In patients, a one-hour discussion of "stressful subjects" caused diuresis with increased 17-OHCS, nitrogen, sodium and potassium excretion.

Bliss, E. L., Migeon, C. J., Branch, C. H. H., Samuels, L. T.: "Reaction of the adrenal cortex to emotional stress." *Psychosom. Med.* **18**: 56-76 (1956). C13,032/56

In normal people and psychiatric patients, emotional stress (subjectively estimated by manifestations of anxiety and tension)

whether occurring spontaneously or elicited experimentally, caused consistent but very modest increases in blood and urinary 17-OHCS. These changes were always much less pronounced than those produced by ACTH, Piromen, insulin, electroshock or moderate physical exercise.

Venning, E. H., Dyrenfurth, I.: "Effect of stress upon excretion of aldosterone." *J. Clin. Endocrinol. Metab.* **16**: 961 (1956).

C14,919/56

In healthy individuals urinary aldosterone excretion was frequently raised during "stressful experiences such as examinations or the presentation of papers at meetings."

Schwartz, T. B., Shields, D. R.: "Urinary excretion of formaldehydogenic steroids and creatinine. A reflection of emotional tension." *Psychosom. Med.* **18**: 159-172 (1956).

C25,345/56

In students undergoing stressful final examinations, increased urinary corticoid excretion occurs fairly regularly but urinary volume and creatinine elimination are not clearly related to the stressor.

Mason, J. W., Brady, J. V., Sidman, M.: "Plasma 17-hydroxycorticosteroid levels and conditioned behavior in the rhesus monkey." *Endocrinology* **60**: 741-752 (1957).

C35,278/57

In rhesus monkeys, conditioned anxiety and avoidance caused marked elevations of plasma 17-OHCS comparable to those elicited by intravenous ACTH in maximally effective doses. The animals also showed a substantial rise in plasma corticoids the first time they were brought to the experimental cage, but not on subsequent occasions.

Venning, E. H., Dyrenfurth, I., Beck, J. C.: "Effect of anxiety upon aldosterone excretion in man." *J. Clin. Endocrinol. Metab.* **17**: 1005-1008 (1957).

C38,804/57

In students sitting for oral examinations, the degree of anxiety was approximately graded in terms of an arbitrary scale. The rise in aldosterone excretion roughly paralleled the extent of anxiety, and was associated with enhanced 17-OHCS elimination.

Mason, J. W., Harwood, C. T., Rosenthal, N. R.: "Influence of some environmental factors on plasma and urinary 17-hydroxycorticosteroid levels in the rhesus monkey." *Am. J. Physiol.* **190**: 429-433 (1957).

C42,224/57

Persky, H.: "Adrenocortical function in anxious human subjects: the disappearance of hydrocortisone from plasma and its metabolic fate." *J. Clin. Endocrinol. Metab.* **17**: 760-765 (1957). J11,139/57

Intravenous cortisol disappears from the plasma more rapidly in anxious than in normal subjects. Despite the greater excretion of endogenous 17-OHCS in anxious patients, their excretion of these steroids following intravenous cortisol is subnormal. They appear to produce cortisol at a faster rate than do normal subjects.

Hammond, W. G., Vandam, L. D., Davis, J. M., Carter, R. D., Ball, M. R., Moore, F. D.: "Studies in surgical endocrinology. IV. Anesthetic agents as stimuli to change in corticosteroids and metabolism." *Ann. Surg.* **148**: 199-211 (1958). C57,405/58

"Preoperative apprehension and preanesthetic medication were not associated with elevations of the free blood 17-OHCS."

Persky, H., Maroc, J., Conrad, E., Breejen, A. D.: "Blood corticotropin and adrenal weight-maintenance factor levels of anxious patients and normal subjects." *Psychosom. Med.* **21**: 379-386 (1959).

D2,894/59

In anxious hypercorticoid patients, the plasma level of "precorticotropin or adrenal weight-maintenance factor (AWMF)" is more significantly increased than that of the classic ACTH or ascorbic acid depletion factor (AADF).

Mason, J. W.: "Psychological influences on the pituitary-adrenal cortical system. *Recent Prog. Horm. Res.* **15**: 345-389 (1959).

C71,311/59

Review lecture on the stressor effects of psychologic stimuli upon the pituitary-adrenocortical axis in man and monkeys. Among the factors discussed are housing conditions, environmental activity, "first-experience" situations (such as the first time monkeys are handled or placed in a new cage, avoidance procedures, sleep deprivation and diurnal variations. The general conclusion drawn is "that the pituitary-adrenal cortical system is remarkably sensitive to psychological influences in both man and the monkey, and that ACTH release occurs, not in association with a specific emotional state, but rather with a wide variety of emotional disturbances which may have the relatively undifferentiated element of distress or arousal" (9 refs. only, but an extensive discussion by the audience).

Persky, H., Korchin, S. J., Basowitz, H., Board, F. A., Sabshin, M., Hamburg, D. A., Grinker, R. R.: "Effect of two psychological stresses on adrenocortical function." *Arch. Neurol. Psychiatry* **81**: 219-226 (1959).

J3,935/59

In anxiety-prone psychiatric patients, anticipation of an anxiety-evoking interview or a perceptual distortion test caused a greater increase in plasma cortisol and urinary corticoid levels than did the experiment itself.

Levitt, E. E., Persky, H.: "Relation of Rorschach factors and plasma hydrocortisone level in hypnotically induced anxiety." *Psychosom. Med.* **22**: 218-223 (1960).

C88,083/60

Melick, R.: "Changes in urinary steroid excretion during examinations." *Australas. Ann. Med.* **9**: 200-203 (1960). D1,916/60

During examination periods, students' urinary corticoid excretion is increased throughout day and night.

Korchin, S. J., Herz, M.: "Differential effects of 'shame' and 'disintegrative' threats on emotional and adrenocortical functioning." *Arch. Gen. Psychiatry* **2**: 640-651 (1960).

D2,941/60

In healthy young men the psychogenic stress of shame, threat (scrambled sentences) or disintegrative threat (picture description) caused a rise in plasma cortisol roughly proportional to the manifest signs of emotional arousal.

Hodges, J. R., Jones, M. T., Stockham, M. A.: "Effect of emotion on blood corticotrophin and cortisol concentrations in man." *Nature* **193**: 1187-1188 (1962).

D20,817/62

In students, blood ACTH and cortisol levels were greatly elevated during the emotional stress of oral examinations.

Fiorica, V., Muehl, S.: "Relationship between plasma levels of 17-hydroxy-corticosteroids (17-OHCS) and a psychological measure of manifest anxiety." *Psychosom. Med.* **24**: 596-599 (1962).

D46,952/62

In normal (nonhospitalized) people, plasma 17-OHCS levels are raised under anxiety-creating conditions.

Hamburg, D.A.: "Plasma and urinary corticosteroid levels in naturally occurring psychologic stresses." In: Korey, S.R., Pope, A., Robins, E., *Ultrastructure and Metabolism of the Nervous System*, pp. 406-413. Baltimore: Williams & Wilkins, 1962.

J5,097/62

Review of the literature showing that even minor psychogenic stressors (academic exams, surgical interventions or mere anticipation of these) increase plasma and urinary glucocorticoid levels.

Davis, J., Morrill, R., Fawcett, J., Upton, V., Bondy, P. K., Spiro, H. M.: "Apprehension and elevated serum cortisol levels." *J. Psychosom. Res.* **6**: 83-86 (1962).

J11,154/62

In subjects unfamiliar with blood drawing procedures, the blood cortisol levels rise much more than in those for whom this is not a "first time" experience. Presumably, "data taken in a so-called 'control' situation may not provide a true baseline value, particularly if the subjects are not familiar with the procedures, but rather may be elevated due to the stress of the 'first time' effect."

Cooper, C. E., Nelson, D. H.: "ACTH levels in plasma in preoperative and surgically stressed patients." *J. Clin. Invest.* **41**: 1599-1605 (1962) (33 refs.). D29,555/62

Wadeson, R. W., Mason, J. W., Hamburg, D. A., Handlon, J. H.: "Plasma and urinary 17-OHCS responses to motion pictures." *Arch. Gen. Psychiatry* **9**: 146-156 (1963).

E22,691/63

"Significant elevations in plasma 17-OHCS levels were observed during a war movie in one group. Marked decreases in plasma 17-OHCS levels occurred rather consistently during the viewing of Disney nature films. Plasma and urinary values did not consistently correlate well, and plasma measurements were regarded as more reliable."

Jensen, C. C., Ek, J. I.: "The excretion of certain adrenal steroids during mental stress in healthy persons." *Acta Psychiatr. Scand.* **38** No. 4: 302-306 (1963). G11,917/63

Analysis of the different corticoid fractions in students during the emotional stress of examinations.

Mason, J. W., Sachar, E. J., Fishman, J. R., Hamburg, D. A., Handlon, J. H.: "Corticosteroid responses to hospital admission." *Arch. Gen. Psychiatry* **13**: 1-8 (1965). G31,187/65

Mefferd, R. B. Jr., Wieland, B. A.: "Comparison of responses to anticipated stress and stress." *Psychosom. Med.* **28**: 795-807 (1966). G42,966/66

Young airmen were exposed to actual or

anticipated severe hypoxia, with catecholamine and corticoid secretion as well as other metabolic changes being measured as objective indicators of stress. There were great individual variations in the response to anticipated stress: "some reacted hardly at all, while others had an alarm reaction. Upon actual exposure to hypoxia (except for those compensatory adaptations specific to hypoxia) these general responses simply increased in magnitude in all subjects, i.e., they maintained their rank-order positions during the stress."

Bridges, P. K., Jones, M. T.: "Personality, physique and the adrenocortical response to a psychological stress." *Br. J. Psychiatry* **113**: 601-605 (1967). G47,391/67

In male medical students, plasma cortisol levels rose considerably during oral examinations.

Mason, J. W.: "A review of psychoendocrine research on the pituitary adrenal cortical system." *Psychosom. Med.* **30**: 576-607 (1968).

H29,040/68

Excellent review on the effect of psychologic stimuli and psychiatric disease upon the pituitary-adrenocortical axis. "Elevation of 17-OHCS levels is not related to a highly specific affective state, but rather appears to reflect a relatively undifferentiated state of emotional arousal or involvement, perhaps in anticipation of activity or coping. The elements of novelty, uncertainty, or unpredictability are particularly potent influences in eliciting 17-OHCS elevations" (222 refs.).

Oyama, T., Shibata, S., Kimura, K., Takazawa, T.: "Objective evaluation of pentobarbital as preanesthetic medication: effect on adrenocortical function." *Anesth. Analg. (Cleve.)* **48**: 367-372 (1969).

G66,262/69

In a series of surgical patients "preoperative emotional reactions such as fear and apprehension significantly elevated the plasma cortisol levels on the day of operation, just before induction."

Nyakas, C., Endrőczi, E.: "Activation of pituitary-adrenocortical function by conditioned fear in infant and adult rats." *Acta Physiol. Acad. Sci. Hung.* **36**: 401-405 (1969).

G76,185/69

In rats, conditioned fear was induced by association of tactile and acoustic stimuli with electric shocks. The latter caused a significant decrease in adrenal ascorbic acid in

fourteen-day-old rats, whereas conditioned fear had no such effect in rats at that age but was demonstrable in eighteen-day-old rats. The electric shocks were more effective than conditioned fear during the third week, but a reversal in the magnitude of stimulus response rates was observed in adults.

Weiss, J. M., McEwen, B. S., Silva, M. T. A., Kalkut, M. F.: "Pituitary-adrenal influences on fear responding." *Science* **163**: 197-199 (1969). H5,347/69

In passive avoidance situations, hypophysectomized rats show less, and adrenalectomized rats more, fear than normal. This may be due to the fact that the hypophysectomized rat lacks ACTH which increases arousal, whereas adrenalectomy enhances ACTH production. Presumably, ACTH and glucocorticoids have opposite effects on the regulation of fear-motivated behavior.

Weiss, J. M., McEwen, B. S., Silva, M. T., Kalkut, M.: "Pituitary-adrenal alterations and fear responding." *Am. J. Physiol.* **218**: 864-868 (1970). H21,817/70

Hypophysectomy diminishes the avoidance behavior of the rat while adrenalectomy increases it. ACTH enhances the decreased avoidance behavior of the hypophysectomized rat, and corticosterone reduces the supernormal response of the adrenalectomized rat. "It is suggested that ACTH increases excitability which leads to an increase in generalized fear or anxiety in fear situations, while corticosterone counteracts this influence because it acts to restore a normal level of excitability."

Katz, J. L., Weiner, H., Gallagher, T. F., Hellman, L.: "Stress, distress, and ego defenses. Psychoendocrine response to impending breast tumor biopsy." *Arch. Gen. Psychiatry* **23**: 131-142 (1970). G77,008/70

Women waiting for breast tumor biopsy showed widely differing psychologic defense patterns and anxiety. The associated corticoid excretion also varied considerably and was only roughly proportional to the psychiatric score that was regarded as indicative of stress.

Bloch, S., Brackenridge, C. J.: "Psychological, performance and biochemical factors in medical students under examination stress." *J. Psychosom. Res.* **16**: 25-33 (1972). J10,655/72

In medical students undergoing stressful oral examinations, females showed higher

emotionality and lower uric acid levels. "Scores on worry and emotionality, two components of test anxiety, and two self-ratings of success achieved and emotional interference experienced during the test situation, were all significantly interrelated. The most prominent psychological-biochemical relationship found was the positive one between cortisol and emotionality. Cholesterol was negatively related to self-rating of success." Furthermore, plasma cholesterol levels were inversely, while uric acid concentrations were directly, related to achievement (43 refs.).

Bridges, P. K., Jones, M. T.: "Relationships between some psychological assessments, body-build, and physiological stress responses." *J. Neurol. Neurosurg. Psychiatry* **36**: 839-845 (1973). J7,429/73

During oral academic examinations, constitutional factors greatly influenced the stress reaction. "Students of primarily linear physique had significantly higher plasma corticosteroid values than the predominantly muscular subjects at the time of the examination, as found previously. They also had significantly higher analogue measures of the degree of anxiety experienced at the examination (assessed both by the subject and by an observer)."

Bridges, P. K.: "Practical aspects of the use of some psychological tests of anxiety in a situation of stress." *Br. J. Psychiatry* **123**: 587-596 (1973). J8,356/73

In students undergoing the stress of examinations, respiration and heart rate, blood pressure, plasma corticoids, 17-KGS and urine flow were used as "physiologic variables" to be correlated with different psychologic tests, namely: the Taylor Manifest Anxiety Scale (TMAS), the Minnesota Multiphasic Personality Inventory (MMPI), the Eysenck Personality Inventory (EPI), the Institute for Personality and Ability Testing (IPAT) Anxiety Scale and the Stimulus-Response Inventory (S-R Inventory). "The psychological instruments used showed close relationships together, but there were few associations between the overall psychological test results and the physiological responses. The linear analogue scale is a useful measure of situational anxiety. The other tests used purported to be measures of trait anxiety and should therefore have been relatively stable, but most were found to increase significantly when completed by subjects during states of anxiety."

Bassett, J. R., Cairncross, K. D., King, M. G.: "Parameters of novelty, shock predictability and response contingency in corticosterone release in the rat." *Physiol. Behav.* **10**: 901-907 (1973). J4,385/73

Houser, V. P., Paré, W. P.: "Long-term conditioned fear modification in the dog as measured by changes in urinary 11-hydroxycorticosteroids, heart rate and behavior." *Pavlovian J. Biol. Sci.* **9**: 85-96 (1974).

J12,193/74

→**STH.** Greenwood, F. C., Landon, J.: "Growth hormone secretion in response to stress in man." *Nature* **210**: 540-541 (1966).

F65,986/66

In man, anxiety-causing emotional stress or injection of pyrogen (kind not specified) increased plasma STH levels.

Mason, J. W., Wool, M. S., Wherry, F. E., Pennington, L. L., Brady, J. V., Beer, B.: "Plasma growth hormone response to avoidance sessions in the monkey." *Psychosom. Med.* **30**: 760-773 (1968). H6,463/68

In rhesus monkeys, plasma immunoreactive STH levels usually rise during conditioned avoidance sessions. Venipuncture in itself tends to elevate the "baseline" level (45 refs.).

Greene, W. A., Conron, G., Schalch, D. S., Schreiner, B. F.: "Psychologic correlates of growth hormone and adrenal secretory responses of patients undergoing cardiac catheterization." *Psychosom. Med.* **32**: 599-614 (1970). G80,365/70

In patients undergoing cardiac catheterization, "behavioral differences in categories of affect, arousal and degree of interpersonal engagement were used to reliably delineate four major types of psychologic reaction designated anxious-engaged, anxious-not-engaged, depressed and calm. There were no elevations of cortisol or growth hormone during the procedure in either the calm or the depressed patients. Anxious-not-engaged patients showed major elevations of both cortisol and growth hormone. All the anxious-engaged patients showed initial high and even increasing levels of cortisol but no increases in growth hormone."

→**TTH.** Kracht, J., Spaethe, M.: "Ueber Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. II. Mitteilg. Untersuchungen über den 'Hypophysenhemmstoff' p-Oxypropiophenon" (Interrelation between

the thyroid and the adrenal cortex. II. Report: Studies on the "hypophyseal inhibitor" p-oxypropiophenone). *Virchows Arch. [Pathol. Anat.]* **323**: 629-644 (1953).

B85,143/53

Wild rabbits respond to frightening stimuli not only with adrenocortical enlargement, but also with a marked discharge of TTH which causes thyroid hypertrophy. This peculiar response can be prevented by hypophsectomy or methythiouracil.

Kracht, J., Spaethe, M.: "Ueber Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. III. Mitt. Die thyreotrope Belastungsreaktion" (Interrelation between the thyroid and the adrenal cortex. III. Report: The thyrotropic stress reaction). *Virchows Arch. [Pathol. Anat.]* **324**: 83-109 (1953).

B87,399/53

In wild rabbits, fear produces an acute discharge of TTH, often with an actual inhibition of ACTH secretion. "The symptomatology and the cause of fear thyrotoxicosis can be classified in terms of the phases of the alarm reaction, resistance, and exhaustion (Selye). Increased thyrotropic function causes inhibition of ACTH secretion."

Gupta, R. C., Prasad, G. C., Udupa, K. N.: "Experimental production of thyrotoxicosis." *5th Asia and Oceania Congr. Endocr.*, p. 178. Chandigarh, India, 1974. H82,223/74

Rats exposed to fear by keeping them in front of a dog's cage showed enhanced ^{131}I uptake and increased PBI with histologic changes in the thyroid indicative of thyrotoxicosis. Serum cholesterol and body weight were lowered. "These observations suggest that experimental thyrotoxicosis can be produced in animals using this method."

→**Other Hormones and Hormone-like Substances.** Connell, A. M., Cooper, J., Redfearn, J. W.: "The contrasting effects of emotional tension and physical exercise on the excretion of 17-ketogenic steroids and 17-ketosteroids." *Acta Endocrinol.* **27**: 179-194 (1958). C47,363/58

In a group of medical students, the psychogenic stress of an important examination significantly increased 17-KGS and slightly raised 17-KS excretion. Muscular activity (treadmill exercise, route march) elicited a moderate decrease in 17-KS and no marked change in 17-KGS elimination. "It is suggested that emotional stress causes an increase in the formation of adrenal cortical hormones; this formation is in preparation

for the physical stress and effort which, under 'natural' conditions, could be expected to follow on the initial emotional strain."

Handlon, J. H.: "Hormonal activity and individual responses to stresses and easements in everyday living." In: Roessler, R. and Greenfield, N. S., *Physiological Correlates of Psychological Disorder*, pp. 157-170. Madison: University of Wisconsin Press, 1962.

D55,075/62

Brady, J. V.: "Emotion and the sensitivity of psychoendocrine systems." In: Glass, D. C., *Biology and Behavior. Neurophysiology and Emotion*, pp. 70-95. New York: Rockefeller University Press, 1967.

J11,133/67

→**Metabolites.** Folin, O., Denis, W., Smillie, W. G.: "Some observations on 'emotional glycosuria' in man. *J. Biol. Chem.* **17**: 519-520 (1914). 58,703/14

Among students undergoing academic examinations, 18 percent exhibited at least traces of sugar in the urine. Hence "mental and emotional strain may produce temporary glycosuria in man."

Rydin, H., Verney, E. B.: "The inhibition of water-diuresis by emotional stress and by muscular exercise." *Q. J. Exp. Physiol.* **27**: 343-374 (1938).

A14,575/38

In dogs, emotional excitement and muscular exercise inhibit diuresis. This response is unaltered by transection of the renal nerves, extirpation of one adrenal and denervation of the other or by decentralization of the whole abdominal sympathetic system with removal of ganglia L2 to S1 inclusive. The course of this inhibition is matched by intravenous vasopressin. "The post-pituitary equivalent of this stress in terms of the standard powder is of the order of 1 µg."

Schneider, R. A., Zangari, V. M.: "Variations in clotting time, relative viscosity, and other physicochemical properties of the blood accompanying physical and emotional stress in the normotensive and hypertensive subject." *Psychosom. Med.* **13**: 290-303 (1951).

B62,983/51

Review on *blood clotting* changes induced in normotensive and hypertensive individuals by various stressors (30 refs.).

Gitelson, S., Tiberin, P.: "Effect of emotional stress on the blood pyruvic acid level." *Acta Endocrinol. (Kbh.)* **11**: 345-350 (1952).

B76,933/52

In patients showing obvious signs of anxiety before surgery, the blood *pyruvic acid* level rises. "It is suggested that hyperpyruvicism occurring in these cases is the result of emotional stress caused by fear of operation and is part of the general 'alarm reaction'."

Basowitz, H., Korchin, S. J., Grinker, R. R.: "Anxiety in a life stress." *J. Psychol.* **38**: 503-510 (1954). B29,178/54

Earlier research has shown that subjects having free anxiety (a feeling of intense dread and foreboding with generalized undirected apprehensiveness) exhibited an elevated *hippuric acid* tolerance in the absence of other evidence of liver dysfunction. Moreover, as anxiety is reduced, hippuric acid synthesis is lowered. In the present study, persons with initially elevated hippuric acid tolerance developed higher levels of anxiety under the stress of paratroop training than those with originally low values, although prior to training the two groups were indistinguishable in their self-ratings of anxiety. Hippuric acid elimination not only distinguishes between neurotics with free anxiety and normal persons, but also shows that "normal individuals whose excretion values are very high, although still below levels typifying the condition of free anxiety, are prone toward heightened anxiety in a life stress."

Hetzel, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man." *J. Clin. Endocrinol. Metab.* **15**: 1057-1068 (1955).

C8,424/55

In patients, a one-hour discussion of "stressful subjects" caused diuresis with increased 17-OHCS, *nitrogen*, *sodium* and *potassium* elimination.

Schwartz, T. B., Shields, D. R.: "Urinary excretion of formaldehydogenic steroids and creatinine. A reflection of emotional tension." *Psychosom. Med.* **18**: 159-172 (1956).

C25,345/56

In students undergoing stressful final examinations, increased urinary corticoid excretion occurs fairly regularly but urinary volume and *creatinine* excretion are not clearly related to the stressor.

Wertlake, P. T., Wilcox, A. A., Haley, M. I., Peterson, J. E.: "Relationship of mental and emotional stress to serum cholesterol

levels." *Proc. Soc. Exp. Biol. Med.* **97**: 163-165 (1958). C47,228/58

In male medical students the mental stress of examinations caused a considerable increase in serum *cholesterol*, which is considered to be a manifestation of the G.A.S.

Thomas, C. B., Murphy, E. A.: "Further studies on cholesterol levels in the Johns Hopkins medical students: the effect of stress at examinations." *J. Chronic Dis.* **8**: 661-668 (1958). C80,790/58

In fifty-two male medical students, serum cholesterol values rose whereas blood eosinophils decreased during an anatomy examination. "Stress such as accompanies the first few weeks of medical school or important final examinations is accompanied by a significant mean rise in *cholesterol* level."

Grundy, S. M., Griffin, A. C.: "Effects of periodic mental stress on serum cholesterol levels." *Circulation* **19**: 496-498 (1959).

C66,837/59

Blood *cholesterol* levels in male medical students rose significantly during final examinations.

Dreyfuss, F., Czaczkes, J. W.: "Blood cholesterol and uric acid of healthy medical students under the stress of an examination." *Arch. Intern. Med.* **103**: 708-711 (1959).

C81,688/59

In medical students, the psychic stress of examinations raised the serum *cholesterol* levels. "The α -, β -*lipoprotein* distribution of blood cholesterol seemed to show that the increased amount of cholesterol tended to accumulate in the α -fraction. Blood uric acid levels remained approximately unchanged" (25 refs.).

Grundy, S. M., Griffin, A. C.: "Relationship of periodic mental stress to serum lipoprotein and cholesterol levels." *J.A.M.A.* **171**: 1794-1796 (1959). C86,084/59

In medical students, the psychogenic stress of examinations caused a rise in plasma *cholesterol* and low-density *lipoprotein* levels.

Wolf, S., McCabe, W. R., Yamamoto, J., Adsett, C. A., Schottstaedt, W. W.: "Changes in serum lipids in relation to emotional stress during rigid control of diet and exercise." *Circulation* **26**: 379-387 (1962).

J10,367/62

Striking increases in serum *cholesterol* and *triglycerides* occurred in people on a constant diet upon exposure to various situations inducing anxiety, including difficulties in the

family, on the job, and so on. Stress interviews caused such changes within sixty minutes. "No inferences are drawn with respect to the significance of emotional stress in the pathogenesis of coronary atherosclerosis or myocardial infarction, but it is clear that the mechanisms that govern the serum concentration of certain lipids are connected with and capable of responding to impulses from the higher centers of the brain."

Back, K. W., Bogdonoff, M. D.: "Plasma lipid responses to leadership, conformity, and deviation." In: Liederman, P. H. and Shapiro, D., *Psychobiological Approaches to Social Behavior*, pp. 24-42. Stanford, Cal.: Stanford University Press, 1964.

J11,130/64

Detailed review on plasma *FFA* as an objective indicator of stress in man, particularly in social interrelations. Plasma *FFA* levels are very sensitive to changes in autonomic nervous activity and are especially useful in assessing situational demands and group interactions.

Goldberg, G. A., Nikitin, U. P.: "Changes in blood lipids in physicians during examinations." *Ter. Arkh.* **37** No. 5: 71-74 (1965) (Russian).

J22,374/65

During examinations, physicians exhibit an increase in blood *cholesterol*. "The level of lecithin and the lecithin/*cholesterol* ratio decrease during examinations. There is a reliable correlation between changes of the cholesterol titer in the blood serum and the arterial pressure and pulse."

Scrimshaw, N. S., Habicht, J. P., Piché, M. L., Cholakos, B., Arroyave, G.: "Protein metabolism of young men during university examinations." *Am. J. Clin. Nutr.* **18**: 321-324 (1966).

J15,921/66

Vandenbergh, R. L., Sussman, K. E., Titus, C. C.: "Effects of hypnotically induced acute emotional stress on *carbohydrate* and *lipid* metabolism in patients with diabetes mellitus." *Psychosom. Med.* **28**: 382-390 (1966).

G40,600/66

Back, K. W., Bogdonoff, M. D.: "Buffer conditions in experimental stress." *Behav. Sci.* **12**: 384-390 (1967).

J9,369/67

Detailed report on the conditions under which psychologic stimuli, particularly those causing anxiety, raise the plasma *FFA* level in man.

Carlson, L. A., Levi, L., Orö, L.: "Plasma lipids and urinary excretion of catechol-

amines in man during experimentally induced emotional stress, and their modification by nicotinic acid." *J. Clin. Invest.* **47**: 1795-1805 (1968). H1,440/68

In male volunteers, emotional stressors (dazzling light, standardized criticism, sorting steel balls of different sizes) caused a rise in plasma FFA and triglycerides and greater catecholamine excretion. Concurrent treatment with nicotinic acid prevented the elevation in FFA and triglycerides but not the stressor-induced increase in catecholamine elimination or the associated rise in heart rate and blood pressure.

Beneš, V., Hrubes, V.: "Serum free fatty acid level after an experimentally induced emotional stress and its modification by nicotinic acid in rats with different characteristics of higher nervous activity." *Activ. Nerv. Sup. (Praha)* **10**: 395-399 (1968). J11,743/68

The fear of intermittent electric shocks elevated serum FFA, particularly in rats with extremely low spontaneous exploratory activity. Intraperitoneal nicotinic acid completely blocked this change.

Yordanova, L., Gotsev, T.: "Alterations in the enzyme activity of students with increased body temperature during examinations." *J. Physiol. (Paris)* **63**: 463-464 (1971). J20,215/71

Among students under "examination stress," the most outstanding objective changes were tachycardia, hypertension, dilatation of the pupils, increased intraocular pressure, sweating, alterations in erythrocytes and platelets, a rise in body temperature and in the blood levels of carbonic anhydrase and cholinesterase.

Kakizaki, T.: "Stress response during mental task. 2. Biochemical response of human subjects under arithmetical calculation tasks." *Ind. Health (Kawasaki)* **9**: 105-112 (1971). J10,263/71

Kakizaki, T.: "3. Three factors affecting the stress responses in man under arithmetical calculation tasks." *Ind. Health (Kawasaki)* **9**: 153-161 (1971). H79,739/71

Kakizaki, T.: "4. A principal factor inducing the stress responses in man under arithmetical calculation tasks." *Ind. Health (Kawasaki)* **9**: 162-170 (1971). J10,264/71

Kakizaki, T.: "5. Effect of unpleasant feeling toward task performance on the stress response to arithmetical calculation tasks."

Ind. Health (Kawasaki) **11**: 8-18 (1973). J10,265/73

Kakizaki, T. "6. Effect of unpleasant feeling due to pure sound noise on the stress response during arithmetical calculation tasks." *Ind. Health (Kawasaki)* **11**: 77-83 (1973). J10,266/73

Detailed description of a test in which responses (corticoid, FFA, blood pressure, electrolytes, blood proteins, cholesterol and so on) are used as indicators of the stress produced by arithmetic calculations. Both the difficulty and the duration of the task are of significance, but curiously, several interfering unpleasant factors (for example, sound) do not significantly affect the results.

Critz, J. B.: "The effect of the mental stress of examination writing on plasma enzyme activity" (abstracted). *Physiologist* **17**: 203 (1974). H89,885/74

→**Morphology.** Mora, J. M., Amtman, L. E., Hoffman, S. J.: "Effect of mental and emotional states on the leukocyte count." *J.A.M.A.* **86**: 945-946 (1926). B26,023/26

In man, various "mental and emotional states" elicited polymorphonuclear leukocytosis. The practical importance of this phenomenon lies in the fact that it "may have to be considered as a not infrequent cause of leukocytosis, especially in operative cases, and may be confused with infective or other types of leukocytic change." [Published ten years before the formulation of the stress concept! (H. S.).]

Humphreys, R. J., Raab, W.: "Response of circulating eosinophils to norepinephrine, epinephrine and emotional stress in humans." *Proc. Soc. Exp. Biol. Med.* **74**: 302-303 (1950). B49,646/50

In medical students, the stress of examination caused profound eosinopenia; this response was much more readily duplicated by EP than by NEP.

Renold, A. E., Quigley, T. B., Kennard, H. E., Thorn, G. W.: "Reaction of the adrenal cortex to physical and emotional stress in college oarsmen." *N. Engl. J. Med.* **244**: 754-757 (1951). B65,108/51

Harvard-Yale boat race crews showed a marked eosinopenia which was interpreted as a sign of stress-induced corticoid secretion. Muscular effort was not the only stressor, for the coxswain likewise responded with pronounced eosinopenia although he was almost exclusively under emotional stress.

Dreyfuss, F., Feldman, S.: "Eosinopenia induced by emotional stress." *Acta Med. Scand.* **144**: 107-113 (1952). B82,162/52

Eosinopenia occurred in medical students just before examinations and sometimes persisted afterwards. The same phenomenon was noted in women during the anxiety related to diagnostic curettage. It was "ascribed to the considerable emotional stress undergone in the two situations."

Mahl, G. F., Brody, E. B.: "Chronic anxiety symptomatology, experimental stress, and HCl secretion." *Arch. Neurol. Psychiatry* **71**: 314-325 (1954). J13,190/54

Review of the literature on the effects of stress upon gastric acidity in animals and man. Among patients, chronic anxiety is associated with increased gastric hydrochloric acid secretion and may be related to ulcerogenesis (18 refs.).

Markkanen, A., Pekkarinen, A., Pulkkinen, K., Simola, P. E.: "On the emotional eosinopenic reaction caused by examination." *Acta Physiol. Scand.* **35**: 225-239 (1956). C12,841/56

Kerr, A. C.: "The effect of mental stress on the eosinophil leucocyte count in man." *Q. J. Exp. Physiol.* **41**: 18-24 (1956).

C35,686/56

Eosinopenia was observed in students during examinations in dental surgery. Controls performing similar operations in daily practice showed no such changes in blood counts.

Hill, S. R. Jr., Goetz, F. C., Fox, H. M., Murawski, B. J., Krakauer, L. J., Reifenstein, R. W., Gray, S. J., Reddy, W. J., Hedberg, S. E., St. Marc, J. R., Thorn, G. W.: "Studies on adrenocortical and psychological response to stress in man." *Arch. Intern. Med.* **97**: 269-298 (1956). C35,720/56

The intense muscular and psychogenic stressor effect of crew racing caused eosinopenia with increased urinary excretion of 17-OHCS, 17-KS and uropepsin, but signs of adrenal hyperactivity were also obvious during the prerace tension. In earlier studies it was found that eosinopenia developed in both the coxswain and coach during the race; hence "the physical exertion of rowing was not the only stress involved capable of inducing a marked eosinopenia."

McDonald, R. D., Yagi, K.: "A note on eosinopenia as an index of psychological

stress." *Psychosom. Med.* **22**: 149-150 (1960). C84,340/60

In subjects induced to believe that they had accidentally caused serious injury to a companion through misuse of explosives, attempts to repair an inoperative telephone switchboard to call for medical assistance led to pronounced eosinopenia. Controls asked to fix the same switchboard merely as a psychomotor test showed no such change. Hence, eosinopenia appears to be a reliable index of psychogenic stress.

Gollender, M., Law, O. T., Isaacson, R. L.: "Changes in the circulating eosinophil level associated with learned fear: conditioned eosinopenia." *J. Comp. Physiol. Psychol.* **53**: 520-523 (1960). G50,316/60

In rats, intermittent electroshock causes eosinopenia. After conditioning, this reaction can be elicited by mere anticipation of shock.

Milin, R.: "The effect of fright on morphodynamics of testes." *Med. Pregl.* **19**: 453-458 (1966) (Serbo-Croatian). G60,378/66

In hares kept in captivity in the presence of a hunting dog, testicular atrophy occurs as a consequence of fear.

→Nervous System (including performance in general). Cowen, E. L.: "The influence of varying degrees of psychological stress on problem-solving rigidity." *J. Abnorm. Soc. Psychol.* **47** Supp.: 512-519 (1952). B29,093/52

The psychogenic stress of anxiety causes "problem-solving rigidity," defined as the tendency to adhere to an induced method of problem-solving even when this is no longer the most economic means to achieve the goal (24 refs.).

Cowen, E. L.: "Stress reduction and problem-solving rigidity." *J. Consult. Psychol.* **16**: 425-428 (1952). B26,453/52

Subjects were arbitrarily told that they did well or badly in examinations, irrespective of their actual performance. When exposed to a second test, the praised group did significantly better, presumably because their anxiety had diminished (14 refs.).

Lazarus, R. S., Deese, J., Osler, S. F.: "The effects of psychological stress upon performance." *Psychol. Bull.* **49**: 293-317 (1952). B36,729/52

Extensive review on the effects of various psychogenic stress situations upon verbal, perceptual and motor performance. The rela-

tionships to the G.A.S. are only briefly touched upon (46 refs.).

Lazarus, R. S., Eriksen, C. W.: "Effects of failure stress upon skilled performance." *J. Exp. Psychol.* **43**: 100-105 (1952).

E60,272/52

Hamburg, D. A.: "Psychological adaptive processes in life-threatening injuries." *Symposium on Stress*, pp. 222-235. Washington, D. C.: Army Medical Service Graduate School, 1953.

B89,532/53

Detailed discussion of the various mental defense reactions with which people having different psychologic characteristics meet the challenge of life-threatening situations, particularly severe injuries and imminent stress. Among these responses, there are three general types: "those which tend to make the patient feel that his life is not really in danger; those which tend to make him feel unafraid of impending death; and those which tend to make him feel that he will recover. All of these emergency defenses are usually facilitated by the diffuse impairment of brain function often associated with severe injury. This impairment makes it easier for the patient to restrict his awareness, to perceive only what he wants to perceive, and to delay recognition of the threat to life."

Berg, I. A.: "Observations concerning obsessive tunes in normal persons under stress." *J. Clin. Psychol.* **11**: 300-302 (1953).

J8,066/53

Marital discord, financial worries, academic failure, vocational indecision and other stressors caused certain persons to experience "tunes in the head" which they could not stop reproducing for long periods.

Hammock, J. C., Prince, A. L.: "Rifle marksmanship as a function of manifest anxiety and situational stress" (abstracted). *Am. Psychol.* **9**: 389-390 (1954).

J13,186/54

Stopol, M. S.: "The consistency of stress tolerance." *J. Pers.* **23**: 13-29 (1954).

B28,524/54

Through the use of the Rorschach and Digit-Symbol tests it was found that: "(a) Tolerance for failure stress and for distraction stress are independent of each other; no significant relationship exists between them. (b) The amount of poststress recovery is positively related to the degree of failure stress and distraction stress tolerance, especially during the second introduction of

stress. (c) Variability of performance during the poststress phase is inversely related to the degree of tolerance for failure stress and distraction stress during the second introduction of stress; no significant relationship exists during the initial administration of stress. (d) During the second administration of stress there is a greater decrement in performance, regardless of the nature of the stress. (e) No significant difference exists between the effects of the particular kinds of failure stress and distraction stress employed in this study if the temporal sequence of presentation is controlled. (f) During the second introduction of stress, generalization occurs in the form of a tendency to respond in a similar manner to both stimulus conditions of stress and nonstress."

Parsons, O. A., Phillips, L., Lane, J. E.: "Performance on the same psychomotor task under different stressful conditions." *J. Psychol.* **38**: 457-466 (1954).

E84,297/54

Kohn, H., "The effect of variations of intensity of experimentally induced stress situations upon certain aspects of perception and performance." *J. Genet. Psychol.* **85**: 289-304 (1954).

J13,188/54

Kubzansky, P. E.: "Anxiety, stress, and flicker fusion measurements" (abstracted). *Am. Psychol.* **9**: 410-411 (1954).

J13,187/54

"There were no effects in the flicker measures attributable to stress."

Beam, J. C.: "Serial learning and conditioning under real-life stress." *J. Abnorm. Soc. Psychol.* **51**: 543-551 (1955).

J10,605/55

The stress of academic examinations seriously interfered with serial learning of a list of nonsense syllables. Stress was appraised by the palmar-sweat index.

Smock, C. D.: "The influence of psychological stress on the 'intolerance of ambiguity'." *J. Abnorm. Soc. Psychol.* **50**: 177-182 (1955).

B29,284/55

In university students of both sexes, feelings of anxiety inspired by the examiner produced an intolerance of ambiguity, as manifested by a tendency to attempt solving problems quickly on the basis of insufficient evidence (13 refs.).

Smock, C. D.: "The influence of stress on the perception of incongruity." *J. Abnorm. Soc. Psychol.* **50**: 354-356 (1955).

B29,336/55

Psychologic stress results in a special intolerance of ambiguity and incongruity. The latter is defined as a stimulus configuration composed of elements that conflict with the expectancies of the individual. Psychogenic stress causes "a tendency to adhere to expectancies (prerecognition hypothesis) in ambiguous task situations. From these two sets of data it is inferred that stress or anxiety results in cognitive and perceptual processes that tend to preserve a 'familiar' perceptual and behavioral field for the individual." [Here again, the causative agent is difficult to identify as nonspecific and hence as a stressor in the classic sense of the word. It might be referred to more accurately as strain (H.S.).]

French, E. G.: "Interrelation among some measures of rigidity under stress and non-stress conditions." *J. Abnorm. Soc. Psychol.* **51**: 114-118 (1955). J11,475/55

In testing Air Force personnel it was found that various psychogenic stressors did not increase rigidity in problem solving (16 refs.).

Wiener, M.: "The effects of two experimental counseling techniques on performances impaired by induced stress." *J. Abnorm. Soc. Psychol.* **51**: 565-572 (1955).

J13,309/55

Farber, I. E., Spence, K. W.: "Effects of anxiety, stress, and task variables on reaction time." *J. Pers.* **25**: 1-18 (1956).

B29,418/56

In man, variations in the degree of anxiety did not consistently affect reaction time to visual stimuli (41 refs.).

Pronko, N. H., Leith, W. R.: "Behavior under stress: a study of its disintegration." *Psychol. Rep.* **2**: 205-222 (1956).

B28,732/56

Review of the literature and personal observations on the effects of psychogenic stress (particularly anxiety) upon perception and performance in various tests, some of which are described in detail (29 refs.).

Davidson, W. Z., Andrews, T. G., Ross, S.: "Effects of stress and anxiety on continuous high-speed color naming." *J. Exp. Psychol.* **52**: 13-17 (1956).

J13,313/56

Kalish, H. I., Garmezy, N., Rodnick, E. H., Bleke, R. C.: "The effects of anxiety and experimentally-induced stress on verbal learning." *J. Gen. Psychol.* **59**: 87-95 (1958).

B66,644/58

Review of the literature and personal observations on the effect of anxiety as a stressor on verbal learning in subjects with high and low anxiety (TMAS) (17 refs.). [It is questionable whether such psychologic effects of certain mental states should be ascribed to stress in the classic sense, since there is no evidence of their nonspecificity. It might be preferable to refer to these and any other specific physiologic demands as "strain" (H.S.).]

Taylor, J. A.: "The effects of anxiety level and psychological stress on verbal learning." *J. Abnorm. Soc. Psychol.* **57**: 55-60 (1958).

J2,414/58

Tests using the MAS showed that while "high anxiety subjects under neutral instructions were significantly superior to the low anxious, as predicted, and the subjects operating under stress were inferior to their neutral controls, the predicted interaction between anxiety level and stress was not found."

Katchmar, L. T., Ross, S., Andrews, T. G.: "Effects of stress and anxiety on performance of a complex verbal-coding task." *J. Exp. Psychol.* **55**: 559-564 (1958). J10,039/58

Psychologic study on the effects of anxiety upon performance. No attempt is made to coordinate these findings with the somatic manifestations of the G.A.S.

Dowis, J. L., Diethelm, O.: "Anxiety, stress, and thinking: an experimental investigation." *J. Psychol.* **45**: 227-238 (1958).

J10,609/58

In man, experimentally induced anxiety interferes with problem solving as indicated by various tests.

Caron, A. J., Wallach, M. A.: "Personality determinants of repressive and obsessive reactions to failure-stress." *J. Abnorm. Soc. Psychol.* **59**: 236-245 (1959). G82,249/59

Harvard freshmen received a complete battery of tests used in factor analysis either under normal conditions or when submitted to a failure-stress. Their performance was related to their personality characteristics, particularly ego strength, need achievement and hysteria. The influence of these characteristics upon repressive and obsessive forms of defense is discussed.

Visotsky, H. M., Hamburg, D. A., Goss, M. E., Lebovits, B. Z.: "Coping behavior under extreme stress." *Arch. Gen. Psychiatry* **5**: 423-448 (1961).

J3,934/61

Observations on adaptive behavior (or its failure) in patients with severe poliomyelitis.

Mechanic, D.: *Students Under Stress. A Study in the Social Psychology of Adaptation*, p. 231. Glencoe, Ill.: Free Press, 1962.

E10,421/62

A detailed analysis based mainly on observations of psychogenic stress in students preparing for and taking examinations for the Ph.D. degree. One of the most important objectives of the study was to attempt a correlation between the somatic aspects of the G.A.S. and psychologic stress responses (about 75 excellent references, especially to monographs on psychogenic stress).

Speisman, J. C., Lazarus, R. S., Mordkoff, A., Davison, L.: "Experimental reduction of stress based on ego-defense theory." *J. Abnorm. Soc. Psychol.* **68**: 367-380 (1964).

J7,194/64

The same anxiety-producing film was shown with three different sound tracks, one of which was designed to increase its stressor effect by emphasizing threatening aspects while the other two were based upon the theory of ego defense, encouraging defensive and cognitive interpretations. Skin conductance (used as evidence of psychogenic stress) was decreased by the defensive sound tracks, "permitting the conclusion that the same visual stimulus varies in the amount of stress produced depending upon the nature of the cognitive appraisal the person makes regarding its significance for him."

Suinn, R. M., Geiger, J.: "Stress and the stability of self- and other attitudes." *J. Gen. Psychol.* **73**: 177-180 (1965). J10,615/65

In students undergoing examinations, "the prediction that anxiety increases the correlation between self-acceptance and acceptance of others was not confirmed."

Lazarus, R. S.: *Psychological Stress and the Coping Process*, p. 466. New York, Toronto and London: McGraw-Hill, 1966.

E750/66

Detailed and very competent discussion of stress in relation to psychology, with special reference to the problem of coping with threatening situations. Correlations between the adaptive mechanisms of the CNS and the G.A.S. are given adequate attention throughout this volume.

Feather, N. T.: "Effects of prior success and failure on expectations of success and subsequent performance." *J. Pers. Soc. Psychol.* **3**: 287-298 (1966). J11,249/66

Nomikos, M. S., Opton, E. Jr., Averill, J. R., Lazarus, R. S.: "Surprise versus suspense in the production of stress reaction." *J. Pers. Soc. Psychol.* **8**: 204-208 (1968).

J8,972/68

In viewers of films depicting wood-mill accidents that occurred either unexpectedly or after long anticipation and suspense, it was found that "long anticipation was more stressful than short anticipation, consistently producing higher levels of autonomic disturbance. Moreover, most of the physiological stress reaction occurred during the periods of anticipation, rather than during the actual confrontations with accident scenes." The literature on the comparative stressor effect of exposure to unpleasant experiences with and without forewarning is discussed.

Hackman, J. R.: "Tasks and task performance in research on stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 202-237. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970.

E10,325/70

Lecture analyzing how task-induced stress relates to behavior.

Cattell, R. B.: "Measurement of neuroticism and anxiety." In: Sahakian, W. S., *Psychopathology Today: Experimentation, Theory and Research*, pp. 173-181. Itasca, Ill.: F E Peacock, 1970.

E10,330/70

In a monograph on psychopathology, this chapter is devoted to the relationship between stress and psychologic changes as its cause or result. Anxiety appears when an individual evades reality and suffers internal conflicts whereas "effort stress" occurs when he forcefully grapples with reality.

Martens, R., Landers, D. M.: "Motor performance under stress: a test of the inverted-U hypothesis." *J. Pers. Soc. Psychol.* **16**: 29-37 (1970).

J12,679/70

High school boys were exposed to various intensities of anxiety by the threat of punishment with electroshock if they performed standard motor tasks poorly. Heart rate, palmar sweat and questionnaire responses served as indicators of stress, and the Children's Manifest Anxiety Scale was used to appraise anxiety. The results "supported the inverted-U hypothesis for the stress factor and the anxiety factor separately." The inverted-U hypothesis states that increased arousal is associated with better performance up to a certain point, after which additional increases in arousal impair performance.

Bey, D. R., Lange, J.: "Waiting wives: women under stress." *Am. J. Psychiatry* **131**: 283-286 (1974). J10,401/74

Description of the psychologic problems met by wives of men ordered into combat.

→**Accident Proneness.** Schulzinger, M. S.: *The Accident Syndrome. The Genesis of Accidental Injury*, p. 234. Springfield, Ill.: Charles C Thomas, 1956. E10,655/56

Monograph concerning statistical data on the frequency of accidents under various conditions, and the factors responsible for accident proneness. No special attention is given to stress as such (73 refs.).

Kerr, W.: "Complementary theories of safety psychology." *J. Soc. Psychol.* **45**: 3-9 (1957). D54,998/57

Discussion of an "adjustment stress theory" which holds that distracting stress increases accident proneness. Literature is cited in which earlier investigators found that the following stress factors significantly correlated with accident rates: employee age, workplace temperature, illumination, comfort of shop, operator congestion, anxiety, alcohol and preexistent disease (24 refs.).

Rogg, S. G.: "The role of emotions in industrial accidents." *Arch. Environ. Health* **3**: 519-522 (1961). D92,957/61

Psychogenic stress predisposes to industrial accidents.

Sachs, B. C.: Psychosomatic aspects of accidents. *Ind. Med. Surg.* **31**: 525-532 (1962). J13,761/62

Brody, L.: "The accident phenomenon." *Person. Admin.* **26**: 11-14 (1963).

D84,924/63

Various types of stressors can cause accident proneness.

Thomae, H.: "Accident and psychological stress." *Int. J. Prod. Res.* **2**: 229-233 (1963). J16,323/63

Jonderko, G.: "Effect of work mechanization upon the improvement of working condition and the accident rate in coal mining" *Med. Pracy* **15**: 237-243 (1964) (Polish).

J16,122/64

Wells, R. L.: Psychosocial influences on accidents. *Arch. Environ. Health* **13**: 496-500 (1966). D99,572/66

General review on the effect of psychogenic stress upon accident proneness.

Selzer, M. L., Rogers, J. E., Kern, S.: "Fatal accidents: the role of psychopathology, social stress, and acute disturbance." *Am. J. Psychiatry* **124**: 1028-1036 (1968).

E84,312/68

"Significantly more psychopathology and social stress were present in 96 drivers causing fatal accidents than in a matched control group." Twenty percent of the drivers had acutely disturbing experiences within six hours of causing a fatal accident (20 refs.).

Neves, F. I.: "Adaptación social y accidentes del trabajo" (Social adaptation and accidents on the job). *Rev. Interamer. Psicol.* **3**: 139-162 (1969). J16,327/69

Review of the literature on the role of psychosocial stressors in accident proneness among manual workers (21 refs.).

Felton, J. S.: "Sensitivity to emotional ill health." *Proc. Ann. Conf. NASA Clin. Dir., Environm. Hlth. Off. Med. Advisors*, New Orleans, La. Oct. 21-23, 1969. Abstracted in *Staff Century Res. Corp. pamphlet* Vol. 2, 923rd Abstr. Arlington, Va. 1973.

J16,125/69

Statistical studies suggest that accident proneness is often referable to intolerable and frustrating conditions at work.

McMurray, L.: "Emotional stress and driving performance: the effect of divorce." *Behav. Res. Highway Safety* **1**: 100-114 (1970).

J16,599/70

Gass, G. Z.: "Hardcore personality and industrial illnesses and accidents." *Ind. Med. Surg.* **39**: 174-178 (1970). J13,408/70

McGuire, F. L.: "A typology of accident proneness." *Behav. Res. Highway Safety* **1**: 26-32 (1970).

J16,598/70

A review of the role of stress in accident proneness, particularly in relation to driving.

Baruch, D.: "Some medical aspects in agricultural flights relating to fatigue among agricultural pilots." *Aerosp. Med.* **41**: 447-450 (1970).

G36,975/70

A study in Israel showed that "as a result of agricultural flights under hard weather conditions there were significant changes in the pilot's body such as loss of weight, increase of body temperature, decrease of eosinophil cells, tendency to decrease of blood sugar level. All these changes in combination with lack of sleep may reduce the alertness of the pilot and may be considered an im-

portant factor in aircraft accidents in agricultural flights."

Andersson, A. L., Nilsson, A., Henriksson, N. G.: "Personality differences between accident-loaded and accident-free young car drivers." *Br. J. Psychol.* **61**: 409-421 (1970). J15,060/70

Henderson, M.: "The accident-prone car driver—does he exist?" *Med. J. Austr.* **2**: 909-912 (1971). J13,987/71

Accident proneness in motor car drivers is positively correlated with their stress experiences in daily life. The concept that certain individuals are inherently accident prone is rejected, but stress increases the probability of accidents in virtually any profession.

Viney, L.: "Accident proneness: some psychological research." *Med. J. Austr.* **2**: 916-918 (1971). J14,016/71

Review of clinical data indicating that previous exposure to stressors increases accident proneness.

Yanowitch, R. E., Mohler, S. R., Nichols, E. A.: "Psychosocial reconstruction inventory: a postdictal instrument in aircraft accident investigation." *Aerosp. Med.* **43**: 551-554 (1972). J14,847/72

Review of data on the role of stress in increasing accident proneness, especially in pilots.

"Problems in occupational safety and health: a critical review of select physical and psychological factors." *Staff Century Res. Corp.* pamphlet, Vol. 2, p. 90, and 1317 Abstr. Arlington, Va. 1973. J13,172/73

Annotated bibliography of 1317 articles concerning occupational safety and accident proneness.

Rodstein, M.: "Accident proneness." *J.A.M.A.* **229**: 1495 (1974). H91,883/74

Concise summary of principal factors responsible for accident proneness under stressful conditions, with special reference to automobile accidents.

→ **Suicide.** Neuringer, C.: "Reactions to interpersonal crises in suicidal individuals." *J. Gen. Psychol.* **71**: 47-55 (1964). J23,844/64

Bunney, W. E. Jr., Fawcett, J. A.: "Possibility of a biochemical test for suicidal potential. An analysis of endocrine findings prior to three suicides." *Arch. Gen. Psychiatry* **13**: 232-239 (1965). J12,529/65

Increased urinary 17-OHCS excretion may be a useful indicator of suicidal intent.

Hoch-Ligeti, C.: "Adrenal cholesterol concentration in cases of suicide." *Fed. Proc.* **25**: 552 (1966). F65,019/66

The highest adrenal cholesterol concentrations were found in patients who committed suicide and in hypertensives, being much above those of persons who died in accidents. Presumably, the changes are related to stress.

Rosenberg, P. H., Latimer, R.: "Suicide attempts by children." *Ment. Hyg.* **50**: 354-359 (1966). J22,930/66

Anxiety about handling stress situations and acute distress owing to frustration are among the most frequent causes of suicide attempts in children.

Bunney, W. E. Jr., Fawcett, J. A., Davis, J. M., Gifford, S.: "Further evaluation of urinary 17-hydroxycorticosteroids in suicidal patients." *Arch. Gen. Psychiatry* **21**: 138-150 (1969). G67,923/69

Urinary 17-OHCS levels were elevated in patients who committed or attempted to commit suicide (16 refs.).

Naftulin, D. H.: "The potentially suicidal patient. Detection and management in office practice." *Calif. Med.* **111** No. 3: 169-176 (1969). J21,184/69

Use of the SPRS in patients under stress.

Krieger, G.: "Biochemical predictors of suicide." *Dis. Nerv. Syst.* **31**: 478-482 (1970). H47,537/70

In psychiatric patients considered to be suicidal risks, a large percentage of those with high plasma cortisol levels subsequently killed themselves. "The elevated plasma cortisol may reflect the vulnerability to suicide and be causative" (17 refs.).

Pichot, P., Menahem, R.: "Constitutional factors in suicide." In: Waldenström, J., Larsson, T. et al., *Suicide and Attempted Suicide (Skandia Sixth International Symposium, 1971)*, pp. 102-113. Stockholm: Nordiska Bokhandelns Förlag, 1972. E10,485/72

A review suggesting a possible association between suicidal tendencies and derangements in corticoid and 5-HT production.

Sanborn, D. E., Sanborn, C. J., Cimbolic, P., Niswander, G. D.: "Suicide and stress-related dermatoses." *Dis. Nerv. Syst.* **33**: 391-394 (1972). J21,824/72

Brooksbank, B. W. L., Brammall, M. A.,

Cunningham, A. E., Shaw, D. M., Camps, F. E.: "Estimation of corticosteroids in human cerebral cortex after death by suicide, accident, or disease." *Psychol. Med.* **2**: 56-65 (1972). G97,911/72

The cortisol content of the frontal cerebral cortex of healthy individuals who had committed suicide was as low or lower than that of control patients who died suddenly without antecedent illness. "It is concluded therefore that neither the presumed severe emotional stress preceding suicide nor depressive illness itself is associated with high levels of cortisol in the cerebral cortex." On the other hand, in patients who died from stressful somatic disease, brain cortisol was raised proportionately to the duration and severity of their physical illness.

Brooksbank, B. W. L., Brammall, M. A., Shaw, D. M.: "Estimation of cortisol, cortisone and corticosterone in cerebral cortex, hypothalamus and other regions of the human brain after natural death and after death by suicide." *Steroids Lipids Res.* **4**: 162-183 (1973). H82,485/73

Comparative studies on the cortisol, corticosterone and cortisone levels in various parts of the human brain after accidental death or suicide. "In 8 sudden-death control and 6 suicide brains, the concentration of cortisol and of corticosterone was higher in the controls, in both cerebral cortex and in hypothalamus. In most specimens, the levels were higher in the hypothalamus, but there was no difference between controls and suicides in the relationship between the two steroids or between the two brain regions. Cortisone levels were often too low to be measurable, but appeared to parallel the level of cortisol." It is assumed that suicide is associated with stress.

Kreitman, N., Chowdhury, N.: "Distress behaviour: a study of selected Samaritan clients and parasuicides ('attempted suicide' patients). Part I: General aspects." *Br. J. Psychiatry* **123**: 1-8 (1973). J19,559/73

Kiev, A.: "Prognostic factors in attempted suicide." *Am. J. Psychiatry* **131**: 987-990 (1974). J15,969/74

Krieger, G.: "The plasma level of cortisol as a predictor of suicide." *Dis. Nerv. Syst.* **35**: 237-240 (1974). J12,780/74

High plasma cortisol levels are frequently noted in anxious and depressed patients who

subsequently commit suicide, and may be used as a warning sign.

→**Cardiovascular System** (See also Diseases of Adaptation). Morris, D. P.: "Blood pressure and pulse changes in normal individuals under emotional stress; their relationship to emotional instability." *Psychosom. Med.* **3**: 389-398 (1941). B26,186/41

In student nurses undergoing examinations and student pilots performing different flying exercises for the first time, a rise in blood pressure was quite constant, while pulse rate was more variable and sometimes actually decreased during the stress. Pallor, tremor, flushing, excessive sweating, restlessness and apprehensive facial expression were also studied as possible indicators of stress but the results proved more difficult to interpret.

Loftus, T. A., Gold, H., Diethelm, O.: "Cardiac changes in the presence of intense emotion." *Am. J. Psychiatry* **101**: 697-698 (1945). B26,677/45

In man, intense emotional arousal and anxiety evoke ECG changes but these appear to be largely independent of the type of emotion experienced.

Funkenstein, D. H., King, S. H., Drolette, M.: "The direction of anger during a laboratory stress-inducing situation." *Psychosom. Med.* **16**: 404-413 (1954).

C1,759/54

When exposed to stress-inducing "problem situations" in which failure is rudely criticized, some individuals react with anger, others with anxiety. Each of these response types is associated with different effects upon blood pressure and ballistocardiographic measures.

Jost, H., Epstein, L. J.: "The Rorschach as a physiological stress." *J. Clin. Psychol.* **12**: 259-263 (1956). C17,467/56

The Rorschach test is a stressor as indicated by its effect on heart rate, blood pressure and GSR in young adults.

Fencl, V., Hejl, Z., Jirka, J., Madlaousek, J., Brod, J.: "Changes of blood flow in forearm muscle and skin during an acute emotional stress (mental arithmetic)." *Clin. Sci.* **18**: 491-498 (1959). C81,538/59

Brod, J., Fencl, V., Hejl, Z., Jirka, J.: "Circulatory changes underlying blood pressure elevation during acute emotional stress (mental arithmetic) in normotensive and hypertensive subjects." *Clin. Sci.* **18**: 269-279 (1959). C85,146/59

Extensive studies on man led to the conclusion that "the detailed haemodynamic response to emotional stress resembles that occurring on strenuous muscular exercise. It is suggested that it is probably the same reaction, activated by situations which might necessitate strenuous muscular action" (33 refs.).

Thackray, R. I., Pearson, D. W.: "The effects of cognitive appraisal of stress on heart rate and task performance." *Federal Aviation Administration, Aviation Med. pamphlet*, p. 6. Washington, D.C., 1968. G65,881/68

Studies on tachycardia produced by the fear of an electric shock, which might or might not be given depending upon performance on a pursuit rotor. Male undergraduates were divided into those who did and those who did not fear shocks. "High fear of shock subjects revealed significantly greater heart rate acceleration and performance impairment, but only under the condition in which the subjects were told that receipt of shock would be contingent on prior performance level."

Jones, M. T., Bridges, P. K., Leák, D.: "Relationship between the cardiovascular and sympathetic responses to the psychological stress of an examination." *Clin. Sci.* **35**: 73-79 (1968). G60,678/68

Rashman, S. M.: "Changes in the body functions in students under the effect of examinations." *Fiziol. Zh. (Kiev)* **17** No. 1: 97-100 (1971) (Ukrainian). J20,490/71

Students taking examinations show typical stress ECGs.

→Varia. Mahl, G. F.: "Effect of chronic fear on the gastric secretion of HCl in dogs." *Psychosom. Med.* **11**: 30-44 (1949). B26,004/49

Wadsworth, H. M. M.: "The relationship between experimentally induced stress and the characteristic mode of expression and level of anxiety." *Diss. Abstr.* **15**: 883-884 (1955). J11,022/55

Doctoral thesis showing that in man, different modes of inducing anxiety increase GSR and pulse rate while decreasing performance.

Dreyfuss, F.: "Coagulation time of the blood, level of blood eosinophils and thrombocytes under emotional stress." *J. Psychosom. Res.* **1**: 252-257 (1956). C26,923/56

In medical students during final examinations, eosinopenia and accelerated *blood clotting* were not accompanied by significant variations in platelet count.

Johnsson, T., Lavender, J. F., Marsh, J. T.: "The influence of avoidance-learning stress on resistance to Coxsackie virus in mice" (abstracted). *Fed. Proc.* **18**: 575 (1959). C66,433/59

Pruitt, R. D.: "Death as an expression of functional disease." *Mayo Clin. Proc.* **49**: 627-663 (1974). H93,314/74

General review in which death, including "Voodoo Death" and death from fright (as, for example, among canaries exposed to but beyond the reach of a leopard) is explained by nervous reflexes, especially those regulating heartbeat (excellent bibliography).

+Genetics. Kracht, J. Spaethe, M.: "Ueber Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. II. Mitteilg. Untersuchungen über den 'Hypophysenhemmstoff' p-Oxypropiophenon" (Interrelation between the thyroid and the adrenal cortex. II. Report. Studies on the "hypophysial inhibitor" p-oxypropiophenone). *Virchows Arch. [Pathol. Anat.]* **323**: 629-644 (1953).

B85,143/53

Wild rabbits respond to frightening stimuli not only with adrenocortical enlargement, but also with a marked discharge of TTH which causes thyroid hypertrophy. This peculiar response can be prevented by hypophysectomy or methylthiouracil.

Kracht, J., Spaethe, M.: "Ueber Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. III. Mitt. Die thyreotrope Belastungsreaktion" (Interrelation between the thyroid and the adrenal cortex. III. Report. The thyrotropic stress reaction). *Virchows Arch. [Pathol. Anat.]* **324**: 83-109 (1953). B87,399/53

In wild rabbits, fear produces an acute discharge of TTH, often with an actual inhibition of ACTH secretion. "The symptomatology and the cause of fear thyrotoxicosis can be classified in terms of the phases of the alarm reaction, resistance and exhaustion (Selye). Increased thyrotropic function causes inhibition of ACTH secretion."

Bridges, P. K., Jones, M. T.: "Relationship of personality and physique to plasma cortisol levels in response to anxiety." *J.*

Neurol. Neurosurg. Psychiatry **31**: 57-60
(1968). G56,652/68

During academic examinations, the plasma level of cortisol in medical students rose considerably as a consequence of anxiety. The degree of response was correlated with both the physical and mental constitution of the candidates. "It is suggested that there is an intrinsic sensitivity in anxiety responses to psychological stress that has an important association with physique."

Moore, T.: "Stress in normal childhood." *Hum. Relat.* **22** No. 3: 235-250 (1969).

E67,152/69

Effect of psychologic stressors upon the mentality of children, including neonates.

Bridges, P. K., Jones, M. T., Leak, D.: "A taxonomic study of physiological responses to a psychological stress." *J. Neurol. Neurosurg. Psychiatry* **33**: 180-187 (1970).

J11,245/70

Taxonomic studies were performed in students to establish the relationship between the stressor effect of examinations (plasma cortisol, catecholamine excretion, blood pressure, and so on) and constitutional factors (body build, personality types).

Hodges, W. F., Felling, J. P.: "Types of stressful situations and their relation to trait anxiety and sex." *J. Cons. Clin. Psychol.* **34**: 333-337 (1970).

J20,483/70

+**Restraint.** Mikhail, A. A.: "Relationship of conditioned anxiety to stomach ulceration and acidity in rats." *J. Comp. Physiol. Psychol.* **68**: 623-626 (1969). G68,624/69

In rats, conditioned anxiety did not aggravate the production of stress ulcers by restraint.

Caul, W. F., Buchanan, D. C., Hays, R. C.: "Effects of unpredictability of shock on incidence of gastric lesions and heart rate in immobilized rats." *Physiol. Behav.* **8**: 669-672 (1972). G91,264/72

In restraint-conditioned rats, unpredictable electric shocks produced a higher incidence of gastric ulcers than did predictable shocks.

+**Electroshock.** Taylor, R. H., Gross, M., Ruby, I. J.: "Nonconvulsive electrostimulation and the pituitary-adrenocortical system." *J. Nerv. Ment. Dis.* **114**: 377-383 (1951). J8,693/51

Both convulsive and nonconvulsive electrostimulation produced marked eosinopenia even in schizophrenic patients, although earlier investigators claimed that these usually failed to show such a response. Pentothal anesthesia did not prevent this eosinopenia, and it was therefore attributed not to stress but to a direct action of electric current on the hypothalamus. The literature on the effect of electroshock upon blood eosinophils is reviewed (17 refs.).

Vogel, J. R., Haubrich, D. R.: "Chronic administration of electroconvulsive shock effects on mouse-killing activity and brain monoamines in rats." *Physiol. Behav.* **11**: 725-728 (1973). J7,248/73

In rats, mouse-killing activity is blocked by chronic electroconvulsive shocks as well as by antidepressive drugs. At the same time, brain NEP concentrations rise (23 refs.).

+**Drugs, Hormones.** Steinberg, H.: "Effects of nitrous oxide on reactions to stress." *Bull. Br. Psychol. Soc.* **24**: 12 (1954).

J13,306/54

In men under the stress of being asked to solve insoluble problems, inhalation of small amounts of nitrous oxide (sufficient to cause euphoria) reduced stress. [The brief abstract gives no details about how this was measured (H.S.).]

Russell, R. W., Steinberg, H.: "Effects of nitrous oxide on reactions to 'stress'." *Q. J. Exp. Psychol.* **7**: 67-73 (1955).

D81,503/55

"The present investigation using insoluble and soluble problems has demonstrated that both nitrous oxide and exposure to stress impair learning; but that, when subjects are exposed to stress while under the influence of the drug, the effects of the stress on subsequent learning are abolished."

Frankenhaeuser, M., Post, B.: "Catecholamine excretion during mental work as modified by centrally acting drugs." *Acta Physiol. Scand.* **55**: 74-81 (1962). D35,589/62

In medical students the stress of various "intellectual tests" increased urinary EP excretion, and this change could be suppressed by methamphetamine and pentothenal. It appears that "urinary excretion of adrenaline provides a sensitive measure of reactions to mental stress, and that centrally acting drugs may influence adrenaline excretion during mental work."

Frankenhaeuser, M., Kareby, S.: "Effect of meprobamate on catecholamine excretion during mental stress." *Percept. Mot. Skills* **15**: 571-577 (1962). E30,225/62

In students, the psychogenic stress of problem solving (and, to a lesser extent, even the anticipation of it) caused an increase in EP and NEP excretion. After simultaneous administration of meprobamate, EP output rose but NEP decreased during stress. Thus "meprobamate in moderate doses counteracted the increase in the catecholamine response of normal individuals subjected to mental stress in a laboratory situation."

Baumann, R.: "Die Bedeutung des Stress für die Regulation des Kohlenhydratstoffwechsels und den Insulineffekt" (The importance of stress in regulating carbohydrate metabolism and the effects of insulin). *Zentralbl. Chir.* **92**: 1324-1334 (1967).

F91,158/67

In rats, psychogenic stress increases blood sugar and makes insulin hypoglycemia and the associated shock phenomena more intense and acute, although the latter are not

directly dependent upon the dose of insulin or the blood sugar level.

+Varia. Colehour, J. K., Graybiel, A.: "Excretion of 17-hydroxycorticosteroids, catechol amines, and uropepsin in the urine of normal persons and deaf subjects with bilateral vestibular defects following acrobatic flight stress." *Aerospace Med.* **35**: 370-373 (1964). G11,705/64

Deaf persons with *vestibular defects* who accompanied experienced pilots on acrobatic flights failed to show the usual increase in corticoids and catecholamines, presumably because their appropriate sensory organs in the inner ear were not functional.

Patton, G. W. R.: "Combined autonomic effects of concurrently-applied stressors." *Psychophysiology* **6**: 707-715 (1970).

H47,514/70

In U.S. soldiers, the stress effects (pulse rate, blood pressure, skin conductance) of solving anagrams and exposure to *cold* were greater than when each stressor was applied alone.

Public Speaking

Public speaking is extraordinarily stressful for many people and tends to cause a curious mixture of distress and eustress, depending largely upon the response of the audience. In this respect, success is often most exhilarating, whereas evidence of an adverse response (facial expressions of boredom, enmity and disagreement on the part of the audience, or the departure of many people before the end of the speech) usually causes considerable distress. But often both positive and negative responses elicit the characteristics of stress, such as evidence of enhanced adrenergic activity, acceleration of the heart rate (up to 180 per minute), a rise in blood pressure, increases in plasma NEP and FFA, excessive mental arousal and so on.

Most of these manifestations can be suppressed by β -adrenergic blocking agents (for example, oxprenolol) without noticeably interfering with the ability of the speaker to express his thoughts, although a certain amount of arousal is indispensable for optimal efficiency.

Every public speaker has experienced the fact that manifestations of approval by the public improve his performance, whereas the reverse is true if the speech is badly received. Under these conditions, many people, especially beginners, become virtually inarticulate. Experience usually improves the performance even of poor speakers, particularly during question and answer periods. Since, during delivery of many speeches, they have met most of the problems likely to arise, an appropriate statement becomes virtually a reflex response requiring no embarrassing delays and hesitations.

Public Speaking

(See also our earlier stress monographs, p. xiii)

Levin, H., Baldwin, A. L., Gallwey, M., Paivio, A.: "Audience stress, personality, and speech." *J. Abnorm. Soc. Psychol.* **61**: 469-473 (1960). J23,720/60

Dreppleman, L. F., McNair, D. M.: "An experimental analog of public speaking." *J. Cons. Clin. Psychol.* **36**: 91-96 (1971). J21,290/71

Somerville, W.: "Emotions, catecholamines and coronary heart disease." *Adv. Cardiol.* **8**: 162-173 (1973). J16,987/73

A statistical study shows that "certain experienced motor-car drivers with a history of coronary heart disease when driving in busy traffic develop angina, sinus tachycardia, ectopic beats and various arrhythmias. Healthy racing drivers, stimulated by the emotions of competition and danger, develop high-grade sinus tachycardia, raised plasma catecholamines and free fatty acids immediately before and after a race. Public speaking induces in normal persons similar changes in heart rate and rhythm and elevations in plasma catecholamines and free fatty acids. In both drivers and public speakers, triglycerides show a peak elevation 1-2 h after the event. Oxprenolol inhibits the increase in heart rate, plasma catecholamines, free fatty acids and triglycerides."

MacLeod, R. D. M.: "Unaccustomed speakers." *Lancet* August 25, 1973, pp. 440-441. J19,608/73

Although β -adrenergic blockade by oxprenolol has been recommended to alleviate

the unpleasant symptoms, especially the cardiovascular manifestations in anxious public speakers. the author feels that a more realistic aim would be "to encourage adaptation to stress rather than attempting to shield individuals throughout their lives from the problems of living."

Taggart, P., Carruthers, M., Somerville, W.: "Electrocardiogram, plasma catecholamines and lipids, and their modification by oxprenolol when speaking before an audience." *Lancet* August 18, 1973, pp. 341-346.

H74,091/73

In normal subjects and patients with coronary heart disease, speaking before an audience caused tachycardia (up to 180 per minute) and increases in plasma catecholamine and FFA levels. Ectopic heart beats were noted in about 25 percent of the subjects. A single dose of the β -adrenergic blocker, oxprenolol, suppressed most of the cardiac anomalies in both the normal and the coronary subjects, although plasma NEP levels were not significantly affected. Presumably, "emotional challenges may produce conspicuous cardiovascular effects, especially in susceptible persons. It is suggested that β -blockade could be used to alleviate the unpleasant symptoms associated with speaking before an audience."

Vaisrub, S.: "Unaccustomed as I am to..." *J.A.M.A.* **226**: 1226-1227 (1973).

H78,576/73

Report on various stress indices (tachycardia, rise in plasma catecholamine and FFA concentrations) in people immediately after they address an audience. These responses can be prevented by prophylactic administration of β -adrenergic-blocking agents.

Sleep Deprivation

The unpleasant effects of sleep deprivation are so well known, especially to insomniacs, that they hardly require any detailed discussion here. Yet, on the basis of observations on four young men deprived of sleep for 120 hours, in whom neither corticoid nor catecholamine production appeared to be altered, it was "concluded that although sleep deprivation is stressful it does not operate through Selye's model." In a more extensive study on 600 subjects, 112 hours of sleep deprivation elicited characteristic EEG changes, irritability, loss of memory, hallucinations, and occasional symptoms resembling acute schizophrenia, not unlike those seen in sensory deprivation. However, blood sugar hemoglobin, white cell count and various indicators of corticoid production were barely affected. Perhaps sleep deprivation, isolation and

monotony are not potent stressors in that they make no great demands on any function and, though unpleasant, they act somewhat like leisure or TM.

In soldiers performing on a shooting range for seventy-five hours without sleep, catecholamine excretion was increased and the amplitudes of the circadian rhythm of EP excretion were accentuated, while NEP elimination curves became more irregular. However, in these studies, it is difficult to distinguish pure sleep deprivation from the associated psychomotor performance as a possible stressor.

In young men, lack of sleep for 120 hours deactivated the CNS, as indicated by EEG α -waves, but produced a mixed pattern of deactivation of the ANS with a gradual return to the predeprivation level toward the fifth day. This coincided with increased 17-OHCS excretion. Despite such a rise in corticoid elimination, it was concluded that prolonged sleep loss "did not produce a Selye-type generalized stress reaction."

Yet other studies on university students showed that sleep deprivation can initially raise pulse rate and GSR, with a secondary decline during a later phase. Recent investigations indicate that even moderate sleep loss increases plasma cortisol levels in man; indeed, 11-OHCS excretion has been claimed to be inversely correlated with the amount of sleep during an average night.

These apparently contradictory results show that the stressor effect of sleep deprivation is still far from clearly established. Perhaps further studies should give more attention to the all-important conditioning factors, especially to the type of activity performed during sleep deprivation. Furthermore, it may be worth examining the possibility that sleep deprivation (like the "pseudohypophysectomy" of prolonged undernutrition) could specifically interfere with the hypothalamus pituitary-adrenocortical axis, for example, by inhibiting the function of the neurotransmitter mechanisms.

Sleep Deprivation

(See also our earlier stress monographs, p. xiii)

Tyler, D. B., Marx, W., Goodman, J.: "Effect of prolonged wakefulness on the urinary excretion of 17-ketosteroids." *Proc. Soc. Exp. Biol. Med.* **62**: 38-40 (1946).

B1,301/46

In man, 112 hours of forced wakefulness failed to alter the urinary excretion of 17-KS (taken as an indicator of corticoid production). These observations on twenty-four-hour samples contradict earlier data based on comparatively short periods of stress.

Tyler, D. B.: "The 'fatigue' of prolonged wakefulness." *Fed. Proc.* **6**: 218 (1947).

B26,692/47

In six hundred subjects, sleep deprivation for up to 112 hours caused characteristic EEG changes, irritability, loss of memory, hallucinations and occasional symptoms resembling acute schizophrenia. The ability to maintain sustained effort and performance

was also diminished. However, "blood sugar, hemoglobin, red and white cell count, body weight, and body temperature show little variation from the normal. The excretion of 17-ketosteroids, total nitrogen and creatinine, and the level of adrenal-like substances in the blood are little affected."

Murawski, B. J., Crabbé, J.: "Effect of sleep deprivation on plasma 17-hydroxycorticosteroids." *J. Appl. Physiol.* **15**: 280-282 (1960). C83,739/60

Hasselman, M., Schaff, G., Metz, B.: "Influences respectives du travail, de la température ambiante et de la privation de sommeil sur l'excrétion urinaire de catécholamines chez l'homme normal" (Influence of work, ambient temperature and sleep deprivation on urinary catecholamine secretion in normal men). *C. R. Soc. Biol. (Paris)* **154**: 197 (1960). C88,413/60

In people performing multiple-choice psychomotor muscular work, catecholamine excretion rose; this effect was particularly

pronounced following periods of sleep deprivation.

Gifford, S., Murawski, B. J.: "Minimal sleep deprivation alone and in small groups: Effects on ego-functioning and 24-hour body temperature and adrenocortical patterns." *Symposium on the Medical Aspects of Stress in the Military Climate*, pp. 157-185. Washington, D.C., 1964 (43 refs.). B45,972/64

Mandell, A. J., Sabbot, I. M., Mandell, M. P., Kollar, E. J.: "The stress responsive indole substance in sleep deprivation." *Arch. Gen. Psychiatry* **10**: 299-305 (1964).

G2,556/64

In man, sleep deprivation and other stressors as well as ACTH and functioning adrenocortical tumors produce in the urine a "stress responsive indole substance (SRIS)" whose physical and chemical characteristics are described, although it could not be definitely identified.

Edholm, O. G., Bacharach, A. L. (eds.): *The Physiology of Human Survival*, p. 581. New York and London: Academic Press, 1965. E6,283/65

A monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal and muscular exercise. Each chapter is written by a specialist in the corresponding field, and numerous references indicate the difference between specific defense mechanisms and the stressor effect of the agents used.

Luce, G. G., Segal, J.: *Sleep*, p. 335. New York: Coward-McCann, 1966. E1,208/66

Semipopular monograph on sleep, with sections on the effect of stress upon insomnia. An extensive bibliography lists both technical and popularized references on sleep.

Kollar, E. J., Slater, G. R., Palmer, J. O., Docter, R. F., Mandell, A. J.: "Stress in subjects undergoing sleep deprivation." *Psychosom. Med.* **28**: 101-113 (1966).

G39,265/66

In four young men deprived of sleep for 120 hours, "corticoid and psycho-physiologic measurements did not reveal an adrenosympathetic activation. Both subjects and observers concluded that although sleep deprivation is stressful it does not operate through Selye's model." Neither personal observations nor the literature have convinced the authors

that loss of sleep could produce psychoses (36 refs.).

Cartwright, R. D., Monroe, L. J., Palmer, C.: "Individual differences in response to REM deprivation." *Arch. Gen. Psychiatry* **16**: 297-303 (1967). J22,691/67

Fiorica, V., Higgins, E. A., Iampietro, P. F., Lategola, M. T., Davis, A. W.: "Physiological responses of men during sleep deprivation." *J. Appl. Physiol.* **24**: 167-176 (1968). G55,182/68

Metabolic studies and resistance to cold in man after eighty-four to eighty-six hours of sleep deprivation showed no very constant and significant deviations from the norm. Plasma catecholamines were increased during cold in both experimental and control subjects.

Solomon, G. F.: "Stress and antibody response in rats." *Int. Arch. Allergy Appl. Immunol.* **35**: 97-104 (1969). G64,541/69

"Overcrowding stress, but not the stress of apprehension-electric shock, administered for a week prior to immunization with a potent bacterial antigen, flagellin, and continued during the course of observation significantly reduced both primary and secondary antibody response in inbred male rats. The stress of remaining on a small platform (with rapid eye-movement sleep deprivation) or medium sized platform (without REM deprivation) over a pan of water significantly reduced primary but not secondary response" (31 refs.).

Kuhn, E., Brodan, V., Brodanová, M., Rysánek, K.: "Metabolic reflection of sleep deprivation." *Activ. Nerv. Sup. (Praha)* **11**: 165-174 (1969). J23,076/69

Polis, B. D., Polis, E., DeCani, J., Schwarz, H. P., Dreisbach, L.: "Effect of physical and psychic stress on phosphatidyl glycerol and related phospholipids." *Biochem. Med.* **2**: 286-312 (1969). G65,013/69

In rats exposed to ionizing radiation or "acceleration stress," the plasma concentration of phosphatidylglycerol was consistently increased. "Extension of the studies to humans stressed by acceleration to grayout, sleep deprivation, schizophrenia, combat, etc., revealed that all stresses were accompanied by significant increments in plasma phosphatidyl glycerol." In rats, hypophysectomy prevented the increase in phosphatidylglycerol induced by acceleration stress, but a

rise in the brain level of this compound remained even in the absence of the pituitary.

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Conditions of work and their influence on psychological and endocrine stress reactions." *Rep. Lab. Clin. Stress Res.* (Stockh.) No. 8: 1-19 (1969).

G69,180/69

In Swedish officers deprived of sleep for seventy-five hours and performing on an electronic shooting range or engaged in military staff work, NEP and EP excretion was increased, as were the erythrocyte sedimentation rate and the amount of protein-bound iodine, whereas serum iron was decreased. Some subjects developed ECG anomalies, particularly ST-T depression, and it took several days of rest for the ECG patterns to return toward normal. Stressors imitating situations in civilian life produced essentially similar changes proportional to their severity.

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Circadian rhythms in catecholamine excretion, psychomotor performance and ratings of stress and fatigue during a 75-hour vigil." *Studia Laboris et Salutis* No. 4 (1969).

G87,093/69

Observations on thirty-one men of different ages who were deprived of sleep for seventy-five hours. Considerable fatigue and a decline in motor performance developed with a rise in EP excretion. The highest rates occurred during early afternoon, the lowest during the night and early morning hours. The amplitude of the circadian rhythm in EP excretion was increased by sleep deprivation. NEP elimination curves were much less regular.

Mark, J., Heiner, L., Godin, Y.: "Le stress au cours de la privation expérimentale du sommeil paradoxal" (Stress during experimental deprivation of paradoxical sleep). *J. Physiol. (Paris)* **62** Supp. 1: 185 (1970).

J21,828/70

Shiotsuka, R. N., Reinberg, A., Ungar, F., Sonstroem, R., Sothern, R. B., Nelson, W., Kahane, Z., Vestergaard, P. B., Esser, A. H., Fröberg, J., Levi, L., Kline, N. S., Halberg, F.: "Circadian variation of norepinephrine ratio (NER) in health, sleep deprivation and schizophrenia." *Physiologist* **14**: 230 (1971).

H41,969/71

Naitoh, P., Pasnau, R. O., Kollar, E. J.: "Psychophysiological changes after prolonged

deprivation of sleep." *Biol. Psychiatry* **3**: 309-320 (1971).

H73,911/71

In young adult males, "sleep loss of up to 120 hr. deactivated the central nervous system (CNS) as judged by EEG alpha time, but it produced a mixed pattern of deactivation of the ANS. Around the 'fifth day' of sleep loss, a yet-undefined adaptive mechanism was actuated, allowing a slow shift of the oral temperature as well as EEG alpha time toward the predeprivation level, coincident with increased secretion of 17-hydroxycorticosteroid. A simple notion of generalized activation and deactivation could not account for a complex bodily mechanism during sleep loss, and the vigil did not produce a Selye-type generalized stress reaction." Despite increased corticoid excretion, it is concluded that prolonged wakefulness cannot be regarded as a generalized Selye-type stressor: "it introduced a profound change in the subjects by actuating an adaptive mechanism which was only slowly stopped after more than three nights of recovery sleep."

Utting, J. E., Whitford, J. H. W.: "Assessment of premedicant drugs using measurements of plasma cortisol." *Br. J. Anaesth.* **44**: 43-46 (1972).

G88,755/72

Even moderate sleep deprivation increases plasma cortisol in man. Hence, normalization of plasma cortisol in preoperative patients may be due to the soporific rather than to the anxiolytic effect of drugs used for premedication.

Fenz, W. D., Graig, J. G.: "Autonomic arousal and performance during sixty hours of sleep deprivation." *Percept. Mot. Skills* **34**: 543-553 (1972).

H73,792/72

In university students, performance of psychologic tests "remained unimpaired during the early phases of sleep loss while heart rate and skin conductance increased; the deficit in performance became evident in the last phase of the deprivation period when heart rate and skin conductance declined."

Stern, W. C., Hartmann, E. L.: "Reduced amphetamine lethality following chronic stress." *Psychopharmacologia* (Berlin) **23**: 167-170 (1972).

G88,947/72

"Rats stressed for up to four days by desynchronized sleep deprivation or repeated immersions in cold water showed adrenal gland hypertrophy and thymus gland atrophy. These chronically stressed rats survived

markedly longer following a high dose of amphetamine than non-stressed rats."

Narinskaya, A. L.: "The diurnal dynamics of mental performance during 72 hr continuous wakefulness." *Kosm. Biol. Med.* **6**: 64-69 (1972). H80,310/72

In men deprived of sleep for seventy-two hours, the circadian rhythmicity of mental performance is subject to considerable individual variations.

Radulovački, M.: "Comparison of effects of paradoxical sleep deprivation and immobilization stress on 5-hydroxyindoleacetic acid in cerebrospinal fluid." *Brain Res. (Amst.)* **60**: 255-258 (1973). J21,552/73

Sagales, T., Domino, E. F.: "Effects of stress and REM sleep deprivation on the patterns of avoidance learning and brain acetylcholine in the mouse." *Psychopharmacologia (Berlin)* **29**: 307-315 (1973).

J2,883/73

Goodyear, M. D. E.: "Stress, adrenocortical activity and sleep habits." *Ergonomics* **16**: 679-681 (1973). J8,266/73

There appears to be a close relationship between stress, adrenocortical activity and sleep habits in students. 11-OHCS excretion is inversely correlated with the amount of sleep, that is, enhanced elimination is associated with less sleep.

Buck, L.: "Sleep deprivation effects on accuracy and speed of response selection and execution." *Q. Bull. No. 1973 (2)*, p. 12. National Research Council pamphlet, Ottawa: Division of Med. Eng., 1973. J11,330/73

Performance of a step-tracking task after zero, one and two nights without sleep showed no change in accuracy but there was a progressive reduction in speed.

Hockey, R.: "Changes in information-selection patterns in multisource monitoring as a function of induced arousal shifts." *J. Exp. Psychol.* **101**: 35-42 (1973).

J17,213/73

Review on the stressor effects of shift work and sleep deprivation.

Kapen, S., Boyar, R. M., Finkelstein, J. W., Hellman, L., Weitzman, E. D.: "Effect of sleep-wake cycle reversal on luteinizing hormone secretory pattern in puberty." *J. Clin. Endocrinol. Metab.* **39**: 293-299 (1974).

H89,310/74

In pubertal children, plasma LH levels

rose during sleep at night or during the daytime. Plasma LH concentrations remained elevated during nocturnal waking but not during daytime waking, showing that sleep-wake reversal does not prevent increased LH secretion at night. "Therefore, it is unlikely that the stress associated with sleep deprivation or reversal of the sleep-wake patterns was responsible for the elevated nocturnal waking secretion of LH found in this study" (35 refs.).

Inoue, S., Nagasaki, H., Iriki, M.: "Total sleep deprivation and weight increases of the reproductive organs in male rats." *Endocrinol. Jap.* **21**: 283-286 (1974).

H92,991/74

Rats exposed to long-term sleep loss in a cage where they were forced to move continuously in order to avoid electric shocks experienced hypertrophy of the adrenals, testes, ventral prostates and seminal vesicles. "It is supposed that either the sleep deprivation *per se* or stressful conditions accompanied with the treatment caused a hypersecretion of hypophyseal and testicular hormones." [It is unusual for chronic stress to produce hypertrophy of the sex organs, and these observations appear to be incompatible with the pituitary-shift theory (H.S.).]

Matussek, N., Ackenheil, M., Athen, D., Beckmann, H., Benkert, O., Dittmer, T., Hippius, H., Loosen, P., Rüther, E., Scheller, M.: "Catecholamine metabolism under sleep deprivation therapy of improved and not improved depressed patients." *Pharmakopsychiatrie* **7**: 108-114 (1974). J12,520/74

Sleep deprivation is often but not invariably effective as a transitory treatment in certain types of depressed patients. Only in those showing definite improvement is NEP and VMA elimination increased.

Mendelson, W., Guthrie, R. D., Guynn, R., Harris, R. L., Wyatt, R. J.: "Rapid eye movement (REM) sleep deprivation, stress and intermediary metabolism." *J. Neurochem.* **22**: 1157-1159 (1974). J14,449/74

Rats divided into four groups show "a range of values for lactate, pyruvate and malate. With the baseline at the low end, the two stress control groups in the middle, and the REM sleep deprived group at the upper end, only the difference between the two extremes reaches statistical significance. One possible implication is that the changes in these three metabolites may be related to

both the 'stress' of the experimental condition and REM sleep deprivation, perhaps in a cumulative manner."

Fröberg, J. E.: "Circadian rhythms in catecholamine excretion, performance and selfratings." *Rep. Lab. Clin. Stress Res.* (Stockh.) **36**: 1-22 (1974). J17,328/74

Observations on man "have shown that adrenaline excretion, performance and subjective arousal are low during the night and high during the day even under conditions of sleep deprivation and regularly spaced meals and other activities. Both the physiological and the psychological arousal rhythms had crests in the small hours."

Palmlad, J., Cantell, K., Strander, H.,

Fröberg, J., Karlsson, C. G., Levi, L.: "Stressor exposure and human interferon production." *Rep. Lab. Clin. Stress Res.* (Stockh.) **35**: 1-8 (1974). J17,329/74

In women exposed to a seventy-seven-hour vigil and showing hormonal changes characteristic of stress, the ability of the blood cells to produce interferon following addition of Sendai virus to blood samples rose considerably.

Saario, I., Linnoila, M., Mäki, M.: "Interaction of drugs with alcohol on human psychomotor skills related to driving: effect of sleep deprivation or two weeks' treatment with hypnotics." *J. Clin. Pharmacol.* **15**: 52-59 (1975). H96,783/75

Motivation

The stressor effect of motivation does not lend itself well to strict scientific analysis because of the innumerable conditioning factors that influence it and the many specific actions of the tasks selected as tests.

In an extensive study on 185 preparatory school boys, predominantly achievement-oriented and affiliation-oriented subjects were separated, and further subdivided into successful and unsuccessful individuals. Stress was appraised by autonomic reactions, including pulse rate, blood pressure, and GSR. Successful subjects were more easily aroused by minimally threatening conditions and less disturbed by severe stressors. Intrinsic motivation, the type of task, and the subject's past history of success and failure also influenced reactivity, but broad generalizations could not be made from this or similar studies.

The same difficulty arises in the interpretation of an investigation on a U.S. Navy underwater demolition team, in which a positive correlation was found between serum uric acid levels and subjective estimates of motivation. The serum cholesterol concentrations demonstrated a negative correlation with the intensity of motivation and pleasure in doing the work. The reverse was true for those who found the task unpleasant, and thus serum cholesterol values could not be said to correlate very consistently with these indicators of motivation.

Motivation

(See also our earlier stress monographs, p. xiii)

Berkeley, A. W.: "Level of aspiration in relation to adrenal cortical activity and the concept of stress." *J. Comp. Physiol. Psychol.* **45**: 443-449 (1952). B85,457/52

Through the use of a special manual dex-

terity test, "the level of performance (achievement) was calculated, and an estimate of performance on the next trial (aspiration) was obtained....The extent of discrepancy between aspiration and achievement with respect to both success and failure conditions was related to increase in rate of 17-ketosteroid excretion. Greater discrepancies were accompanied by increases in steroid

excretion." The literature on stress and goal-oriented aspiration is discussed (12 refs.).

Maslow, A. H.: *Motivation and Personality*, p. 411. New York: Harper and Brothers, 1954. C68,728/54

Perceptive analysis of motivation in general by an author trained in Gestalt psychology, psychoanalysis and anthropology. Relationships to physiology and stress reactions in particular are not dealt with.

Iverson, M. A., Reuder, M. E.: "Ego involvement as an experimental variable." *Psychol. Rep.* 2: 147-181 (1956).

J11,126/56

Extensive review on ego involvement in psychogenic stress (173 refs.).

Vogel, W., Raymond, S., Lazarus, R. S.: "Intrinsic motivation and psychological stress." *J. Abnorm. Soc. Psychol.* 58: 225-233 (1959). J4,021/59

One hundred and eighty-five preparatory school boys were grouped on the basis of different tests as predominantly achievement-oriented or affiliation-oriented, each group being subdivided into successful and unsuccessful subjects. Stress was appraised by autonomic reactions including pulse rate, blood pressure and GSR. The induction of stress depended upon the relationship between the motive pattern and the type of stressor used. "The relative effect of stress on a sensory-motor task was facilitative, while on a conceptual task it produced impairment. Successful subjects were more easily aroused by minimally threatening conditions than unsuccessful subjects, and less disturbed by more severe stressor conditions." Intrinsic motivation, the type of task and the subject's history of success or failure are basic components in psychogenic stress.

Appley, M. H.: "Motivation, threat perception and the induction of psychological stress." *Proc. Sixteenth Int. Congr. Psychol. Bonn*, pp. 880-881. Amsterdam: 1962.

J13,078/62

Eysenck, H. J. (ed.): *Experiments in Motivation*, p. 424. Oxford and London: Pergamon Press, 1964. E10,635/64

Compilation of numerous articles on motivation with special reference to stress and particularly to the Eysenck Personality Indices (about 800 refs.).

Kiesler, S. B.: "Stress, affiliation and performance." *J. Exp. Res. Pers.* 1: 227-235

(1966). J9,321/66

Studies on grade school students "(1) support a drive-theory prediction that stress facilitates performance on speed tasks with low intratask competition (simple) and hinders performance on speed tasks with high intratask competition (complex); (2) suggest that under low stress conditions, the presence of others may raise drive and affect performance in an analogous fashion to stress; and that under high stress, the presence of others may reduce drive, hindering performance on simple tasks and facilitating it on complex tasks as compared to the performance of those working alone."

Hermann, M. G.: "Testing a model of psychological stress." *J. Pers.* 34: 381-396 (1966). J23,350/66

Kahn, R. L., French, J. R. P. Jr.: "Status and conflict: two themes in the study of stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 238-263. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,326/70

Lecture summarizing earlier studies on status and status incongruity as determinants of health; role conflict and ambiguity; shift work as a factor in personal and family adjustment and other subjects.

Fine, B. J.: "Intrinsic motivation, intelligence and personality as related to cognitive and motor performance." *Percept. Mot. Skills* 34: 319-329 (1972). J19,075/72

Rahe, R. H., Rubin, R. T., Gunderson, E. K. E.: "Measures of subjects' motivation and affect correlated with their serum uric acid, cholesterol, and cortisol." *Arch. Gen. Psychiatry* 26: 357-359 (1972).

G90,674/72

Among trainees of a U.S. Navy underwater demolition team, "predominantly positive correlations were seen between the subjects' serum uric acid levels and their estimates of their own motivation. Their serum cholesterol concentrations demonstrated consistently negative correlations with their motivational and pleasant affect scores. Highest correlations were positive ones found between the subjects' serum cholesterol levels and their unpleasant affect scores. Serum cortisol correlations with the three psychological criteria demonstrated wide variability around a zero correlation baseline."

Cognition

Most of the evidence on the relationship between stress and cognition is discussed with other functional changes induced by stressors, under the special headings of Performance and Learning Ability. However, learning itself can act as a stressor.

Although the literature on the subject is very limited, it suggests that there is a positive relationship between pituitary-adrenocortical activity and facilitated avoidance learning, which appears to be a function of age. Furthermore, cardiac rhythm and urinary catecholamine excretion increase in men under the influence of intense mental work, while even mere calculating may suffice to produce eosinopenia in women. The performance of arithmetic tasks has also been shown to cause elevated levels of plasma corticoids, FFA, and blood pressure, as well as changes in blood electrolytes, proteins and cholesterol.

Cognition

(See also our earlier stress monographs, p. xiii)

Haggard, E. A.: "Experimental studies in affective processes: I. Some effects of cognitive structure and active participation on certain autonomic reactions during and following experimentally induced stress." *J. Exp. Psychol.* **33**: 257-284 (1943).

B33,896/43

Experiments on man using a test consisting of three periods. "I, the conditioning or stressful session, during which the S's were asked to give chained associations to each of 42 stimulus words. They were always (and only) shocked between 10 and 12 sec. after the stimulus word *sword*, which recurred five times during the list; II, the therapy session, in which one of three experimental procedures was employed to alleviate the general disturbance and extinguish the specific reactions initiated during the first session; and finally, III, a test period to measure the relative effectiveness of the therapies." A strong electric shock was employed as the stressor, and GSR was used as the principal indicator of autonomic activity. "In general, those individuals who knew most about the conditions involved in the situation and who took an active attitude or role in facing this experience consistently showed less disturbance on all measures of autonomic reactivity during the stressful and therapy sessions" (87 refs.).

Tatai, K., Mori, Y., Ito, K.: "Response of the pituitary-adrenocortical system to mental strain in healthy women." *Jap. J. Physiol.* **1**: 316-319 (1951).

B59,995/51

In women, the stressor effect of calculating or operating a telephone switchboard sufficed to produce pronounced eosinopenia.

Barcroft, H., Brod, J., Heil, Z., Hirşjärvi, E. A., Kitchin, A. H.: "The mechanism of the vasodilatation in the forearm muscle during stress (mental arithmetic)." *Clin. Sci.* **19**: 577 (1960).

D2,280/60

Ulrych, M.: "Changes of general haemodynamics during stressful mental arithmetic and non-stressing quiet conversation and modification of the latter by beta-adrenergic blockade." *Clin. Sci.* **36**: 453-461 (1969).

G67,814/69

Hemodynamic studies on forty-seven subjects showed that "both stressful mental arithmetic and quiet speaking resulted in similar increases in mean arterial pressure (12.7% and 13.8%) and cardiac output (22.6% and 23.6%) and therefore in similar changes in total peripheral vascular resistance. In the case of stressful mental arithmetic the increased cardiac output was exclusively due to an increase in heart rate (28.8%) but during quiet conversation both heart rate (14.4%) and stroke volume (8.3%) contributed to this rise." The considerable hemodynamic changes caused even by quiet conversation are apparently due to activation, since they can be prevented by β -adrenergic blockade.

Weingarten, G., Alexander, J. F.: "Effects of physical exertion on mental performance of college males of different physical fitness level." *Percept. Mot. Skills* **31**: 371-378 (1970).

J21,334/70

Eiff, A. W. von, Plotz, E. J., Beck, K. J.,

Czernik, A.: "The effect of estrogens and progestins on blood pressure regulation of normotensive women." *Am. J. Obstet. Gynecol.* **109**: 887-892 (1971). G81,851/71

Both folliculoids and luteoids enhance the rise in blood pressure, respiratory rate, and muscle tone in ovariectomized women performing a simple arithmetic task with or without noise.

McKendry, J. M., Hurst, P. M.: "Adaptation to speed stress in an immediate memory task." *Hum. Factors* **13**: 543-552 (1971).

J20,327/71

In a "speed stress test," the subjects were faced with comparatively simple questionnaires to which responses had to be given at different rates of speed. "Whenever the minimal response time was surpassed, both performance accuracy and the amount of information transmitted per minute fell to a degree that was disproportionately greater than increases in input speed relative to the minimal response time."

Kakizaki, T.: "Stress response during mental task. 2. Biochemical response of human subjects under arithmetical calculation tasks." *Ind. Health* (Kawasaki) **9**: 105-112 (1971).

J10,263/71

Kakizaki, T. "3. Three factors affecting the stress responses in man under arithmetical calculation tasks." *Ind. Health* (Kawasaki) **9**: 153-161 (1971).

H79,739/71

Kakizaki, T. "4. A principal factor inducing the stress responses in man under arithmetical calculation tasks." *Ind. Health* (Kawasaki) **9**: 162-170 (1971).

J10,264/71

Kakizaki, T. "5. Effect of unpleasant feeling toward task performance on the stress response to arithmetical calculation tasks." *Ind. Health* (Kawasaki) **11**: 8-18 (1973).

J10,265/73

Kakizaki, T. "6. Effect of unpleasant feeling due to pure sound noise on the stress response during arithmetical calculation tasks." *Ind. Health* (Kawasaki) **11**: 77-83 (1973).

J10,266/73

Detailed description of a test in which responses (corticoid, FFA, blood pressure, electrolytes, blood proteins, cholesterol and so on) are used as indicators of the stress produced by arithmetic calculations. Both the difficulty and the duration of the task are of significance, but curiously, several interfering unpleasant factors (for example, sound) do not significantly affect the results.

O'Neil, H. F. Jr.: "Effects of stress on state anxiety and performance in computer-assisted learning." *J. Ed. Psychol.* **63**: 473-481 (1972).

J19,657/72

Kilpatrick, D. G.: "Differential responsiveness of two electrodermal indices to psychological stress and performance of a complex cognitive task." *Psychophysiology* **9**: 218-226 (1972).

J19,072/72

Danev, S. G., de Winter, C. R., Wartna, G. F.: "Information processing and psychophysiological functions in a task with and without time stress." *Act. Nerv. Sup. (Praha)* **14**: 8-12 (1972).

J18,091/72

Zwaga, H. J. G.: "Psychophysiological reactions to mental tasks: effort or stress?" *Ergonomics* **16**: 61-67 (1973).

J8,259/73

Neufeldt, A. H., Raulston, P., Peterson, G.: "Personal factors in human learning: II. Learning ability and subjective stress." *J. Gen. Psychol.* **88**: 87-91 (1973).

J19,605/73

Kato, M., Ogino, T., Suzuki, T.: "Cardiac rhythm and urinary excretion of catecholamine under mental work and physical exercise." *Tohoku J. Exp. Med.* **112**: 111-118 (1974).

H86,189/74

Johnston, R. E., Miya, T. S., Paolino, R. M.: "Facilitated avoidance learning and stress-induced corticosterone levels as a function of age in rats." *Physiol. Behav.* **12**: 305-308 (1974).

J11,624/74

"Older animals acquired the conditioned avoidance response (CAR) faster and required a longer time to extinguish, than the younger animals. The enhanced CAR performance of the older animals could not be attributed to an altered pain threshold but was correlated with a significantly higher plasma corticosterone response to ether-stress. The data are interpreted as being consistent with the notion of a positive relationship between pituitary-adrenal activity and facilitated avoidance learning."

Friedman, M., Byers, S. O., Diamant, J., Rosenman, R. H.: "Plasma catecholamine response of coronary-prone subjects (Type A) to a specific challenge." *Metabolism* **24**: 205-210 (1975).

H98,918/75

In a nonphysical competitive struggle (puzzle solving), the plasma NEP content of type A persons rises 30 percent above that of type B individuals, whereas plasma EP remains essentially unchanged in both groups.

Fighting, Anger, Hate

Actual fighting, anger, aggressiveness and hate occur so often in association that it would be practically impossible to isolate each of them in a stress reaction. Many pertinent data in relation to the special case of military activities will be found in the section, Combat. Most of the relevant publications deal with the psychologic consequences of aggressive behavior, but there is considerable evidence to show that combativeness also elicits other manifestations of the classic stress syndrome. For example, voles kept in a cage viciously attack any stranger of the same species introduced among them. This leads to adrenal enlargement, thymic atrophy and other characteristic manifestations of the alarm reaction. Curiously, instead of the usual splenic atrophy in these animals, the spleen enlarges after fighting, perhaps because of secondary infections.

In rats, fighting causes adrenal enlargement and other characteristic signs of stress. In isolated male mice exposed to trained fighters several times a day, adrenal hypertrophy is associated with a rise in plasma corticosterone, whereas the seminal vesicles decrease in size, indicating diminished testicular function. Adrenal hyperactivity is particularly pronounced in mice that have previously experienced defeat, presumably because they are more frightened than are usually victorious animals.

The rate of brain catecholamine synthesis is lower in isolated than in grouped mice, but fighting rapidly accelerates the synthesis of both catecholamines and 5-HT in the brain. Deposition of cortisol crystals into the ME of rats did not influence electro-shock-induced fighting behavior. Yet, immediately after the last fight, the plasma corticosterone levels and adrenal weight indicated complete suppression of ACTH activity in the animals.

Much research has also been done on human aggression, particularly in the socio-political context. Among aggressive stressor agents, special attention has been given to anti-Semitism and other types of common race hatred, destructive student protests, anger towards traditionally, though irrationally, selected targets (scapegoats), and various movements to change society by violence.

Fighting, Anger, Hate

(See also our earlier stress monographs, p. xiii)

Clarke, J. R.: "The effect of fighting on the adrenals, thymus and spleen of the vole (*Microtus agrestis*)."*J. Endocrinol.* 9: 114-126 (1953). B77,639/53

Voles (*Microtus agrestis*) kept in a cage viciously attack any strangers of the same species introduced among them. The fighting results in adrenal enlargement and thymic atrophy characteristic of the alarm reaction, but instead of the usual splenic atrophy there is hypertrophy—perhaps due to secondary infection.

Funkenstein, D. H., King, S. H., Drolette, M.: "The direction of anger during a labora-

tory stress-inducing situation."*Psychosom. Med.* 16: 404-413 (1954).

C1,759/54

When exposed to stress-inducing "problem situations" in which failure is rudely criticized, some individuals react with anger, others with anxiety. Each of these response types is associated with different effects upon blood pressure and ballistocardiographic measures.

Barnett, S. A.: "Physiological effects of 'social stress' in wild rats—I. The adrenal cortex."*J. Psychosom. Res.* 3: 1-11 (1958).

J11,151/58

In wild male rats kept in groups, fighting produces enlargement of the adrenal, and there is occasional sudden death unrelated to wounds. "It may have resulted from dis-

turbed carbohydrate metabolism or from 'vagal syncope'."

Lemonde, P.: "Influence of fighting on leukemia in mice." *Proc. Soc. Exp. Biol. Med.* **102**: 292-295 (1959). C77,947/59

In leukemic strains of mice, fighting among males tends to delay the development of the disease, probably through the stress-induced discharge of ACTH and corticosterone.

Bronson, F. H., Eleftheriou, B. E.: "Chronic physiological effects of fighting in mice." *Gen. Comp. Endocrinol.* **4**: 9-14 (1964). F7,501/64

When isolated male mice were exposed to trained fighters several times a day, the adrenal weight and plasma corticosterone levels rose, whereas seminal vesicle weight decreased. Adrenal corticosterone concentrations paralleled the increase in adrenal weight.

Bronson, F. H., Eleftheriou, B. E.: "Adrenal response to fighting in mice: separation of physical and psychological causes." *Science* **147**: 627-628 (1965). F31,060/65

The plasma concentration of free corticosterone in mice exposed to the presence of a trained fighter is much greater if they have previously experienced defeat under similar conditions. The change is of essentially the same magnitude as in actual defeat. Apparently, the psychologic stress is more important than the physical damage of bites.

Thorne, F. C.: "Differing reactions of friendly and fear-biting dogs to severe stress." *J. Clin. Psychol.* **24**: 181-184 (1968). J23,708/68

Sigg, E. B.: "Relationship of aggressive behaviour to adrenal and gonadal function in male mice." In: Garattini, S. and Sigg, E. B., *Aggressive Behaviour*, pp. 143-149. Amsterdam: Excerpta Medica Foundation, 1969.

J10,865/69

The aggressive behavior of isolated mice was studied by extirpation of various endocrine glands and treatment with diverse hormones. It is concluded that "the male gonadal hormones are critically involved in this response whereas other endocrine changes (adreno-cortical, adreno-medullary and thyroid) may be contributory and consequential."

Fischer, D., Rule, B. G.: "Anti-Semitism, stress, and anchor effects on interpersonal

judgements." In: Presse, A. W. and Zubeck, J. P., *Readings in General Psychology: Canadian Contributions*, pp. 343-346. Toronto: McClelland and Stewart, 1970. E8,858/70

Purely psychologic studies on the effect of stress upon interpersonal judgments in subjects with varying degrees of anti-Semitism.

Parker, R. S.: "Anger, identification, and irrational target selection." In: Parker, R. S., *The Emotional Stress of War, Violence, and Peace*, pp. 12-70. Pittsburgh, Pa.: Stanwix House, 1972. E10,441/72

Hostility is regarded as a defensive adaptive response accompanied by anger and often expressed toward irrationally selected targets. The term stress is used in its broadest sense only.

Riscalla, L. M.: "The violence of non-violence. A barrier to enlightenment." In: Parker, R. S., *The Emotional Stress of War, Violence, and Peace*, pp. 128-132. Pittsburgh, Pa.: Stanwix House, 1972. E10,443/72

General discussion of demonstrations, student protests and other efforts to change society. The term stress is used essentially as a synonym for difficulty, and not in its medical connotation.

Hucklebridge, F. H., Nowell, N. W., Dilks, R. A.: "Plasma catecholamine response to fighting in the male albino mouse." *Behav. Biol.* **8**: 785-800 (1973). H92,272/73

"Mice which fought victories showed no evidence of an increase in plasma catecholamines, whereas plasma epinephrine, and to a lesser extent, norepinephrine were elevated in defeated mice and this response tended to be greater in mice which fought back when attacked. Attack by a trained fighter mouse was found to be a particularly effective stimulus for the release of epinephrine from the adrenal medulla."

Modigh, K.: "Effects of isolation and fighting in mice on the rate of synthesis of noradrenaline, dopamine and 5-hydroxytryptamine in the brain." *Psychopharmacologia* **33**: 1-17 (1973). J7,891/73

The rate of brain catecholamine synthesis is lower in isolated than in grouped mice and intense fighting rapidly accelerates the synthesis of both catecholamines and 5-HT in the brain.

Erskine, M. S., Levine, S.: "Suppression of pituitary-adrenal activity and shock-induced fighting in rats." *Physiol. Behav.* **11**: 787-790 (1973). J8,675/73

Deposition of cortisol acetate crystals into the ME of the hypothalamus did not influence the shock-induced fighting behavior of rats. Yet, immediately following the last fighting session, plasma corticosterone levels and adrenal weight showed complete suppression of pituitary-adrenal activity in the implanted group. Apparently, aggressive behavior is not mediated through ACTH and corticoids. The previously reported suppression by cortisol of muricidal behavior in rats could have been due to inhibition of ACTH secretion.

Allikmets, L. H.: "Cholinergic mechanisms in aggressive behaviour." *Med. Biol.* **52**: 19-30 (1974). J14,512/74

A review on brain 5-HT and catecholaminergic systems in aggressive behavior. It is suggested that the cholinergic trigger mechanism of aggressive behavior depends

on brain 5-HT and catecholaminergic processes (75 refs.).

Hucklebridge, F. H., Nowell, N. W.: "Plasma catecholamine response to physical and psychological aspects of fighting in mice." *Physiol. Behav.* **13**: 35-40 (1974).

J14,548/74

Plasma EP and, to a lesser degree, NEP levels were elevated in mice attacked daily by a trained fighter. The mere presence of the attacker caused no such change, but plasma corticosterone levels were raised. "It is suggested that, unlike adrenal corticosterone release which is induced by a relatively non specific state of hyperalertness or arousal, adrenomedullary epinephrine release is stimulated only under specific circumstances which, for the mice in the present experiment, were not met by a 'psychological' stimulus" (32 refs.).

Sensory Deprivation, Boredom, Monotony

The study of sensory deprivation illustrates the difficulties encountered in any attempt to interpret the stress concept correctly, that is, in accordance with its contemporary definition as the nonspecific reaction of the body to any demand: At first sight, it would appear that complete rest in the virtual absence of any external stimulus, psychic or somatic, would represent the state closest to total freedom from stress. This view is definitely incorrect.

Many experiments have shown that maximal sensory deprivation--when the subject lies quietly in a most comfortably cushioned bed, every effort being made to protect him against sound, temperature variations, air pollutants, physical or mental work, and all other stimuli that may make a "demand" upon his adaptive mechanisms--hardly provides protection against stress. Actually, under such conditions, the subject experiences "an intense desire for extrinsic sensory stimuli and bodily motion, increased suggestibility, impairment of organized thinking, oppression and depression, and, in extreme cases, hallucinations, delusions and confusion." Living beings are constructed for work, and if they have no outlet for their pent-up energy they must make extreme efforts at adaptation to this unphysiologic state of inactivity which has been named "deprivation stress" and which has been incorporated into the G.A.S. concept by Galdston.

Normal function of the brain depends on constant arousal generated in the reticular formation by continuous sensory input. Thus, hallucinations, which may cause accidents, have been noted in pilots, astronauts and long-distance truck drivers, the monotony of whose work presumably acts as a form of sensory deprivation.

Several excellent chambers have been described for sensory deprivation experiments, and the psychic manifestations of more or less prolonged residence in them have been carefully recorded; however, up to now, little is known about the associated somatic indicators, such as hormonal responses.

Although virtually complete sensory deprivation for prolonged periods is rare in daily life, a decrease in sensory input below the normal level is a common cause of boredom. It will undoubtedly represent a major pathogen, not only in astronauts on long voyages, but in all those whose work becomes increasingly monotonous as mass-production techniques develop.

Separation of infants from their mothers, and all types of relocation of people into strange environments which leave few possibilities for interpersonal contacts, are very common forms of sensory deprivation; they may become major factors in psychosomatic disease.

In infant rhesus monkeys, catecholamine synthesis is stimulated by mother-infant separation, and this process is neurally mediated.

Studies on female undergraduates showed that even ninety minutes of total isolation is stressful, as indicated by the rise in GSR. In children, prolonged emotional deprivation caused a kind of "hypopituitarism" with diminished ACTH and STH secretion, which was abolished by return to a normal environment. Undoubtedly, growth is inhibited, but according to another investigation, fasting serum STH is usually increased in emotionally deprived children, while the STH and ACTH responses to hypoglycemia are diminished.

In policemen, both understimulation and overstimulation enhanced NEP release. Subjects excreting more EP performed better during understimulation, whereas those with less EP output were more efficient during overstimulation.

Sensory Deprivation, Boredom, Monotony

(See also our earlier stress monographs, p. xiii
and cf. Isolation)

Wyatt, S., Fraser, J. A., Stock, F. G. L.:
The Effects of Monotony in Work. Industrial
Fatigue Research Board Report No. 56
(1929). B27,759/29

Galdston, I.: *Beyond the Germ Theory*, p.
182. New York, Minneapolis: Health Education
Council, 1954. C1,722/54

Very readable book with major emphasis upon the disease-producing effects of "deprivation stress" in relation to the G.A.S. Special sections on deprivation of food and emotional stimuli.

Bexton, W. H., Heron, W., Scott, T. H.:
"Effects of decreased variation in the sensory environment." *Can. J. Psychol.* 8: 70-76
(1954). J20,482/54

In man, sensory deprivation can cause hallucinations, confusion, headaches and fatigue, with unusual emotional lability.

Wulfften Palthe, P. M. van: "Sensory and motory deprivation as a psycho-pathological stress." *Aeromed. Acta* (Soesterberg) 4:
155-168 (1955). J23,252/55

Murphy, C. W., Kurlents, E., Cleghorn,

R. A., Hebb, D. O.: "Absence of increased corticoid excretion with the stress of perceptual deprivation." *Can. J. Biochem.* 33:
1062-1063 (1955). C9,602/55

In healthy male volunteers, long periods of perceptual deprivation failed to cause any significant increase in 11-OHCS excretion. "As far as our data go, it appears that under these circumstances the adrenal cortex is not activated to a greater degree than it is by the minor exigencies of everyday life."

Heron, W.: "The pathology of boredom." *Sci. Am.* 196: 52-56 (1957). B28,802/57

Semipopular description of the experiments of D. O. Hebb and his group on sensory deprivation in specially constructed chambers. Subjects developed various types of hallucinations and became unable to concentrate on any particular topic. "The most striking finding was that when subjects emerged after several days of isolation, the whole room appeared to be in motion. In addition there was a tendency for surfaces to appear curved, and for objects to appear to be changing their size and shape. Asked to match a disk that was handed to them to one in a row of disks of various sizes 12 feet away, the subjects consistently chose a larger disk than did control subjects." Recent studies indicate that normal function

of the brain requires constant arousal generated in the reticular formation which in turn depends upon continuous sensory input. Hallucinations are also common among pilots, astronauts and long-distance truck drivers, and may predispose to accidents.

Solomon, P., Leiderman, P. H., Mendelson, J., Wexler, D.: "Sensory deprivation, a review." *Am. J. Psychiatry* **114**: 357-363 (1957). B29,588/57

Review on the effects of sensory deprivation in man showed that the most evident results are an "intense desire for extrinsic sensory stimuli and bodily motion, increased suggestibility, impairment of organized thinking, oppression and depression, and, in extreme cases, hallucinations, delusions, and confusion" (28 refs.).

Wexler, D., Mendelson, J., Leiderman, P. H., Solomon, P.: "Sensory deprivation. A technique for studying psychiatric aspects of stress." *Arch. Neurol. Psychiatry* **79**: 225-233 (1958). B69,786/58

Sensory deprivation is considered to be a suitable technique for studying the psychiatric aspects of stress. Men placed in a tank-type respirator for periods of up to thirty-six hours experienced perceptual and sensory deprivation which led to an impaired ability to concentrate, distortions in time judgment and anxiety. Several subjects had pseudosomatic delusions, illusions or hallucinations. Correlation of these findings with the pertinent literature led to the conclusion that the most common manifestations are: "(1) the inability of most subjects to tolerate or adapt to the stress of sensory isolation; (2) the subjects' increasing need for and attempts to obtain extrinsic physical and social stimuli; (3) the progressive failure, in certain subjects, of reality contact with the emergence of pathological thought processes and behavior."

Kraft, J. A.: "Measurement of stress and fatigue in flight crews during confinement." *J. Aviat. Med.* **30**: 424 (1959). C70,483/59

Description of an elaborate facility for the automatic registration of various stress indices (skin temperature, heart rate, respiratory cycle, muscular tension, skin conductance, and so on) under the influence of stressors to which flight crews and astronauts are likely to be exposed (for example, gravity forces, loneliness, confinement, isolation, sensory deprivation, and so on).

Gauron, E. F., Becker, W. C.: "The ef-

fects of early sensory deprivation on adult rat behavior under competition stress: an attempt at replication of a study by Alexander Wolf." *J. Comp. Physiol. Psychol.* **52**: 689-693. (1959). J23,322/59

Ruff, G. E., Levy, E. Z., Thaler, V. H.: "Studies of isolation and confinement." *Aerospace Med.* **30**: 599-604 (1959). B71,838/59

Brief description of the psychologic consequences of isolation and sensory deprivation under conditions simulating those of space flights. The parameters measured are mentioned, but the results are not reported in sufficient detail for evaluation.

McBain, W. N.: "Noise, the 'arousal hypothesis,' and monotonous work." *J. Appl. Psychol.* **45**: 309-317 (1961). E53,909/61

Wieser, S.: "Psychische Überforderungsreaktionen. I. Monotonie und Stress" (Mental reactions to excessive demands. I. Monotony and stress). *Arch. Psychiatr. Nervenkr.* **203**: 452-461 (1962). D47,718/62

Discussion of the relationship between monotony and the G.A.S.

Miller, S. C.: "Ego-autonomy in sensory deprivation, isolation, and stress." *Int. J. Psychoanal.* **43**: 1-20 (1962) (151 refs.). D52,100/62

Zuckerman, M., Albright, R. J., Marks, C. S., Miller, G. L.: "Stress and hallucinatory effects of perceptual isolation and confinement." *Psychol. Monogr.* **76** No. 30: 1-15 (1962). J3,941/62

Observations on student nurses subjected to perceptual isolation through various techniques. The resulting loss of orientation, difficulties in directed thinking, anxiety from personal thoughts and increasing somatic discomfort led to a mounting stress reaction in most subjects. Hallucinations were also common.

Burns, N. M., Kimura, D.: "Isolation and sensory deprivation." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 167-192. Glencoe, Ill.: Free Press, 1963.

E10,429/63

Brief review on isolation, loneliness and sensory deprivation in relation to prolonged space flights.

Winters, W. D.: "Various hormone changes during simulated space stresses in the monkey." *J. Appl. Physiol.* **18**: 1167-1170 (1963). E35,060/63

In *Macacca nemestrina* monkeys, diuresis and urinary excretion of 17-KGS and catecholamines were examined under simulated space stressor conditions, namely, centrifugation, vibration and isolation with restraint. The results varied with the type of stressor used, but reduction in urine volume was obvious in all instances. "A fall in steroid and slight elevation in catecholamine excretion were observed following vibration and centrifugation. The centrifugation appeared to be slightly more stressful. Isolation with restraint appears to be a severe stress to the animals as demonstrated by a marked elevation of amine and a marked reduction in both urine output and steroid excretion."

Zuckerman, M.: "Perceptual isolation as a stress situation." *Arch. Gen. Psychiatry* **11**: 255-276 (1964). G19,879/64

Careful evaluation of the literature (68 refs.) on biochemical and physiologic responses to isolation produced by various techniques in normal and abnormal individuals. "Sensory deprivation" (darkness and quiet) is compared with "perceptual deprivation" (unpatterned light and constant "white noise").

Zuckerman, M., Levine, S., Biase, D. V.: "Stress response in total and partial perceptual isolation." *Psychosom. Med.* **26**: 250-260 (1964). J7,193/64

In studies on female undergraduates, the GSR (recorded by the Tissue Resistance Monitor) showed that a ninety-minute period of "total isolation is more stressful than partial isolation. Verbal indices indicate that all types of isolation are equally stressful. The results indicate that a social set theory is not sufficient to explain the stressful effects of perceptual restriction."

Dohrenwend, B. S., Dohrenwend, B. P.: "Stress situations, birth order, and psychological symptoms." *J. Abnorm. Psychol.* **71**: 215-223 (1966). J8,713/66

Studies on college students suggest that—in confirmation of earlier observations—the stress of sensory deprivation is modified by birth order. "First borns show high levels of symptoms when their situation is such that, faced with an anxiety-arousing condition, they have difficulty finding others with whom to share the experience. Later borns show high levels of symptoms when, in the face of anxiety, they are forced into intense interaction with others."

Zubek, J. P., Schutte, W.: "Urinary excre-

tion of adrenaline and noradrenaline during prolonged perceptual deprivation." *J. Abnorm. Psychol.* **71**: 328-334 (1966).

J24,049/66

In young men who successfully completed a week of perceptual isolation, there was no significant change in urinary EP or NEP excretion. However, "quitters" had a significantly lower baseline of EP even months after the isolation experiment, but exhibited an increased excretion during isolation. "These results seem to suggest that isolation quitters may be biochemically or 'constitutionally' different from volunteers who can successfully complete a prolonged period of perceptual isolation."

Shurley, J. T.: "Stress and adaptation as related to sensory perceptual isolation research." *Milit. Med.* **131**: 254-258 (1966).

J23,108/66

Biase, D. V., Zuckerman, M.: "Sex differences in stress responses to total and partial sensory deprivation." *Psychosom. Med.* **29**: 380-390 (1967). G48,990/67

Haythorn, W. W., Altman, I.: "Personality factors in isolated environments." In: Appley, M. H. and Trumbull, R., *Psychological Stress. Issues in Research*, pp. 363-399. New York: Appleton-Century-Crofts, 1967.

E10,418/67

Guidelines for the analysis of performance in task-oriented isolated groups with special reference to space travel.

Powell, G. F., Brasel, J. A., Raitt, S., Blizzard, R. M.: "Emotional deprivation and growth retardation simulating idiopathic hypopituitarism. II. Endocrinologic evaluation of the syndrome." *N. Engl. J. Med.* **276**: 1279-1283 (1967). F80,128/67

In children, prolonged emotional deprivation resulted in a syndrome similar to hypopituitarism with diminished ACTH and STH secretion. Once removed from the pathogenic environment, they began to grow at a remarkable rate; STH and ACTH discharge returned to normal (42 refs.).

Suedfeld, P.: "Anticipated and experienced stress in sensory deprivation as a function of orientation and ordinal position." *J. Soc. Psychol.* **76**: 259-263 (1968). J21,696/68

Suedfeld, P.: "Sensory deprivation stress: birth order and instructional set as interacting variables." *J. Pers. Soc. Psychol.* **11**: 70-74 (1969). J23,471/69

Grandjean, E. P.: "Fatigue." *Am. Ind. Hyg. Assoc. J.* July-August, 1970, pp. 401-411. J16,329/70

Review of neurophysiologic interrelations regulating fatigue, especially in connection with particularly stressful mental or monotonous work (27 refs.).

Krieger, I., Mellinger, R. C.: "Pituitary function in the deprivation syndrome." *J. Pediatr.* 79: 216-225 (1971). G85,342/71

In children deprived of emotional stimulation and food, fasting serum STH was usually increased but STH and ACTH responses to hypoglycemia were diminished.

Frankenhaeuser, M., Nordheden, B., Myrsten, A. L., Post, B.: "Psychophysiological reactions to understimulation and overstimulation." *Acta Psychol. (Amst.)* 35: 298-308 (1971). G99,743/71

Student policemen were subjected to understimulation (vigilance test) and overstimulation (complex sensorimotor test), both of which caused increased NEP in comparison to controls under conditions of a medium amount of stimulation. Subjects excreting relatively more EP performed better during understimulation, whereas efficiency was greater during overstimulation in those releasing small amounts of EP.

Cohen, S., Taylor, L.: *Psychological Survival. The Experience of Long-term Imprisonment*, p. 217. New York: Pantheon Books, 1972. E10,656/72

Monograph on the effects of captivity, especially long-term imprisonment. Particular attention is given to psychologic changes and to studies on stress and deprivation (few key refs.).

Rayner, P. H. W., Rudd, B. T.: "Emo-

tional deprivation in three siblings associated with functional pituitary growth hormone deficiency." *Austr. Paediatr. J.* 9: 79-84 (1973). J4,141/73

In three siblings with severe emotional deprivation, growth retardation was evident. When placed in a residential school, they showed dramatic improvement.

Breese, G. R., Smith, R. D., Mueller, R. A., Howard, J. L., Prange, A. J. Jr., Lipton, M. A.: "Induction of adrenal catecholamine synthesizing enzymes following mother-infant separation." *Nature [New Biol.]* 246: 94-96 (1973). J8,088/73

It is concluded that "mother-infant separation stimulates adrenal catecholamine synthesis in the infant rhesus monkey and that this effect is neurally mediated."

Thackray, R. I., Jones, K. N., Touchstone, R. M.: "Personality and physiological correlates of performance decrement on a monotonous task requiring sustained attention." *Federal Aviation Administration, Aviation Med. pamphlet*, p. 13. Washington, D.C., 1973. J15,364/73

"Reductions in task load resulting from the increasing automation of air traffic control may actually increase the requirement for controllers to maintain high levels of sustained attention in order to detect infrequent system malfunctions. A previous study indicated that individuals scoring high on a distractibility scale found it difficult to maintain sustained attention on a monotonous, but perceptually demanding, task."

Frankenhacuser, M., Johansson, G.: "On the psychophysiological consequences of understimulation and overstimulation." *Rep. Psychol. Lab. Univ. Stockholm*, Supp. 25: 1-19 (1974). J19,040/74

Pleasure

There is surprisingly little scientific literature on objectively demonstrable indices of stress elicited by pleasure. It is of course common knowledge that sudden joy—like pain or grief—can produce increased adrenergic activity with acceleration of the pulse, a rise in blood pressure and excessive mental arousal. In fact, it was this type of observation that led to the creation of the "eustress" concept, according to which gratifying or health-promoting demands upon the body represent stress just as distress does.

That there is a lack of positive laboratory data supporting this view is probably due primarily to the difficulty encountered in producing chronic states of extreme pleasure for experimental purposes. However, some pertinent observations have been

made quite independently of the research on stress in human beings during sexual intercourse, and several publications make reference to the possibility of sudden death in predisposed people as a consequence of extreme unexpected joy.

Pleasure

(See also our earlier stress monographs, p. xiii)

Engel, G. L.: "Sudden and rapid death during psychological stress. Folklore or folk wisdom?" *Ann. Intern. Med.* **74**: 771-782 (1971). G83.212/71

Excellent and detailed review of the sociologic-demographic literature shows that the causes of sudden death in man may be classified into eight categories: "1) on the impact of the collapse or death of a close person; 2) during acute grief; 3) on threat

of loss of a close person; 4) during mourning or on an anniversary; 5) on loss of status or self-esteem; 6) personal danger or threat of injury; 7) after the danger is over; 8) reunion, triumph, or happy ending" (89 refs.).

Tejmar, J.: "Berlin wall and sudden death." *Ann. Intern. Med.* **78**: 620 (1973).

J19,555/73

Sudden death during joyful meetings after long years of separation has been described, but undoubtedly it is a very rare occurrence.

Handling and Gentling

(See also Age—Perinatal)

Handling and gentling of young animals may influence their subsequent stress resistance, but the underlying mechanism of this phenomenon is not yet clear. First, it must be realized that handling can be experienced as an attack or a friendly gesture, depending upon the individual's reaction to the situation. Surely, handling of fish or other animals that are unaccustomed to it will be experienced by them as an aggression, whereas newborn babies like to be taken up and handled by their mothers.

In animals, especially rats (in which most of the corresponding experiments were performed) it is difficult to judge their associated mental reactions, but in any event, it has been claimed that taking the young away from the mother and placing them in a cage for handling may act as a stressor merely by reducing their surrounding temperature.

Handling and Gentling

(See also our earlier stress monographs, p. xiii, and Chapter V: Treatment)

Borda-Bossana, D., Elrick, H., Bernstein, L., Atkinson, H.: "Effects of handling in the adrenalectomized rat treated with corticosterone." *J. Psychosom. Res.* **5**: 206-210 (1961). J23,513/61

Schaefer, T. Jr., Weingarten, F. S., Towne, J. C.: "Temperature change: the basic variable in the early handling phenomenon?" *Science* **135**: 41-42 (1962). J22,952/62

Spence, J. T., Maher, B. A.: "Handling

and noxious stimulation of the albino rat: II. Effects on subsequent performance in a learning situation." *J. Comp. Physiol. Psychol.* **55**: 252-255 (1962). J22,950/62

Bernardis, L. L., Skelton, F. R.: "Effect of gentling on development of adrenal regeneration hypertension in immature female rats." *Proc. Soc. Exp. Biol. Med.* **113**: 955-957 (1963). E28,036/63

"Gentling acts as a stressor and increases blood pressure in adrenal-enucleated as well as intact rats."

Salama, A. A., Hunt, J. M.: "'Fixation' in the rat as a function of infantile shocking,

handling, and gentling." *J. Genet. Psychol.*
105: 131-162 (1964) (82 refs.).

J23,019/64

Goldman, J. R.: "The effects of handling and shocking in infancy upon adult behavior in the albino rat." *J. Genet. Psychol.* **104:** 301-310 (1964). J22,967/64

Hucklebridge, F. H., Nowell, N. W.: "Effect of infantile handling upon plasma catecholamine response to acute noxious stimulation in adulthood." *Behav. Biol.* **9:** 563-579 (1973). J22,755/73

Umminger, B. L., Gist, D. H.: "Effects of thermal acclimation on physiological responses to handling stress, cortisol and aldosterone injections in the goldfish, *Carassius auratus*." *Comp. Biochem. Physiol.* **44A:** 967-977 (1973). H64,677/73

"Goldfish subjected to stressful handling and sham injection procedures responded with a hyperglycemia and a decline in serum chloride and sodium concentrations. Carcass water content was not affected."

Varia

Kowalski, R.: "L'effet des émissions radiophoniques sur l'image radiologique du tube digestif chez l'enfant" (The effect of radiophonic emission on the radiologic appearance of the gut in childhood). *Ann. Radiol.* **12:** 827-833 (1969). J21,830/69

In children *listening to the radio*, intestinal motility may be greatly altered.

Mahood, W. H.: "How stressful is *endoscopy*?" *Gastrointest. Endosc.* **19:** 146-147 (1973). J19,553/73

Orlandi, F., Serra, D.: "La risposta ipotalamo-ipofisaria all'elettrostimolazione del nervo olfattivo" (Hypothalamo-hypophyseal reaction to electric stimulation of the olfactory nerve). *Folia Endocrinol. (Roma)* **26:** 441-446 (1973). H83,463/73

In man, direct electric *stimulation of the nasal mucosa* elicits rapid increases in plasma cortisol with other manifestations of stress, presumably because the olfactory nerve is directly connected with the CRF-producing hypothalamic centers.

CLIMATE, ENVIRONMENT

(See also Drugs—especially individual toxicants acting as pollutants; Physical Agents—psychogenic stressors, occupations and other factors likely to affect the environment)

Generalities

(See also our earlier stress monographs, p. xiii)

Randolph, T. G.: "Human ecology and susceptibility to the chemical environment." *Ann. Allergy* **19:** 518-540; 657-677; 779-799; 908-929 (1961). D5,214/61

Extensive review on the influence of the chemical environment upon resistance, with a section on stress. The author creates the concept of the "specific adaptation syndrome," defined as "a clinical counterpart of Selye's general adaptation syndrome." [It is not clear how specific adaptation to each agent can result in a single stereotyped syndrome common to all stressors (H.S.).]

Budd, G. M.: "Acclimatization to cold in Antarctica as shown by rectal temperature response to a standard cold stress." *Nature* **193:** 886 (1962). D41,090/62

Lawton, R. W.: "The physiological effects of unusual environments." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 3-31. Glencoe, Ill.: Free Press, 1963. E10,424/63

Brief review on the physiologic changes in man that occur in unusual environments, especially during space flights.

Fraser, T. M.: "Men under stress." *Sci. Technol.* No. 73: 38-44; 82 (1968). F98,050/68

Semipopular review on men under stress with special reference to environmental factors.

Olivereau, J. M.: "Incidences psychophysioliques des facteurs climatiques de l'environnement" (Psychophysiological effects of environmental climatic factors). *Bull. Psychol.* **24:** 597-606 (1971). G87,046/71

Rather speculative review on the stressor effect of climatic factors, including pollution.

Hall, S. A.: "Heat stress in outdoor manual workers in East Africa." *Ergonomics* **14**: 91-94 (1971). J19.719/71

Beals, K. L.: "Head form and climatic stress." *Am. J. Phys. Anthropol.* **37**: 85-92 (1972). J20.343/72

"Based on a sample of 339 populations, the magnitude of the index is statistically different between zones of predominantly dry heat, wet heat, wet cold and dry cold. There is an inverse relationship between the mean cephalic index and temperature. It is argued that the occupation of cold climates is one of the circumstances increasing the frequency of brachycephaly through time," and that a relationship exists between climatic stress and head form.

Hanlon, J. J.: "Environmental hazards." *Fed. Proc.* **31**: TF101-TF120 (1972). H57,805/72

Review of physical, biologic, psychologic and chemical environmental hazards to man, with brief sections on noise and the roles of adaptive steroids (65 refs.).

Lindvall, T., Radford, E. P.: "Measurement of annoyance due to exposure to environmental factors." *Environ. Res.* **6**: 1-36 (1973). J15,317/73

Review on various environmental factors, especially sound, pollution, crowding and stressful interpersonal relations, as objective indicators of somatic stress (about 150 refs.).

Moos, R. H.: "Conceptualizations of human environments." *Am. Psychol.* **29**: 652-665 (1974). J19,057/74

Review of the stressor effect of environmental factors (about 100 refs.).

Davidson, A. F., Blake, W. J.: "Challenge of the Arctic." *J. R. Nav. Med. Serv.* **60**: 17-21 (1974). J20,063/74

Vollrath, L., Brabant, G.: "Umweltbedingte Anpassung und Schädigung endokriner Organe" (Climatic factors affecting adaptation and the endocrine system). *Dtsch. Med. Wochenschr.* **99**: 1568-1573 (1974). H88,840/74

Excellent and extensive review, with special reference to the stressor effect of climate (90 refs.).

Pollution

In view of the increasing importance of air and water pollution there exists an enormous literature on this subject. But although chemical agents, microbes, sound, and in a broader sense, "social pollution" by overcrowding of our cities represent potent stressors, comparatively few data are available on their truly nonspecific, measurable stressor effects as such. Most of the relevant publications deal with the psychologic effects of life in polluted, overcrowded, urbanized areas and in concentration camps; in the special sections of this chapter, the reader will find data on the typical stressor effects of these and many other environmental agents.

Pollution

(See also our earlier stress monographs, p. xiii)

Blumer, W.: "Nervöse Störungen durch Autoabgase" (Nervous disturbances caused by automobile exhaust gases). *Praxis* **59**: 1809-1816 (1970). H35,115/70

Automobile exhaust gases are considered to produce stress in man as judged by the resulting symptoms, although elimination of

lead furnishes a rather specific therapeutic measure.

Lindvall, T., Radford, E. P.: "Measurement of annoyance due to exposure to environmental factors." *Environ. Res.* **6**: 1-36 (1973). J15,317/73

Review on various environmental factors, especially sound, pollution, crowding and stressful interpersonal relations, on objective indicators of somatic stress (about 150 refs.).

Levi, L., Andersson, L.: *Population, En-*

vironment and Quality of Life, p. 142. Stockholm: Goteborgs Offsettryckeri AB, 1974.

E10,629/74

Effects of social factors, crowding, pollution and urbanization upon stress-induced diseases (several hundred refs.).

Bolduan, N. W., Taguchi, S.: "Air pollu-

tion, exercise, and heat stress." *Arch. Environ. Health* **28**: 177-181 (1974).

J11,428/74

Studies on the effects of air pollution (particularly of carbon monoxide and peroxyacetyl nitrate) upon work tolerance at various temperatures, with special reference to the Los Angeles area (20 refs.).

Social, Cultural, Family

Social and cultural stressors are difficult to separate from related agents with which they often overlap. For example, it would be impossible to dissociate the social from the cultural influences which may act as stressors in the life of a particular primitive tribe, or to distinguish these from genetic factors, climate, diet, prevalent diseases, overcrowding, isolation and innumerable other elements to which the social group is exposed.

The stressor effects of epidemics, wars and economic changes are met very differently by people of distinct cultural and ethnic backgrounds. The term "situational stress" has been used to designate the behavior of people acting in groups, but here it is employed in its broadest sense, essentially as a synonym of "difficulty," which is quite unjustified.

The fact that, in Japan, arteriosclerotic CHD is uncommon in comparison with its incidence among the North American white population has led to some speculation about the roles of social and cultural elements in the pathogenesis of this rather typical disease of adaptation to stress. However, the striking differences in nutrition as well as genetic predisposition must also be considered.

Special attention has been given to what is termed "culture stress" or "cross-cultural stress" in relation to the G.A.S. These studies are mainly concerned with the stressors encountered by migrants, "guest workers" and others who are often regarded as undesirable intruders by host populations. These people may suffer from the lack of friendly social contact in addition to being obliged to follow customs, diets and a general philosophy which is foreign to them.

Most of the investigators in this field have limited their assessment of these stressor conditions to questionnaires or the frequency of typical "diseases of adaptation," such as hypertension, gastric ulcers, mental illness. Only a few somewhat inconclusive data are available with respect to the secretion of stress hormones, that is, corticoids or catecholamines.

A rise in plasma FFA is said to be a very sensitive indicator of interpersonal stress.

A special index of culture stress was constructed by comparing traditions and social habits in thirty-seven totally dissimilar societies and races. It was concluded that protest suicide, defiant homicide, drunken brawling, and witchcraft attribution are suitable tentative indicators of this type of stress.

Extensive studies on "the theory of leadership in interpersonal behavior under stress" led to the conclusion that moderate stress tends to improve, whereas severe stress disorganizes, performance.

In any event, there appears to be a consensus that severe social and cultural stress

predisposes to a number of maladies, not only to typical psychosomatic diseases but even to infections, by decreasing resistance.

Even birth order may act as a social stress. In one study, college students faced with anxiety-arousing conditions manifested more distress and had more difficulty in finding others with whom to share their experiences than did their siblings. Of course, conflicts in the family and with coworkers are particularly common social stressors.

Allegedly, chronic alcoholics drink most when stress and socialization periods coincide.

A comparative study in high and low stress areas of Detroit revealed that social and economic factors predispose to hypertension, especially among blacks.

Much attention has also been given to social stress in animals. The well-known "pecking order" is a common source of stress in chickens, and dominance, especially among males, often causes conflict in various mammals.

In chickens subjected to various social groupings, resistance to different infections may be increased or decreased depending upon circumstances; this has been ascribed to nonspecific cross-resistance phenomena characteristic of the G.A.S. Allegedly, the resistance of poultry to certain infections coincides with a rise in blood corticoid levels.

In adult *Tupaia belangeri* (tree shrews), the confrontation of two males immediately results in fighting associated with loss of body weight, liver glycogen, blood hemoglobin and kidney weight, eventually resulting in fatal uremia. This allegedly shows "the great significance which social stress may have in the origin of renal disease—possibly in man as well as in animals." When a male *Tupaia* is defeated by a trained fighter, and separated from him by wire mesh to be protected from further attack, the conquered *Tupaia* exhibits adrenal enlargement with increased ascorbic acid concentrations. Plasma corticoid levels initially drop and then rise above normal. The defeated shrew dies after about twenty days of such "psychosocial stress." Curiously, *Tupaias* exposed to various other stressors also exhibit increased adrenal ascorbic acid, in contrast to most other species.

Studies on colonized squirrel monkeys indicated an elevation of 17-OHCS but unchanged catecholamine and 17-KS excretion. Dominant animals had the highest 17-OHCS and the lowest catecholamine levels, whereas their subordinates showed decreased 17-OHCS and increased catecholamine concentrations. 17-KS levels were related to dominance rank. It was concluded that high adrenocortical activity is perhaps necessary for the maintenance of dominance.

Social, Cultural, Family

(See also our earlier stress monographs, p. xiii)

Hallowell, A. I.: "Psychic stresses and culture patterns." *Am. J. Psychol.* 92: 1291-1310 (1936). B30,003/36

Interesting anthropologic study on the cultural stresses characteristic of various (mostly primitive) races of man.

Halliday, J. L.: *Psychosocial Medicine*, p.

278. New York: W W Norton, 1947.

B42,543/47

Popular volume on psychosocial medicine, with only occasional references to stress.

Romano, J. (ed.): *Adaptation*, p. 113. Ithaca, N.Y.: Cornell University Press, 1949. B90,996/49

Anthology of papers on adaptation to various environmental factors, with main emphasis upon emotional, intellectual and neurotic reactions. The G.A.S. is not mentioned.

Honigmann, J. J.: "Culture patterns and human stress. A study in social psychiatry." *Psychiatry* 13: 25-34 (1950).

D78,160/50

Caudill, W.: "Cultural perspectives on stress." *Symposium on Stress*, pp. 194-208. Washington, D.C.: Army Medical Service Graduate School, 1953. B89,530/53

The stressor effects of epidemics, wars, drastic technologic changes and economic or physiologic deprivation are very different in people of differing cultural and ethnic backgrounds.

Gerard, D. L., Phillips, L.: "Relation of social attainment to psychological and adrenocortical reactions to stress." *Arch. Neurol. Psychiatry* 69: 350-354 (1953).

G85,802/53

A pinball-like device, the Rotter aspiration board, was manipulated by an experimenter so that the subject became inept after a period of successful performance. Subjects with high social attainment showed better adaptive responses and less pronounced increases in corticoid excretion than others because they shifted their goals more realistically after failure.

Lanzetta, J. T.: "Group behavior under stress." *Hum. Relat.* 8: 29-52 (1955).

J10,234/55

An extensive study on the effects of situational stress on the behavior of individuals acting in small groups. [The significance of the term stress as used here is not defined but appears to be equated with the need to overcome difficulties (H.S.).]

Ames, M. M.: "Reaction to stress: a comparative study of nativism." *J. Anthropol.* 3: 17-30 (1957). J2,333/57

Studies on four cultures, Manus (Mead, 1956), Klamath, Modoc and Paviotso (Nash, 1937), and their responses to the stress of culture contact which took various forms of nativistic reactions. An attempt was made "to show the importance of the cultural variable in an analysis of stress and its consequences, and to present an analytic scheme by which nativistic movements can be compared and classified."

Caudill, W.: "Effects of Social and Cultural Systems in Reactions to Stress." *Preventive Medicine and Social Research* (pamphlet), p. 34. New York, 1958. J10,111/58

Review on the roles of stress factors in "developing areas of research of mutual in-

terest to social scientists and specialists in the fields of public health and preventive medicine," prepared under the auspices of the Committee on Preventive Medicine and Social Science Research. The author examines the responses of people living under the most diverse social and cultural conditions throughout the world. "The basic idea in this paper is that stress can manifest itself in one or more of a number of linked open systems, and that the strain on one system can be transmitted to others so that several become involved in the process of adaptation and defense" (51 refs.).

Hill, R.: "Social stresses on the family. I. Generic features of families under stress." *Social Casework* 39: 139-150 (1958).

J3,942/58

Interdisciplinary conference (jointly sponsored by the Family Service Association of America and the Elizabeth McCormick Memorial Fund) on the behavior of families under stress. Analysis of the respective roles of stressor agents, hereditary predisposition and interpersonal relationships that may affect adjustment to crises. Special emphasis is placed upon advice to social agencies regarding policies and practice.

Naroll, R.: "A tentative index of culture-stress." *Int. J. Soc. Psychiatry* 5: 107-116 (1959).

J11,585/59

A tentative index of culture stress in thirty-seven totally dissimilar societies and races, based upon comparison of four symptoms: protest suicide, defiant homicide, drunken brawling and witchcraft attribution. This report reviews the theoretical grounds for supposing each indicator to be a symptom of culture stress, and offers a formal set of definitions, rules and corollaries to delineate each. "The construction of the index is described and its validity and reliability discussed."

Scotch, N. A.: "A preliminary report on the relation of sociocultural factors to hypertension among the Zulu." *Ann. N.Y. Acad. Sci.* 84: 1000-1009 (1960). B42,444/60

Studies on the influence of urbanization upon the incidence of hypertension in Zulus of two African communities.

Barnett, S. A., Eaton, J. C., McCallum, H. M.: "Physiological effects of 'social stress' in wild rats. II. Liver glycogen and blood glucose." *J. Psychosom. Res.* 4: 251-260 (1960). C93,978/60

Hamburg, D. A.: "The relevance of recent evolutionary changes to human stress biology." In: Washburn, S., *Social Life of Early Man*, pp. 278-288. Chicago: Aldine, 1961.

J16,062/61

Torrance, E. P.: "A theory of leadership and interpersonal behavior under stress." In: Petrullo, L. and Bass, B. M., *Leadership and Interpersonal Behavior*, pp. 100-117. New York: Holt, Rinehart and Winston, 1961.

J10,652/61

A theory of the relationship between the G.A.S., leadership and interpersonal behavior is developed and summarized in the following table:

cultural Study of Culture Stress, p. 198. Glencoe, Ill.: Free Press, 1962.

E10,632/62

A monograph on culture stress with reference to the G.A.S. Special attention is given to witchcraft attribution as a symptom of culture stress, and an extensive bibliography on this topic is provided. There is also an index of culture stress, based upon this phenomenon and such others as drunken brawling, defiant homicide, and protest suicide among numerous peoples of different racial and ethnic backgrounds.

Fishman, J. R., Hamburg, D. A., Handlon, J. H., Mason, J. W., Sachar, E.: "Emotional

Stressors	Mediating Variables	Consequences
Failure of group mission or objectives; unrealistic goals		Panic, disorganization, lack of group-task efficiency
Attack by hostile individuals or groups		Apathy, lack of effort, loss of will-to-live
Difficult tasks; frequent repetition of events	DURATION	Excessive hostility, defiance, destructiveness, lawlessness
Sudden emergencies		Exhaustion, collapse, dissolution of group
Deprivation of physical, social, emotional, cognitive, and/or esthetic needs		Overcompensation, all-out effort, victory over superior forces
Discomfort from cold, heat, fatigue, lack of sleep	INTENSITY	Increased speed and group-task efficiency
Lack of group-task structure		Control of panic, maintenance of will-to-live (continue adaptation)
Rigid group-task structure		Excessive disharmony, interpersonal strife, "survival of fittest"
Presence of an incompetent, competitive, hostile, erratic, unpredictable, disloyal, or other deviate member	LEADERSHIP AND INTERPERSONAL BEHAVIOR	Lack of trust, mutiny
History of internal strife		Planning, good group decisions, cooperation
Inadequate training for individual and group tasks		Mutual support and self-sacrifice of members
Loss of a group member		Inventiveness and creativity

Reproduced from *Leadership and Interpersonal Behavior*, Fig. 1, p. 103, 1961, with permission of E. P. Torrance.

[Moderate stress tends to produce performance increments, whereas severe stress results in disorganized performance.]

Naroll, R.: *Data Quality Control: A New Research Technique. Prolegomena to a Cross-*

and adrenal cortical responses to a new experience. Effect of social environment." *Arch. Gen. Psychiatry* 6: 271-278 (1962).

J11,153/62

Graham, D. T., Stevenson, I.: "Disease as

response to life stress. I. The nature of the evidence." In: Lief, H. I. and Lief, V. F., *The Psychological Basis of Medical Practice*, pp. 115-136. New York, Evanston, Ill. and London: Hoeber Medical Division, 1963.

J8,246/63

A review of the literature and personal observations led to the conclusion that "there is a considerable body of evidence that social stresses are etiologically important in many diseases."

Farber, S. M., Mustacchi, P., Wilson, R. H. L. (eds.): *Man Under Stress*, p. 173. Berkeley: University of California Press, 1964.

E4,227/64

Proceedings of a symposium organized by the University of California. A group of physicians, surgeons and basic research men (among them Brock Chisholm, René Dubos, Seymour Farber, Stanley Sarnoff, Hans Selye, Paul Dudley White) discussed various aspects of stress, particularly in relation to the philosophy of life, social environment, cardiovascular disease, space medicine and so on. Most of the speakers refrained from highly technical discussions, but key references to scientific papers are given.

Rahe, R. H., Meyer, M., Smith, M., Kjaer, G., Holmes, T. H.: "Social stress and illness onset." *J. Psychosom. Res.* **8**: 35-48 (1964).

G18,232/64

Statistical studies suggest that various types of social stressors can predispose to tuberculosis, skin diseases and even inguinal hernia.

Konopka, G., Wallinga, J. V.: "Stress as a social problem." *Am. J. Orthopsychiatry* **34**: 536-542 (1964).

J23,543/64

Southwick, C. H.: "Peromyscus leucopus: an interesting subject for studies of socially induced stress responses." *Science* **143**: 55-56 (1964).

F35/64

The white-footed mouse is particularly suitable for the study of social interactions in stress physiology. It possesses "tolerance of very high cage densities among social congeners; marked behavioral intolerance among social strangers; exceptionally large adrenal glands; and adrenal and eosinophil responses sensitive to social disturbance."

Robey, A., Rosenwald, R. J., Snell, J. E.: "The runaway girl: a reaction to family stress." *Am. J. Orthopsychiatry* **34**: 762-767 (1964).

J23,545/64

Kahn, R. L., Wolfe, D. M., Quinn, R. P., Snoek, J. D.: *Organizational Stress: Studies*

in Role Conflict and Ambiguity

, p. 470. New York, London and Sydney: John Wiley & Sons, 1964.

E10,438/64

A monograph on organizational stress, particularly in social and industrial groups. There are some highly interesting data on the roles of conflict and ambiguity as they affect various personalities, but the word stress is used essentially as synonymous with difficulties and not in its now generally accepted medical meaning (about 125 refs.).

Back, K. W., Bogdonoff, M. D.: "Plasma lipid responses to leadership, conformity, and deviation." In: Leiderman, P. H. and Shapiro, D., *Psychobiological Approaches to Social Behavior*, pp. 24-42. Stanford, Cal.: Stanford University Press, 1964.

J11,130/64

Detailed review on plasma FFA as an objective indicator of stress in man, particularly in social interrelations. Plasma FFA levels are very sensitive to changes in autonomic nervous activity, and are especially useful in assessing situational demands and group interactions.

Barnett, S. A.: "Social stress. The concept of stress." In: Carthy, J. D. and Duddington, C. L., *Viewpoints in Biology*, Vol. 3, pp. 170-218. London: Butterworths, 1964.

J15,351/64

Kissel, S.: "Stress-reducing properties of social stimuli." *J. Pers. Soc. Psychol.* **2**: 378-384 (1965).

J8,704/65

Psychogenic stress, measured primarily by GSR, was induced by having subjects solve problems in a laboratory setting. Such situations were less stressful in the presence of a friend than before a stranger. However, "the hypothesis that individuals with strong affiliative motives will show a greater reduction in stress responses than will individuals with weak affiliative motives in the presence of another person was not confirmed."

Gross, W. B., Siegel, H. S.: "The effect of social stress on resistance to infection with *Escherichia coli* or *Mycoplasma gallisepticum*." *Poult. Sci.* **44**: 998-1001 (1965).

J11,921/65

Social stress was induced in chickens by moving males into cages with other birds according to a schedule which kept contact with previously encountered birds to a minimum. After two weeks their resistance to *E. coli* inoculation was increased, but their sensitivity to *Mycoplasma gallisepticum* remained unchanged.

Siegel, H. S., Gross, W. B.: "Social grouping, stress and resistance to coliform infection in cockerels." *Poult. Sci.* 44: 1530-1536 (1965). G37,829/65

In cockerels subjected to various types of social grouping "evidences of mild stress such as lower total leucocytes, increased adrenal weight, reduced bursa weight and/or reduced adrenal cholesterol concentrations were discernible." *E. coli* infection caused more severe leukopenia and raised plasma corticosterone, but under certain conditions there was also evidence of "cross" or 'nonspecific' resistance as suggested by Selye."

Reuck, A. de, Knight, J.: *Conflict in Society*, p. 467. London: J and A Churchill, 1966. E7,234/66

Symposium on conflict in animal and human societies. Stress, in the medical sense, is only occasionally touched upon.

Loudon, J. B.: "Private stress and public ritual." *J. Psychosom. Res.* 10: 101-108 (1966). G39,736/66

Speculations on stress in relation to public ritual, especially in developing countries. Contrary to the belief that people instinctively resist change, it was found that many natives welcome it as long as it does not disrupt their personal lives. The authors present several examples of rituals which presumably began as means of combatting stress.

Kasanen, A., Forsström, J.: "Social stress and living habits in the etiology of peptic ulcer." *Ann. Med. Intern. Fenn.* 55: 13-22 (1966). G39,590/66

Statistical studies on one hundred male patients with peptic ulcers of the stomach or duodenum showed that most of them were self-employed or working on temporary jobs. They were more frequently worried about their economic status, although they were no more in debt than were control patients. "The type of work was assessed to be the same in both groups. The peptic ulcer patients often neglected to take an annual holiday because of their work.... The way of life and character of peptic ulcer patients bear a great resemblance to the ways and nature of patients with coronary disease. Persons who feel that life is hectic and tension-producing and who consume stimulants on a liberal scale run a greater risk of contracting these diseases."

Dohrenwend, B. S., Dohrenwend, B. P.: "Stress situations, birth order, and psycho-

logical symptoms." *J. Abnorm. Psychol.* 71: 215-223 (1966). J8,713/66

Studies on college students suggest—in confirmation of earlier observations—that the stress of sensory deprivation is modified by birth order. "First borns show high levels of symptoms when their situation is such that, faced with an anxiety-arousing condition, they have difficulty finding others with whom to share the experience. Later borns show high levels of symptoms when, in the face of anxiety, they are forced into intense interaction with others."

Syme, S. L., Borhani, N. O., Buechley, R. W.: "Cultural mobility and coronary heart disease in an urban area." *Am. J. Epidemiol.* 82: 334-346 (1966). J8,893/66

The terms social and cultural mobility are used to designate the tendency of certain people to move frequently from one social setting or occupation to another. A study on a rural population showed that some factors associated with residential or sociocultural mobility are especially conducive to CHD. The relevant literature on urbanization, industrialization and so on is discussed (24 refs.).

Lazarus, R. S., Tomita, M., Opton, E. Jr., Kodama, M.: "A cross-cultural study of stress-reaction patterns in Japan." *J. Pers. Soc. Psychol.* 4: 622-633 (1966).

J15,487/66

Comparative studies on the responses of Japanese students and middle-aged adults to stressful motion picture films. "The pattern of mood and the degree and timing of reported distress were similar, and the defensive orientations reduced stress reaction for both subjective and physiological measures. However, the hypothesized interaction between MMPI-scaled personality disposition and defensive orientations was not observed. Unlike Americans, Japanese Ss' skin conductance was almost as high during the benign film as during the stressful film, and their conductance during the stressful film was poorly correlated to the specific stressful scenes."

Levi, L.: *Stress. Sources, Management, and Prevention* (Foreword by Hans Selye), p. 192. New York: Liveright, 1967.

E250/67

Very readable volume on the sources, management and prevention of distress, emphasizing both the purely medical and the psychologic aspects of everyday experiences.

- Wolff, K.: "Family conflicts and aging." *Northw. Med.* January, 1967, pp. 50-55. G44,145/67
 Theoretical discussion of the role of stress and the exhaustion of adaptation energy during family conflicts.
- Gross, W. B., Colmano, G.: "Further studies on the effects of social stress on the resistance to infection with Escherichia coli." *Poul. Sci.* **46**: 41-46 (1967). J11,174/67
 Social stress induced in poultry by isolation and regrouping in cages, increased resistance to certain infections with a concurrent rise in blood corticoid levels.
- Altman, I., Haythorn, W. W.: "The effects of social isolation and group composition on performance." *Hum. Relat.* **20**: 313-340 (1967). J10,969/67
 Extensive review on the effect of social isolation and crowding upon performance in man.
- Reeder, L. G., Chapman, J. M., Coulson, A. H.: "Socioenvironmental stress, tranquilizers and cardiovascular disease." *Proc. Int. Symp. on Psychotropic Drugs in Internal Medicine*, Baia Domizia, Italy, 1968. J17,504/68
 Chance, N. A.: "Implications of environmental stress. Strategies of developmental change in the North." *Arch. Environ. Health* **17**: 571-577 (1968). G61,519/68
 Lantis, M.: "Environmental stresses on human behavior. Summary and suggestions." *Arch. Environ. Health* **17**: 578-585 (1968). G61,520/68
 Review of the literature and personal observations on the importance of social stresses during adaptation to unusual environments with special reference to North American Indians and Eskimos, particularly in Canada.
- Dohrenwend, B. P., Dohrenwend, B. S.: *Social Status and Psychological Disorder: a Causal Inquiry*, p. 207. New York, London and Sydney: Wiley-Interscience, 1969. E10,660/69
 A monograph on social stressors in various ethnic groups (about 250 refs.)
- Rahe, R. H.: "Multi-cultural correlations of life change scaling: America, Japan, Denmark, and Sweden." *J. Psychosom. Res.* **13**: 191-195 (1969). J13,505/69
 Social stress among inhabitants of various countries was compared using the SRRQ.
- "Despite many cross-cultural differences, similarities between twentieth century cultures are far more pronounced" (15 refs.).
- Dohrenwend, B. P.: "Social status, stress and psychological symptoms." *Milbank Mem. Fed. Q.* **47**: 137-150 (1969). J13,506/69
 Brenner, M. H.: "Patterns of psychiatric hospitalization among different socioeconomic groups in response to economic stress." *J. Nerv. Ment. Dis.* **148**: 31-38 (1969) (30 refs.). J14,816/69
 Dohrenwend, B. S., Dohrenwend, B. P.: "Class and race as status-related sources of stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 111-140. Chicago: Aldine, 1970. B44,378/70
 McGrath, J. E.: "Settings, measures, and themes: an integrative review of some research on social-psychological factors in stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 58-96. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,317/70
 Review on psychosocial factors in human stress reactions.
- Mechanic, D.: "Some problems in developing a social psychology of adaptation to stress." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 104-123. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,319/70
 Theoretical outline for the study of psychosocial stress with special reference to adaptation.
- Steiner, I. D.: "Strategies for controlling stress in interpersonal situations." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 140-158. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,322/70
 Description of various psychologic techniques for coping with interpersonal stress situations.
- Haythorn, W. W.: "Interpersonal stress in isolated groups." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 159-176. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,323/70
 Brief lecture attempting to correlate the psychologic factors in interpersonal stress with the somatic aspects of the G.A.S.

Dodge, D. L., Martin, W. T.: *Social Stress and Chronic Illness: Mortality Patterns in Industrial Society*, p. 331. Notre Dame, Ind. and London: Notre Dame University Press, 1970. E10,654/70

Monograph attempting to evaluate modern concepts of systemic stress within the body in relation to social stresses.

Matsumoto, Y. S.: "Social stress and coronary heart disease in Japan." *Milbank Mem. Fed. Q.* **48**: 9-36 (1970).

G73,150/70

The incidence of arteriosclerotic CHD among the Japanese is extremely low as compared to its incidence among white North Americans. "Although the diet factor remains dominant in current thinking, the stress hypothesis merits the most intensive probing as alternate or associated explanations of observed relations and differentiations" (87 refs.).

Levine, S., Scotch, N. A. (eds.): *Social Stress*, p. 295. Chicago: Aldine, 1970.

E10,711/70

An anthology on social stress with contributions by numerous specialists.

Levine, S., Scotch, N. A.: "Social stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 1-16. Chicago: Aldine, 1970.

E10,712/70

Introductory chapter to an anthology with frequent references to the G.A.S.

Croog, S. H.: "The family as a source of stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 19-53. Chicago: Aldine, 1970.

E10,713/70

Teele, J. E.: "Social pathology and stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 228-256. Chicago: Aldine, 1970.

E10,716/70

Levine, S., Scotch, N. A.: "Perspectives on stress research." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 279-290. Chicago: Aldine, 1970.

E10,717/70

Martin, R. D.: "Social Stress." *New Society* December 17, 1970, pp. 1086-1088.

J13,723/70

McMurray, L.: "Emotional stress and driving performance: the effect of divorce." *Behav. Res. Highway Safety* **1**: 100-114 (1970).

J16,599/70

Harmon, D. K., Masuda, M., Holmes, T. H.: "The social readjustment rating scale: a cross-cultural study of Western Europeans

and Americans." *J. Psychosom. Res.* **14**: 391-400 (1970). J13,507/70

The SRRQ is described in detail. In French translation it was administered to French, Belgian and Swiss subjects of widely different cultural backgrounds. In comparison with Americans "a high correlation of relative rank ordering of readjustment required by life events was observed ($r_s = 0.89$), but differences in cultures and living conditions were reflected in the SRSS obtained."

Weiss, J. H.: "Birth order and physiological stress response." *Child Dev.* **41**: 461-470 (1970). J21,251/70

Born, D. O.: "Psychological adaptation and development under acculturative stress: toward a general model." *Soc. Sci. Med.* **3**: 529-547 (1970). J21,191/70

Scott, R., Howard, A.: "Models of stress." In: Levine, S. and Scotch, N., *Social Stress*, pp. 259-278. Chicago: Aldine, 1970.

J13,722/70

Analysis of prototypes ("models") of social stress situations in relation to the G.A.S.

Crider, A.: "Experimental studies of conflict-produced stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 165-188. Chicago: Aldine, 1970 (above 50 refs.).

J12,698/70

Sos, J., Gati, T., Csalay, L., Dési, I.: *Pathology of Civilization Diseases*, p. 174. Budapest: Akadémia Kiadó, 1971. E8,933/71

Many maladies largely due to stress are considered to be "diseases of civilization." A special section is devoted to the role of corticoids and stress in the development of peptic ulcers.

Eisenstadt, S. N.: "Problems in theories of social structure, personality and communication in their relation to situations of change and stress." In: Levi, L., *Society, Stress and Disease*. Vol. 1. *The Psychosocial Environment and Psychosomatic Diseases*, pp. 79-84. London, New York and Toronto: Oxford University Press, 1971. E9,306/71

Averill, J. R., Opton, E. M. Jr., Lazarus, R. S.: "Cross-cultural studies of psychophysiological responses during stress and emotion." In: Levi, L., *Society, Stress and Disease*. Vol. 1. *The Psychosocial Environment and Psychosomatic Diseases*, pp. 110-124. London, New York and Toronto: Oxford University Press, 1971. E9,309/71

"Society, stress, and disease." *WHO Chron.* **25**: 168-178 (1971). G85,103/71

Brief review on a meeting of the WHO. Special attention is given to psychosomatic derangements due to social changes.

Corson, S. A.: "The lack of feedback in today's societies. A psychosocial stressor." In: Levi, L., *Society, Stress and Disease*. Vol. 1. *The Psychosocial Environment and Psychosomatic Diseases*, pp. 181-189. London, New York and Toronto: Oxford University Press, 1971. E9,311/71

Predominantly philosophic considerations on the importance of feedback systems in combating psychosocial stressors in today's society.

Naumenko, E. V., Popova, N. K., Starygin, A. G.: "Pituitary-adrenal system of animals in groups and in isolation." *Zh. Obshch. Biol.* **32**: 731-739 (1971) (Russian).

J21,443/71

"The reaction of the pituitary-suprarenal system to seasonal influences in the isolated rats differed markedly from that in the rats kept in groups; in the former the level of corticosterone in May sharply increased as compared with that in winter, while in the latter it decreased." It is concluded that reactivity to stressors is weakened during the summer. In rats with the highest index of dominance, plasma corticosterone levels were particularly low during the winter.

Wan, T.: "Status stress and morbidity: a sociological investigation of selected categories of work-limiting chronic conditions." *J. Chron. Dis.* **24**: 453-468 (1971).

G86,863/71

Graham, S., Snell, L. M., Graham, J. B., Ford, L.: "Social trauma in the epidemiology of cancer of the cervix." *J. Chron. Dis.* **24**: 711-725 (1971).

J20,331/71

Contrary to some data in the earlier literature, the incidence of cervical cancer was not found to be dependent upon social stressors in a group of 447 women of various backgrounds.

Eisler, R. M., Polak, P. R.: "Social stress and psychiatric disorder." *J. Nerv. Ment. Dis.* **153**: 227-233 (1971). G87,329/71

In patients, various "situational or social stressors" can precipitate psychologic disorders, but the subject's predisposition will determine whether the resulting derangement will be of a schizophrenic, depressive, or other type.

Beck, J. D., Cassel, J. C.: "Role inconsistency and health status." *Soc. Sci. Med.* **6**: 737-751 (1972).

J19,667/72

Bryant, M. J.: "The social environment: behaviour and stress in housed livestock." *Vet. Rec.* **90**: 351-358 (1972).

J20,517/72

Fine, R.: "The stress of peace." In: Parker, R. S., *The Emotional Stress of War, Violence, and Peace*, pp. 92-100. Pittsburgh, Pa.: Stanwix House, 1972.

E10,442/72

Discussion of the forces in peacetime which lead to periodic outbreaks of war and usually have their roots in frustration. The term stress is used essentially as a synonym for nervous tension, and not in its accepted medical sense.

Allen, H. M.: "Gastrointestinal erosions in wild rats subjected to 'social stress'." *Life Sci. [I]* **11**: 351-356 (1972). G90,995/72

Leshner, A. I., Candland, D. K.: "Endocrine effects of grouping and dominance rank in squirrel monkeys." *Physiol. Behav.* **8**: 441-445 (1972). G90,599/72

17-OHCS, 17-KS and total catecholamine excretions were used as indices of social stress in colonized and isolated squirrel monkeys. "Compared to the isolated animals, the colonized monkeys showed elevated 17-OHCS but unchanged catecholamine and 17-KS levels. In the colonized group the dominant animals had the highest 17-OHCS levels and the lowest catecholamine levels, while the subordinate animals showed lower 17-OHCS levels and elevated catecholamine levels. 17-KS levels were related to dominance rank by a J-shaped function." Presumably, high adrenocortical output is necessary for the maintenance of dominance. These results on primates differ from most studies on rodents, which use other methods to determine dominance.

Holst, D. von: "Renal failure as the cause of death in *Tupaia belangeri* exposed to persistent social stress." *J. Comp. Physiol.* **78**: 236-273 (1972). G93,301/72

When two adult male tree shrews are introduced, they immediately begin to fight. Subsequently, merely seeing the victor induces stress manifestations in the defeated *Tupaia*. This is associated with a constant decline in body weight, liver glycogen, blood hemoglobin and kidney weight, eventually resulting in fatal uremia. "The

evidence from natural populations, when examined along with the findings from tree-shrews, show the great significance which social stress may have in the origin of renal disease—possibly in man as well as in animals."

Holst, D. von: "Die Funktion der Nebennieren männlicher Tupaia belangeri. Nebennierengewicht, Ascorbinsäure und Glucocorticoide im Blut bei kurzem und andauerndem soziopsychischem Stress" (The function of the adrenals in male Tupaia belangeri. Adrenal weight, ascorbic acid and glucocorticoids in the blood after acute and prolonged psychosocial stress). *J. Comp. Physiol.* **78**: 289–306 (1972). G93,303/72

Male *Tupaias*, after being defeated by a trained fighter, were separated from him by a wire mesh so that they could continually see the victor without being attacked. The fight was repeated every one to two days. Under these conditions, the defeated *Tupaias* died in less than twenty days owing to the "psychosocial stress" associated with adrenal enlargement and increased ascorbic acid concentrations. Plasma glucocorticoid levels initially dropped and then rose above normal. An elevation of adrenal ascorbic acid also occurred in *Tupaias* exposed to various other stressors, in contrast to the characteristic depletion in most other species.

Allman, L. R., Taylor, H. A., Nathan, P. E.: "Group drinking during stress: effects on drinking behavior, affect, and psychopathology." *Am. J. Psychiatry* **129**: 669–678 (1972). G96,807/72

A group of three chronic alcoholics "drank most when stress and socialization periods coincided; they drank least when stress and periods of isolation occurred together."

Levi, L. (ed.): *Stress and Distress in Response to Psychosocial Stimuli* (Foreword by Hans Selye), p. 166. Oxford, New York, Toronto, Sydney and Braunschweig: Pergamon Press, 1972. H53,062/72

Very thoughtful analysis of the literature and of the author's personal observations on the G.A.S. in relation to psychosocial stimuli. Detailed description of methodology, including hormone determinations. Special emphasis is placed upon pleasant and unpleasant psychosocial stimuli, stress reactions to sexual stimulation and the relationship between psychologic and physiologic reactions during acute and chronic exposure to stressors in man

Levi, L.: "A synopsis of ecology and psychiatry: some theoretical psychosomatic considerations, review of some studies and discussion of preventive aspects." *Lab. Clin. Stress Res.* (Stockholm) Rep. No. 30: 1–17 (1972). J4,975/72

Theoretic considerations on the role of social and ecologic factors in the development of stress in human society.

Grotjahn, M., Mensen, H.: "Was ist Stress?" (What is stress?). *Hippokrates* **44**: 355–367 (1973). J17,047/73

Review on the sociologic implications of the stress concept.

Bronner, K., Levi, L.: *Stress in Arbeitsleben. Ursachen und Folgen. Möglichkeiten zur Vorbeugung und Heilung* (Stress in everyday working conditions. Causes and consequences. Possibilities for prevention and cure), p. 174. Göttingen, Zürich and Frankfurt: Musterschmidt, 1973. E10,281/73

Very readable, popularized translation of the original Swedish monograph which appeared under the same title.

Roghmann, K. J., Haggerty, R. J.: "Daily stress, illness, and use of health services in young families." *Pediatr. Res.* **7**: 520–526 (1973). J5,991/73

Statistical studies and speculations suggest that family crises increase morbidity, precipitating demands for medical services.

Frankenhaeuser, M.: "Sympathetic-adrenomedullary activity, behaviour, and the psychosocial environment." In: Venables, P. H. and Cristie, M. J., *Research in Psychophysiology*. New York, London and Sydney: John Wiley & Sons, 1973. J5,999/73

Review on the effects of the psychosocial environment upon catecholamine production in man.

Harburg, E., Erfurt, J. C., Chape, C., Hauenstein, L. S., Schull, W. J., Schork, M. A.: "Socioecological stressor areas and black-white blood pressure: Detroit." *J. Chron. Dis.* **26**: 595–611 (1973). J8,243/73

Comparative studies in high and low stressed areas of Detroit revealed that social and economic stressors definitely predispose to increased blood pressure, especially in blacks.

Dohrenwend, B. S.: "Social status and stressful life events." *J. Pers. Soc. Psychol.* **28**: 225–235 (1973). J24,104/73

Allodi, F. A., Coates, D. B.: "Social stress, psychiatric symptoms and help-seeking pat-

- ters." *Can. Psychiatr. Assoc. J.* **18**: 153-158 (1973). J2,498/73 (Selye)" but no definite recommendation is made (12 refs.).
- Bruppacher, R.: "Somatische Auswirkung sozialer Ereignisse: das Beispiel der asymptomatischen Bakteriurie der Frau" (Somatic consequences of social events: the example of asymptomatic bacteriuria in women). *Therap. Umsch.* **30**: 112-116 (1973). J20,520/73
- Davidson, P. O., Kelley, W. R.: "Social facilitation and coping with stress." *Brit. J. Soc. Clin. Psychol.* **12**: 130-136 (1973). J19,552/73
- Bugard, P.: *Stress, Fatigue et Dépression. (L'homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue and depression. Man and the aggression of daily life), Vol. 1, p. 294, Vol. 2, p. 302. Paris: Doin Edit., 1974. E10,487/74
- Extensive discussion of psychosocial problems in daily life.
- Levi, L., Andersson, L.: *Population, Environment and Quality of Life*, p. 142. Stockholm: Goteborgs Offsettryckeri AB, 1974. E10,629/74
- Effects of social factors, crowding, pollution and urbanization upon stress-induced diseases (several hundred refs.).
- Ierodiakonou, C. S., Kokantzis, N., Fekas, L.: "Stressful factors in Greek life leading to illness." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 189-194. Springfield, Ill.: Charles C Thomas, 1974 (10 refs.). E10,690/74
- Wilkins, W. L.: "Social stress and illness in industrial society." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 242-254. Springfield, Ill.: Charles C Thomas, 1974. E10,694/74
- Discussion of the various definitions of stress. Special attention is given to "stress
- Myers, J. K., Lindenthal, J. J., Pepper, M. P.: "Social class, life events, and psychiatric symptoms: a longitudinal study." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 191-205. New York, London and Sydney: John Wiley & Sons, 1974. E10,790/74
- Hinkle, L. E. Jr.: "The effect of exposure to culture change, social change, and changes in interpersonal relationships on health." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 9-44. New York, London and Sydney: John Wiley & Sons, 1974. E10,780/74
- Kiritz, S., Moos, R. H.: "Physiological effects of social environments." *Psychosom. Med.* **36**: 96-114 (1974). J18,916/74
- Review on stress in relation to the social environment (91 refs.).
- Insel, P. M., Moos, R. H.: "Psychological environments. Expanding the scope of human ecology." *Am. Psychol.* **29**: 179-188 (1974). J19,056/74
- Newman, L. R.: "Family stresses in the 1970's: What does the pediatrician have to learn and transmit?" *Clin. Pediatr.* **13**: 987-989 (1974). J18,887/74
- Chilman, C. S.: "Home: safe harbor or storm center?" *Stress. Blue Print for Health* **25** No. 1: 42-47. Chicago: Blue Cross Association, 1974. E10,817/74
- Levi, L.: "Stress, distress and psychosocial stimuli." In: McLean, A., *Occupational Stress*, pp. 31-46. Springfield, Ill.: Charles C Thomas, 1974. E10,886/74
- El-Islam, M. F.: "Culture bound neurosis in Qatari women." *Soc. Psychiatr.* **10**: 25-29 (1975). J21,684/75

Crowding

A great many observations on animals and man show that at least under certain circumstances crowding may act as a powerful stressor and produce typical manifestations of the G.A.S., such as adrenal enlargement and hyperactivity, thymicolympathic and gonadal involution with decreased fertility, a special tendency toward the formation of peptic ulcers and sensitivity to infections. Allegedly, crowding can help to maintain normal population density.

In mice and rats, crowding at an early age may even cause lasting changes in the offspring of surviving females, perhaps as a result of deficient lactation.

The direct effects of crowding may be complicated by social rank within a community. For example, among wild mice, low-ranking subjects have the largest adrenals, possibly because they are subjected to more physical and psychologic stress than their "social superiors." Likewise, it has been maintained that grouping of previously isolated mice resulted in the greatest adrenal hypertrophy among the subordinate individuals, and that this change could not be related to the extent of injury caused by fighting.

In chickens, overcrowding definitely diminishes egg production and concurrently produces adrenal hypertrophy, although the two do not run strictly parallel. In any event, this factor is of practical importance in raising poultry.

Especially instructive observations have been made on wild rabbits showing that population growth is significantly inhibited in overcrowded colonies. Similar findings have been reported for a large number of other rodents as well as for dogs, guinea pigs, monkeys, woodchucks, deer and man.

The fact that, in rats, under certain conditions, production of gastric ulcers by restraint was inhibited by crowding may have been related to the rise in ambient temperature of animals kept close together.

The curious phenomenon of "group toxicity" has been described in crowded colonies of mice. It is characterized by emotional paroxysms and high mortality, with myocardial necrosis following treatment with catecholamine precursors and MAO inhibitors. This phenomenon could be prevented by reserpine or chlorpromazine. Allegedly, crowding is a more effective stressor for male than for female mice.

A population study on human behavior under crowded conditions suggested that men become more competitive, somewhat more severe, and like each other less, whereas women tend to be more cooperative and lenient and like each other more. On the other hand, a study on young Swedish soldiers, confined to a small shelter for fifty-two hours, revealed no significant adverse effects upon their social compatibility or psychomotor performance (as judged by pistol shooting skill).

An especially interesting study has been done among hunter-gatherers in Botswana and South-West Africa. The !Kung Bushmen live under crowded conditions by choice; the population density in the total area is 1 person per 10 square miles, and yet they form camps in which they occupy only about 188 square feet per person. Typically, their huts are so near that people sitting at different hearths can hand items back and forth without getting up. Yet their blood pressure is low, even at an advanced age, and their serum cholesterol levels are among the lowest in the world. Apparently, "residential crowding alone does not produce symptoms of psychological stress;" in fact, it seems that interpersonal contact "is supportive rather than stressful" as long as the people know they have the space to get away from each other whenever they so desire. Of course, interpretation of this study is extremely difficult since the tribesmen do not suffer from air pollution, competitive strife, noise and the many other stressors associated with urbanization in Western society.

Crowding

(See also our earlier stress monographs, p. xiii)

Christian, J. J.: "The adreno-pituitary system and population cycles in mammals." *J. Mammal.* 31: 247-259 (1950).

B51,490/50

Review on population cycles in various mammals. These can be largely explained by "exhaustion of the adreno-pituitary system subsequent to the stresses inherent in a high population level, severe climatic conditions, and the demands of the spring breeding season."

Bullough, W. S.: "Stress and epidermal mitotic activity. I. The effects of the adrenal hormones." *J. Endocrinol.* 8: 265-274 (1952). B72,094/52

In rats, the stress of overcrowding causes a more pronounced increase in the size of the adrenal medulla than of the cortex. Simultaneously, the epidermal mitotic rate decreases by 60 percent. "It is suggested that the antimitotic effects of stress may be due to a high rate of secretion of either, or both, of these adrenal [cortical and medullary] hormones." All the reactions are regarded as manifestations of the G.A.S.

Christian, J. J.: "Effect of population size on the adrenal glands and reproductive organs of male mice in populations of fixed size." *Am. J. Physiol.* 182: 292-300 (1955).

C8,490/55

In male mice kept under crowded conditions, adrenal enlargement with involution of the thymus, testes, preputial glands and seminal vesicles is attributed to "density-dependent stress."

Tobach, E., Bloch, H.: "Effect of stress by crowding prior to and following tuberculous infection." *Am. J. Physiol.* 187: 399-402 (1956). J5,559/56

Exposure of mice to the stressor effect of crowding can enhance resistance to subsequent tuberculous infection.

Christian, J. J.: "Reserpine suppression of density-dependent adrenal hypertrophy and reproductive hypoendocrinism in populations of male mice." *Am. J. Physiol.* 187: 353-356 (1956). C27,420/56

Davis, D. E., Christian, J. J.: "Relation of adrenal weight to social rank of mice." *Proc. Soc. Exp. Biol. Med.* 94: 728-731 (1957). C32,828/57

In male "wild-strain mice" kept in groups, there is a significant relationship between adrenal weight and social rank. High-ranking mice have smaller adrenals than low-ranking ones, presumably because the latter group is "subjected to more physical and psychological stressing stimuli."

Christian, J. J.: "A review of the endocrine responses in rats and mice to increasing population size including delayed effects on offspring." *Naval Med. Res. Inst.* August 6, 1957, pp. 443-462. C53,409/57

Rats and mice living under crowded conditions show many manifestations of stress, including a decrease in fertility which may

act as a regulator of population density to maintain an optimal level. Crowding can also cause lasting changes in the offspring of surviving females, probably due to lactational deficiencies.

Christian, J. J., Lemunyan, C. D.: "Adverse effects of crowding on lactation and reproduction of mice and two generations of their progeny." *Endocrinology* 63: 517-529 (1958). C59,942/58

Christian, J. J.: "Lack of correlation between adrenal weight and injury in grouped male albino mice." *Proc. Soc. Exp. Biol. Med.* 101: 166-168 (1959). C68,931/59

Grouping previously isolated mice caused adrenal hypertrophy which was least marked in dominant and most prominent in subordinate animals. Yet the amount of scarring and adrenal weight after such grouping showed no correlation that could be attributed to the degree of injury caused by fighting.

Siegel, H. S.: "The relation between crowding and weight of adrenal glands in chickens." *Ecology* 40: 495-498 (1959). J10,863/59

In laying chickens, crowding increases the adrenal weight, although pituitary and thyroid weights remain unaffected.

Siegel, H. S.: "Egg production characteristics and adrenal function in White Leghorns confined at different floor space levels." *Poult. Sci.* 38: 893-898 (1959). J10,896/59

Crowding definitely diminished egg production in chickens. This was usually accompanied by adrenal hypertrophy, although the two changes did not strictly parallel each other. Presumably, both changes were due to stress.

Griffiths, M. E., Calaby, J. H., McIntosh, D. L.: "The stress syndrome in the rabbit." *C. S. I. R. O. Wildl. Res.* 5: 134-148 (1960). D12,295/60

A review of the literature and observations on wild rabbits indicate that overcrowding of rodents in confined colonies can inhibit population growth—possibly through a stress response, although other factors must be considered. [Curiously, the extensive studies of Kracht on acute hyperthyroidism in stressed rabbits are not even mentioned (H.S.).]

Christian, J. J.: *Naval Med. Res. Inst. Lect. Rev. Ser.* 60/2: 1-49 (1960). J12,691/60

Christian, J. J.: "Phenomena associated

with population density." *Proc. Natl. Acad. Sci. U.S.A.* **47**: 428-449 (1961).

D79,921/61

Crowding produces typical manifestations of the G.A.S. in a variety of species, including *Mus*, *Rattus*, *Microtus*, *Clethrionomys*, *Marmota*, *Oryctolagus*, *Lepus*, *Sylvilagus*, *Cervus*, *Myocastor*, dog, guinea pig, monkey and man. The diminution in gonadotropic hormone production that is associated with increased ACTH secretion characteristic of stress, is an important factor in regulating population density (73 refs.).

Keeley, K.: "Prenatal influence on behavior of offspring of crowded mice." *Science* **135**: 44-45 (1962). D16,058/62

Calhoun, J. B.: "Population density and social pathology." *Sci. Am.* **206**: 139-148 (1962). J11,144/62

Popular article on the role of stress as a cause of abnormal behavior patterns in rats kept under crowded conditions.

Bronson, F. H., Eleftheriou, B. E.: "Adrenal responses to crowding in *Peromyscus* and C57BL/10J mice." *Physiol. Zool.* **36**: 161-166 (1963). D63,122/63

Calhoun, J. B.: "The social use of space." In: Mayer, W. V. and van Gelder, R. G., *Physiological Mammalogy*, Vol. 1, pp. 1-187. New York and London: Academic Press, 1963. E313/63

Very detailed review and statistical analysis of information on the physiologic effects of crowding and the social use of space among animals and man (about 50 refs.).

Christian, J. J.: "Endocrine adaptive mechanisms and the physiologic regulation of population growth. Part 1-2." In: Mayer, W. V. and van Gelder, R. G., *Physiological Mammalogy*, Vol. 1, pp. 189-353. New York and London: Academic Press, 1963. E314/63

Extensive review on endocrine adaptive mechanisms and the effects of crowding upon population growth, with special reference to the G.A.S. (several hundred refs.).

Christian, J. J.: "The pathology of overpopulation." *Milit. Med.* **128**: 571-603 (1963). E22,467/63

A review of the literature on the effects of overpopulation in various species. In the mouse, woodchuck (*Marmota monax*) and Japanese deer (*Cervus nippon*), increased population density elicits structural and functional adrenal hyperactivity which—depend-

ing upon the species—is associated with decreased fertility, aggressiveness or renal glomerular disease.

Bashenina, N.: "Importance of the theory of stress for the understanding of population dynamics of small rodents." *Bull. Mosk. Naturforsch. Gesamte. Biol.* **68**: 5-13 (1963). J12,746/63

Bernardis, L. L., Skelton, F. R.: "Effect of crowding on hypertension and growth in rats bearing regenerating adrenals." *Proc. Soc. Exp. Biol. Med.* **113**: 952-954 (1963). E28,035/63

Christian, J. J.: "Pathopoietic consequences of increasing population." *Proc. R. Soc. Med.* **57**: 169-174 (1964). F29,985/64

Dickson, A. D.: "Delay of implantation in super-ovulated mice subjected to crowded conditions." *Nature* **201**: 839-840 (1964). F9,776/64

Soave, O. A.: "Reactivation of rabies virus in a guinea pig due to the stress of crowding." *Am. J. Vet. Res.* **25**: 268-269 (1964). J16,324/64

Welch, B. L.: "Psychophysiological response to the mean level of environmental stimulation: A theory of environmental integration." *Symposium on the Medical Aspects of Stress in the Military Climate*, pp. 39-99. Washington, D.C.: GPO, 1965. G41,327/65

Review on the relationship between stress and Mean Level of Environmental Stimulation (MLES). Detailed survey of the literature and personal observations on the effects of isolation with sensory deprivation or crowding upon nonspecific responsiveness. Particular attention is given to the influence of the Ascending Reticular Activating System (ARAS) upon the hypothalamus and through it upon ACTH, glucocorticoid and catecholamine discharges. The numerous feedbacks in several mechanisms involved in arousal and relaxation are critically analyzed (205 refs.).

Robert, A., Phillips, J. P., Nezamis, J. E.: "Production, by restraint, of gastric ulcers and of hydrothorax in the rat." *Gastroenterology* **51**: 75-81 (1966). G40,473/66

In rats, restraint produced gastric ulcers and hydrothorax within four to six hours. Overnight fasting prevented the hydrothorax and reduced the gastric ulcerations (contrary to previous reports). Restraint ulcers and

hydrothorax "were also inhibited by crowding of the animals, a rise in ambient temperature, or administration of prednisolone."

Zalis, E. G., Kaplan, G.: "The effect of aggregation on amphetamine toxicity in the dog." *Arch. Int. Pharmacodyn. Ther.* **159**: 196-199 (1966). F62,080/66

Chernov, H. I., Furness, P., Partyka, A. D., Plummer, A. J.: "Age, confinement and aggregation as factors in amphetamine group toxicity in mice." *J. Pharmacol. Exp. Ther.* **154**: 346-349 (1966). F73,732/66

Sethy, V. H., Sheth, U. K.: "Factors affecting amphetamine toxicity in aggregated mice." *Indian J. Med. Sci.* **22**: 364-379 (1968). G60,792/68

Halpern, B., Drudi-Baracco, C., Bessirard, D., Martineau, F.: "Brain monoamines and thyroid hormones on the emotional stress induced by sympathomimetic agents in aggregated animals." In: Jasmin, G., *Endocrine Aspects of Disease Processes*, pp. 47-73. St. Louis, Mo.: Warren H Green, 1968.

E7,616/68

In mice, crowding elicited the syndrome of "group toxicity," characterized by emotional paroxysms and high mortality with myocardial necrosis, following administration of certain catecholamine precursors and MAO inhibitors. Reserpine and chlorpromazine inhibited this phenomenon, whereas thyroid hormones increased sensitivity to it.

Bronson, F. H., Chapman, V. M.: "Adrenal-oestrous relationships in grouped or isolated female mice." *Nature* **218**: 483-484 (1968). F98,042/68

When grouped together in a room with no males, female mice exhibit suppression of estrous cycle, increase of adrenal weights and no change in plasma corticosterone concentrations. "It can be concluded that social stressors do not provide a basis for explaining the suppression of oestrus found in groups of females." The literature suggests that crowding acts as a stressor in males, but this has not been definitely established for females.

Bliss, E. L., Ailion, J.: "Response of neurogenic amines to aggregation and strangers." *J. Pharmacol. Exp. Ther.* **168**: 258-263 (1969). H15,845/69

Aggregation of mice unaccustomed to each other caused a decrease in brain NEP and an acceleration of its catabolism. 5-HT levels remained unchanged, although 5-HIAA con-

centrations in the brain rose, indicating an increased catabolism of 5-HT. "Dopamine levels in brain and its catabolism were unaffected. At the same time no changes in norepinephrine metabolism could be detected in the adrenal, heart or spleen. The intermingling of strangers without aggregation also decreased brain norepinephrine. A more severe stress of footshock to rats not only diminished brain norepinephrine but also radically reduced catecholamine levels in the adrenal and spleen. These observations suggest that emotional disturbances activate the norepinephrine and serotonin systems in brain."

Lidberg, L., Seeman, K.: "Psychomotor performance before and after confinement in a shelter." *Lab. Clin. Stress Res.* (Stockholm) Rep. No. 9: 1-7 (1969). G74,277/69

In young Swedish infantrymen, confinement to a shelter for fifty-two hours did not consistently or markedly influence psychomotor performance as judged by pistol shooting skill.

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Behaviour and social interaction in an experimental shelter." *Lab. Clin. Stress Res.* (Stockholm) Rep. No. 11: 1-16 (1969). G74,276/69

Young soldiers of the Swedish infantry were confined to a shelter for a fifty-two hour period. "Absence of individual role or sub-group differentiation, subdued activity, and generally positive and bland interpersonal perceptions were noted. Adverse reactions were minor and infrequent."

Fröberg, J., Karlsson, C. G., Lidberg, L., Seeman, K.: "Effects of confinement in an experimental shelter on behaviour, social interaction and psychomotor performance." *Försvarsmed.* **6**: 254-262 (1970).

G85,149/70

In healthy young Swedish soldiers confined to a shelter for fifty-two hours under crowded conditions, objective evidence of stress was minimal.

Friedman, S. B., Glasgow, L. A., Ader, R.: "Differential susceptibility to a viral agent in mice housed alone or in groups." *Psychosom. Med.* **32**: 285-299 (1970).

G76,988/70

"In two strains of mice, individually housed animals were more susceptible to encephalomyocarditis (EMC) virus than those housed in groups." Interferon and antibody levels following virus inoculation did

not explain the differences in resistance. Corticosterone levels at the peak of the circadian rhythm were higher in individually housed mice.

Naumenko, E. V., Popova, N. K., Starygin, A. G.: "Pituitary-adrenal system of animals in groups and in isolation." *Zh. Obshch. Biol.* **32**: 731-739 (1971) (Russian).

J21,443/71

"The reaction of the pituitary-suprarenal system to seasonal influences in the isolated rats differed markedly from that in the rats kept in groups; in the former the level of corticosterone in May sharply increased as compared with that in winter, while in the latter it decreased." It is concluded that reactivity to stressors is weakened during the summer. In rats with the highest index of dominance, plasma corticosterone levels were particularly low during the winter.

Mitchell, R. E.: "Some social implications of high density housing." *Am. Sociol. Rev.* **36**: 18-29 (1971).

J21,162/71

Champlin, A. K.: "Suppression of oestrus in grouped mice: the effects of various densities and the possible nature of the stimulus." *J. Reprod. Fertil.* **27**: 233-241 (1971).

H47,870/71

Ehrlich, P., Freedman, J.: "Population, crowding and human behaviour." *New Scientist Sci. J.* **50**: 10-14 (1971).

J13,725/71

Studies in urban areas led to the conclusion that "under crowded conditions, men become more competitive, somewhat more severe, and like each other less, whereas women become more cooperative and lenient and like each other more."

Leshner, A. I., Candland, D. K.: "Endocrine effects of grouping and dominance rank in squirrel monkeys." *Physiol. Behav.* **8**: 441-445 (1972).

G90,599/72

17-OHCS, 17-KS and total catecholamine excretions were used as indices of social stress in colonized and isolated squirrel monkeys. "Compared to the isolated animals, the colonized monkeys showed elevated 17-OHCS but unchanged catecholamine and 17-KS levels. In the colonized group the dominant animals had the highest 17-OHCS levels and the lowest catecholamine levels, while the subordinate animals showed lower 17-OHCS levels and elevated catecholamine levels. 17-KS levels were related to dominance rank by a J-shaped function." Presum-

ably, high adrenocortical output is necessary for the maintenance of dominance. These results on primates differ from most studies on rodents, which use other methods to determine dominance.

Daniels-Severs, A., Goodwin, A., Keil, L. C., Vernikos-Danellis, J.: "Effect of chronic crowding and cold on the pituitary-adrenal system: responsiveness to an acute stimulus during chronic stress." *Pharmacology* **9**: 348-356 (1973).

H77,763/73

Kutner, D. H. Jr.: "Overcrowding: human responses to density and visual exposure." *Hum. Relat.* **26** No. 1: 31-50 (1973).

E78,120/73

Draper, P.: "Crowding among hunter-gatherers: The !Kung Bushmen." *Science* **182**: 301-303 (1973).

H76,199/73

"Highly crowded living conditions exist among the !Kung Bushmen, hunter-gatherers who live on the edges of the Kalahari Desert in Botswana and South-West Africa. The !Kung appear to be crowded by choice, and biological indicators of stress are absent. Data indicate that residential crowding alone does not produce symptoms of pathological stress." The population density is approximately one person per 10 square miles, and hence among the lowest in the world. Yet they form camps in which they occupy only about 188 square feet per person. Typically, their huts are so close that people sitting at different hearths can hand items back and forth without getting up. They are hypotensive and their blood pressures do not rise with age; serum cholesterol levels are among the lowest in the world. "The !Kung are unfazed by the press and are able to maintain a multi-sensory, diffuse contact with each other that is supportive rather than stressful."

Gärtner, K., Reznik-Schüller, H., Reznik, G.: "The influence of overcrowding on spermatogenesis, size of Leydig-cell nuclei (histometrical investigation), and the adrenal corticosterone contents in mice." *Acta Endocrinol. (Kbh.)* **74**: 783-791 (1973).

H80,017/73

In mice kept alone or under different conditions of crowding, the adrenal corticosterone levels increased twofold with increasing population, whereas spermatogenesis and Leydig cell size decreased.

DeFeudis, F. V., Marks, J. H.: "Studies on the time course of entry and subcellular distribution of radioactivity of (³H) d-ampheta-

mine in the brains of differentially-housed mice." *Experientia* **29**: 1518-1520 (1973).

H81,970/73

In mice, the accumulation of radio-marked d-amphetamine in synaptic particles of the brain increased after prolonged isolation. [The authors do not specifically relate this to stress (H.S.).]

Hull, E. M., Langan, C. J., Rosselli, L.: "Population density and social, territorial, and physiological measures in the gerbil (*Meriones unguiculatus*)."*J. Comp. Physiol. Psychol.* **84**: 414-422 (1973). J5,208/73

Mongolian gerbils possess a ventral sebaceous gland that they rub against low objects in their environment to mark territorial claims. "Crowding depressed several social interaction measures as well as body, ventral gland, and testis weights. In the mixed-sex groups, paired males and females had heaviest adrenal glands, ventral glands, and marking scores, as well as the highest reproductive rate. Mixed-sex crowding did not depress either social or physiological measures as much as did same-sex crowding."

Svare, B. B., Leshner, A. I.: "Behavioral correlates of intermale aggression and grouping in mice."*J. Comp. Physiol. Psychol.* **85**: 203-210 (1973). J6,969/73

Studies on isolated and group-housed mice "suggest that fear is inversely related to, and reactivity directly related to, aggressiveness. It was speculated that differences in fearfulness and reactivity might contribute to the determination of an animal's particular level of aggressiveness and that certain hormonal manipulations might affect aggressiveness through their effects on these related behaviors."

Lindvall, T., Radford, E. P.: "Measurement of annoyance due to exposure to environmental factors."*Environ. Res.* **6**: 1-36 (1973). J15,317/73

Review on various annoyance-producing environmental factors, especially sound, pollution, crowding and stressful interpersonal relations, as objective indicators of somatic stress (about 150 refs.).

Hull, E. M., Chapin, E., Kastaniotis, C.: "Effects of crowding and intermittent isolation on gerbils (*Meriones unguiculatus*)."*Physiol. Behav.* **13**: 723-727 (1974). J19,281/74

In gerbils, crowding depressed all social and reproductive activities but did not stimulate cortisol production. Intermittent isola-

tion actually aggravated the effects of crowding and caused more fighting, but also failed to elicit any marked adrenocortical stimulation.

Levi, L., Andersson, L.: *Population, Environment and Quality of Life*, p. 142. Stockholm: Goteborgs Offsettryckeri AB, 1974.

E10,629/74

Effect of social factors, crowding, pollution and urbanization upon stress-induced diseases (several hundred refs.).

Welch, B. L., Brown, D. G., Welch, A. S., Lin, D. C.: "Isolation, restrictive confinement or crowding of rats for one year. I. Weight, nucleic acids and protein of brain regions."*Brain Res.* **75**: 71-84 (1974). J14,176/74

Rats living for one year under stressful conditions of isolation or crowding have a diminished DNA content in their telencephalon. The authors suggest the tentative working hypothesis that "stress or high levels of environmental stimulation may accelerate the natural aging-associated loss of neurons from the brain."

Prinz, A. F.: "Alt werden wie Methusalem. Modelldenken und Bedenken für die Menschen von morgen" (To be as old as Methuselah. Model-thinking and reflection for the man of tomorrow). *Eur. Med. Mag.* **14**: 22-26 (1974). J14,317/74

Critical analysis of !Kung bushmen from Botswana in whom crowding fails to cause distress, possibly because, unlike urban existence, it is voluntary and has no negative effect upon the quality of life as they see it.

Hamburgh, M., Mendoza, L. A., Rader, M., Lang, A., Silverstein, H., Hoffman, K.: "Malformations induced in offspring of crowded and parabiotically stressed mice."*Teratology* **10**: 31-37 (1974). J15,934/74

Malformations were induced in fetuses of mice kept under crowded conditions or parabiotically joined during pregnancy. "The abnormalities included amputation of peripheral limb structures, open neural folds, exencephaly, blisters, head, face, and tail malformation, and generalized growth retardation. The hypothesis that the teratogenic and other effects were consequences of prolonged prenatal stress induced by the experimental conditions is supported by the observation that both procedures led in a short time to significant increases in mean maternal adrenal weight."

Isolation

(See also Sensory Deprivation, Crowding, Aerospace Medicine, Captivity, and other sections in which agents are discussed in relation to isolation)

In recent years, special attention has been given to isolation and loneliness in connection with the problems encountered by pilots and astronauts during prolonged flights, but these have already been discussed in their corresponding sections, jointly with the techniques and apparatus recommended for such investigations.

In prisoners who volunteered for solitary confinement, it was found that social isolation may produce a change in subjective feelings, but does not in itself cause considerable mental or psychomotor deterioration. Other studies suggest that there exists a definite difference between the stressor effects of perceptual isolation and those of social isolation. In comparisons of the performance of people working alone or in small groups, it was noticed that task motivation, emotional composure and social compatibility are the main determinant factors; in groups, leadership requires a balance between social distance and ability to mix with people.

In rats, isolation allegedly increases the voluntary consumption of ethanol when drinking water is available as an alternative choice.

In confined puppies, the presence of another puppy decreases the level of emotional distress and helps to maintain homeostasis.

Most of the pertinent studies have been performed on mice, among which certain strains tend to become extremely aggressive during isolation. When male mice are isolated they develop eosinopenia, and brain NEP is significantly lower in groups of twenty than in isolated controls. Allegedly, this may have some influence upon the development of aggressiveness. "Isolation stress" may also be associated with increased metabolic and adrenal activity. Gland extirpation studies have suggested that testoid hormones are probably involved in this response, but corticoids, catecholamines and thyroid hormones also play a role. Adrenalectomy and ACTH injections reduce fighting in isolated mice, whereas dexamethasone increases it.

The production of gastric ulcers in fasting mice is facilitated by isolation.

Increases in adrenal weight and plasma corticosterone with pronounced thymus involution were observed in isolated nonfighters as compared with isolated fighter or paired nonfighter mice. Paired fighters were not used for comparison to exclude the complications of fighting itself. However, isolated fighters had significantly higher adrenal catecholamine levels than did isolated nonfighters. Presumably, isolation-induced aggression in the female mice used in these experiments was directly related to increased sympathetic-adrenal activity but not to corticoid secretion.

In three strains of mice, brain NEP and 5-HT determinations during acquisition of shuttle box avoidance and the development of aggressiveness revealed genetic differences. However, in this series of experiments, no clearcut relationship was found between learning ability, aggressiveness and biogenic amine turnover.

In mice, aggressiveness induced by isolation diminished after adrenalectomy but was restored by dexamethasone though not by testosterone. ACTH decreased aggressiveness in both intact and steroid-treated mice.

The rate of catecholamine synthesis is lower in isolated than in grouped mice, and

intense fighting accelerates the synthesis of both catecholamines and 5-HT in the brain.

In isolated people, circadian rhythms of catecholamines and corticoids are disturbed but become normalized soon after synchronization with the usual social stimuli.

Isolation

(See also our earlier stress monographs, p. xiii)

Generalities. Fredericson, E.: "Perceptual homeostasis and distress vocalization in puppies." *J. Pers.* **20**: 472-477 (1952).

E97,850/52

Tests on puppies have shown that "the presence of another puppy in a confining situation tends to decrease the level of emotional distress and thus to favor the maintenance of perceptually homeostatic conditions. The indicator of emotional stress was yelping, in terms of number of yelps per unit time."

Mullin, C. S. Jr.: "Some psychological aspects of isolated antarctic living." *Am. J. Psychiatry* **117**: 323-325 (1960).

J3,365/60

Sells, S. B.: *Military Small Group Performance Under Isolation and Stress*. Vol. 1. *An Annotated Bibliography*. Technical Report No. 61-19, Project No. 8243-11. Fort Worth: Dept. of Psychology, Texas Christian University, 1961.

J13,019/61

Sells, S. B.: *Military Small Group Performance Under Isolation and Stress*. Vol. 2. *Critical Review*. Technical Report No. 62-31, Project No. 8243-11. Fort Worth: Dept. of Psychology, Texas Christian University, 1962.

J13,020/62

Wulfften-Palthe, P. M. van: "Fluctuations in level of consciousness caused by reduced sensorial stimulation and by limited motility in solitary confinement." *Psychiatr. Neurol. Neurochir.* **65**: 377-401 (1962).

J23,625/62

Gorbov, F. D., Miasnikov, V. I., Iazdovskii, V. I.: "On the state of strain and fatigue under conditions of isolation." *Zh. Vyssh. Nerv. Deiat.* **13**: 585-592 (1963) (Russian).

J24,284/63

Walters, R. H., Callagan, J. E., Newman, A. F.: "Effect of solitary confinement on prisoners." *Am. J. Psychiatry* **119**: 771-773 (1963).

J4,752/63

Observations on prisoners in a federal penitentiary who volunteered for solitary confinement.

ment revealed that although social isolation may produce some change in subjective feelings, it does not in itself cause mental or psychomotor deterioration. Objective indicators of stress were not examined.

Burns, N. M., Chambers, R. M., Hendler, E. (eds.): *Unusual Environments and Human Behavior. Physiological and Psychological Problems of Man in Space*, p. 438. Glencoe, Ill.: Free Press, 1963. E10,423/63

Monograph composed of articles by many specialists on the stressor effects elicited by aerospace flights, such as psychologic factors, isolation and sensory deprivation, weightlessness, vibration and radiation. Relationships to the G.A.S. and to performance are given considerable attention.

Hatch, A. M., Wiberg, G. S., Zawidzka, Z., Cann, M., Airth, J. M., Grice, H. C.: "Isolation syndrome in the rat." *Toxicol. Appl. Pharmacol.* **7**: 737-745 (1965).

F64,169/65

Zuckerman, M., Haber, M. M.: "Need for stimulation as a source of stress response to perceptual isolation." *J. Abnorm. Soc. Psychol.* **70**: 371-377 (1965). J11,250/65

People who had shown a greater stress reaction (skin conductance) to perceptual isolation needed more stimulation than others, as indicated by their voluntary use of available visual or auditory stimuli. [The relation of these findings to the stress syndrome is not specifically discussed (H.S.).]

Zuckerman, M., Persky, H., Hopkins, T. R., Murtaugh, T., Basu, G. K., Schilling, M.: "Comparison of stress effects of perceptual and social isolation." *Arch. Gen. Psychiatry* **14**: 356-365 (1966). J11,155/66

Review and personal observations on the effects of perceptual isolation as compared to those of confinement and social isolation with regard to the classic parameters of stress (50 refs.).

Wilkins, W. L.: "Group behavior in long-term isolation." In: Appley, M. H. and Trumbull, R., *Psychological Stress. Issues in Research*, pp. 278-296. New York: Appleton-Century-Crofts, 1967. E10,416/67

Recommendations for "men who comprise task-oriented groups isolated for long periods include these three characteristics: (1) task motivation, with a complete commitment to the group's goals and the skill and pertinacity to carry them out; (2) emotional composure, involving tolerance for the variability in other people's conduct and sensitivity to how one's own conduct may bother others; and, finally (3) social compatibility. The leadership requires a nice balance between social distance—sufficient to maintain the group's perception of who the leader is—and an ability to meet and mix and work along with any colleague."

Raab, W., Bajusz, E., Kimura, H., Herrlich, H. C.: "Isolation-stress, myocardial electrolytes and epinephrine cardiotoxicity in rats." *Proc. Soc. Exp. Biol. Med.* **127**: 142-147 (1968). F96,287/68

Taylor, D. A., Wheeler, L., Altman, I.: "Stress relations in socially isolated groups." *J. Pers. Soc. Psychol.* **9**: 369-376 (1968).

J22,707/68

Review of the literature and personal observations on the stressor effect of solitary confinement in man.

Baer, H.: "Long-term isolation stress and its effects on drug response in rodents." *Lab. Anim. Sci.* **21**: 341-349 (1971).

J20,127/71

A review of the literature shows that "isolation stress, especially long-term isolation stress in rats and mice, can affect the growth, behavior, physiological condition, and response to a wide variety of drugs" (41 refs.).

Robertson, J., Robertson, J.: "Quality of substitute care as an influence on separation responses." *J. Psychosom. Res.* **16**: 261-265 (1972). J19,670/72

Psychologic observations on "separation distress" in very young children isolated from their mothers.

Grelk, D. F., Papson, B. A., Cole, J. E., Rowe, F. A.: "The influence of caging conditions and hormone treatments on fighting in male and female hamsters." *Horm. Behav.* **5**: 355-366 (1974). J18,996/74

Eleftheriou, B. E., Bailey, D. W., Denenberg, V. H.: "Genetic analysis of fighting behavior in mice." *Physiol. Behav.* **13**: 773-777 (1974) (16 refs.). J19,282/74

Alexander, N.: "Psychosocial hypertension in members of a Wistar rat colony." *Proc.*

Soc. Exp. Biol. Med. **146**: 163-169 (1974). H87,183/74

Various social conditions (particularly aggregation and isolation) can cause hypertension in the rat.

Parker, L. F., Radow, B. L.: "Isolation stress and volitional ethanol consumption in the rat." *Physiol. Behav.* **12**: 1-3 (1974).

J9,601/74

Isolation increases the voluntary consumption of ethanol by rats given the alternative of drinking water. This change is ascribed to "isolation stress."

→**Morphology.** Southwick, C. H.: "Eosinophil response of C57BR mice to behavioral disturbance." *Ecology* **40**: 156-157 (1959). J11,123/59

When isolated male mice were placed in groups of four or into strange cages, pronounced stress-eosinopenia resulted.

Hatch, A. M., Wiberg, G. S., Balazs, T., Grice, H. C.: "Long-term isolation stress in rats." *Science* **142**: 507 (1963).

J22,956/63

Rats isolated for thirteen weeks become aggressive and show adrenal and thyroid enlargement with splenic and thymic atrophy.

Essman, W. B., Frisone, J. D.: "Isolation-induced facilitation of gastric ulcerogenesis in mice." *J. Psychosom. Res.* **10**: 183-188 (1966). G41,114/66

In mice, isolation facilitates gastric ulcerogenesis induced by fasting. "The data suggest that isolation contributes to food intake and food disposition and differences in the duration of aggregation or isolation and resulting ulcer development may be accounted for in terms of: (1) differences in motor activity, or (2) age at the time of change in population density."

Gärtner, K.: "Der Anteil sozialer Ursachen an der Varianz physiologischer und morphologischer Größen, demonstriert am Beispiel des Serumcorticosterongehaltes und der Gewichte von Nebennieren, Testes und Samenblasen bei Ratten" (The socially-caused component of phenotypic variance in physiologic or morphologic data demonstrated in corticosterone content of serum and the weight of adrenals, testes, prostate and seminal vesicles in rats). *Berl. Münch. Tierärztl. Wochenschr.* **84**: 451-455 (1971). J15,950/71

The parameters mentioned in the title are compared in isolated and grouped rats.

Hughes, R. E., Nicholas, P.: "Effects of caging on the ascorbic acid content of the adrenal glands of the guinea-pig and gerbil." *Life. Sci. [II]* **10**: 53-55 (1971).

G84,434/71

Ascorbic acid determinations in the adrenals of guinea pigs and gerbils suggest that "individual caging would appear to 'stress' the animals less than group caging" (8 refs.).

Brain, P. F., Nowell, N. W.: "Isolation versus grouping effects on adrenal and gonadal function in albino mice. I. The male. II. The female." *Gen. Comp. Endocrinol.* **16**: 149-159 (1971). H36,177/71

Brain, P. F., Nowell, N. W., Hucklebridge, F. H.: "Further studies on isolation-induced adrenal hypertrophy in the female albino mouse." *J. Endocrinol.* **49**: xix-xx (1971).

H39,343/71

Truhaut, R., Dechambre, R. P.: "Modalités de l'induction chez la souris de tumeurs pulmonaires par le benzo-(α)-pyrène; influence de la dose d'hydrocarbure aromatique et de facteurs écologiques" (Methods of induction in mice of pulmonary tumors with benzo-(α)-pyrene; influence of the dose of the aromatic hydrocarbon and of ecological factors). *C.R. Acad. Sci. (Paris)* **274**: 2263-2267 (1972). J20,220/72

In isolated mice, benzopyrene produces pulmonary tumors more rapidly than in those kept in groups of ten.

Ely, D. L., Henry, J. P.: "Effects of prolonged social deprivation on murine behavior patterns, blood pressure, and adrenal weight." *J. Comp. Physiol. Psychol.* **87**: 733-740 (1974). J17,421/74

→**Hormones.** Welch, B. L., Welch, A. S.: "Effect of grouping on the level of brain nor-epinephrine in white Swiss mice." *Life Sci.* **4**: 1011-1018 (1965). J8,692/65

Mice housed for one week in a group of twenty had significantly lower levels of brain NEP than controls isolated for the same period. These differences may explain isolation-induced aggression and excitability.

Weltman, A. S., Sachler, A. M., Sparber, S. B.: "Endocrine, metabolic and behavioral aspects of isolation stress on female albino mice." *Aerosp. Med.* **37**: 804-810 (1966). G36,883/66

In mice isolated for sixteen weeks, there was increased irritability, viciousness, heightened activity and head-twitching. The results

suggest that in the third to eleventh weeks isolation stress was associated with enhanced metabolic and adrenal activity with suggestions of hypothyroidal trends during the terminal period of the study. Possible relationships between these changes and the pathogenesis of psychoses were noted.

Sigg, E. B.: "Relationship of aggressive behaviour to adrenal and gonadal function in male mice." In: Garattini, S. and Sigg, E. B., *Aggressive Behaviour*, pp. 143-149. New York: Wiley-Interscience, 1969.

J10,865/69

The aggressive behavior of isolated mice was studied by extirpation of various endocrine glands and treatment with diverse hormones. It was concluded that "the male gonadal hormones are critically involved in this response whereas other endocrine changes (adreno-cortical, adreno-medullary and thyroid) may be contributory and consequential."

Gilbert, F. F., Bailey, E. D.: "Visual isolation and stress in female ranch mink particularly during the reproductive season." *Can. J. Zool.* **47**: 209-212 (1969). J20,525/69

"Visual isolation is apparently more stressful to female mink during the anoestrous period but reduces stress during oestrus and pregnancy. The increased adrenal steroid output of control mink as part of the stress syndrome during the critical reproductive period might be responsible for increased *in utero* losses. But increased adrenocortical output associated with the stress of long term visual isolation might result in insufficient gonadal stimulation resulting in fewer pregnancies."

Brain, P. F., Nowell, N. W., Wouters, A.: "Some relationships between adrenal function and the effectiveness of a period of isolation in inducing intermale aggression in albino mice." *Physiol. Behav.* **6**: 27-29 (1971). J10,867/71

In male mice, isolation causes aggressiveness (fighting) which is reduced by adrenalectomy and ACTH injection but enhanced by dexamethasone (17 refs.).

Kriebel, J.: "Exogenous modifications of circadian rhythms of adrenal hormones in man." *J. Interdiscipl. Cycle Res.* **3**: 233-241 (1972). G93,758/72

In a healthy young man, circadian rhythms of EP, NEP, corticoids, 17-KS and other metabolic parameters were examined (1)

under normal conditions, (2) during complete isolation without indication of time and (3) after subsequent return to synchronization with the usual social stimuli. Apparently, such stimuli are important in determining the shape of circadian rhythms owing to "(1) the relative late maxima of the catecholamines in synchronization; (2) the increased amplitude during social activity; (3) the abrupt increase in the level of urinary catecholamine excretion at the conclusion of isolation."

Lovely, R. H., Pagano, R. R., Paolino, R. M.: "Shuttle-box-avoidance performance and basal corticosterone levels as a function of duration of individual housing in rats." *J. Comp. Physiol. Psychol.* **81**: 331-335 (1972).

H79,737/72

In rats, isolation increased plasma corticosterone levels and facilitated both the acquisition and the extinction of shuttle-box avoidance responses. "These findings, together with the recent literature implicating the pituitary-adrenal axis in the control of responding in appetitively motivated tasks, suggest that the condition of housing may be a major parameter affecting performance in a variety of learning paradigms."

Leshner, A. I., Walker, W. A., Johnson, A. E., Kelling, J. S., Kreisler, S. J., Svare, B. B.: "Pituitary adrenocortical activity and intermale aggressiveness in isolated mice." *Physiol. Behav.* **11**: 705-711 (1973).

J7,247/73

In mice, the aggressiveness induced by isolation was diminished following adrenalectomy and was restored by dexamethasone but not by testosterone. ACTH decreased aggressiveness in both intact mice and those with controlled levels of corticosterone and/or testosterone. Presumably, ACTH rather than glucocorticoid levels are the critical parameters in the control of aggressiveness by hormones of the pituitary adrenocortical axis: "ACTH affects aggressiveness independently of its effects on either adrenocortical or gonadal activity."

Modigh, K.: "Effects of isolation and fighting in mice on the rate of synthesis of noradrenaline, dopamine and 5-hydroxytryptamine in the brain." *Psychopharmacologia* **33**: 1-17 (1973).

J7,891/73

The rate of brain catecholamine synthesis is lower in isolated than in grouped mice, and intense fighting rapidly accelerates the synthesis of both catecholamines and 5-HT in the brain.

Goldberg, M. E., Insalaco, J. R., Hefner, M. A., Salama, A. I.: "Effect of prolonged isolation on learning, biogenic amine turnover and aggressive behaviour in three strains of mice." *Neuropharmacology* **12**: 1049-1058 (1973). J8,664/73

In three strains of mice, brain NEP and 5-HT levels were measured during acquisition of shuttle-box avoidance and the development of aggressiveness following isolation of some of the mice. "It is concluded that no clearcut relationship exists among learning ability, aggressive behaviour and biogenic amine turnover rates in isolated or aggregated mice."

Hull, E. M., Chapin, E., Kastaniotis, C.: "Effects of crowding and intermittent isolation on gerbils (*Meriones unguiculatus*)."
Physiol. Behav. **13**: 723-727 (1974).

J19,281/74

In gerbils, crowding depressed all social and reproductive activities but did not stimulate cortisol production. Intermittent isolation actually aggravated the effects of crowding and caused more fighting, but also failed to elicit any marked adrenocortical stimulation.

Schwartz, R., Sackler, A. M., Weltman, A. S.: "Adrenal relationships to aggressiveness in isolated female mice." *Experientia* **30**: 199-200 (1974). H85,604/74

Good review of the literature on the effects of isolation on aggressiveness and adrenal activity in female mice. The present observations revealed an increase in adrenal weight and plasma corticosterone with pronounced thymus involution in isolated nonfighter mice as compared to isolated fighter or paired non-fighter mice (paired fighters were not studied to exclude complications caused by the fighting itself). On the other hand, isolated fighters had significantly higher adrenal catecholamine levels than did isolated nonfighters. From these and other investigations, it was concluded "that isolation-induced aggression in female mice was directly related to increased sympathetic-adrenal activity. Conversely, no direct relationship was noted between adrenocortical activity and aggressiveness" (25 refs.).

Holley, D. C., Evans, J. W.: "Effect of confinement on ovine glucose and immunoreactive insulin circadian rhythms." *Am. J. Physiol.* **226**: 1457-1461 (1974).

H88,015/74

In rams "the plasma glucose rhythm

peaked at 0000, reached a low value at 1600, and was not affected by cage restraint. During cage restraint, the time of maximum plasma insulin concentration was shifted 4 h from 0000 to 0400, and the daily mean concentration was increased 160%, suggesting an increased sensitivity of pancreatic β -cells to glucose."

Hutchins, D. A., Pearson, J. D. M., Sharman, D. F.: "An altered metabolism of dopamine in the striatal tissue of mice made aggressive by isolation." *Br. J. Pharmacol.* **51**: 115-116 (1974). H89,221/74

Hodge, G. K., Butcher, L. L.: "5-Hydroxytryptamine correlates of isolation-induced aggression in mice." *Eur. J. Pharmacol.* **28**: 326-337 (1974). H93,909/74

Stolk, J. M., Conner, R. L., Barchas, J. D.: "Social environment and brain biogenic amine metabolism in rats." *J. Comp. Physiol. Psychol.* **87**: 203-207 (1974). J15,239/74

In rats, isolation caused increased NEP turnover in the brain whereas brain 5-HT metabolism showed minimal changes.

Wise, D. A.: "Aggression in the female golden hamster: effects of reproductive state and social isolation." *Horm. Behav.* **5**: 235-250 (1974). J16,161/74

In female hamsters (which are notoriously more aggressive than males, even under ordinary conditions), isolation enhances aggressive behavior. "Considering social isolation as stressful, increases in prolactin levels could be responsible for high aggression following prolonged isolation, since in rats, stress has been reported to increase prolactin secretion."

Modigh, K.: "Effects of social stress on the turnover of brain catecholamines and

5-hydroxytryptamine in mice." *Acta Pharmacol. Toxicol. (Kbh.)* **34**: 97-105 (1974).

J16,345/74

Male mice that were at first isolated and then brought together immediately started to fight, and exhibited characteristic changes in the turnover of brain catecholamines and 5-HT.

→Metabolites. Sabbot, I. M., McNew, J. J., Hoshizaki, T., Sedgwick, C. J., Adey, W. R.: "Effect of a 30 day isolation stress on calcium, phosphorus and other excretory products in an unrestrained chimpanzee." *Aerosp. Med.* **43**: 142-148 (1972).

H73,921/72

Observations on chimpanzees kept in isolation for thirty days suggest that "the calcium to phosphorus excretion ratio might serve as a physiological stress indicator of Selye's adaptation syndrome (period of resistance)."

Hattingh, J., van Pletzen, A. J. J.: "The influence of capture and transportation on some blood parameters of fresh water fish." *Comp. Biochem. Physiol. [A]* **49**: 607-609 (1974). H93,884/74

Welch, B. L., Brown, D. G., Welch, A. S., Lin, D. C.: "Isolation, restrictive confinement or crowding of rats for one year. I. Weight, nucleic acids and protein of brain regions." *Brain Res.* **75**: 71-84 (1974).

J14,176/74

Rats living for one year under stressful conditions of isolation or crowding have a diminished DNA content in their telencephalon. The authors suggest the tentative working hypothesis that "stress or high levels of environmental stimulation may accelerate the natural aging-associated loss of neurons from the brain."

Captivity

(See also Anxiety, Climate)

Death may be caused by the so-called "shock disease" that develops in some captive wild animals after exposure to minor stressors, such as transfer to new quarters or repairs to an adjacent cage. In these animals, the lymphoid tissues are hyperplastic, the adrenal glands and heart small, liver glycogen stores depleted, and death usually occurs in hypoglycemia. The syndrome has been compared to the exhaustion phase of the G.A.S., but the supportive evidence is not entirely conclusive.

Captive wild Norway rats have comparatively large adrenals and atrophic thymus

glands with other typical manifestations of the G.A.S. in comparison with domesticated controls; this has been ascribed to the more sheltered existence of the latter.

In certain strains of hares kept confined in the presence of a hunting dog, testicular atrophy results as a consequence of fear, but of course, in studying the effects of captivity upon any animal it is difficult to estimate the role of anxiety.

Numerous publications deal with the effects of captivity upon various species, including fish, shrews, ground squirrels, mongooses, dolphins and squirrel monkeys. In general, fertility decreases and the changes noted correspond to those of the stress reaction, but for details the reader must be referred to the abstract section.

Captivity

(See also our earlier stress monographs, p. xiii)

Richter, C. P.: "Domestication of the Norway rat and its implications for the problem of stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 19-47. Baltimore: Williams & Wilkins, 1950.

B51,893/50

In wild Norway rats, organ weights (large adrenals, small thymus and so on) as well as many functional characteristics resemble those typical of the G.A.S. In this respect they differ from those of domesticated rats. Presumably, this can be ascribed to the more sheltered existence of the laboratory animals.

Christian, J. J., Ratcliffe, H. L.: "Shock disease in captive wild mammals." *Am. J. Pathol.* **28**: 725-737 (1952).

B74,160/52

In various captive wild animals, shock disease and death occurred after minor stress, such as transfer to new quarters or disturbance by repairs to adjacent cages. In these animals the lymphoid tissues were hyperplastic, the adrenal glands and hearts small, the liver glycogen stores depleted, and the immediate cause of death was hypoglycemia. "Shock disease, therefore, corresponds to the exhaustion phase of Selye's syndrome of general adaptation." [Lymphatic atrophy is not usually associated with the exhaustion phase of the G.A.S. (H.S.).]

Hediger, H.: *Studies of the Psychology and Behaviour of Captive Animals in Zoos and Circuses*, p. 166. London: Butterworths, 1955.

E3,952/55

Extensive monograph on the behavior of wild animals in captivity and during training. [The G.A.S. is not discussed, but many pertinent facts can be deduced from the innumerable observations described (H.S.).]

Nagle, J. P., Cammock, E. E., Nyhus, L. M., Harkins, H. N.: "Evidence for adre-

nal insufficiency in acutely stressed captive monkeys." *J. Appl. Physiol.* **20**: 131-133 (1965).

G24,473/65

Milin, R.: "The effects of fright on morphology of testes." *Med. Pregl.* **19**: 453-458 (1966) (Serbo-Croatian).

G60,378/66

In hares kept in captivity in the presence of a hunting dog, testicular atrophy occurs as a consequence of fear.

Hane, S., Robertson, O. H., Wexler, B. C., Krupp, M. A.: "Adrenocortical response to stress and ACTH in Pacific salmon (*Oncorhynchus tshawytscha*) and steelhead trout (*Salmo gairdnerii*) at successive stages in the sexual cycle." *Endocrinology* **78**: 791-800 (1966).

F63,818/66

In the Pacific salmon, plasma 17-OHCS concentrations rose at various phases of migration upstream during the spawning season, as well as after bleeding, confinement in a tank or treatment with ACTH. Spawning steelhead trout showed an even greater increase in plasma corticoids than did spawning salmon after ACTH injection.

Sorenson, M. W., Conaway, C. H.: "Observations on the social behavior of tree shrews in captivity." *Folia Primatol.* (Basel) **4**: 124-145 (1966).

J11,006/66

General review and personal observations on the effects of captivity upon behavior—particularly stress manifestations—in various tree shrews.

Schmidt, J. P., Rehkemper, J. A.: "Myocardial lesions: spontaneous development in captive ground squirrels." *Proc. Soc. Exp. Biol. Med.* **125**: 213-215 (1967).

F80,175/67

In Arctic ground squirrels (*Citellus undulatus*), numerous areas of focal myocardial necrosis developed during captivity. "The etiology of these degenerative changes may be associated with the stress of captivity, but remains to be determined."

Harrison, R. J., Boice, R. C., Brownell, R. L. Jr.: "Reproduction in wild and captive dolphins." *Nature* **222**: 1143-1147 (1969).

H13,797/69

Among various types of dolphins, ulceration of the forestomach occurred during captivity, while the number of pregnancies decreased considerably.

Stemmermann, G. N., Hayashi, T.: "A survey of the normal and morbid anatomy of the Hawaiian feral mongoose." *Am. J. Pathol.* **55**: 67a-68a (1969). H13,927/69

Among Hawaiian feral mongooses, acute stress ulcers are common, and are probably related to the method of capture. Yet the presence of healing ulcers demonstrates that these lesions also occur in the wild.

Vlodaver, Z., Medalie, J., Neufeld, H. N.: "Coronary arteries in young monkeys." *Isr. J. Med. Sci.* **5**: 639-643 (1969). H16,811/69

In young rhesus or vervet monkeys, intimal changes develop in the coronary arteries during captivity, especially if the animals are restricted to small cages and have little exercise. "The possible relation between stress and physical activity and the development of

intimal changes in the captive young monkey are emphasized."

Brown, G. M., Grotta, L. J., Penney, D. P., Reichlin, S.: "Adrenal regulation in the wild captive squirrel monkey: a model of chronic stress." *Can. Psychiatr. Assoc. J.* **15**: 425-431 (1970). G78,935/70

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971). H37,353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound and aversive conditioning) increase plasma STH and cortisol levels, but the two responses are not parallel and are presumably regulated by diverse mechanisms. In the case of chair restraint, STH values fall to resting levels whereas cortisol continues to rise.

Hattingh, J., van Pletzen, A. J. J.: "The influence of capture and transportation on some blood parameters of fresh water fish." *Comp. Biochem. Physiol. [A]* **49**: 607-609 (1974). H93,884/74

Concentration Camps, POWs

(See also Isolation)

A very large number of publications deal with the problems of concentration camp inmates and with the "concentration camp survivor syndrome" which may develop long after liberation.

Principal emphasis has been placed upon the psychologic problems related to coping behavior, but of course, it is difficult to distinguish the relative roles played by loss of freedom, poor nutrition, bad treatment, fear and generally deficient hygiene. In these studies, considerable attention has been given not only to the psychologic defense reactions which enabled the prisoners to endure the hardships but also to the actions of their masters who had come to terms with their own entirely inhuman behavior by shifting responsibility to those who gave the orders.

Internees in diverse concentration and labor camps developed remarkably similar symptoms. In general, an initial reactive depression was followed by varying degrees of adaptation, and new cases of psychoneuroses rarely occurred until after liberation.

Many of the survivors developed depression with irrational guilt feelings about the fact that they continued to live, while so many of their fellow inmates died. Several investigators mention that the damage was particularly marked in those imprisoned at an early age and in those who suffered not only psychic injury but perhaps also physical trauma, malnutrition and/or illness.

A fairly constant phenomenon resulted from conflicts at an unconscious level between the wish to get well after liberation and the need to suffer for purposes of

revenge and expiation of the "guilt of survival." These observations show that it is incorrect to ascribe the late symptoms to a "constitutional inadequacy" and to reject compensation claims because the disturbances developed only after liberation.

In both male and female concentration camp survivors, libido and fertility were often diminished owing to deficiencies in sperm formation and amenorrhea. Psychosomatic skin disorders were also common.

Due to the unending process of mourning and the emotionally depleted state of the inmates, life in a concentration camp even affected the second generation at times. Parents were often so handicapped that they regarded their children's normal robust activity as an interference with the mourning process or as an extra burden on their already taxed resources. Consequently, the children became anxious and more disruptive.

In POWs repatriated after captivity in China or North Korea, the "prisoner-of-war syndrome" was described as being mainly characterized by apathy and withdrawal as defensive adjustments.

Concentration Camps, POWs

(See also our earlier stress monographs, p. xiii and cf. Isolation)

Bondy, C.: "Problems of internment camps." *J. Abnorm. Soc. Psychol.* 38: 453-475 (1943). B27,407/43

The effects and after-effects of life in a Nazi concentration camp were analyzed while World War II was still in progress. Principal emphasis was placed upon psychosocial problems.

Bettelheim, B.: "Individual and mass behavior in extreme situations." *J. Abnorm. Soc. Psychol.* 38: 417-452 (1943).

B27,881/43

Detailed review of life in a Nazi concentration camp presented by a former inmate. Major emphasis is placed upon psychologic reactions.

Lipscomb, F. M.: "Medical aspects of Belsen Concentration Camp." *Lancet* September 8, 1945, pp. 313-315. B45,379/45

Uehlinger, E.: "Die pathologische Anatomie der Hungerkrankheit und des Hungerödems" (The pathologic anatomy of famine and nutritional edema). *Helv. Med. Acta* 14: 584-601 (1947). B24,304/47

Study of inmates who died in Nazi concentration camps.

Kral, V. A.: "Psychiatric observations under severe chronic stress." *Am. J. Psychiatry* 108: 185-192 (1951). G85,150/51

Internees in the Theresienstadt concentration camp exhibited remarkably similar psychologic responses—an initial reactive de-

pression followed by varying degrees of adaptation. No new cases of psychoneuroses developed; in fact, "old and long-lasting conditions of that kind improved to such an extent that the patients could be considered as practically cured. After the liberation, however, neurotic reactions could be observed in some of the former internees" (22 refs.).

Cohen, E. A.: *Human Behavior in the Concentration Camp*, p. 295. New York: Universal Library, 1953. E10,422/53

An extensive and very objective report of life in a German concentration camp written by a Dutch-Jewish physician who was a prisoner in Auschwitz for three years. It presents a remarkable description of the adaptive reactions of prisoners under extreme circumstances of ill-treatment, malnutrition, cruel experiments and constant fear of death, and attempts to explain the psychologic defense reactions which enabled many of them to endure these hardships. The author suggests that strict discipline helped their masters come to terms with an entirely inhuman behavior by shifting responsibility to those who gave the orders which were blindly accepted as being justified. According to the *London Times* "it is a human document that is one of the most moving and at the same time scientifically most distinguished books to have come out of the postwar period" (157 refs.).

Cohen, B. M., Cooper, M. Z.: *A Follow-up Study of World War II Prisoners of War*, p. 81. Washington, D.C.: Veterans Administration Medical Monograph, 1954.

E10,273/54

A very extensive compilation of data by the U.S. Army on white male survivors of imprisonment by the Japanese and Germans during World War II, with special emphasis on after-effects (morbidity, mortality). Statistical analysis suggests lasting unfavorable after-effects, but evaluation of the role of stress as such, or of more specific factors (malnutrition, infection, trauma), is difficult.

Strassman, H. D., Thaler, M. B., Schein, E. H.: "A prisoner of war syndrome: Apathy as a reaction to severe stress." *Am. J. Psychiatry* **112**: 998-1003 (1956).

C17,232/56

Psychiatric interviews were conducted with American POWs repatriated by the Chinese and North Koreans to examine the psychologic aspects of the "prisoner of war syndrome," which is characterized mainly by apathy and withdrawal as a defensive adjustment.

Oury, P., Day, J.: "Les troubles digestifs chez les déportés" (Gastrointestinal disturbances in concentration camp inmates). *Presse Méd.* **65**: 2078-2081 (1957).

J11,138/57

Chodoff, P.: "Effects of extreme coercive and oppressive forces: brainwashing and concentration camps." *Am. Handb. Psychiatry* **3**: 384-405 (1959).

G73,927/59

Description of the "concentration camp syndrome" among inmates of Nazi and Chinese camps. Special emphasis is placed upon brain-washing and the development of depression with guilt feelings (78 refs.).

Chodoff, P.: "Late effects of the concentration camp syndrome." *Arch. Gen. Psychiatry* **8**: 323-333 (1963).

G73,925/63

Neurotic symptoms are typical late effects that appear in Nazi concentration camp survivors after liberation. "This stress supplies the necessary and essential conditions responsible for the initial development of the traumatic neurosis which occurs to a greater or lesser extent in all individuals who have been subjected to any considerable degree of the stress." The damage is particularly pronounced in those exposed to stress at an early age, suffering not only psychic injury but perhaps physical trauma, malnutrition or illness. A curious but fairly constant phenomenon results from "conflicts, at an unconscious level between the wish to get well, and the need to suffer for purposes of revenge and

expiation, expressed at the symptomatic level in feelings of guilt over survival."

Lyon, E.: "Das peptische Geschwür, eine Stresskrankheit der Verfolgten. (Neue Gesichtspunkte für die Begutachtung)" (Peptic ulcer as a stress disease of the persecuted. [New viewpoints on testimony]). *Med. Klin.* **58**: 1514-1517 (1963). E27,706/63

In concentration camp survivors, stress ulcers are particularly common, and this has been recognized even in legal testimony.

Cleave, T. L.: "A new approach to peptic ulcer." *Am. J. Proctol.* **15**: 297-307 (1964).

F16,659/64

The common occurrence of peptic ulcers in POWs and concentration camp inmates is not due exclusively to stress but also to a lack of dietary protein and the unappetizing nature of the food received. During stress, gastric emptying-time is prolonged and hence the action of acid upon the mucosa is intensified.

Copelman, L. S.: "Etudes et recherches sur les facteurs endocriniens et psychologiques dans la pathogénie et le traitement de la stérilité" (Studies and research on endocrine and psychologic factors in the pathogenesis and treatment of sterility). *Thérapie* **20**: 459-465 (1965). G30,661/65

In both male and female concentration camp survivors, libido and fertility are often diminished. Sperm formation tends to be abnormal and amenorrhea is common as a consequence of stress, as was shown in the original experiments on the G.A.S.

Hocking, F.: "Human reactions to extreme environmental stress." *Med. J. Aust.* **2**: 477-483 (1965). G34,377/65

Review on stress reactions in men exposed to extreme conditions, particularly starvation, natural disasters and life in concentration camps. It is important to remember that in concentration camp survivors, symptoms often appear late, after liberation. "In the past, their claims for compensation have often been dismissed on the grounds that the persistence of their symptoms indicates that they are 'constitutionally inadequate'."

Venzlaff, U.: "Akute und chronische psychiatrische Syndrome nach Extrembelastungen" (Acute and chronic psychiatric syndromes following extreme stress). *Med. Klin.* **62**: 701-706 (1967). F81,248/67

Observations on inmates of Nazi concen-

tration camps and on very badly treated POWs (39 refs.).

Kral, V. A., Pazder, L. H., Wigdor, B. T.: "Long-term effects of a prolonged stress experience." *Can. Psychiatr. Assoc. J.* **12**: 175-181 (1967). G46,466/67

In a group of twenty ex-Hong Kong POWs it was found that "the accumulation of severe stresses endured over a period of three-and-a-half years led to significant impairment in various areas of nervous and psychological functioning which is still easily detectable twenty years after liberation."

"The survivor syndrome: concentration camp effects." *Sciences* **8**: 32-37 (1968).

F94,111/68

Review of the "survivor syndrome" based on observations by various physicians who examined a large number of former concentration camp inmates. Both the acute and delayed manifestations are described as regards somatic and psychic damage. An important pathogenic factor, "survivor guilt, persists long after relatives have died because the survivor unconsciously identifies with the aggressor."

Chodoff, P.: "The Nazi concentration camp and the American poverty ghetto. A comparison." *J. Contemp. Psychother.* **1**: 27-36 (1968). G73,926/68

Hoppe, K. D.: "Psychosomatische Reaktionen und Erkrankungen bei Überlebenden schwerer Verfolgung" (Psychosomatic reactions and diseases in survivors of severe persecution). *Psyche* (Stuttg.) **22**: 464-477 (1968). J23,711/68

Haefner, H.: "Psychosocial changes following racial and political persecution. *Res. Publ. Assoc. Nerv. Ment. Dis.* **47**: 101-117 (1969). J22,418/69

Cohen, E. A., "Het post-concentratiekamp-syndroom" (The post-concentration camp syndrome). *Ned. Tijdschr. Geneesk.* **113**: 2049-2054 (1969) (Dutch). H19,380/69

Review of psychologic observations on former inmates of Nazi camps.

Shanon, J.: "Stress and conflict as criteria for the classification of psychosomatic skin disorders." *Arch. Belg. Dermatol. Syphiligr.* **25**: 429-437 (1969). J2,894/69

Psychosomatic skin disorders are common among survivors of Nazi concentration camps. Stress and conflict are of pathogenic importance here.

Chodoff, P.: "The German concentration camp as a psychological stress." *Arch. Gen. Psychiatry* **22**: 78-87 (1970). G71,936/70

Anecdotal description of the psychologic and physical damage caused by life in Nazi concentration camps.

Hocking, F.: "Extreme environmental stress and its significance for psychopathology." *Am. J. Psychother.* **24**: 4-26 (1970). G72,373/70

Review on "some of the immediate and possible long-term effects of a number of situations involving severe to extreme stress, including semistarvation, sensory deprivation, natural disasters, military combat, concentration camps, Russian labor camps, and nuclear bombing" (78 refs.).

Thygesen, P., Hermann, K., Willanger, R.: "Concentration camp survivors in Denmark. Persecution, disease, disability, compensation. A 23-year follow-up: A survey of the long-term effects of severe environmental stress." *Dan. Med. Bull.* **17**: 65-108 (1970).

H26,387/70

Extensive description of the somatic effects and an even more detailed description of the psychic effects of imprisonment in German concentration camps as noted during a twenty-three-year followup study of Danish subjects.

Shanon, J.: "The subconscious motivation for the appearance of psychosomatic skin disorders in concentration camp survivors and their rehabilitation." *Psychosomatics* **11**: 178-182 (1970). H28,927/70

Among 128 Nazi concentration camp survivors suffering from psychosomatic skin disorders, fifty were found to be "conflictogenic, largely motivated by guilt."

Shanon, J.: "Delayed psychosomatic skin disorders in survivors of concentration camps." *Br. J. Dermatol.* **83**: 536-542 (1970). J10,417/70

Description of the delayed appearance of psychosomatic skin disorders in survivors of concentration camps. "The mechanism of the delayed reaction has been discussed in terms of stress and conflict and their interaction."

Halloran, A. V.: "Comparison of World War II, Korean, and Vietnamese prisoners of war." *Minn. Med.* **53**: 919-922 (1970).

J21,198/70

Lumry, G. K.: "Psychological effects of prisoner-of-war experience." *Minn. Med.* **53**: 915-918 (1970). J21,194/70

Eitinger, L.: "Organic and psychosomatic aftereffects of concentration camp imprisonment." *Int. Psychiatry Clin.* 8: 205-215 (1971). J20,185/71

Wind, E. de: "Psychotherapy after traumatization caused by persecution." *Int. Psychiatry Clin.* 8: 93-114 (1971).

J20,182/71

Klein, H.: "Families of holocaust survivors in the kibbutz: psychological studies." *Int. Psychiatry Clin.* 8: 67-92 (1971).

J20,181/71

Hoppe, K. D.: "The aftermath of Nazi persecution reflected in recent psychiatric literature." *Int. Psychiatry Clin.* 8: 169-204 (1971). J20,184/71

Review of the literature (including medico-legal problems of compensation) in relation to Nazi persecution (195 refs.).

Trautman, E. C.: "Violence and victims in Nazi concentration camps and the psychopathology of the survivors." *Int. Psychiatry Clin.* 8: 115-133 (1971) (42 refs.).

J19,884/71

Krystal, H.: "Trauma: considerations of its intensity and chronicity." *Int. Psychiatry Clin.* 8: 11-28 (1971). J20,179/71

Krystal, H.: "Review of the findings and implications of this symposium." *Int. Psychiatry Clin.* 8: 217-229 (1971). J20,186/71

Review of a symposium on "Psychic Traumatization. Aftereffects in Individuals and Communities." Major emphasis is laid upon concentration camp survivors and victims of wars, tornados, floods and other types of disaster.

Nemeth, M. C.: "Psychosis in a concentration camp survivor. A case presentation." *Int. Psychiatry Clin.* 8: 135-146 (1971).

J20,183/71

Sigal, J. J.: "Second-generation effects of massive psychic trauma." *Int. Psychiatry Clin.* 8: 55-65 (1971). J19,883/71

Sigal, J. J., Rakoff, V.: "Concentration camp survival. A pilot study of effects on the second generation." *Can. Psychiatr. Assoc. J.* 16: 393-397 (1971). G86,390/71

Concentration camp survivors manifested great difficulties in self-control and in their ability to handle their children. "The most significant effects appeared to be attributable to the insurmountable process of mourning

and the emotionally depleted state of the parents."

Sigal, J. J., Silver, D., Ellin, B.: "Some Second-generation Effects of Survivors of Nazi Persecution," p. 15. Paper presented at the International Congress of Psychiatry, Mexico City, 1971 (mimeographed).

G87,038/71

Even the children of Nazi concentration camp survivors show behavioral anomalies because of their contact with parents "preoccupied with the unending mourning of the loss of their parents, siblings, etc., and with the various psychological and physical illnesses that have beset them since the war. Because they are so preoccupied, they respond to their children's normal robust activity and need for control as an interference with this mourning process or as an extra burden imposed on their already taxed resources. As a result, the children become anxious and more disruptive."

Straker, M.: "The survivor syndrome: theoretical and therapeutic dilemmas." *Laval Méd.* 42: 37-41 (1971). H34,052/71

Description of the late psychologic consequences characteristic of the "survivor syndrome" in former inmates of Nazi concentration camps.

Neiderland, W. G.: "Clinical observations on the survivor syndrome." In: Parker, R. S., *The Emotional Stress of War, Violence, and Peace*, pp. 284-288. Pittsburgh, Pa.: Stanwix House, 1972. E10,446/72

The "concentration camp survivor syndrome" is discussed and compared to the after-effects of other types of catastrophes. Many interesting observations are reported but are not connected with the stress syndrome as it is known in medicine.

Cohen, S., Taylor, L.: *Psychological Survival. The Experience of Long-term Imprisonment*, p. 217. New York: Pantheon Books, 1972. E10,656/72

Monograph on the effects of captivity, especially long-term imprisonment. Particular attention is given to psychologic changes and to studies on stress and sensory deprivation (only a few key refs.).

Spaulding, R. C., Ford, C. V.: "The Pueblo incident: psychological reactions to the stresses of imprisonment and repatriation." *Am. J. Psychiatry* 129: 17-26 (1972).

G91,346/72

Psychologic studies on the eighty-two surviving crew members of the U.S.S. Pueblo,

two to three days after their release from North Korean captivity. "Previous descriptions of a repatriation syndrome in prisoners of war, consisting of initial apathy followed by anger and hostility, were confirmed."

Klein, H.: "Holocaust survivors in kibbutzim: readaptation and reintegration." *Isr. Ann. Psychiatry* **10**: 78-91 (1972) (15 refs.). J19,904/72

Sonnenberg, S. M.: "A special form of survivor syndrome." *Psychoanal. Q.* **41**: 58-62 (1972). J20,337/72

Warnes, H.: "The traumatic syndrome." *Can. Psychiatr. Assoc. J.* **17**: 391-396 (1972). J19,545/72

Bolewski, M.: "Neurose, Stress und psychische Beanspruchung. Eine tiefenpsychologische Untersuchung an Spätheimkehrern" (Neurosis, stress and psychic load. Psychologic studies on returning prisoners-of-war). *Z. Psychosom. Med.* **18**: 48-61 (1972) (19 refs.). G88,778/72

Lipkowitz, M. H.: "The child of two survivors. A report of an unsuccessful therapy." *Isr. Ann. Psychiatry* **11**: 141-155 (1973).

J21,854/73

Description of the morbid changes that may occur in the children of concentration camp survivors.

Ford, C. V., Spaulding, R. C.: "The Pueblo incident. A comparison of factors related to coping with extreme stress." *Arch. Gen. Psychiatry* **29**: 340-343 (1973). J19,551/73

Horowitz, M. J.: "Phase oriented treatment of stress response syndromes." *Am. J. Psychother.* **27**: 506-515 (1973).

J17,978/73

In concentration camp survivors, psychologic "stress response syndromes" may persist for decades. Their characteristics are classified and treatment schedules recommended. Even viewing "stress films" may induce persistent, intrusive and repetitive thoughts in normal subjects (23 refs.).

Dimsdale, J. E.: "The coping behavior of Nazi concentration camp survivors." *Am. J. Psychiatry* **131**: 792-797 (1974).

J13,409/74

Haine, J. C.: "Evaluation des sequelles invalidantes tardives de la captivité trente ans après le conflit 40-45" (Evaluation of delayed consequences of captivity thirty years after the war of 1940-45). *Brux. Méd.* **54**: 639-653 (1974) (39 refs.). H97,404/74

Kestenberg, J.: "Kinder von Überlebenden der Naziverfolgungen. Psychoanalytische Beiträge" (Psychoanalytic contributions to the problems of children of survivors of Nazi persecution). *Psyche* (Stuttg.) **28**: 249-265 (1974). J23,866/74

Segall, A.: "Spätreaktion auf Konzentrationslagererlebnisse" (Delayed reaction to concentration camp experiences). *Psyche* (Stuttg.) **28**: 221-230 (1974).

J23,864/74

Bastiaans, J.: "The KZ-syndrome. A thirty year study of the effects on victims of Nazi concentration camps." *Rev. Med. Chir. Iași* **78**: 573-578 (1974). J21,042/74

"The best frame of reference for the description of the KZ-syndrome is given in Selye's General Adaptation Syndrome with the four phases of shock, alarm, adaptation and exhaustion. The shock phase was reality already during the war, immediately following the first exposure to war stress. The post-concentration camp syndrome consists of the three phases of alarm, adaptation and exhaustion."

Busse, E. W.: "Criteria for determination of premature aging attributed to prisoner-of-war status." *J.A.M.A.* **231**: 521 (1975).

H98,500/75

"Secondary aging refers to changes resulting from stress, trauma, and infection (all factors in combat and internment)." The life expectancy of POWs after release may be normal or increased, depending upon circumstances during internment.

Relocation and Travel

(See also Circadian Variations, Diseases of Adaptation in Animals—shipping fever; Aerospace, and other sections dealing with stressors likely to be encountered during relocation and travel)

Considerable literature exists on the stressor effect of relocation from a familiar to an unfamiliar environment. Most of this work is concerned with voluntary or en-

forced transfers of entire populations, often into an environment totally differing in climate, culture and ethnic characteristics. Various studies have analyzed the problems of nomads, migrant workers and explorers of Arctic or tropical regions, as well as the effects of long-distance travel. Other experiments have indicated the difficulties of becoming accustomed to prolonged life in hospitals, homes for the aged or schools far removed from home. However, most of these studies have been limited to psychosocial observations with only occasional references to somatic manifestations of the G.A.S.

In psychiatric patients, increased corticoid excretion was noted following their journey to the hospital.

In men on an Antarctic expedition, 17-OHCS elimination as well as blood cholesterol and phospholipid levels were enhanced during the first month of the winter. But most of the pertinent studies have been performed on small groups in which it was virtually impossible to separate the effects of relocation itself from those of numerous incidental associated factors, such as desynchronization of the circadian cycle, variations in temperature, atmospheric pressure and the psychosocial elements that induce people to change their environments.

The classic indicators of stress subject to quantitative measurements have received more attention in animal experiments. Thus, in rats, a slight environmental change caused by transfer from one room to another may be associated with an enormous increase in plasma free corticoid concentrations. In squirrel monkeys captured in Colombia, serum cholesterol rose significantly during transportation to North Carolina. However, most of the changes characteristic of stress in captive wild animals have already been considered in a preceding section.

Relocation, Travel

(See also our earlier stress monographs, p. xiii)
and *cf.* *Shipping Fever*)

Pedersen, S.: "Psychopathological reactions to extreme social displacements (refugee neuroses)." *Psychoanal. Rev.* **36**: 344-354 (1949). B35,072/49

Discussion of psychologic problems and their relation to social displacement, particularly forced emigration to foreign environments including concentration camps.

Jasmin, G.: "Stress and travel." *Int. Rec. Med.* **168**: 528-532 (1955). C5,856/55

Popular outline of the G.A.S. in relation to travel.

Maule, H. G., Martin, F. M.: "Social and psychological aspects of rehousing." *Adv. Sci.* **12**: 443-453 (1956). D83,114/56

Martin, F. M., Brotherston, J. H. F., Chave, S. P. W.: "Incidence of neurosis in a new housing estate." *Br. J. Prev. Soc. Med.* **11**: 196-202 (1957). J11,592/57

The high incidence of stress-induced neu-

roses in the population of new housing estates is attributed to adaptive difficulties created by relocation.

Sloane, R. B., Saffran, M., Cleghorn, R. A.: "Autonomic and adrenal responsiveness in psychiatric patients. Effect of methacholine and corticotropin." *Arch. Neurol. Psychiatry* **79**: 549-553 (1958). C52,524/58

In psychiatric patients, corticoid excretion is raised following "the stress of their special journey to hospital and their relative unfamiliarity with the setting."

Fortier, C.: "Sensitivity of the plasma free corticosteroid response to environmental change in the rat." *Arch. Int. Physiol.* **66**: 672-673 (1958). C61,758/58

In rats, "the slight environmental change resulting from the transfer of the animals from one room to the next, possibly associated with fright and a higher level of sensory stimulation, resulted in a 223% increase of the plasma free corticosteroid concentration."

Koranyi, E. K., Kerenyi, A., Sarwer-Foner, G. J.: "On adaptive difficulties of some Hun-

garian immigrants. A sociopsychiatric study." *Med. Serv. J. Can.* **14**: 383-405 (1958).

J11,573/58

Juszkiewicz, T., Jones, L. M.: "Effects of chlorpromazine and ascorbic acid in rats during simulated transportation conditions at normal and high temperatures." *Am. J. Vet. Res.* **22**: 544-548 (1961). J24,117/61

"Under simulated transport conditions, chlorpromazine protects rats against excessive weight losses, excessive depletion of the adrenal ascorbic acid, and the excessive mortality experienced at high temperature. The simultaneous administration of ascorbic acid with chlorpromazine seemed to promote anti-stress effects, particularly at high temperatures."

Blank, P., Owen, S., Peay, R.: "Stressful experiences among hospitalized patients." *Hospitals* **35**: 55-60 (1961). J23,942/61

Mehta, J. N.: "Emotional stress on patients due to hospitalisation." *J. Ind. Med. Assoc.* **41**: 268-269 (1963). J22,392/63

Budd, G. M.: "General acclimatization to cold in men studied before, during and after a year in Antarctica." *ANARE Repl. Ser. B* **4**: 1-84 (1964). G43,355/64

The results of an expedition showed that "in Antarctica a highly significant improvement occurred in the men's ability to maintain rectal temperature during acute cold stress." Heat production and skin temperature did not change significantly (114 refs.). [Various metabolic studies have been performed but alterations characteristic of non-specific stress have not been reported, and hence it is difficult to draw general conclusions beyond those applicable to the Antarctic climate as a whole (H.S.).]

Fried, M.: "Transitional functions of working-class communities: implications for forced relocation." In: Kantor, M. B., *Mobility and Mental Health*. pp. 123-165. Springfield, Ill.: Charles C Thomas, 1965. J15,335/65

Review especially concerned with forced relocation of working populations and the need for adaptation to change.

Friedman, S. B., Ader, R.: "Parameters relevant to the experimental production of 'stress' in the mouse." *Psychosom. Med.* **27**: 27-30 (1965). G26,082/65

"Merely moving mice from standard laboratory cages to experimental cages resulted in a significant decrease in weight gain."

Hall, P.: "Some clinical aspects of moving house as an apparent precipitant of psychiatric symptoms." *J. Psychosom. Res.* **10**: 59-70 (1966). J23,660/66

Wolpert, J.: "Migration as an adjustment to environmental stress." *J. Soc. Issues* **22**: 92-102 (1966). F75,120/66

Theoretical discussions on the sociologic factors causing migration to distant areas or from and to city regions predominantly occupied by certain ethnic or racial groups. [No reference is made to the somatic aspects of stress (H.S.).]

Sainsbury, P., Collins, J.: "Some factors relating to mental illness in a new town." *J. Psychosom. Res.* **10**: 45-51 (1966).

J13,502/66

Description of neurotic changes in people who moved from London to Crawley New Town in Sussex, England.

Fernea, R. A., Kennedy, J. G.: "Initial adaptations to resettlement: a new life for Egyptian Nubians." *Curr. Anthropol.* **7**: 349-354 (1966). J15,344/66

Simpson, H. W.: "Field studies of human stress in polar regions." *Br. Med. J.* March 4, 1967, pp. 530-533. F78,155/67

In men at a British Antarctic sledging base, eosinopenia was especially marked in the evening after a full day of travel. Similarly, in a party skiing 400 miles across Greenland, 17-OHCS excretion was high during the forty days of crossing from coast to coast. No adaptation to stress occurred.

Novick, L. J.: "Easing the stress of moving day." *Hospitals* **41**: 64-74 (1967).

J24,294/67

Friedman, S. B., Ader, R.: "Adrenocortical response to novelty and noxious stimulation." *Neuroendocrinology* **2**: 209-212 (1967).

F90,171/67

In rats placed in a new experimental cage, plasma corticosterone levels rose almost equally regardless of whether they were exposed to electric shocks. Apparently, "exposure to a new environment, or novelty, may contribute significantly to the adrenocortical response often attributed entirely to the effects of noxious or painful stimulation."

St. Clair, R. W., MacNinch, J. E., Middleton, C. C., Clarkson, T. B., Lofland, H. B.: "Changes in serum cholesterol levels of squirrel monkeys during importation and acclimation." *Lab. Invest.* **16**: 828-832 (1967).

H1,895/67

In squirrel monkeys (*Saimiri sciureus*) captured in Colombia, serum cholesterol rose significantly after transportation to North Carolina. This response was much less obvious in animals kept in a semisecluded environment than in those caged in laboratories with relatively high noise levels and frequent contact with men. The cholesterol changes could be completely accounted for by a similar fluctuation in β -lipoprotein cholesterol without any alteration in α -lipoprotein cholesterol. "It is suggested that the observed changes in serum cholesterol may reflect the squirrel monkeys' reaction to 'stress' resulting from changes in environment." However, the relative importance of relocation, captivity, noise and contact with men is difficult to appraise.

Kral, V. A., Grad, B., Berenson, J.: "Stress reactions resulting from the relocation of an aged population." *Can. Psychiatr. Assoc. J.* **13**: 201-209 (1968). G58,342/68

In subjects relocated to homes for the aged, plasma corticoid levels increased, especially among men who developed organic signs of disease. Of the normal men, 25 percent died within the first six months of relocation, while all normal women survived. More psychotics died than normal subjects.

Tobin, S. S., Etigson, E.: "Effect of stress on earliest memory." *Arch. Gen. Psychiatry* **19**: 435-444 (1968). G61,195/68

With elderly people for whom institutionalization was a severe stressor, reconstruction of their earliest memories was often considerably impaired.

Skipper, J. K. Jr., Leonard, R. C.: "Children, stress and hospitalization: a field experiment." *J. Health Soc. Behav.* **9**: 275-287 (1968). J23,681/68

Parker, S., Kleiner, R. J., Needelman, B.: "Migration and mental illness. Some reconsiderations and suggestions for further analysis." *Soc. Sci. Med.* **3**: 1-9 (1969). J22,108/69

Report on migratory groups which provides "little support for 'culture shock' as an explanatory concept. Such variables as goal-striving stress, reference group orientation, and self-esteem are found to be useful, particularly when the presence or absence of certain pathology-linked characteristics in the same individual is considered."

Markus, E., Blenkner, M., Bloom, M., Downs, T.: "Relocation stress and the aged."

In: Blumenthal, H. T., *The Regulatory Role of the Nervous System in Aging*, pp. 60-71. Basel, München and New York: S Karger, 1970. E8,832/70

Relocation of aged persons from an accustomed to an unknown environment increases morbidity and mortality because it "generates stress and discomfort which call forth coping responses from the relocated person beyond those required by familiar routines." Relocation is particularly damaging to males, especially those with severe mental dysfunctions.

Hashmi, F.: "Immigrants and emotional stress." *Proc. R. Soc. Med.* **63**: 631-632 (1970). H26,830/70

"Immigration causes considerable stress, and in dealing with the problems arising from it and the consequent struggle there are bound to be casualties in the form of psychological or even physical breakdown." Classic biochemical indicators of stress are not mentioned.

Olinescu, A., Olinescu, E., Istrate, N., Oprisan, R., Potorac, E.: "Modificari ale raspunsului imun la soareciile de laborator supusi aciunii factorului stress-ant de transport" (Changes in the immune response of laboratory mice undergoing transport stress). *Microbiol. (Bucur.)* **16**: 417-422 (1971) (Roumanian). J19,887/71

In mice, "transport stress" decreases the titer of antibodies and increases mortality following inoculation with pathogenic organisms.

Carlson, E. T., Noel, P. S.: "Stress and behavior in the founding Pilgrims." *Bull. N.Y. Acad. Med.* **47**: 147-160 (1971). G88,713/71

Hansburg, H. G.: "Separation problems of displaced children." In: Parker, R. S., *The Emotional Stress of War, Violence, and Peace*, pp. 241-262. Pittsburgh, Pa.: Stanwix House, 1972. E10,444/72

A paper on the problems of displaced children separated from their families. Various tests show that there are characteristic patterns of response to separation which are useful in personality evaluation as well as in therapy. The term stress is used very loosely.

"Emotional stress in immigrant workers." *Lancet* June 10, 1972, p. 1276.

H56,204/72
Report on emotional stress problems in

immigrant workers, especially those who came to Belgian mines from various parts of the world. They suffered from a sense of isolation, homesickness and difficulties of adaptation to strange customs, particularly the feeling of being unwelcome by the natives. Symptoms included complaints about living conditions, absenteeism, fatigue and increased general morbidity.

Kecmanović, D., Marković, B., Cerić, I.: "Mental disorders in economic emigrants." *Acta Med. Jugosl.* **26**: 319-327 (1972) (Serbo-Croatian). H60,878/72

Mental disorders and even psychoses are comparatively common among emigrants and are attributed to culture-deprivation stress, although no data are reported on classic biochemical stress indices.

Khomulo, P. S., Popov, A. A., Dmitrieva, N. A.: "The changes in the lipid metabolism and excretion of 17-oxy corticosteroids in the urine in members of polar expeditions during the period of adaptation in the Antarctic." *Kardiologiya* **12** No. 9: 48-52 (1972) (Russian). H80,108/72

In men on an Antarctic expedition, 17-OHCS excretion and blood levels of cholesterol and phospholipids were increased during the first month of wintering, presumably as a consequence of enhanced adrenal cortical activity. Subsequently, some of these values tended to return to normal.

Lumsden, D. P.: "The Volta River Project: village resettlement and attempted rural animation." *Can. J. Afr. Stud.* **7**: 115-132 (1973). J15,924/73

Discussion of the stressor effect of Ghana's Volta River Hydroelectric and Resettlement Project upon the local population.

Dobsinska, E., Lehky, F.: "Effect of transportation as a stress factor on the blood picture of the German shepherd-dog" (Ab-

stracted). *Vet. Med. (Praha)* **18**: 499-506 (1973). J24,388/73

Volicer, B. J.: "Perceived stress levels of events associated with the experience of hospitalization: development and testing of a measurement tool." *Nurs. Res.* **22**: 491-497 (1973). J22,493/73

Moron, P., Gayral, L., Monnier, J., Escande, M., Jourdan, M. C.: "A propos de la psychopathologie des travailleurs immigrés de la région toulousaine. Données étiopathogéniques et cliniques" (The psychopathology of immigrant workers in the Toulouse region. Etio-pathogenic and clinical data). *Bordeaux Méd.* **7**: 633-640 (1974). H85,680/74

Review on the emotional stressor effect of relocation upon immigrants (9 refs.).

Baldwin, D. M., Colombo, J. A., Sawyer, C. H.: "Plasma prolactin, LH, and corticosterone in rats exposed to a novel environment." *Am. J. Physiol.* **226**: 1366-1369 (1974). H88,007/74

In rats exposed to a novel environment, plasma corticosterone levels rose, but the changes in prolactin secretion were greatly dependent upon the presence of other gonadotropic or ovarian hormones.

Lasry, J. C., Sigal, J. J.: "Stress et santé mentale chez un groupe d'immigrants montréalais" (Stress and mental health in a group of Montreal immigrants). *Ann. ACFAS* **41**: 202 (1974). H88,199/74

Walton, J. R.: "Indirect consequences of low-level use of antimicrobial agents in animal feeds." *Fed. Proc.* **34**: 205-208 (1975). H98,529/75

In mammals treated with antimicrobial agents, "one form of stress may be defined in terms of a disturbance of intestinal flora brought on by relocation, group mixing, change of diet, or travel."

Urbanization

(See also Climate, Environment—social, cultural, pollution)

The literature on the stressor effect of urbanization is concerned mainly with problems of town planning, and the avoidance of noise, pollution and psychosocial complications resulting from life in a modern city. However—as in many of the preceding sections on environmental problems—it is difficult to distinguish the stressor effect of urbanization as such from that of its individual components.

In connection with our main topic, it is of interest that in a Zulu population, the stress of urbanization apparently increased the incidence of hypertension, and statistical data suggest that citification predisposes to CHD. In Bedouins and other nomadic Arabs, ulcerative colitis has been noted after settlement in Kuwait City, presumably as a consequence of urbanization. The high incidence of neuroses in certain housing estates has been similarly interpreted.

American blacks of both sexes have higher blood pressure and mortality from heart disease and strokes than do corresponding whites. Pertinent studies in different areas of Detroit suggested that "blood pressure levels were significantly correlated with different patterns of life stress for the essentially working class persons in the high stress area and for the middle class persons in the low stress area."

Urbanization

(See also our earlier stress monographs, p. xiii)

Martin, F. M., Brotherston, J. H. F., Chave, S. P. W.: "Incidence of neurosis in a new housing estate." *Br. J. Prev. Soc. Med.* **11**: 196-202 (1957). J11,592/57

The high incidence of stress-induced neuroses in the population of new housing estates is attributed to adaptive difficulties created by relocation.

Scotch, N. A.: "Sociocultural factors in the epidemiology of Zulu hypertension." *Am. J. Public Health* **53**: 1205-1213 (1963).

J10,864/63

Mean blood pressure was significantly higher in urban than in rural Zulu populations. "There was a relationship between variables observed to be stressful and hypertension."

Bernard, A.: "Vue d'ensemble sur les maladies du progrès" (Survey of the diseases of progress). *J. Sci. Méd. Lille* **81**: 487-496 (1963). J23,713/63

Spencer, J.: *Stress and Release in an Urban Estate. A Study in Action Research*, p. 355. London: Tavistock, 1964.

E10,633/64

Very practical discussion of the stress of urban life and the means to avoid it. However, little attention is given to the purely somatic aspects of the stress mechanism.

Hare, E. H.: "Mental health in new towns: What next?" *J. Psychosom. Res.* **10**: 53-58 (1966). J13,503/66

"Recent studies of mental health in new towns have, I think, added to our knowledge of stress disorders because they have illuminated for neurotic illness some aspects of the relation between organism and environment" (21 refs.).

Martin, A. E.: "Environment, housing, and health." *Urban Studies* **4**: 1-21 (1967). B46,049/67

Detailed analysis of the stress of urban life with special reference to social factors, crowding and housing conditions.

Salem, S. N., Shubair, K. S.: "Non-specific ulcerative colitis in Bedouin Arabs." *Lancet* March 4, 1967, pp. 473-475. F77,588/67

In Bedouins and other nomadic Arabs, ulcerative colitis has been noted after settlement in Kuwait city. Presumably, "the sudden shift from a simple life to a complicated one predisposes these people to the disease."

Marks, R. U.: "A review of empirical findings." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 51-107 (1967). J10,924/67

Extensive review on demographic variables, particularly urbanization, in relation to CHD (154 refs.).

Selye, H.: "Stress and urban development." *A.I.A. Journal* September, 1969, pp. 74-75. Also in: *Arkitektur* **70**: 41-42 (1970). G60,081/69

Brief summary of a lecture on stress in relation to urbanism.

Harburg, E., Schull, W. J., Erfurt, J. C., Schork, M. A.: "A family set method for estimating heredity and stress. I. A pilot survey of blood pressure among Negroes in high and low stress areas, Detroit, 1966-1967." *J. Chron. Dis.* **23**: 69-81 (1970). G78,153/70

American blacks of both sexes have higher blood pressure and mortality from heart disease and strokes than do corresponding whites. A pilot study of blacks in low and high stress areas of Detroit suggested that "blood pressure levels were significantly correlated with different patterns of life stress for the essentially working class persons in

the high stress area, and for the middle class persons in the low stress area. Briefly, working class persons in the high stress area with higher blood pressure levels (adjusted for sex, age and weight) reported greater economic frustration and more satisfaction (sic) with their marital life and their neighborhood than did their normotensive counterparts in the same tract. In contrast, middle class persons with higher blood pressure levels had higher occupational achievements and aspired to even more than did their normotensive neighbors."

Carlestam, G.: "Stress—människoförstöring" (Stress—disturbances in man). *Arkitektur* 79: 4-9 (1970) (Swedish).

H31,000/70

General considerations on the application of the stress concept to urbanism and architecture.

Gutmann, M. C., Benson, H.: "Interaction of environmental factors and systemic arterial blood pressure: a review." *Medicine* (Baltimore) 50: 543-553 (1971).

G33,290/71

Excellent epidemiologic and experimental study showing that hypertension is related to environmental conditions (especially urbanization) requiring continuous behavioral and physical readjustments. "Operant conditioning techniques may be useful in training humans to lower their blood pressure in environmental situations previously associated with pressor responses" (85 refs.).

Glass, D. C., Singer, J. E.: *Urban Stress: Experiments on Noise and Social Stressors*, p. 182. New York and London: Academic Press, 1972.

E3,951/72

Monograph on the stressor effect of noise mainly as a function of predictability and subject control. Despite the title, little is said about other stressors in urban life, but the book—which earned its authors the 1971 Socio-Psychological Prize of The American Association for the Advancement of Science—undoubtedly contains many valuable data

on human responses to psychosocial stressors (about 120 refs.).

Coates, D., Moyer, S., Wellman, B.: "The Yorklea study of urban mental health: symptoms, problems and life events." In: Boydell, C. L., Grindstaff, C. F. et al., *Deviant Behaviour and Societal Reaction*, pp. 420-434. Toronto and Montreal: Holt, Rinehart and Winston, 1972. J16,063/72

Lebowitz, M. D., Toyama, T., McCarroll, J.: "The relationship between air pollution and weather as stimuli, and daily mortality as responses in Tokyo, Japan with comparisons with other cities." *Environ. Res.* 6: 327-333 (1973). J6,551/73

Bugard, P.: *Stress, Fatigue et Dépression. (L'homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue and depression. Man and the aggression of daily life), Vol. 1, p. 294; Vol. 2, p. 302. Paris: Doin Edit., 1974.

E10,487/74

Discussion of urban stress.

Lachnit, V.: "Paraprofessionale Erkrankungen. (Ursachen und Versuch ihrer Verhütung)" (Paraprofessional diseases. Causes and attempts at their prevention). *Wien Med. Wochenschr.* 124: 193-197 (1974).

H84,018/74

A review on the pathogenic effects of various environmental factors such as noise, air pollutants and interpersonal tension, with practical considerations concerning their prophylaxis.

Uhlenhuth, E. H., Lipman, R. S., Balter, M. B., Stern, M.: "Symptom intensity and life stress in the city." *Arch. Gen. Psychiatry* 31: 759-764 (1974). J19,757/74

Miller, F. T., Bentz, W. K., Aponte, J. F., Brogan, D. R.: "Perception of life crisis events: a comparative study of rural and urban samples." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 259-273. New York, London and Sydney: John Wiley & Sons, 1974. E10,794/74

Catastrophe, Accidents

(See also Anxiety)

The psychologic responses to catastrophes and disasters of various kinds—particularly those brought about by bombings, earthquakes, floods, combat, tornadoes, or extreme emotional traumas—have certain elements in common which may be ascribed

to their stressor effect. These have been described as apprehensive avoidance, stunned immobility, apathy, depression, docile dependency, aggressive irritability. The literature contains interesting descriptions of behavior during catastrophes as well as suggestions on protective measures against irrational behavior during disasters, but little is said about the purely medical, especially biochemical, aspects of the associated stress responses.

Catastrophe, Accidents

(See also our earlier stress monographs, p. xiii)

Selye, H., MacLean, A.: "Prevention of gastric ulcer formation during the alarm reaction." *Am. J. Dig. Dis.* **11**: 319-322 (1944). A75,010/44

Brief review of the literature on the frequent occurrence of perforating gastric ulcers among the population of heavily bombed areas during the war, as well as in sailors and soldiers exposed to continual physical and mental strain.

Janis, I. L.: *Air War and Emotional Stress. Psychological Studies of Bombing and Civilian Defense*, p. 280. New York, Toronto and London: McGraw-Hill, 1951. E4,323/51

Monograph on the psychologic consequences of bombing in Hiroshima and Nagasaki, air war in general, and civil defense. [No reference is made to the stress concept in the medical sense, and such terms as adrenal, adrenaline, corticoids, hypothalamus or adaptation syndrome are not even mentioned in the index. The word stress appears to be used as synonymous with mental upset but is nowhere defined, although it is in the title of the book (H.S.).]

Janis, I. L.: "Problems of theory in the analysis of stress behavior." *J. Soc. Issues* **10**: 12-25 (1954). B26,918/54

General discussion of psychologic reactions to catastrophes, particularly tornadoes, bombings, earthquakes, floods and combat. The typical emotional responses to danger are discussed under the following headings: apprehensive avoidance, stunned immobility, apathy and depression, docile dependency and aggressive irritability (15 refs.).

Wallace, A. F. C.: *Human Behavior in Extreme Situations: A Survey of the Literature and Suggestions for Further Research*, p. 35. National Academy of Science, National Research Council Publ. No. 390 (pamphlet). Washington, D.C., 1956. J6,763/56

Susser, M., Stein, Z.: "Civilisation and peptic ulcer." *Lancet* January 20, 1962, pp. 115-119. D46,685/62

"The immediate effects of war are evident in the rise in perforations and deaths from peptic ulcer which followed air-raids and the stress of war." Statistical studies suggest that "because of the sharp rise in morbidity and mortality during this century, peptic ulcer, particularly of the duodenum, has earned a place as one of the 'diseases of civilisation'."

Baker, G. W., Chapman, D. W.: *Man and Society in Disaster*, p. 442. New York: Basic Books, 1962. E10,447/62

Symposium on the roots and consequences of various catastrophes in war and peace. Somatic stress reactions have been considered only by some contributors, but the book does contain interesting observations on the behavior of individuals and groups during disasters.

Latané, B., Wheeler, L.: "Emotionality and reactions to disaster." *J. Exp. Soc. Psychol. Supp.* 1: 95-102 (1966). J17,242/66

Men who observed death and dismemberment in commercial airplane accidents, and who were "independently designated as emotionally nonresponsive, increased communicative behaviors as a function of stress, while emotionally responsive men decreased communication."

Barton, A. H.: *Communities in Disaster. A Sociological Analysis of Collective Stress Situations*, p. 352. Garden City, N. Y.: Doubleday, 1969. E8,320/69

A detailed sociologic study of behavior at times of catastrophe in war and peace. The author speaks of "collective stress" in referring to extreme disaster situations in entire communities, but the purely medical, especially biochemical, aspects of stress reactions are not considered. The volume is of greater value to sociologists than to physicians.

Abram, H. S. (ed.): *Psychological Aspects*

of Stress, p. 98. Springfield, Ill.: Charles C Thomas, 1970. E9,826/70

Proceedings of a symposium sponsored by the University of Virginia School of Medicine and Medical Education for National Defense (MEND). Seven specialists in different aspects of stress discuss psychologic and physiologic reactions to extremely stressful situations such as disasters, life-threatening illness, combat or life in concentration camps and outer space.

Haas, J. E., Drabek, T. E.: "Community disaster and system stress: a sociological perspective." In: McGrath, J. E., *Social and Psychological Factors in Stress*, pp. 264-286. New York, Chicago and San Francisco: Holt, Rinehart and Winston, 1970. E10,327/70

Sociologic studies on stress, especially in connection with group reactions to extreme situations such as community disasters.

Luchterhand, E. G.: "Sociological approaches to massive stress in natural and man-made disasters." *Int. Psychiatry Clin.* 8: 29-53 (1971). J20,180/71

Psychosocial studies on victims of floods, hurricanes, wars and genocide.

Parker, R. S.: *The Emotional Stress of War, Violence, and Peace*, p. 292. Pittsburgh, Pa.: Stanwix House, 1972. E10,440/72

An anthology of papers presented at the symposiums sponsored by the Brooklyn Psychological Association in November 1968 at which representatives of various countries, particularly the U.S.A., spoke about the stressor effects of violence, especially war. Mainly social and psychologic problems are discussed, and the term stress is used rather loosely as a synonym for tension.

Milburn, T. W.: "A comparison of the effects of crises and disasters on values." In: Parker, R. S., *The Emotional Stress of War Violence, and Peace*, pp. 270-283. Pittsburgh, Pa.: Stanwix House, 1972. E10,445/72

Various crises and disasters are considered as "social stressors," and mechanisms of adjustment to them are discussed. The term stressor is used essentially to refer to a state of tension, without being related to medical indices of the stress syndrome.

Luff, K., Karger, J. von: "Zur Frage der Verhaltenskontrolle von Kraftfahrern nach Verkehrsunfällen unter Berücksichtigung des Schuldmasses" (Behavioral self-control of drivers following road accidents with reference to the degree of guilt). *Beitr. Gerichtl. Med.* 31: 18-21 (1973). J17,717/73

The stressor effect of an automobile accident may lead to an immediate disturbance of decision making, conducive to flight from the scene of the accident. The legal implications in German courts are described.

Ziv, A., Israeli, R.: "Effects of bombardment on the manifest anxiety level of children living in kibbutzim." *J. Cons. Clin. Psychol.* 40: 287-291 (1973). J20,147/73

A Hebrew version of the Children's Manifest Anxiety Scale was administered to children in frequently shelled kibbutzim and in others where life was peaceful. Contrary to expectations, there was no great difference in the anxiety level of the two groups.

Kinston, W., Rosser, R.: "Disaster: effects on mental and physical state." *J. Psychosom. Res.* 18: 437-456 (1974) (117 refs.).

J19,269/74

BIORHYTHMS

(See also Characteristic Manifestations of Stress—sexual cycle)

Stress in relation to such biorhythms as circadian, lunar and seasonal variations, menstrual cycles and so on, has attracted much attention, but comparatively few investigators have described quantitative alterations in parameters indubitably related to nonspecific, that is, stressor effects.

Circadian

Among all biorhythms, circadian variations have probably received the greatest attention, especially in connection with desynchronization as a result of ever more com-

mon travel from one time zone to another. Of course, prolonged space or submarine voyages, and life in subterranean caves or polar regions, where some of the diurnal changes in lighting, sunshine and social activities, including feeding times, deviate from the norm, as well as working in variable shifts during the day make this aspect of "chronobiology" especially timely. For rapid orientation the reader is advised to consult some of the excellent general *review* articles mentioned below. The topics most immediately concerned with the stressor effect of circadian variations are: changes in CRF, corticoids, ACTH, catecholamines, insulin, 5-HT and histamines. Also, there are some data on fluctuations in blood count, stress ulcer formation, and particularly, data comparing the activity of diverse drugs given at different times of the day.

In man, the blood and urinary levels of *corticoids* and their metabolites are generally high between 06:00 and 08:00, and low between 20:00 and 22:00, but this may vary with the time people arise or go to sleep and is considerably deranged among shift workers with uncommon sleeping times. The usual pattern may be interrupted by sudden bursts of corticoid secretion at irregular times throughout the day. According to some investigators, the periodicity is not changed in night workers or blind people, whereas others maintain that the dark-light cycle is an important synchronizer of pituitary-adrenal activity.

Observations on people kept in underground chambers with artificial dark-light cycles, and later in complete darkness, led investigators to the conclusion that social cues are sufficient to maintain the human circadian rhythm in the absence of light. Yet it has been claimed that the dark-light cycle may be an important regulator of circadian pituitary-adrenal activity.

In mice, the circadian rhythm of blood corticosterone changes during various phases of the circannual cycle and differences in lighting are thought to play an important role here.

Perhaps many external signals can act alternately as cues regulating the circadian cycle, and if one pathway is blocked, another can replace it if it recurs regularly at twenty-four-hour periods. This may explain why, under certain circumstances, disturbance of the light-dark cycle or of social cues in daily activities does derange circadian fluctuations in hormone secretion, at least temporarily. The situation is somewhat comparable to that of a blind man who previously depended on his sight for orientation but who has since learned to a remarkable degree how to be guided by touch, sound and other stimuli. However, it appears to be well established, as we shall see later, that the "cue" must be external, since a total interruption of sensory input into the hypophysiotropic area of the hypothalamus definitely abolishes circadian cycles in hormone production. We must abandon the idea of finding "the" signal for circadian rhythms, because we now have definite evidence that many exogenous rhythms can act as time signals (the Germans call them *Zeitgeber*).

In patients with diabetes insipidus, the circadian variations in plasma cortisol are normal, which suggests that vasopressin is not an important neurohumoral regulator of ACTH secretion. One group of investigators claims that approximately half of man's daily cortisol production is achieved during early morning hours and sleep, when secretory episodes are temporally related to REM sleep. It is estimated that corticoids are synthesized during only six hours of the day.

In animals, the circadian cycles in corticoid production are essentially similar, al-

though on this point observations on various species have yielded dissimilar results. In monkeys, cortisol is secreted episodically, increasing in frequency and concentration during the latter part of the night and the early morning hours.

Many of the apparent contradictions in the literature are due to the fact that animals differ in their sleep-wake cycles. For example, rats—so commonly used for this type of experimentation—are essentially nocturnal animals that sleep during most of the day.

In rats, sectioning of the fornix abolishes the circadian variations in plasma corticosterone by raising the lowest and decreasing the highest daily values. The circadian rhythm is also prevented by total deafferentation or selective transection of the anterior pathways to the MBH, but not by transection of the lateral or dorsal and posterior connections to it; yet a basal ACTH secretion is maintained in the absence of neural input.

Allegedly, in rats the pituitary-adrenal response to ether or restraint is not markedly altered by circadian variations in plasma corticosterone levels, but injection of dexamethasone at noon suppresses it, without affecting a rise in corticoids during stress (ether, restraint, handling).

Much less attention has been given to circadian fluctuations in *ACTH* production. The few available data confirm that—as might be expected—it roughly parallels corticoid synthesis.

We also have evidence of circadian variations in *CRF* production. In rats, hypothalamic tissue obtained every three hours revealed an increase in CRF activity from early morning through the midafternoon, coincident with elevated levels of plasma corticosterone. The peak concentration of plasma corticosterone was reached approximately two hours prior to the onset of the dark period; concurrently, there was a precipitous drop in CRF activity, followed by a rapid return to a high level within three hours.

In the rat, CRF activity of the hypothalamus reached a peak at 18:00 and a minimum at 20:00, paralleling plasma corticosterone levels. This CRF rhythm is not significantly affected by adrenalectomy, and hence is presumably independent of a corticoid feedback mechanism.

In pigeons, plasma *STH* reaches a peak at 06:00 and a nadir at 18:00. This curve is correlated with corresponding changes in plasma FFA levels.

The circadian cycles of *catecholamine* production are much less clearcut and are readily influenced by desynchronization and numerous incidental stressors that may affect animals or man during the day.

Also, there is some evidence of diurnal variations in *STH*, *insulin*, *5-HT* and *histamine* production in mammals, but in all these respects the available data are insufficient to justify generalizations. Some results suggest that serotonergic neurons play a role in circadian fluctuations of pituitary-adrenal function, because the *5-HT* content of the hippocampus and amygdala exhibits a circadian rhythm which roughly parallels that of plasma corticosterone; this rhythm can be eliminated by p-chlorophenylalanine, which blocks *5-HT* synthesis. However, this drug has such strong stressor actions in itself that it reduces food intake and causes hypertrophy of the adrenals along with other signs of the alarm reaction, so that “the proposed relation between decreased brain 5-hydroxytryptamine content and pituitary-adrenal periodicity is questioned.”

In mice, eosinopenia is most pronounced at about 03:00 and least between 14:00 and 17:00. The reverse is true in man, but in both species strong light causes eosinopenia at all times, presumably owing to its stressor effect.

In rats, restraint-induced *stress ulcers* of the stomach develop more rapidly during the active night period than during the day. This is another indication of circadian variations in stress responses.

In general, various physiologic and psychologic indicators of desynchronization following flights from *east to west* are of shorter duration than after comparable trips in the opposite direction.

The circadian rhythms in *body temperature* are too well-known to deserve special discussion here, but they also are deranged during desynchronization.

Generalities

(See also our earlier stress monographs, p. xiii)

Sollberger, A.: *Biological Rhythm Research*, p. 461. Amsterdam, London, and New York: American Elsevier, 1965.

E6,390/65

Monograph on biologic rhythms (circadian, lunar, seasonal), with models and a mathematical-statistical analysis of cybernetic mechanisms in general. Their relationship to the G.A.S. is considered in many connections (several hundred refs.).

Luce, G. G.: *Body Time: Physiological Rhythms and Social Stress*, p. 394. New York: Pantheon, 1971. E10,777/71

Monograph on biorhythms, with special reference to their effect upon stress reactions (about 1,200 refs.).

Hatotani, N. (ed.): *Psychoneuroendocrinology*. (Workshop Conf. Int. Soc. Psycho-neuroendocrinology, Mieken, 1973), p. 312. Basel, München and Paris: S Karger, 1974. E10,797/74

Report on a symposium with the participation of numerous experts (predominantly Japanese). Special sections are devoted to "Stress and Biological Rhythm" and "Regulation of Hypothalamo-Pituitary Function."

Kawakami, M. (ed.): *Biological Rhythms in Neuroendocrine Activity*, p. 353. Tokyo: Igaku Shoin, 1974. E10,857/74

Valuable monograph summarizing data on the effect of various biorhythms in relation to hormones and nervous activity, and stress responses (several hundred refs.).

Circadian

(See also our earlier stress monographs, p. xiii)

Generalities. Aschoff, J., Gerecke, U., Wever, R.: "Desynchronization of human circadian rhythms." *Jap. J. Physiol.* **17**: 450-457 (1967). J11,331/67

Mohler, S. R., Dille, J. R., Gibbons, H. L.: "The time zone and circadian rhythms in relation to aircraft occupants taking long-distance flights." *Am. J. Public Health* **58**: 1404-1409 (1968). G60,504/68

Mohler, S. R., Dille, J. R., Gibbons, H. L.: *Circadian Rhythms and the Effects of Long-Distance Flights*. Federal Aviation Administration, Aviation Med. pamphlet, p. 5. Washington, D.C., 1968. G60,824/68

Description of disturbances in air travelers due to desynchronization after crossing several time zones. Special emphasis is placed on behavioral changes and performance (16 refs.).

Klein, K. E., Wegmann, H. M., Brüner, H.: "Circadian rhythm in indices of human performance, physical fitness and stress resistance." *Aerosp. Med.* **39**: 512-518 (1968). G63,722/68

Haus, E., Halberg, F., Nelson, W., Hillman, D.: "Shifts and drifts in phase of human circadian system following intercontinental flights and in isolation." *Fed. Proc.* **27**: 224 (1968). H64/68

As indicated by various physiologic and psychologic indicators, desynchronization following flights from *east to west* is of shorter duration than after flights in the opposite direction.

Halberg, F.: "Chronobiology." *Annu. Rev. Physiol.* **31**: 675-725 (1969). H8,562/69

Review on "chronobiology" which includes various types of biologic rhythms. Particular attention is given to circadian variations and their relation to steroid metabolism, susceptibility to several harmful agents and the conditioning effect of the external environment (341 refs.).

Siegel, P. V., Gerathewohl, S. J., Mohler, S. R.: "Time-zone effects on the long distance air traveler." *Science* **164**: 1249-1255 (1969). H13,629/69

Review on the principal factors involved in desynchronization during air travel through various time zones, with practical suggestions for treatment.

Aschoff, J.: "Desynchronization and resynchronization of human circadian rhythms." *Aerosp. Med.* **40**: 844-849 (1969).

J7,198/69

Review of various environmental changes that can cause desynchronization and resynchronization of circadian rhythms in man (24 refs.).

Aschoff, J.: "Circadian rhythm of activity and of body temperature." In: Hardy, J. D., Gagge, A. P. et al., *Physiological and Behavioral Temperature Regulation*, pp. 905-919. Springfield, Ill.: Charles C Thomas, 1970.

J7,195/70

Monograph on circadian rhythms of body temperature and their derangements during desynchronization (50 refs.).

Rafikov, A. M., Agadzhanyan, N. A.: "The problem of studying the 24-hour variations of body resistance to stress effects." *Pat. Fiziol. Éksp. Ter.* **15** No. 1: 60-62 (1971) (Russian).

H57,841/71

Aschoff, J.: "Das circadiane System" (The circadian system). *Ergeb. 79. Tag. Dtsch. gesamte inn. Med. Wiesbaden* (1973).

J7,196/73

Review on circadian rhythms in man and the factors that can disrupt them (70 refs.).

Stepanova, S. I.: "Study of the possibility of human adaptation to days of 16-hour duration." *Kosm. Biol. Med.* **7** No. 3: 68-75 (1973) (Russian). Transl. in: *Space Biol. Med.* **7**: 100-109 (1973). H91,915/73

"The body temperature did not change under the influence of a new daily schedule and remained related to the real time of

day." However, sleep cycles were disturbed under these conditions.

Scheving, L. E., Mayersbach, H. von, Pauly, J. E.: "An overview of chronopharmacology." *J. Eur. Toxicol.* **7**: 203-227 (1974). J19,636/74

Review with a large section on circadian variations in drug resistance (over 200 refs.).

→**Hypophyseal Hormones.** Curtis, G. C., Fogel, M. L., McEvoy, D., Zarete, C.: "The effect of sustained affect on the diurnal rhythm of adrenal cortical activity." *Psychosom. Med.* **28**: 696-713 (1966) (61 refs.). G41,456/66

Halász, B., Slusher, M. A., Gorski, R. A.: "Adrenocorticotrophic hormone secretion in rats after partial or total deafferentation of the medial basal hypothalamus." *Neuroendocrinology* **2**: 43-55 (1967). F81,329/67

In rats, a few weeks after deafferentation of the MBH by means of the Halász knife, plasma and adrenal corticosterone levels were greatly increased except in the venous effluent. Unilateral adrenalectomy under ether further elevated the corticosterone levels, and the remaining adrenal underwent compensatory hypertrophy. The circadian rhythm was abolished either by total deafferentation or by selective transection of the anterior pathways to the MBH, but not by transection of the lateral, dorsal and posterior connections to it. Presumably, the anterior pathways convey afferent input for circadian variations. "It is concluded that ACTH secretion of the anterior pituitary is maintained by the MBH in the absence of neural input. For normal ACTH function, however, afferent impulses to the MBH are required."

Matsuyama, H., Ruhmann-Wennhold, A., Nelson, D. H.: "Radioimmunoassay of plasma ACTH in intact rats." *Endocrinology* **88**: 692-695 (1971). H36,540/71

In rats, the ACTH (radioimmunoassay) content of the plasma was higher between 18:00 and 03:00 than between 08:00 and 12:00. This is the opposite of the circadian pattern in man. Metyrapone increased plasma ACTH after two to eight hours. Five minutes after exposure to stress even more pronounced rises were observed.

Dunn, J. D., Arimura, A., Scheving, L. E.: "Effect of stress on circadian periodicity in

serum LH and prolactin concentration." *Endocrinology* **90**: 29-33 (1972).
H50,464/72

Nelson, D. H., Ruhmann-Wennhold, A.: "The assay of ACTH in plasma." *Mt. Sinai J. Med.* **40**: 315-322 (1973). J3,809/73

Description of a sensitive and accurate radioimmunoassay of ACTH in plasma which revealed an almost tenfold increase in patients exposed to various stressors, particularly surgical trauma. However, the peaks were relatively short and might readily be missed in single determinations. The circadian variations generally peaked around 06:00.

McKeown, B. A., John, T. M., George, J. C.: "Circadian rhythm of plasma growth hormone levels in the pigeon." *J. Interdiscipl. Cycle Res.* **4**: 221-227 (1973). J9,766/73

Radioimmunoassays in pigeons revealed a definite circadian cycle of plasma STH reaching a peak at 06:00 and a low at 18:00. This rhythm was correlated with corresponding changes in FFA levels.

Dunn, J. D.: "Circadian variation in adrenocortical and anterior pituitary hormones." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 119-139. Tokyo: Igaku Shoin, 1974.

E10,864/74

Imura, H., Kato, Y., Yoshimoto, Y., Nakai, Y.: "The role of biogenic amines in the regulation of pituitary hormone release in man, with special reference to circadian rhythmicity." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 140-150. Tokyo: Igaku Shoin, 1974.

E10,865/74

Brodish, A.: "Hormonal and behavioral influences on the circadian rhythmicity of the hypothalamic-pituitary-adrenal system." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 253-266. Tokyo: Igaku Shoin, 1974.

E10,873/74

Jacoby, J. H., Sassin, J. F., Greenstein, M., Weitzman, E. D.: "Patterns of spontaneous cortisol and growth hormone secretion in rhesus monkeys during the sleep-waking cycle." *Neuroendocrinology* **14**: 165-173 (1974). H86,424/74

"Cortisol was secreted episodically, increasing in frequency and concentration during the latter portion of the night and early morning hours. Growth hormone was also

secreted episodically but bore no apparent relationship to either sleep stage or time of day."

Angeli, A., Bocuzzi, G., Frairia, R., Biscocci, D.: "Importanza dello studio del ritmo circadiano corticotropinico nella semeiotica funzionale dell'asse ACTH-surrene" (Importance of the study of the corticotropic circadian rhythm in the functional symptomatology of the ACTH-adrenal axis). *Minerva Med.* **65**: 2499-2512 (1974) (about 150 refs.).
J17,017/74

Weitzman, E. D., Nogaire, C., Perlow, M., Fukushima, D., Sassin, J., McGregor, P., Gallagher, T. F., Hellman, L.: "Effects of a prolonged 3-hour sleep-wake cycle on sleep stages, plasma cortisol, growth hormone and body temperature in man." *J. Clin. Endocrinol. Metab.* **38**: 1018-1030 (1974).
H87,274/74

Allen, C. F., Allen, J. P., Greer, M. A.: "Absence of nyctohemeral variation in stress-induced ACTH secretion in the rat." *Aviat. Space Environ. Med.* **46**: 296-299 (1975).
J22,153/75

→**Steroids.** Pincus, G.: "A diurnal rhythm in the excretion of urinary ketosteroids by young men." *J. Clin. Endocrinol. Metab.* **3**: 195-199 (1943). A57,653/43

In healthy young men, 17-KS excretion at night is regularly lower than during the day. Maximum values tend to occur in the morning. The rise may reflect "ordinary daily stresses."

Sandberg, A. A., Eik-Nes, K., Samuels, L. T., Tyler, F. H.: "The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man." *J. Clin. Invest.* **33**: 1509-1516 (1954). B99,413/54

Human blood 17-OHCS levels are highest at 08:00 and decline during the day.

Migeon, C. J., Tyler, F. H., Mahoney, J. P., Florentin, A. A., Castle, H., Bliss, E. L., Samuels, L. T.: "The diurnal variation of plasma levels and urinary excretion of 17-hydroxycorticosteroids in normal subjects, night workers and blind subjects." *J. Clin. Endocrinol. Metab.* **16**: 622-633 (1956).

C15,075/56
The circadian rhythm in plasma 17-OHCS levels reached a peak at about 06:00 and a nadir around midnight. It was followed about two hours later by a similar variation in 17-OHCS excretion. This periodicity was not changed in night workers or blind persons.

Nakadate, G. M., Groot, J. de: "Fornix transection and adrenocortical function in rats." *Anat. Rec.* **145**: 338 (1963).

J11,290/63

After complete bilateral transection of the fornix in rats, the circadian variations of corticosterone production disappeared.

Ulvedal, F., Roberts, J. J.: "Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. VI. Excretion of steroids and catecholamines." *Aerosp. Med.* **37**: 572-578 (1966).

F93,442/66

Men kept in a double-walled space cabin simulator in an oxygen-helium atmosphere showed no significant disturbance in glucocorticoid or catecholamine output. A reversal of the corticoid excretion rhythm was noted in subjects who slept during the day and worked throughout the night (22 refs.).

Zimmermann, E., Critchlow, V.: "Effects of diurnal variation in plasma corticosterone levels on adrenocortical response to stress." *Proc. Soc. Exp. Biol. Med.* **125**: 658-663 (1967).

F86,246/67

In rats, the acute pituitary-adrenal response to ether or restraint is not markedly altered by circadian variations in plasma corticosterone levels.

Ader, R., Friedman, S. B., Grotta, L. J.: "'Emotionality' and adrenal cortical function: effects of strain, test, and the 24-hour corticosterone rhythm." *Anim. Behav.* **15**: 37-44 (1967).

G46,135/67

Lafontaine, E., Ghata, J., Lavernhe, J., Courillon, J., Bellanger, G., Laplane, R.: "Rythmes biologiques et décalages horaires. Etude expérimentale au cours de vols commerciaux long-courriers" (Biologic rhythm and time zone differences. Experimental study during long commercial flights). *Concours Méd.* **89**: 3731-3746; 3963-3976 (1967).

G47,151/67

In airline employees on flights from Paris to Anchorage, with eleven hours of time zone difference, there occurred a decrease in diuresis followed by a "rebound" and a disruption in the circadian rhythm of catecholamine and corticoid elimination.

Lafontaine, E., Lavernhe, J., Courillon, J., Medvedeff, M., Ghata, J.: "Influence of air travel east-west and vice-versa on circadian rhythms of urinary elimination of potassium and 17-hydroxycorticosteroids." *Aerosp. Med.* **38**: 944-947 (1967).

H3,611/67

Studies on transatlantic flight crews show that, among various metabolic parameters, 17-OHCS exhibits the clearest circadian variations. After a quick round trip with twenty hours of exposure to a negative time zone change of eleven hours, the circadian rhythm of potassium and 17-OHCS immediately re-establishes concordance with the preexisting reference rhythm. With five days of exposure to a similar time zone change, the circadian eliminatory rhythm of 17-OHCS begins to adapt itself to local time on the third day and becomes complete by the fifth day, by then being the antithesis of the pre-established reference rhythm.

Dixit, B. N., Buckley, J. P.: "Circadian changes in brain 5-hydroxytryptamine and plasma corticosterone in the rat." *Life Sci.* **6**: 755-758 (1967).

J12,743/67

Experiments on rats "do not indicate any specific time-relationship between changes in brain 5-HT and plasma corticosterone," although both show circadian rhythmicity.

Czakó, L., László, F. A., Kovács, K., Faredin, I., Tóth, I.: "Diurnal variations of the plasma cortisol level in diabetes insipidus." *Acta Med. Acad. Sci. Hung.* **26**: 197-201 (1969).

G67,342/69

In patients with diabetes insipidus, the circadian variations in plasma cortisol are normal. Thus "the results obtained do not support the view that under physiological conditions vasopressin would be the neurohumoral regulator of ACTH secretion."

Zimmermann, E., Critchlow, V.: "Negative feedback and pituitary-adrenal function in female rats." *Am. J. Physiol.* **216**: 148-155 (1969).

H6,475/69

In female rats, 100 µg. per kg. of dexamethasone injected subcutaneously at noon suppressed diurnal variations in plasma corticosterone but not its rise during stress (ether, restraint, handling). Apparently, "it is possible on the basis of sensitivity to negative feedback, to dissociate mechanisms underlying nonstress pituitary-adrenal function from those which support acute responses to the stresses used in these studies."

Orth, D. N., Island, D. P.: "Light synchronization of the circadian rhythm in plasma cortisol (17-OHCS) concentration in man." *J. Clin. Endocrinol. Metab.* **28**: 479-486 (1969).

H11,056/69

In man, the dark-light cycle may be an important synchronizer of the pituitary-adrenal circadian rhythms.

Ceresa, F., Angeli, A., Bocuzzi, G., Molino, G.: "Once-a-day neurally stimulated and basal ACTH secretion phases in man and their response to corticoid inhibition." *J. Clin. Endocrinol. Metab.* **29**: 1074-1082 (1969). H15,880/69

In man, submaximal infusion doses of 6-methylprednisolone or dexamethasone led to partial inhibition of nocturnal and early morning urinary 17-OHCS excretion, but no suppression occurred from 22:00 to midnight unless very massive doses of dexamethasone were administered. It is concluded that "the ACTH-secreting system has 2 daily activity phases with different control mechanisms. One in the nocturnal early morning hours is the result of neural activity directed to the hypothalamus, superimposed on the basal activity and responsible for the circadian rhythm. This once-a-day impulse would appear to be linked to the rapid eye movement sleep stages. Corticoid-induced inhibition in submaximal doses is possible only during this phase. The second phase is characterized by a steady basal activity lasting 24 hours. It is independent of the early morning hour impulse and is resistant to all but massive doses of corticoids."

Haus, E., Halberg, F.: "Circannual rhythm in level and timing of serum corticosterone in standardized inbred mature C-mice." *Environ. Res.* **3**: 81-106 (1970). G73,872/70

In mice, blood corticosterone levels are highest during the winter and lowest during the spring and summer. The circadian rhythm likewise varies during the phases of the circannual cycle. Lighting plays an important role in these changes, although the mechanism of its effect is not yet clear (95 refs.).

Conroy, R. T. W. L., Elliott, A. L., Mills, J. N.: "Circadian rhythms in plasma concentration of 11-hydroxycorticosteroids in men working on night shift and in permanent night workers." *Br. J. Ind. Med.* **27**: 170-174 (1970). H24,017/70

Comparative studies of plasma corticoids were made in newspaper printing shop employees who regularly worked at night and in engineering factory workers on monthly rotation shifts. Among the newspaper workers, maximal concentrations were noted around 14:00 when they awoke, whereas the pattern was much more irregular in the engineering shift employees. "It appears that the adrenal cortical rhythm can be adapted to night work in a community in which this is universal, ac-

cepted and lifelong, but that such adjustment is unusual in men on night shift work for limited periods, and whose associates are mainly following a usual nyctohemeral existence."

Hellman, L., Nakada, F., Curti, J., Weitzman, E. D., Kream, J., Roffwarg, H., Ellman, S., Fukushima, D. K., Gallagher, T. F.: "Cortisol is secreted episodically by normal man." *J. Clin. Endocrinol. Metab.* **30**: 411-422 (1970). H24,101/70

It was shown by various techniques that the circadian cycle of cortisol secretion in man is not a smooth curve when analyzed at short time intervals but represents a jagged line, even without periodic exposure to stressors. It has been demonstrated that "approximately half the day's cortisol production is achieved in the early morning hours during sleep and the secretory episodes are temporally related to rapid eye movement sleep although the relationship is not episode for episode. There was no evidence for steady-state conditions in cortisol level in any portion of the sleep-wake day. It was estimated that the adrenals were secreting at most only 6 hr in a day and were quiescent for the remaining 18 hr." This regulation may be programmed by the CNS.

Hamanaka, Y., Manabe, H., Tanaka, H., Monden, Y., Uozumi, T., Matsumoto, K.: "Effects of surgery on plasma levels of cortisol, corticosterone and nonprotein-bound-cortisol." *Acta Endocrinol. (Kbh.)* **64**: 439-451 (1970). H27,377/70

In preoperative patients, plasma cortisol levels reached a peak at 06:00 and a minimum at 22:00. Surgery caused a steep rise two to four hours after the end of the operation. Plasma corticosterone levels roughly paralleled these values. The percentage of nonprotein-bound plasma cortisol remained almost the same throughout the day but also increased after the operations.

Aschoff, J., Fatranská, M., Giedke, H.: "Human circadian rhythms in continuous darkness: entrainment by social cues." *Science* **171**: 213-215 (1971). H33,965/71

Earlier observations have shown that "cycles of illumination intensity and, to a lesser degree, cycles of environmental temperature are the most important *Zeitgebers* for animals. It has been suggested that in man also light is an important *Zeitgeber* or that it is, at least, responsible for the entrainment of some human rhythms." In the present experi-

ments, catecholamines, 17-OHCS and sodium excretion as well as rectal temperature were compared in people kept in underground chambers with artificial light-dark cycles and later in complete darkness. "Social cues are sufficient to entrain human circadian rhythms, and absence of light has no immediate effect on the functions measured."

Moberg, G. P., Scapagnini, U., Groot, J. de, Ganong, W. F.: "Effect of sectioning the fornix on diurnal fluctuation in plasma corticosterone levels in the rat." *Neuroendocrinology* **7**: 11-15 (1971). H36,762/71

In rats, sectioning of the fornix abolishes the circadian variations in plasma corticosterone by raising the lowest and decreasing the highest values during the day.

Singley, J. A., Chavin, W.: "Cortisol levels of normal goldfish, *Carassius auratus* L., and response to osmotic change." *Am. Zool.* **11**: 653 (1971). J12,378/71

In goldfish, blood cortisol levels show a clear-cut circadian rhythm and a particularly rapid increase following exposure to a variety of stressors.

Dunn, J., Scheving, L.: "Plasma corticosterone levels in rats killed sequentially at the 'trough' or 'peak' of the adrenocortical cycle." *J. Endocrinol.* **49**: 347-348 (1971). H37,824/71

Dunn, J., Scheving, L., Millet, P.: "Circadian variation in stress-evoked increases in plasma corticosterone." *Am. J. Physiol.* **223**: 402-406 (1972). H58,314/72

Broussard, G.: "Bioritmi e stress lavorativo" (Biorhythms and the stress of work). *Minerva Med.* **63**: 3919-3924 (1972). H64,707/72

Corticoid secretion is largely dependent upon circadian rhythms which in turn influence man's ability to perform various types of work.

Hale, H. B., Hartman, B. O., Harris, D. A., Williams, E. W., Miranda, R. E., Hosenfeld, J. M.: "Time zone entrainment and flight stressors as interactants." *Aerosp. Med.* **43**: 1089-1094 (1972). J2,017/72

In flight crews on fifty-four-hour bi- or tri-directional transmeridian missions, urinary corticoid and catecholamine excretion showed rhythmic variability which corresponded to the crews' home base even after several time zones had been crossed. Corticoid and catecholamine responses to flight stressors were least pronounced at 22:00 and

most marked at 06:00 Eastern Standard Time, which corresponded to home base. Essentially similar findings were obtained on fifty-hour missions.

Sobczyk, W., Markiewicz, L.: "Catecholamine excretion in urine during work with high emotional load." *Acta Physiol. Pol.* **23**: 59-65 (1972). J6,003/72

In control room employees at a heat and power station, three-shift work did not change the circadian rhythm of catecholamine and 17-OHCS excretion. The urinary catecholamine and steroid levels were comparatively low although EP elimination increased in proportion to physical activity.

Kawakami, M., Seto, K., Kimura, F.: "Influence of repeated immobilization stress upon the circadian rhythmicity of adrenocorticoid biosynthesis." *Neuroendocrinology* **9**: 207-214 (1972). H56,042/72

"A diurnal rhythm was observed in the activity of adrenocorticoid biosynthesis in non-stressed rabbits, with a maximum at 18:00 and a minimum at midnight. When the animals were exposed to 6 h of immobilization, the adrenocortical biosynthetic activity showed an 80% increase at 3 h and a 40% increase at 6 h; the normal rhythmicity was thus disturbed by exposure to this stressor. The lowest level was observed at 9:00 on the next morning, with a 9 h delay."

Begue, R. J., Gustafsson, J. Å., Gustafsson, S. A.: "Diurnal variations in excretion of corticosteroid metabolites in bile from male and female rats." *J. Steroid Biochem.* **4**: 393-400 (1973). J6,681/73

Roussel, A., Daniel, J. Y., Assenmacher, I.: "Les glucocorticostéroïdes circulants du Lapin, et leurs fluctuations nycthémérales" (Circulating glucocorticoids and circadian variations in rabbits). *C.R. Acad. Sci. (Paris)* **277**: 341-344 (1973). J6,395/73

In rabbits, most plasma corticosterone and cortisol undergo circadian variations, with a peak during the day and a drop at the end of the night. However, the two corticoids do not show complete parallelism.

Lengvari, I., Halász, B.: "Evidence for a diurnal fluctuation in plasma corticosterone levels after fornix transection in the rat." *Neuroendocrinology* **11**: 191-196 (1973). H68,128/73

In rats, the circadian variations in plasma corticosterone disappeared immediately after transection of the fornix, although they reap-

peared a few weeks after this operation. It is concluded that, "contrary to the assumption of other authors, the fornix is not the key structure in the mediation of extrahypothalamic influences to the medial basal hypothalamus that are essential for the diurnal rhythm in plasma corticosterone levels."

Asano, Y., Moroji, T.: "Effects of methamphetamine on daily rhythms of hypothalamic norepinephrine, serotonin and plasma corticosterone levels in the rat." *Life Sci.* **14**: 1463-1472 (1974). J13,478/74

Szafarczyk, A., Moretti, J. M., Boissin, J., Assenmacher, I.: "Effect of time of administration of an inflammatory agent on plasma corticosterone and haptoglobin levels in the rat." *Endocrinology* **94**: 284-287 (1974).

H80,857/74

Haptoglobin, a plasma glycoprotein, is synthesized in the liver of rats under the influence of corticosterone and represents a fairly accurate index of the intensity of inflammatory reactions. In rats injected with turpentine, the fastest and highest haptoglobin levels occurred concurrently with maximum corticosterone hypersecretion after injections at 09:00 while persistently low haptoglobin levels resulted from the phlogogen administration at the time of minimal circadian adrenal reactivity (03:00). "These data are consistent with the concept of an adrenocortical control of haptoglobin biosynthesis."

Ramaley, J. A.: "Correlation between fertility and the serum corticosterone rhythm in mice." *Fed. Proc.* **33**: 282 (1974).

H84,020/74

Ramaley, J. A.: "The changes in basal corticosterone secretion in rats blinded at birth." *Experientia* **30**: 827 (1974). H90,545/74

In rats blinded soon after birth, a circadian rhythm in plasma corticosterone still develops, although somewhat later than in controls.

Bruckdorfer, K. R., Kang, S. S., Khan, I. H., Bourne, A. R., Yudkin, J.: "Diurnal changes in the concentrations of plasma lipids, sugars, insulin and corticosterone in rats fed diets containing various carbohydrates." *Horm. Metab. Res.* **6**: 99-106 (1974).

H86,042/74

Daly, J. R., Evans, J. I.: "Daily rhythms of steroid and associated pituitary hormones in man and their relationship to sleep." *Adv. Steroid Biochem. Pharmacol.* **4**: 61-110 (1974). J15,152/74

Detailed review on the function of the hypothalamo-pituitary-adrenal axis during sleep, with a description of the methodology for EEG measurement of sleep and a periodic drawing of blood specimens using an intravenous catheter throughout the night. The plasma corticoids drop gradually from a zenith at 08:00 to a nadir at 00:00. The circadian rhythm of plasma testosterone has been less carefully studied but appears to run parallel to that of cortisol; however, unlike the latter it cannot be inhibited by dexamethasone. The circadian variations of FSH and LH likewise receive comparatively little attention, but sleep-related rises in LH secretion are regularly observed during adolescence. There are two phases of cortisol elimination, "basal" and "impulsive"; only the latter shows an early morning peak sensitive to corticoid inhibition (about 220 refs.).

Singley, J. A., Chavin, W.: "Serum cortisol in normal goldfish (*Carassius auratus L.*)."
Comp. Biochem. Physiol. [A] **50**: 77-82 (1975). H96,696/75

Data on the circadian rhythm of serum cortisol in normal and cold-stressed goldfish.

Carroll, B. J., Heath, B., Jarrett, D. B.: "Corticosteroids in brain tissue." *Endocrinology* (In press). J20,878/

"A clear circadian variation of brain corticosteroid values was found in mice, together with a rapid elevation of the tissue levels in response to stress. Reduction of both plasma and tissue concentrations was observed after adrenalectomy and in response to dexamethasone treatment of mice. Between 24 and 48 hours *post mortem* mouse brain corticosteroid values decreased greatly." Brain areas not concerned with adrenocortical regulation contain particularly large amounts of corticoids.

→**Catecholamines.** Kärki, N. T.: "The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it." *Acta Physiol. Scand.* **39** Suppl. 132: 1-96 (1956). C26,120/56

Monograph on catecholamine excretion in man as influenced by circadian variations, age, muscular work, emotional stress and sex (160 refs.).

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Circadian rhythms in catecholamine excretion, psychomotor performance and ratings of stress and fatigue

during a 75-hour vigil." *Studia Laboris et Salutis* No. 4: 1-4 (1969). G87.093/69

Observations on thirty-one men of different ages who were deprived of sleep for seventy-five hours. Considerable fatigue and a decline in motor performance developed with an increase in EP excretion. The highest rates occurred during early afternoon, and the lowest throughout the night and early morning hours. The amplitude of the circadian rhythm in EP output was raised by sleep deprivation. The NEP elimination curves were much less regular.

Pátkai, P.: "Inter-individual differences in diurnal variations in alertness, performance, and adrenaline excretion." *Acta Physiol. Scand.* 81: 35-46 (1971).

G84,261/71

EP elimination was highest in the morning in habitual morning workers, decreasing gradually during the day, while evening workers showed nearly constant excretion values.

Kriebel, J.: "Exogenous modifications of circadian rhythms of adrenal hormones in man." *J. Interdiscipl. Cycle Res.* 3: 233-241 (1972). G93.758/72

In a healthy young man, circadian rhythms of EP, NEP, corticoids, 17-KS and other metabolic parameters were examined (1) under normal conditions, (2) during complete isolation without indication of time and (3) after subsequent return to synchronization with the usual social stimuli. Apparently, such stimuli are important in determining the shape of circadian rhythms owing to "(1) the relative late maxima of the catecholamines in synchronisation; (2) the increased amplitude during social activity; (3) abrupt increase in the level of urinary catecholamine excretion at the conclusion of isolation."

Asano, Y., Morozi, T.: "Effects of methamphetamine on daily rhythms of hypothalamic norepinephrine, serotonin and plasma corticosterone levels in the rat." *Life Sci.* 14: 1463-1472 (1974). J13,478/74

Cymerman, A., Francesconi, R., Robinson, S.: "Alteration of diurnal rhythmicities of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) and vanillylmandelic acid (VMA) in man during cold exposure." *Fed. Proc.* 33: 245 (1974). H83,908/74

Krieger, D. T.: "Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity." *Endocrinology* 95: 1195-1201 (1974). H94,131/74

Studies on rats concerning the effect of disrupting the circadian rhythm upon circulating corticoids and hippocampal NEP and 5-HT levels.

Fröberg, J. E.: "Circadian rhythms in catecholamine excretion, performance and selfratings." *Lab. Clin. Stress Res.* (Stockh.) Rev. No. 36: 1-22 (1974). J17,328/74

Observations on man "have shown that adrenaline excretion, performance and subjective arousal are low during the night and high during the day even under conditions of sleep deprivation and regularly spaced meals and other activities. Both the physiological and the psychological arousal rhythms had crests in the small hours."

→Insulin. Holley, D. C., Evans, J. W.: "Effect of confinement on ovine glucose and immunoreactive insulin circadian rhythms." *Am. J. Physiol.* 226: 1457-1461 (1974).

H88,015/74

In rams, "the plasma glucose rhythm peaked at 0000, reached a low value at 1600, and was not affected by cage restraint. During cage restraint, the time of maximum plasma insulin concentration was shifted 4 h from 0000 to 0400, and the daily mean concentration was increased 160% suggesting an increased sensitivity of pancreatic β-cells to glucose."

Bassett, J. M.: "Diurnal patterns of plasma insulin, growth hormone, corticosteroid and metabolite concentrations in fed and fasted sheep." *Aust. J. Biol. Sci.* 27: 167-181 (1974).

J13,836/74

→CRF. Hiroshige, T., Sakakura, M., Itoh, S.: "Diurnal variation of corticotropin-releasing activity in the rat hypothalamus." *Endocrinol. Jap.* 16: 465-467 (1969).

H20,407/69

In rats, there was a close temporal relationship between the CRF activity of the hypothalamus and plasma corticosterone levels, with a peak at 18:00 and a minimum between 04:00 and 08:00. The animals were placed in a lighted room between 06:00 and 19:00 and in darkness between 19:00 and 06:00.

David-Nelson, M. A., Brodish, A.: "Evidence for a diurnal rhythm of corticotrophin-releasing factor (CRF) in the hypothalamus." *Endocrinology* 85: 861-866 (1969).

H18,530/69

In rats, hypothalamic tissue was obtained every three hours and assayed on recipients which were either corticoid-treated or lesioned in the ventral hypothalamus. CRF activity was estimated by the resulting rise in plasma corticosterone. "A gradual increase in CRF activity was found from early morning through midafternoon coincident with increasing levels of plasma corticosterone. At the time of the peak concentration of plasma corticosterone, approximately 2 hr prior to the onset of the dark period, a precipitous drop in CRF activity was observed, followed by a rapid return of CRF activity at the next 3-hr interval."

Hiroshige, T., Sato, T.: "Postnatal development of circadian rhythm of corticotropin-releasing activity in the rat hypothalamus." *Endocrinol. Jap.* 17: 1-6 (1970).

H27,251/70

In rats, the circadian rhythm of plasma corticosterone (a peak in the evening and a nadir in the morning) as well as concurrent circadian variations in hypothalamic CRF content become detectable only when the animals are about three weeks of age.

Hiroshige, T., Sakakura, M.: "Circadian rhythm of corticotropin-releasing activity in the hypothalamus of normal and adrenalectomized rats." *Neuroendocrinology* 7: 25-36 (1971).

H36,764/71

In the rat, the CRF activity of the hypothalamus shows a definite circadian rhythm with a peak at 18:00 and a minimum at 08:00. This closely parallels plasma corticosterone levels. The CRF rhythm is not significantly affected by adrenalectomy and hence it is presumably of neural origin, independent of the negative corticoid feedback mechanism.

Seiden, G., Brodish, A.: "Persistence of a diurnal rhythm in hypothalamic corticotropin-releasing factor (CRF) in the absence of hormone feedback." *Endocrinology* 90: 1401-1403 (1972).

H54,781/72

Through use of an improved pituitary incubation method, "a diurnal rhythm of hypothalamic CRF activity in hypophysectomized rats was detected which parallels the rhythm found in intact rats. Absolute levels of hypothalamic CRF activity were higher in the hypophysectomized rats than in the intact rats at all times of the day tested." Although ACTH and/or corticoids influence the concentration of CRF, the diurnal rhythm of its activity is independent of hormonal feedback.

Hiroshige, T., Abe, K.: "Dynamics of activity of hypothalamic corticotropin releasing factor in the rat." *J. Physiol. Soc. Jap.* 34: 529-530 (1972). H79,788/72

In rats, the circadian rhythm in hypothalamic CRF content (with a peak in the afternoon and a nadir in the morning) develops after two to three weeks of postnatal life, whereas responses to stress occur as early as the seventh day. The circadian rhythm persists in the absence of circulating corticosterone and hence appears to be dependent only upon nervous regulation, not upon negative feedback.

Takebe, K., Sakakura, M.: "Circadian rhythm of CRF activity in the hypothalamus after stress." *Endocrinol. Jap.* 19: 567-570 (1972).

J17,033/72

In intact, adrenalectomized or hypophysectomized rats, the increment in the CRF content of the ME after ether stress was greatest at 08:00 and smallest at 18:30. The final poststress level was essentially the same, but the resting level was highest in the late afternoon. "Thus it is likely that the response of ACTH release to stimulus is not influenced by the diurnal rhythm of plasma corticoids or ACTH, but is related to other factors such as inherent neural sensitivity to stress."

Hiroshige, T.: "Circadian rhythm of corticotropin-releasing activity in the rat hypothalamus: an attempt at physiological validation." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 267-280. Tokyo: Igaku Shoin, 1974.

J17,356/74

Correlation between the stress-induced increase and the circadian rhythm of CRF activity in the rat hypothalamus (72 refs.).

→ **Other Hormones.** Mandell, A. J.: "Some determinants of indole excretion in man." In: Wortis, J., *Recent Advances in Biological Psychiatry*, Vol. 5, pp. 237-256. New York: Plenum Press, 1963.

D68,081/63

Indole and corticoid excretion showed similar circadian variations and rises after ACTH treatment or exposure to stressors (70 refs.).

Scapagnini, U., Moberg, G. P., Loon, G. R., van Groot, J. de, Ganong, W. F.: "Relation of brain 5-hydroxytryptamine content to the diurnal variation in plasma corticosterone in

the rat." *Neuroendocrinology* 7: 90-96 (1971). H36,747/71

In rats, the 5-HT content of the hippocampus and amygdala exhibits a circadian rhythm which roughly parallels that of plasma corticosterone. p-Chlorophenylalanine (PCPA), which blocks 5-HT synthesis, increases the a.m. and decreases the p.m. plasma corticosterone levels so that the circadian variations are largely eliminated. "The results suggest that 'serotonergic' neurons play a role in the diurnal fluctuation in pituitary-adrenal function."

Vaisf'd, I. L., Il'icheva, R. F.: "Diurnal rhythm of the content of biogenous amines (histamine, serotonin) in human blood under normal conditions and during altered work-sleep cycles." *Kosm. Biol. Med.* 6 No. 5: 56-62 (1972) (English translation of Russian original). H79,765/72

The histamine-diaminoxidase system shows considerable circadian variations in healthy subjects. The blood 5-HT content tends to decrease at night. Changes in the work-sleep cycle cause fluctuations in these parameters "related not only to the stressor applied, but also to the initial state of the organism." These findings are especially important in space medicine.

Delft, A. M. L. van, Kaplanski, J., Smelik, P. G.: "Circadian periodicity of pituitary-adrenal function after p-chlorophenylalanine administration in the rat." *J. Endocrinol.* 59: 465-474 (1973). H80,867/73

Several investigators have suggested that the circadian periodicity of the pituitary-adrenal axis is regulated by 5-HT and abolished by p-chlorophenylalanine (PCPA). It has now been shown that in rats PCPA-induced changes in pituitary-adrenal periodicity coincide with reduced food intake and body growth, adrenal enlargement and other signs of stress. In view of these marked stressor actions of the drug, "the proposed relationship between decreased brain 5-hydroxytryptamine content and pituitary-adrenal periodicity is questioned."

Asano, Y., Moroji, T.: "Effects of methamphetamine on daily rhythms of hypothalamic norepinephrine, serotonin and plasma corticosterone levels in the rat." *Life Sci.* 14: 1463-1472 (1974). J13,478/74

→**Morphology.** Pincus, G.: "Studies of the role of the adrenal cortex in the stress of

human subjects." *Recent Prog. Horm. Res.* 1: 123-145 (1947). 98,426/47

Excellent review on the biochemical changes characteristic of the G.A.S. in man, with special reference to 17-KS excretion and blood count as influenced by circadian variations, the stresses of daily life, operating a Hoagland-Werthessen pursuit meter, flying and exposure to heat. The response of schizophrenics is abnormal in many respects, and the question is raised whether adrenal malfunction may play a pathogenic role in mental disease (20 refs.).

Louch, C., Meyer, R. K., Emlen, J. T.: "Effect of stress on diurnal fluctuations in eosinophils of the laboratory mouse." *Proc. Soc. Exp. Biol. Med.* 82: 668-671 (1953).

B82,222/53

In mice there are pronounced circadian variations in eosinophil counts showing peaks during the day and drops during the night, presumably owing to the characteristic nocturnal activity of this species. Exposure to cold decreases the eosinophil count but does not eliminate the circadian fluctuations. Presumably, nocturnal activity in these experiments acts as a secondary stress superimposed upon the sustained stress of exposure to cold, and the adrenal gland "is capable of responding further to the daily stress of nocturnal activity."

Hollwich, F., Tilgner, S.: "Reaktionen der Eosinophilen-Zahl auf okulare Lichtreize" (Changes in blood eosinophil count after ocular light stimulation). *Dtsch. Med. Wochenschr.* 89: 1430-1436 (1964). F17,971/64

The blood eosinophil count reaches a maximum in man and a minimum in mice at about 03:00. The reverse is true between 14:00 and 17:00. In both species, intense light causes eosinopenia at all times; this is ascribed to its stressor effect and the resulting alarm reaction.

Kreyberg, L., Evensen, A., Iversen, O. H.: "Influence of stress on the diurnal rhythm in the mitotic activity in the epidermis of hairless mice." *Acta Pathol. Microbiol. Scand.* 64: 176-184 (1965). G31,802/65

In hairless mice, epidermal mitotic counts show regular circadian variations due to the duration, not the rate, of mitoses. This is true even after the circadian rhythmicity has been markedly changed by "acoustic stress."

+**Varia.** Ader, R.: "Gastric erosions in the rat: effects of immobilization at different

points in the activity cycle." *Science* **145**: 406-407 (1964). F16,095/64

Ader, R.,: "Behavioral and physiological rhythms and the development of gastric erosions in the rat." *Psychosom. Med.* **29**: 345-353 (1967). H62,749/67

Rats develop stress ulcers of the stomach much more readily if they are *immobilized* during the active (18:00 to 03:00) period than during the inactive period of their diurnal cycle.

Chou, B. J., Besch, E. L.: "Feeding biorhythm alterations in *heat-stressed* rats." *Aerosp. Med.* **45**: 535-539 (1974).

J13,391/74

Fioretti, M. C., Riccardi, C., Menconi, E., Martini, L.: "Control of the circadian rhythm of the body temperature in the rat." *Life Sci.* **14**: 2111-2119 (1974).

J14,493/74

"The circadian rhythm of the rat body

temperature is abolished in rats kept either in constant dark or light or blinded. The suppressive effects act most likely via the retinas. The rhythm can be inverted by reversal of the *lighting* regimen and it is unaffected by pinealectomy. Most likely the circadian rhythm is not related to changes in patterns of motor activity" (15 refs.).

Davies, J. A., Navaratnam, V., Redfern, P. H.: "The effect of phase-shift on the passive avoidance response in rats and the modifying action of chlordiazepoxide." *Br. J. Pharmacol.* **51**: 447-451 (1974).

H92,485/74

"In rats trained to a 12 h light-12 h dark cycle, advancing the phase by 6 h produced a resynchronization of the 24 h variation in passive avoidance response (PAR) which was completed after 10 days." *Chlordiazepoxide* lessened the disruptive effect of phase-shift. The clinical implications of this work are discussed.

Seasonal Variations

In rats, tourniquet shock and traumatic injuries produce greater mortality in November than in June or July. The cause of this seasonal variation is unknown.

The plasma corticosterone and ascorbic acid levels of the rat do not appear to show any consistent seasonal changes. However, in mice, blood corticosterone levels are allegedly highest during the winter and lowest throughout the spring and summer. The circadian rhythms likewise differ during various phases of the circannual cycle; this may explain some contradictory observations on diurnal variations in the corticoid production of rodents.

Seasonal Variations

(See also our earlier stress monographs, p. xiii)

Ankier, S. I., Dawson, W., Karady, S., West, G. B.: "Seasonal variation in the resistance of rats." *J. Pharm. Pharmacol.* **17**: 187-188 (1965). G26,781/65

In the rat, traumatic shock (Noble-Collip drum) and tourniquet shock elicited greater mortality in November than in June or July. The cause of this seasonal variation in stress resistance could not be determined.

Sanchez, C., Miya, T. S., Bousquet, W. F.: "Effects of conditioning upon stress responses in the rat." *Proc. Soc. Exp. Biol. Med.* **123**: 615-618 (1966). F73,973/66

Pretreatment of rats with small amounts of intravenous sodium chloride for five days

inhibited the marked elevation of plasma corticosterone induced by saline in nonpretreated controls. Similar pretreatment offered no protection, however, against the more pronounced stressor effect of intravenous histamine. The resting plasma corticosterone and ascorbic acid levels did not show any consistent seasonal variation and there was no manifest relationship between the two values. This "suggests that caution be employed in relying upon adrenal ascorbic acid determinations as an index of adrenocortical activity or response to stressors."

Aschoff, J.: "Adaptive cycles: their significance for defining environmental hazards." *Int. J. Biometeorol.* **11**: 255-278 (1967).

J7,197/67

Review of various biorhythms (circadian,

lunar, seasonal) that clearly distinguishes the endogenous from those depending upon environmental factors, particularly stress. Among the seasonal rhythms, it is interesting that acts of violence and riots occur most frequently during the warm season, and that in six European countries monthly suicide rates invariably peak during the summer (about 60 refs.).

Fontaine, M.: "Les poissons migrateurs" (Migrating fish). *Atomes* **24**: 715-720 (1969). G81,184/69

Brief semipopular review on the stressor effect of seasonal migration in fish.

Haus, E., Halberg, F.: "Circannual rhythm in level and timing of serum corticosterone in standardized inbred mature C-mice." *Environ. Res.* **3**: 81-106 (1970).

G73,872/70

In mice, blood corticosterone levels are highest during the winter and lowest during the spring and summer. The circadian rhythm likewise varies during the phases of the circannual cycle. Lighting plays an important role in these changes, although the mechanism of its effect is not yet clear (95 refs.).

Naumenko, E. V., Popova, N. K., Starygin, A. G.: "Pituitary-adrenal system of animals in groups and in isolation." *Zh. Obshch. Biol.* **32**: 731-739 (1971) (Russian).

J21,443/71

"The reaction of the pituitary-suprarenal system to seasonal influences in the isolated

rats differed markedly from that in the rats kept in groups; in the former the level of corticosterone in May sharply increased as compared with that in winter, while in the latter it decreased." It is concluded that reactivity to stressors is weakened during the summer. In rats with the highest index of dominance, plasma corticosterone levels were particularly low during the winter.

Morimoto, T., Shiraki, K., Asayama, M.: "Seasonal difference in responses of body fluids to heat stress." *Jap. J. Physiol.* **24**: 249-262 (1974). J15,690/74

Simon, N., Reinboth, R.: "Adenohypophyse und Hypothalamus. Histophysiologische Untersuchungen bei Lepomis (Centrarchidae)" (Adenohypophysis and hypothalamus. Histophysiologic studies on the Lepomis [Centrarchidae]). *Advanc. Anat. Embryol. Cell Biol.* **48**: 1-82 (1974).

J15,761/74

Monograph on the hypothalamus-hypophyseal system of a teleost (*Centrarchidae*) with respect to its anatomy and function under normal conditions, and after various hormone treatments or surgical interventions. Special attention is given to the identification of nerve centers and anterior pituitary cells responsible for the selective secretion of diverse adenohypophyseal hormones, as well as to changes in the pituitary during the annual reproductive cycle and its responsiveness to prolongation of the daily light period (about 160 refs.).

Hibernation

The changes characteristic of hibernation in the hedgehog have been compared to those of the G.A.S. Corresponding studies have also been performed on hamsters, bats, ground squirrels and toads, as well as on guinea pigs during "artificial hibernation." Adrenal hyperactivity is usually most pronounced at arousal and least marked during profound sleep, at which time a significant decrease in brain NEP has also been interpreted as a reflection of hypofunction in the central and sympathetic systems. The turnover of labeled NEP is reduced in most tissues, but particularly in the brain, of hibernating ground squirrels.

Hibernation

(See also our earlier stress monographs, p. xiii)

Suomalainen, P.: "Further investigations

on the physiology of hibernation." *Proc. Finn. Acad. Sci.* 131-144 (1953).

C852/53

The changes characteristic of hibernation in the hedgehog are compared to those of the

G.A.S. Relationships between these two phenomena are discussed.

Raths, P., Schulze, W.: "Die Nebennieren des Goldhamsters im Winterschlaf und bei anderen Aktivitätszuständen" (The adrenals of the golden hamster during hibernation and other activities). *Z. Biol.* **109**: 233-243 (1957). C36,859/57

Detailed description of histologic changes in the adrenal medulla and cortex of the golden hamster during hibernation, awakening from hibernation and during anesthesia induced by cold.

Vašků, J.: "Die Beeinflussung der experimentellen diphtherischen Intoxikation durch den künstlichen Winterschlaf" (The influence of artificial hibernation on experimental diphtheria intoxication). *Z. Gesamte. Inn. Med.* **16**: 885-894 (1961). D80,395/61

Hibernation did not protect guinea pigs against the adrenal changes elicited by diphtheria toxins, but it did increase their sensitivity as indicated by a rise in mortality. The "artificial hibernation" (drugs plus cold) used in these experiments acted as a stressor.

Krutzsch, P. H., Hess, M.: "Studies on the ascorbic acid content of the adrenal of the bat (*Myotis lucifugus*)."*Endocrinology* **69**: 664-666 (1961). D10,630/61

In the bat, captivity *per se* did not influence the vitamin C content of the adrenals during hibernation. "The most marked depletion of the adrenal vitamin occurred in the non-captive hibernating bats stressed by arousal, a finding well correlated with the blood corticosterone content reported for the hamster, another hibernating species, after similar treatment." Less pronounced effects were shown by ACTH in hibernating and by EP in active animals. Thus the bat responds to stress essentially like most other species—at least with regard to the parameters examined.

Uuspää, V. J.: "The catecholamine content of the brain and heart of the hedgehog (*Erinaceus europaeus*) during hibernation and in an active state." *Ann. Med. Exp. Biol. Fenn.* **41**: 340-348 (1963). E36,407/63

In the hedgehog, the brain NEP concentration decreases markedly during hibernation, whereas EP and dopamine levels show comparatively little change. The drop in NEP is interpreted as reflecting a hypofunction of the central sympathetic system.

Draskóczy, P. R., Lyman, C. P.: "Turnover of catecholamines (CA) during hiberna-

tion" (abstracted). *Pharmacologist* **7**: 167 (1965). J8,151/65

In hibernating ground squirrels, the turnover rate of labeled NEP and EP was greatly reduced in most tissues, particularly within the brain.

Canguilhem, B., Bloch, R.: "Evolution saisonnière de l'élimination des hormones surréaliennes chez un hibernant, *Cricetus cricetus*" (Seasonal evolution of adrenal hormone excretion in the hibernating animal, *Cricetus cricetus*). *Arch. Sci. Physiol. (Paris)* **21**: 27-44 (1967). G46,415/67

In the hamster (*Cricetus cricetus*), no seasonal variations in catecholamine output are noted, although such excretion diminishes during adaptation to cold and may last four months even if the animals are placed into surroundings with normal room temperature (23°C). On the other hand, urinary glucocorticoid and aldosterone excretion is subject to definite seasonal changes that are independent of ambient temperature.

Mukherji, M.: "Adrenal cortex in stress and hibernation; a histochemical study in toad (*Bufo melanostictus*)."*Acta Histochem. (Jena)* **29**: 297-303 (1968). F98,729/68

Under ordinary conditions, various stressors (cold, acute dehydration) and ACTH caused depletion of adrenocortical lipids in the toad, but during hibernation the adrenal responded only to dehydration shock.

Romita, G., Montesano, R.: "Aspetti istochimici ed ultrastrutturali delle ghiandole surrenali di Chiropteri durante l'ibernazione, il risveglio ed il periodo estivo" (Histochemical and ultrastructural aspects of adrenal glands in Chiroptera during hibernation, awakening, and the summer period). *Ateneo Parmense [Acta Biomed.]* **43**: 211-235 (1972).

J1,213/72

Detailed description of the histochemical and EM changes in the adrenals of bats, especially with regard to the effects of hibernation. In the adrenal medulla, two types of cells have been differentiated, one synthesized in EP, the other in NEP. "During the winter lethargy a depressed secretory activity has been noticed in the cells of the glomerulosa and moreover a remarkable secretion in the cells of both fasciculata and reticularis. Such activity increased after the awakening and became normal during the summer, demonstrating a tendency to store lipid droplets" (57 refs.).

Meteorologic Influences

(See also Relocation and Travel, Seasonal Variations, Hypoxia--mountaineering)

Numerous studies have dealt with the stressor effects of solar eruptions, magnetism, various types of cosmic rays and other meteorologic factors.

Special attention has been given to certain hot dry winds of Israel called *sharav*, which are similar to the African *khamsin* or *sharkiye* and the European *sirocco* and *Föhn*. They are known by many other names in different countries. Weather-sensitive people can react with an "irritation syndrome" (ascribed to 5-HT overproduction), various types of hyperthyroidism, or an "adrenal exhaustion syndrome" attributed to catecholamine deficiency. These winds cause a wide range of psychologic and somatic disturbances. Despite certain variations in the symptomatology elicited, they all tend to produce migraine headache, cardiac infarcts, changes in mood, predisposition to automobile accidents, loss of sodium, increased corticoid excretion and alterations in catecholamine and 5-HT metabolism.

Meteorologic Influences

(See also our earlier stress monographs, p. xiii, and cf. Catastrophe, Accidents)

Poumailloux, M.: "Ripercussioni umane dell'attività solare interna" (Effects of internal solar activity upon humans). *Minerva Med.* **61**: 5809-5823 (1970). H35,900/70

Theoretical considerations on the stressor effects of meteorologic factors (solar eruptions, magnetism, various types of cosmic rays).

Sulman, F. G., Danon, A., Pfeifer, Y., Tal, E., Weller, C. P.: "Urinalysis of patients suffering from climatic heat stress (Sharav)." *Int. J. Biometeorol.* **14**: 45-53 (1970).

J2,004/70

The hot dry wind ("Sharav" in Israel) tends to elicit discomfort, headaches, irritability and exacerbation of respiratory ailments in weather-sensitive people. On the basis of urinalysis, three patterns are distinguished: "serotonin hypersecretion causing a general 'Irritation Syndrome,' catecholamine deficiency resulting in the 'Exhaustion Syndrome,' histamine and creatinine overproduction combined with clinical 'Hyperthyroidism-Forme Fruste'."

Sulman, F. G.: "Meteorologische Frontverschiebung und Wetterföhligkeit: Föhn-Chamssin-Scharaw" (Sensitivity to movements of the meteorologic front). *Ärztlt. Prax.* **23**: 998-999 (1971).

J2,003/71

Certain movements of the meteorologic front produce curious psychic and somatic

phenomena which are said to be related to the G.A.S. These winds and associated weather constellations have different names and are probably not due to identical meteorologic phenomena. They are called Chamssin or Sharav (Israel), Sharkije (Egypt), Föhn (Siberia, Germany), Sirocco (Italy), Levante (Spain), Xlokk (Malta), Santa Ana Winds (California), Arizona Winds (Arizona), Zonda (Argentina), Thar-Winds (Rajasthan, New Delhi, Agra, India), Northern Winds (Melbourne) and Chinook (Canada). Despite certain differences, they elicit similar results: migraine headache, cardiac infarct, changes in mood, predisposition to automobile accidents, loss of sodium, increased excretion of glucocorticoids, diminution of 17-KS elimination and so on. Studies during Föhn showed three groups of derangements: (1) depletion of catecholamines with increasingly intense exhaustion, hypotension, fatigue, apathy, depression; (2) altered 5-HT production, especially one or two days before Föhn when ionization of the air is common, and (3) symptoms of hyperthyroidism.

Sulman, F. G., Pfeifer, Y., Superstine, E.: "Adrenal medullary exhaustion from tropical winds and its management." *Isr. J. Med. Sci.* **9**: 1022-1027 (1973). H77,285/73

The hot dry winds of Israel called Sharav are similar to the African Khamsin or Sharkije and the European Sirocco and Föhn. In weather-sensitive patients, the Sharav can elicit three different reactions: "1) 'irritation syndrome' (serotonin overproduction), 2) 'thyroid syndrome' (hyper-

thyroidism 'forme fruste'), and 3) 'adrenal exhaustion syndrome' (catecholamine deficiency.) These tropical winds cause many psychologic and somatic disturbances as well as changes in catecholamine, corticoid and 5-HT production and metabolism which are thought to be related to the various stages of the G.A.S. Therapeutic measures, including MAO blockers, restore urinary catecholamine levels.

Ohno, Y., Aoki, N., Horibe, H., Hayakawa, N., Okada, H.: "Biometeorologic studies on cerebrovascular diseases. V. A multivariate analysis of meteorologic effects on cerebrovascular accident." *Jap. Circ. J.* **38**: 195-208 (1974). H88,883/74

Review on meteorologic factors that can participate in the precipitation of cerebrovascular accidents.

Simpson, J. A.: "Weather and myasthenic fatigue." *Lancet* August 24, 1974, pp. 458-459. H90,770/74

"The myasthenic patient responded unfavourably to extremes of cold or heat (especially a hot bath or a stuffy atmosphere)

in the same way as to emotional stress." Numerous other observations indicate that meteorologic conditions, particularly changes in the weather, aggravate myasthenic weakness.

Tramp, S. W.: "The possible effect of meteorological stress on cancer and its importance for psychosomatic cancer research." *Experientia* **30**: 1474-1478 (1974).

H98,793/74

Personal observations and a review of the literature allegedly "confirm the effect of meteorological stresses (in particular thermal stresses) on thermoregulatory processes and cancer development. The similarity in physiological processes during meteorological and psychological stresses may facilitate the studies on the influence of psychosomatic factors on cancer."

Josimovic, I. B.: "Zur Wetterföhligkeit der Ulkuskranken" (Climatic sensitivity in patients with peptic ulcers). *Med. Welt* **26**: 374-376 (1975). J23,813/75

Review on the relationship between the G.A.S. and meteorologic conditions in man.

OCCUPATION

(See also Agents—athletics)

In the following section, we shall discuss the stress associated with certain occupations, such as aerospace travel; parachute jumping; air traffic control; navy, marine, and submarine diving (including underwater demolition); military service and combat; automobile driving; executive work (particularly business management and finance); medicine, dentistry and nursing; law; jobs involving shift work, and the telephone and telegraph industries; as well as a variety of other less common occupations.

Of course, these categories overlap a great deal. For example, civilian and military aerospace problems are discussed conjointly, as is military service in peace or war. However, to avoid excessive repetition (such as bombing attacks involving civilian as well as military populations), the reader is referred to the section, Catastrophe, Accidents, and for the stresses endured by POWs, to Concentration Camps.

Even if these categories—like most others in this treatise—are somewhat artificial, they will considerably accelerate the finding of literature on certain subjects.

Aerospace

Generalities. As an introduction to the various problems posed by aerospace medicine, it may be helpful to peruse some of the reviews listed in the following abstract

section. They deal with generalities of stress in aviation and space travel in relation to the G.A.S., irrespective of the particular specific effects of the task. As far as they specially concern aerospace medicine, some consideration is also given to "stress tests," interpersonal relations, immobilization, isolation, noise, vibration, hypoxia, gravity forces, sound, sonic booms, compression and decompression, temperature variations, pilot fatigue, desynchronization during flights through various time zones, and so on. However, more detailed information concerning each of these subjects is found in the corresponding special sections.

→**Stress Tests.** In selecting crews for planes or spaceships, it is naturally of the utmost practical importance to develop meaningful tests to determine—as accurately and objectively as possible—the suitability of candidates in terms of their ability to withstand the stresses of all the physical and mental demands made by this kind of work. The tests include exposure to simulated flight conditions and measurement not only of performance in properly selected perceptual-motor tasks but also of physical and mental responses, as well as analysis of circulation, pulse rate, ECG, and GSR by more complex systems, such as the "stressalyzer."

In this regard, it will also be useful to consult the special discussion on Stress Tests in the section on the functional characteristics of stress in general, since many of these are applicable to aerospace problems, although they were primarily designed to measure resistance to any kind of stressor.

→**Nervous System.** In civilian and military aviation, as in space travel, the most important causes and results of stress are neuropsychologic disturbances. These also play a principal role in determining efficiency of performance. Hence, virtually all investigations concerned with aeromedicine give prominent attention to the functions of the central and autonomic nervous systems, even if their primary objective is the measurement of some chemical change, the blood count, cardiovascular reactions, GSR or alterations in disease susceptibility.

Extensive studies in England during World War II showed that after repeated missions over enemy territory the initial extreme anxiety of pilots gradually subsided, but eventually their adaptation broke down and they developed a variety of neurotic manifestations. Here we have another example of the triphasic nature of the G.A.S. in that the initial alarm reaction is followed by the stage of resistance and eventually by that of exhaustion. For this reason, even the most courageous and even-minded fighters could perform well for only a limited number of sorties, until their "adaptation energy" was exhausted.

Undoubtedly, not only anxiety but various sensory stimuli can play a part in producing breakdown or "pilot fatigue" following demanding missions. In one interesting experiment, it was observed that deaf persons with vestibular defects who accompanied experienced pilots on acrobatic flights, failed to show the usual increase in corticoid and catecholamine production, presumably because of their impaired sense of equilibrium and hearing.

In general, those men who broke down rapidly under the strain of aerial warfare and who tended to suffer from gastrointestinal disturbances, extreme anxiety or even fainting, would not have done so under peacetime conditions. However, in predisposed individuals, the strain of battle was more likely to bring out latent tendencies than would the stressors of daily civilian life.

→**Corticoids and 17-KS.** Gluco- and mineralocorticoids as well as their metabolites are discussed conjointly with 17-KS, although the latter may be indicative either of corticoids or testoids. In general, it can be said that the stress of life is associated with an increase in the blood level and urinary elimination of corticoids and their degradation products. Such a rise may be seen even under simulated flight conditions. It is frequently associated with diuresis and other typical signs of stress, such as an elevation of catecholamine production, eosinopenia and so on. On long-distance flights, desynchronization may aggravate these changes. The effects of flying upon aldosterone excretion are less clearcut.

→**Epinephrine and Norepinephrine.** In both military and civilian pilots, catecholamine excretion is enhanced during flights as compared to levels on the ground. The findings of various investigators differ with regard to the relative predominance of EP or NEP production, which is presumably dependent upon hitherto unidentified conditioning factors. There is good reason to believe that, in addition to nervous tension, cold and gravity forces play a role here.

In air tanker pilots flying short missions over forest fires, urinary catecholamine and corticoid excretion, heart rate and ECG exhibited no evidence of significant stress. However, during emergencies, the heart rate nearly doubled.

On long flights or repeated shorter flights during six-day missions, urinary EP excretion was always increased, but other endocrine metabolic functions varied considerably. East- and west-bound earth circling missions did not induce essentially different degrees of stress, as judged by these indicators. Naval aviators practicing perilous landings on aircraft carriers showed considerable rises in the urinary elimination of 3-methoxy-4-hydroxyphenylglycol (MHPG), a catecholamine metabolite. These findings were thought to possibly indicate an accelerated metabolism of brain NEP. In inexperienced pilots, the urinary excretion of EP and NEP was not directly proportional to the length of the flight, but increased considerably during landing at unfamiliar airports.

In flight crews on fifty-four-hour bi- or tri-directional transmeridian missions, urinary catecholamine and corticoid output showed rhythmic circadian variations corresponding to the home base of the crew, even after several time zones had been traversed.

→**5-HT and Histamine.** In various species of animals travelling on satellite spaceships, the blood 5-HT level diminished.

Both 5-HT and histamine-diaminioxidase activity in the blood of astronauts showed circadian variations which might play an important role in space medicine.

→**Metabolites.** Pilots under training may exhibit eosinopenia with decreased blood *glutathione* levels at times of stress, but *hippuric acid* formation is not affected. There is some evidence that simulated flights may alter serum *cholesterol phospholipid* and *lipoprotein* concentrations. In pilots flying six-hour over-water missions, *corticoid* levels were increased in plasma but not in urine. Urinary *EP*, *NEP*, *urea* and *uric acid* values were greatly elevated. Allegedly, *hypoglycemia* and *insulin* hypersensitivity may occur in pilots suffering malaise.

The metabolic responses of astronauts on a two-week orbital space flight showed considerable individual variations. In only one of the two participants was there a significant rise in urinary *calcium* during the second week of the flight, but urinary

phosphate elimination increased in both subjects. Some data were also registered on urinary *nitrogen, sulfate, magnesium, sodium, potassium* and *chlorine* in relation to corticoid secretion, but the small number of available observations does not permit far-reaching conclusions.

→**Blood Count.** Operating a pursuit meter, flying and exposure to heat increased 17-KS excretion and caused eosinopenia in normal, but allegedly, not in schizophrenic individuals.

→**Cardiovascular System.** In pilots performing stressful flying exercises for the first time, blood pressure rose consistently, but pulse rate was found to be variable and sometimes actually decreased. There was also pallor, tremor, flushing and excessive sweating. In most instances, tachycardia is noted in conventional aircraft and helicopter pilots during flight.

As astronauts reach weightlessness after takeoff, they exhibit polyuria, and have the illusion of standing on their heads because of increased blood supply to the brain.

→**Varia.** Flying, especially on combat missions, may aggravate preexistent diabetes or elicit an Addisonian syndrome.

A β -adrenergic blocking agent, propranolol, tends to inhibit the cardiovascular changes characteristic of simulated flights or intense muscular exercise.

Generalities

(See also our earlier stress monographs, p. xiii)

Levine, S., Scotch, N. A.: "Toward the development of theoretical models: II." *Milbank Mem. Fed. Q.* 45 No. 2, Part 2: 163–174 (1967). J10,927/67

"In measuring one of the major components of life stress, i.e., job dissatisfaction, the following are some of the indicators which are being used: working overtime, meeting deadlines or rigid time schedules, night work and working closely with unfriendly or inconsiderate people. Similar specific indicators are used to measure the other major areas of possible life stress, such as family dissatisfaction and financial problems."

Margolis, B. K., Kroes, W. H.: "Occupational stress and strain." *Occup. Mental Health* 2: 4–6 (1972). J8,322/72

Brief review on the stressor effects of various occupations, based mainly on subjective indices of "job stress" (no refs.).

Eliot, R. S.: *Stress and The Heart*, Vol. 1, p. 415. Contemporary Problems of Cardiology. Mount Kisco, N.Y.: Futura, 1974.

E10,556/74

Monograph containing many articles by

numerous experts on the role of stress in the production of cardiovascular disease, with special reference to hypertension and myocardial infarction. Among the factors involved in the cardiovascular effects of stress, individual chapters deal with the role of occupation, homeostasis, environmental influences, sex, athletics, emotion, stress tests and the therapeutic value of various techniques for relaxation, including Transcendental Meditation, Yoga, Zen, sentic cycles, hypnosis and related practices.

Carruthers, M.: *The Western Way of Death, Stress, Tension and Heart Attacks*, p. 142. New York: Pantheon Books, 1974.

E10,630/74

Highly simplified, popular description of factors influencing predisposition to heart disease, with brief sections on urban environment, drink, drugs, and diet. Various occupational groups, such as accountants, clerical workers, pilots, bus drivers, industrial employees, public speakers, television performers and athletes are examined.

McLean, A. (ed.): *Occupational Stress*, p. 111. Springfield, Ill.: Charles C Thomas, 1974.

E10,881/74

Margolis, B. K., Kroes, W. H.: "Occupational stress and strain." In: McLean, A.,

Occupational Stress, pp. 15-20. Springfield, Ill.: Charles C Thomas, 1974.

E10,883/74

McLean, A.: "Concepts of occupational stress, a review." In: McLean, A., *Occupational Stress*, pp. 3-14. Springfield, Ill.: Charles C Thomas, 1974.

E10,882/74

McLean, A.: "Occupational 'stress.' A misnomer." In: McLean, A., *Occupational Stress*, pp. 98-105. Springfield, Ill.: Charles C Thomas, 1974.

E10,893/74

McLean, A.: "Clinical concepts." In: McLean, A., *Occupational Stress*, pp. 21-26. Springfield, Ill.: Charles C Thomas, 1974.

E10,884/74

Aerospace

(See also our earlier stress monographs, p. xiii, and cf. Ultra-sound, Sonic Booms)

Generalities. Williams, G. O.: *Fatigue and Flying Accidents*. London: Flying Personnel Research Committee, No. 492, 1942.

E10,662/42

Wright, D. G.: *Notes on Men and Groups Under Stress of Combat: For the Use of Flight Surgeons in Operational Units*, pp. 1-19. Report No. 1 to the Air Surgeon, U.S. Army Air Forces by The Josiah Macy, Jr. Foundation. New York, 1945.

B40,065/45

Drew, G. C.: *Fatigue*. London: Flying Personnel Research Committee, No. 488, 1951.

E10,663/51

Bugard, P., Souvras, H., Valade, P., Coste, E., Salle, J.: "Le syndrome de fatigue et les troubles auditifs des metteurs au point d'aviation" (The fatigue syndrome and hearing problems in aviation ground crews). *Sem. Hôp. Paris* **29**: 3299-3312 (1953).

B89,487/53

Observations on man and animals revealed that stressors common in aviation medicine (immobilization, noise, vibration) reproduce lesions characteristic of the G.A.S.

Barr, N. L., Shepp, B. E., Yarczower, M., Standaert, F.: "Physiologic responses to stressful stratosphere flights." *J. Aviat. Med.* **30**: 334-343 (1959).

C69,056/59

Observations on adrenocortical activity, electrolyte metabolism and white blood cell

count in pilots during balloon flights into the stratosphere.

Hambling, J. (ed.): *The Nature of Stress Disorder*, p. 298. Springfield, Ill.: Charles C Thomas, 1959.

E4,674/59

Proceedings of the Conference of the Society for Psychosomatic Research (Royal College of Physicians, London). Several experts discussed the G.A.S. on the basis of animal experiments and observations in man. Special sections deal with stress in aviation, industry and the family setting, with the role of stress in gastrointestinal disease and skin disorders, and with genetic predisposition to stress disorders.

Burns, N. M., Chambers, R. M., Hendler, E. (eds.): *Unusual Environments and Human Behavior. Physiological and Psychological Problems of Man in Space*, p. 438. Glencoe, Ill.: Free Press, 1963.

E10,423/63

Monograph composed of articles by many specialists on the stressor effects of aerospace flights. Included are psychologic factors, isolation and sensory deprivation, weightlessness, vibration and radiation. Relationships to the G.A.S. and to performance are given considerable attention.

Simons, D. G., Flinn, D. E., Hartman, B.: "Psychophysiology of high-altitude experience." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 127-164. Glencoe, Ill.: Free Press, 1963.

E10,428/63

Brief review on the psychophysiology of high-altitude activity, especially in relation to the stress concept. Particular attention is given to gravity, hypoxia, fatigue and cardiovascular reactions.

Burns, N. M., Kimura, D.: "Isolation and sensory deprivation." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 167-192. Glencoe, Ill.: Free Press, 1963.

E10,429/63

Brief review on isolation, loneliness and sensory deprivation in relation to prolonged space flights.

Nadel, A. B.: "Vibration." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 379-394. Glencoe, Ill.: Free Press, 1963.

E10,433/63

Review on the psychologic and somatic effects of vibration, especially in relation to aerospace medicine.

Schwichtenberg, A. H., Lovelace, W. R.: "Résumé of human stresses in space flight operations and methods of improving man's tolerance." *South. Med. J.* **57**: 522-531 (1964). G13,611/64

Theoretical considerations on stressors that might be encountered by astronauts.

Barron, C. I., Schwichtenberg, A. H., Secrest, R. R.: "Medical evaluation of airmen exposed to altitudes in excess of 50,000 feet." *Aerosp. Med.* **36**: 665-668 (1965).

F69,910/65

Grether, W. F.: "Human performance for military and civilian operations in space." *Ann. N. Y. Acad. Sci.* **134**: 398-412 (1965).

F61,743/65

One article in a Symposium on the Civilian and Military Uses of Aerospace, containing observations on the stressor effect of weightlessness.

Hale, H. B., Duffy, J. C., Ellis, J. P. Jr., Williams, E. W.: "Flying stress in relation to flying proficiency." *Aerosp. Med.* **36**: 112-116 (1965). G26,667/65

"Stress reactions to flight conform to the General Adaptation Syndrome pattern."

Dean, R.: "Human stress in space." *Sci. J.* **2**: 71-75 (1966). G42,593/66

Studies on individual stressors (noise, gravity, temperature, vibration) and their combinations as they may be encountered in space travel. Emphasis is placed on the fact that stressors are not necessarily harmful, that they may be beneficial—"they may improve performance by making subjects more alert."

Mohler, S. R.: "Fatigue in aviation activities." *Aerosp. Med.* **37**: 722-732 (1966).

J10,968/66

Review of the literature on factors that influence physical and mental fatigue during very prolonged or difficult flight tasks, with special reference to the role of stress. There are also definite recommendations for combatting flight fatigue (105 refs.).

Schreuder, O. B.: "Medical aspects of aircraft pilot fatigue with special reference to the commercial jet pilot." *Aerosp. Med.* **37** Sect. 2, No. 4: 1-44 (1966). J10,654/66

Review on the physiologic parameters of aircraft pilot fatigue with special reference to stress, circadian rhythms, accidents, cardiovascular and blood chemistry changes. A major section is devoted to the role of the G.A.S., particularly in connection with stress

and fatigue. The report is based largely upon personal observations (7 refs.).

Roman, J., Older, H., Jones, W. L. Jr.: "Flight research program: VII. Medical monitoring of Navy carrier pilots in combat." *Aerosp. Med.* **38**: 133-139 (1967).

J22,619/67

McKenzie, J. M., Fiorica, V.: "Stress responses of pilots to severe weather flying." *Aerosp. Med.* **38**: 576-580 (1967).

J22,618/67

Lewis, C. E. Jr., Jones, W. L. Jr., Austin, F., Roman, J.: "Flight research program: IX. Medical monitoring of carrier pilots in combat—II." *Aerosp. Med.* **38**: 581-592 (1967).

J22,617/67

Joy, R. J. T.: "Heat stress in army pilots flying combat missions in the Mohawk aircraft in Vietnam." *Aerosp. Med.* **38**: 895-900 (1967).

J22,616/67

Drinkwater, B. L., Cleland, T., Flint, M. M.: "Pilot performance during periods of anticipatory physical threat stress." *Aerosp. Med.* **39**: 994-999 (1968).

J22,489/68

Hale, H. B., Ellis, J. P., Williams, E. W.: "Decompression stress in simulated orbital flight." *Aerosp. Med.* **39**: 1171-1174 (1968).

H22,179/68

Burns, W.: *Noise and Man*, p. 336. Philadelphia: J B Lippincott, 1968.

E8,840/68

Monograph on the effects of noise, sonic booms and vibration on man, with special reference to aerospace problems.

Siegel, P. V., Gerathewohl, S. J., Mohler, S. R.: "Time-zone effects on the long distance air traveler." *Science* **164**: 1249-1255 (1969).

H13,629/69

Review on the principal factors involved in desynchronization during air travel through various time zones, with suggestions for treatment.

Demos, G. T., Hale, H. B., Williams, E. W.: "Anticipatory stress and flight stress in F-102 pilots." *Aerosp. Med.* **40**: 385-388 (1969).

G75,915/69

Jira, F.: "Stress und Fliegen" (Stress and flying). *Wien. Med. Wochenschr.* **120**: 29-32 (1970).

H21,150/70

Brief review on the factors that contribute to stress and its many psychic and somatic manifestations in pilots. "Stress is

the most important problem in aviation medicine."

Cameron, C.: "Fatigue problems in modern industry." *Ergonomics* **14**: 713-720 (1971).
J14,877/71

Study of the relation between stress and fatigue in modern industry, particularly in civil aviation.

Daftuar, C. N.: "Human factors research in India." *Hum. Factors* **13**: 345-353 (1971).
J16,336/71

Review on stress factors affecting jet fighter pilots in the Indian Air Force, with special reference to the influence of sound and fatigue.

Grether, W. F., Harris, C. S., Mohr, G. C., Nixon, C. W., Ohlbaum, M., Sommer, H. C., Thaler, V. H., Veghte, J. H.: "Effects of combined heat, noise and vibration stress on human performance and physiological functions." *Aerosp. Med.* **42**: 1092-1097 (1971).
J16,968/71

Discussion of various parameters that can be used to estimate the effects of combined environmental stressors encountered in aircraft and space vehicles (10 refs.).

Clasing, D., Vogler, G., Burchardt, W., Klaus, E. J.: "Herzfrequenz und psychische Anspannung beim Segelfliegen" (Heart rate and mental stress in gliding). *Med. Welt* **22**: 808-811 (1971). J20,904/71

Bartek, P., Gaume, J. G.: "Pilot incapacitation: an expression of convergent factors." *Aerosp. Med.* **43**: 974-977 (1972).
J19,473/72

Grether, W. F., Harris, C. S., Ohlbaum, M., Sampson, P. A., Guignard, J. C.: "Further study of combined heat, noise and vibration stress." *Aerosp. Med.* **43**: 641-645 (1972). J16,971/72

Vaandrager, K.: "Task of a medical department in civil aviation." *Aerosp. Med.* **43**: 439-445 (1972). J16,969/72

Selye, H.: "Stress and aerospace medicine." *Aerosp. Med.* **44**: 190-193 (1973).
G88,046/73

Brief summary of a lecture on the history and present status of the stress concept. Its applicability to aerospace medicine is mentioned only in passing.

Bugard, P.: *Stress, Fatigue et Dépression. L'homme et les Agressions de la Vie Quotidienne* (Stress, fatigue and depression. Man

and the aggression of daily life). Vol. 1, p. 294; Vol. 2, p. 302. Paris: Doin Edit., 1974.
E10,487/74

Monograph on stress in relation to aero-medical problems.

Mackie, W. A. N., Davies, J. W.: "Human factors in helicopter flying." *J. R. Nav. Med. Serv.* **60**: 39-44 (1974). J20,067/74

Melton, C. E., McKenzie, J. M., Kelln, J. R., Hoffmann, S. M., Saldivar, J. T.: "Effect of a general aviation trainer on the stress of flight training." *Aviat. Space Environ. Med.* **46**: 1-5 (1975). J20,381/75

→ Stress Tests. Brüner, H., Jovy, D., Klein, K. E., Ruff, S.: "Zur Beurteilung der biologischen Leistungsreserve eines Piloten" (Examination of the energy reserve of pilots). *Jarbuch W.G.L.R.* 576-581 (1962).
G23,490/62

Description of a hypoxia resistance test which allegedly measures the energy reserve of a pilot exposed to repeated demands simulating flight conditions. "This method is a simple and time-saving one, and is very suitable for the selection and routine examinations of the flying personnel."

Sem-Jacobsen, C. W., Sem-Jacobsen, I. E.: "Selection and evaluation of pilots for high performance aircraft and spacecraft by in-flight EEG study of stress tolerance." *Aerosp. Med.* **34**: 605-609 (1963).
J23,629/63

Klein, K. E., Brüner, H., Ruff, S.: "Untersuchungen zur Belastung des Bordpersonals auf Fernflügen mit Düsenmaschinen" (Evaluation of resistance to stress in air crew members on transatlantic jet flights). *Z. Flugwissenschaft.* **14**: 109-121 (1966).
G42,395/66

An attempt to evaluate resistance to fatigue using blood circulation, pulse rate, ECG, oral temperature and motor coordination as indices.

Ruff, G. E., Korchin, S. J.: "Adaptive stress behavior." In: Appley, M. H. and Trumbull, R., *Psychological Stress. Issues in Research*, pp. 297-323. New York: Appleton-Century-Crofts, 1967.
E10,417/67

Studies on Mercury astronauts showed "the effectiveness of adaptive responses based on past experience and professional competence. Given a group of men with repeated success in accomplishment of hazardous duties, followed by training which led to

highly organized, efficient patterns of behavior, evidence of disruptive stress behavior was minimal."

Pearson, D. W., Thackray, R. I.: *Consistency of Performance Change and Autonomic Response as a Function of Expressed Attitude toward a Specific Stress Situation*. Federal Aviation Administration, Aviation Med. pamphlet, p. 7. Washington, D. C., 1969. G71,477/69

Comparative studies on fearful and confident pilots performing standard tasks under the threat of receiving electric shocks as a punishment for errors. Half of the subjects were assigned perceptual-motor tasks, others cognitive-interference tasks. The "results indicate significant differences between groups in both sets of measures and support the hypothesis that attitude questionnaires may be used to predict performance and bodily responses to specific stress situations."

Iampietro, P. F., Melton, C. E. Jr., Higgins, E. A., Vaughan, J. A., Hoffmann, S. M., Funkhouser, G. E., Saldivar, J. T.: *High Temperature and Performance in a Flight Task Simulator*. Federal Aviation Administration, Aviation Med. pamphlet, p. 8. Washington, D.C., 1972. G91,965/72

In a flight task simulator, performance definitely declined at high cockpit temperatures. Relationships to the classic manifestations of the stress syndrome are not discussed.

Smith, R. C.: *A Study of the State-Trait Anxiety Inventory and the Assessment of Stress Under Simulated Conditions*. Federal Aviation Administration, Aviation Med. pamphlet, p. 5. Washington, D.C., 1972. G96,466/72

The STAI "produces scores indicating the individual's current level of anxiety, i.e., A-State, and how prone the individual is to experience anxiety, i.e., A-Trait. It is easily administered and scored and, since it contains only 40 items which are to be rated on four-point scales, it takes only a few minutes for the respondent to complete." Its possible use in the study of aviation stress is examined. "It appears that the STAI can be used for measuring the anxiety of air traffic controllers, or workers in other high-demand occupations, with considerable confidence that the validity of findings will not be reduced by the unsuspected effects of biasing response sets."

Sommer, H. C., Harris, C. S.: "Combined effects of noise and vibration on human tracking performance and response time." *Aerosp. Med.* **44**: 276-280 (1973).

H81,610/73

Thackray, R. I., Rylander, R., Touchstone, R. M.: *Sonic Boom Startle Effects. Report of a Field Study*. Federal Aviation Administration, Aviation Med. pamphlet, p. 16. Washington, D.C., 1973. J10,440/73

Review and personal observations on the effects of simulated and real sonic booms upon the "startle response," which measures arm-hand steadiness (11 refs.).

Buck, L., Leonardo, R.: *Sleep Patterns and Psychomotor Performance of Aircrew Flying the North Pacific*. National Research Council, Division Mech. Eng. Report No. LTR-CS-97, p. 22. Ottawa, 1973. J10,491/73

Preliminary data on the stress endured by aircrews flying the North Pacific route from Vancouver to Tokyo as measured by the "stressalyzer." This is an instrument permitting objective assessment of a step-tracking task in which the subject pursues a light as it moves between five horizontally-aligned positions. "The task is subject-paced, target movement depending on pointer alignment, and the coupling between control wheel and pursuit pointer is inverse, the two moving in opposite directions. The instrument yields a number of performance indices relating to the speed and accuracy of decision and movement." Because of various technical difficulties, the application of the machine to this particular task did not provide definitive results.

Strasser, H., Brilling, G., Klinger, K. P., Müller-Limmroth, W.: "Physiological and operational state of a group of aeroplane pilots under the conditions of stressing tracking tests." *Aerosp. Med.* **44**: 1040-1047 (1973). J11,374/73

→ **Nervous System.** McFarland, R. A.: "Fatigue in aircraft pilots." *N. Eng. J. Med.* **225**: 845-855 (1941). B34,718/41

General discussion of the literature on "pilot fatigue" (34 refs.).

Symonds, C. P.: "The human response to flying stress. Lecture I: Neurosis in flying personnel." *Br. Med. J.* December 4, 1943, pp. 703-706. B26,422/43

Symonds, C. P.: "Lecture II. The foundations of confidence." *Br. Med. J.* December 11, 1943, pp. 740-744. B26,422/43

General description of flying stress in Royal Air Force personnel during World War II. Among the most striking manifestations are fatigue, impairment of skill, vision and hearing, gastrointestinal disorders and gradually increasing anxiety.

Bond, D. D.: *How Can the Flight Surgeon Better Treat Anxiety?* pp. 19-23. Report No. 2 to the Air Surgeon, U.S. Army Air Forces by The Josiah Macy, Jr. Foundation. New York, 1945. B40,066/45

Reid, D. D.: "Some measures of the effect of operational stress on bomber crews." *Air Ministry, A.P.* 3139, pp. 245-258. London: HMSO, 1947. B27,155/47

Reid, D. D.: "Fluctuations in navigator performance during operational sorties." *Air Ministry, A.P.* 3139, pp. 321-329. London: HMSO, 1947. B27,164/47

Pilots making repeated sorties over Germany during World War II showed an initial intense anticipatory anxiety with steady deterioration in efficiency on the outward journey, particularly over the enemy coast and on approaching the target. This was maximal in the phase of heavy enemy fighter opposition and persisted as long as the aircraft was over enemy territory. Following numerous sorties, neurotic manifestations and breakdown eventually occurred.

Kahn, L. A.: "A discussion of some causes of operational fatigue in the Army Air Forces." *Psychol. Bull.* 44: 34-53 (1947). B40,068/47

Review on operational fatigue in the Air Force, especially under combat conditions. Undoubtedly, predisposition plays a major role but "clearly, the literature indicates that those men who did break under the strain of battle would in a majority of cases not have done so under the conditions of peace-time living" (12 refs.).

Anderson, R. C.: "The motivations of the flyer and his reactions to the stresses of flight." *J. Aviat. Med.* 18, Sect. 2, Supp.: 18-30 (1947). B26,773/47

Reid, D. D.: "Sickness and stress in operational flying." *Br. J. Soc. Med.* 2: 123-131 (1948). B26,739/48

Field studies in the Bomber Command of the Royal Air Force during World War II suggest that "the acute anxiety caused by a high casualty rate had a much more decisive effect on health and morale than had prolonged or intensive operational effort.

Operational inexperience which also plays a part in determining the incidence of neurosis, is shown to be relevant in the prognosis of cases of sickness occurring in conditions of acute stress on operational sorties." Fainting and other symptoms attributed to the nervous and alimentary systems, especially if they occurred soon after takeoff, were indicative of impending breakdown.

Sem-Jacobsen, C. W.: "Electroencephalographic study of pilot stresses in flight." *Aerosp. Med.* 30: 797-801 (1959).

C77,977/59

Milburn, T. W.: "Space crews, psychology, and American society." *J. Soc. Issues* 17 No. 2: 24-28 (1961). J10,616/61

General discussion of interpersonal conflicts on lengthy space trips. No reference is made to the somatic aspects of the G.A.S.

Tobias, P. R.: "The effects of radiation on integrated behavior." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 395-417. Glencoe, Ill.: Free Press, 1963. E10,434/63

Review on the effects of various intensities of x-irradiation upon the behavior of animals and man, with special reference to aerospace medicine.

Rotondo, G.: "Considerazioni cliniche e medico-legali su una sindrome addisoniana manifestatasi in un pilota militare dopo lunga ed impegnativa attività di volo" (Clinical and medico-legal considerations on an Addisonian syndrome appearing in a military pilot after long and stressful flying activity). *Riv. Med. Aeronaut. Spaz.* 26: 291-306 (1963). E24,219/63

The development of an Addisonian syndrome is ascribed to exhaustion of the adrenals due to pilot's fatigue.

Jongbloed, J.: "Medische vraagstukken in verband met de ruimtevaart. VII. De psychische belasting van de ruimtevaarder" (Medical problems connected with space travel. VII. The psychic stress in the spaceship traveller). *Med. Tijdschr. Geneeskhd.* 107: 1188-1190 (1963) (Dutch). J23,561/63

Rotondo, G.: "Sull'impiego dell'acido adenozintrifosforico e della cocarbossilasi in piloti affetti da lieve o iniziale fatica di volo" (The use of ATP and cocarboxylase in pilots suffering from light or initial flying fatigue). *Riv. Med. Aeronaut. Spaz.* 27: 176-192 (1964). G19,344/64

Flying fatigue in jet pilots, ascribed to the exhaustion of adaptation energy, was effectively treated by oral medications containing ATP and cocarboxylase (19 refs.).

Barron, C. I., Dreher, J. J.: "Effects of electric fields and negative ion concentrations on test pilots." *Aerosp. Med.* **35**: 20-23 (1964). G37,107/64

The results of a study on pilots exposed to ionic or electric fields "neither support nor negate the hypothesis that negative ions or ions plus electric fields may be beneficial in ameliorating the effects of fatigue or stress."

Balke, B., Melton, C. E. Jr., Blake, C.: "Physiological stress and fatigue in aerial missions for the control of forest fires." *Aerosp. Med.* **37**: 221-227 (1966).

G37,796/66

Rotondo, G.: "Contributo sperimentale al trattamento terapeutico e preventivo della fatiga del pilotaggio" (Therapeutic and preventive treatment of pilot fatigue. Experimental contribution). *Riv. Med. Aeronaut. Spaz.* **32**: 231-268 (1969). H18,349/69

Pilot fatigue is compared with the stage of exhaustion of the G.A.S., and presumably is due to depletion of adaptation energy. Allegedly, dehydroisoandrosterone exerts beneficial effects.

Baruch, D.: "Some medical aspects in agricultural flights relating to fatigue among agricultural pilots." *Aerosp. Med.* **41**: 447-450 (1970). G36,975/70

A study in Israel showed that "as a result of agricultural flights under hard weather conditions there were significant changes in the pilot's body such as loss of weight, increase of body temperature, decrease of eosinophil cells, tendency to decrease of blood sugar level. All these changes in combination with lack of sleep may reduce the alertness of the pilot and may be considered an important factor in aircraft accidents in agricultural flights."

Yanowitch, R. E., Mohler, S. R., Nichols, E. A.: "Psychosocial reconstruction inventory: a postdictal instrument in aircraft accident investigation." *Aerosp. Med.* **43**: 551-554 (1972). J14,847/72

Review of data on the role of stress in increasing accident proneness, especially in pilots.

Yanowitch, R. E., Bergin, J. M.: *The Aircraft as an Instrument of Self Destruction*. Federal Aviation Administration, Aviation

Med. pamphlet, p. 5. Washington, D.C., 1973. J5,009/73

Psychologic study suggesting that pilot fatigue, especially if combined with other chronic stressors (for example, family problems), may influence the pilot's behavior so that he provokes a fatal accident for suicidal reasons.

→Corticoids and 17-KS. Pincus, G., Hoagland, H.: "Steroid excretion and the stress of flying." *J. Aviat. Med.* **14**: 173-193 (1943). 84,492/43

Increased urinary 17-KS excretion and diuresis were noted in subjects shown to be fatigued on the "Steven's serial coordination meter, the Hoagland-Werthessen pursuit meter or [in] pilots on test flights or instruction flights." As altitude increased, the response on the Hoagland-Werthessen pursuit meter was associated with poorer performance, owing to reduced oxygen tension. Presumably, "the simulated and actual stress of flying studied induces adrenal steroid hormone hypersecretion that is reflected in the 17-ketosteroid output; this hypersecretion either causes or is accompanied by diuresis."

Craven, C. W., Smith, C. S.: "Steroid excretion in airmen under stress." *J. Aviat. Med.* **26**: 200-205; 213 (1955) (22 refs.). C16,180/55

Marchbanks, V. H.: "Effect of flying stress on urinary 17-hydroxycorticosteroid levels. Observations during a 22 1/2-hour mission." *J. Aviat. Med.* **29**: 676-682 (1958). C58,431/58

Urinary steroids were increased almost twofold in the pilot of a B-52 aircraft on a 22.5 hour nonstop flight from Florida to Argentina to New York. "The 17-OHCS urinary output is a favorable index for measuring stress in flying personnel."

Hale, H. B., Ellis, J. P. Jr., Kratochvil, C. H.: "Effects of piloting supersonic aircraft on plasma corticosteroids and bicarbonate." *J. Appl. Physiol.* **14**: 629-631 (1959). J11,140/59

In pilots flying supersonic military aircraft, no significant correlation was found between the fall in plasma bicarbonate and the rise in corticoids.

Marchbanks, V. H. Jr.: "Flying stress and urinary 17-hydroxycorticosteroid levels during twenty-hour missions." *Aerosp. Med.* **31**: 639-643 (1960). C90,270/60

In B-52 crew members, the highest in-

crease in urinary 17-OHCS output occurred during missions flown at a time most out of phase with the normal sleep cycle. This excretion is regarded "as a favorable index for evaluation of stress in flying personnel."

Bugard, P.: "Etude hormonale et métabolique de la fatigue. II. Personnel volant à bord d'avions intercontinentaux" (Hormonal and metabolic study of fatigue. II. Crew members on transcontinental flights). *Ann. Endocrinol.* (Paris) **22**: 1008-1016 (1961).

D22,366/61

Hyperaldosteronism was more pronounced on jets than on conventional aircraft, and was definitely related to emotional tension. A decrease in 17-KS was evident in men, but not in women. Excretion of 17-OHCS and creatinine was increased. Allegedly, endocrine-metabolic examinations can provide valuable early indices of fatigue among aviators.

Ulvedal, F., Smith, W. R., Welch, B. E.: "Steroid and catecholamine studies on pilots during prolonged experiments in a space cabin simulator." *J. Appl. Physiol.* **18**: 1257-1263 (1963).

E35,063/63

In pilots placed in a space cabin simulator for several weeks, the corticoid and catecholamine variations were no more severe than those caused by extensive medical examinations. "The only significant trend was the continuous linear increase in the excretion of corticosterone-like hormones. There were borderline indications that the excretion of 17-hydroxycorticosteroids and norepinephrine was altitude dependent. Extraordinary occurrences in the simulator were correlated with increased catecholamine and steroid excretion." The space cabin simulator is described in detail.

Marchbanks, V. H. Jr., Hale, H. B., Ellis, J. P. Jr.: "Stress responses of pilots flying 6-hour overwater missions in F-100 and F-104 aircraft." *Aerosp. Med.* **34**: 15-18 (1963).

G2,360/63

In navy pilots flying six-hour overwater missions in F-100 and F-104 aircraft, corticoid levels were increased in the plasma but not in urine. EP and NEP values were considerably above normal, as were the excretion rates of urea and uric acid, while phosphate levels were not altered. The total reaction depended very much upon airplane characteristics and pilot experience.

Colehour, J. K., Graybiel, A.: "Excretion of 17-hydroxycorticosteroids, catechol amines,

and uropepsin in the urine of normal persons and deaf subjects with bilateral vestibular defects following acrobatic flight stress." *Aerosp. Med.* **35**: 370-373 (1964).

G11,705/64

Deaf persons with vestibular defects who accompanied experienced pilots on acrobatic flights failed to show the usual increase in corticoids and catecholamines, presumably because their appropriate sensory organs in the inner ear were not functional.

Litta-Modignani, R., Magid, E. B., Blivais, B. B.: "Effects of whole body vibrations of humans on plasmatic and urinary corticosteroid levels." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 517-525. New York and London: Academic Press, 1965.

E5,496/65

In man, vibrations of a sinusoidal nature performed by a mechanical shake table that attempts to imitate conditions in a jet aircraft seat, did not cause any increase in plasma 17-OHCS, but rather a small decrease. A slight diminution was also found in urinary blue-tetrazolium-reducing steroids (BTS) and 17-KGS. Under these conditions of moderate vibration, "a mild inhibition of the hypothalamic-hypophysis-adrenal axis could have occurred."

Hale, H. B.: "Plasma corticosteroid changes during space-equivalent decompression in partial-pressure suits and in supersonic flight." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 527-534. New York and London: Academic Press, 1965.

E5,497/65

In pilots, decompression to space-equivalent pressure levels in partial-pressure suits caused varying degrees of increase in plasma corticosteroids. However, "on the average, plasma cortisol concentrations, after extreme decompression in these suits, reached levels similar to those observed in human subjects reacting to hypoxia in combination with heat or flying high-performance aircraft."

Elmadjian, F., Forchielli, E.: "Characterization of hormonal steroids of the chimpanzee: changes observed in adrenal cortical function during simulated and actual space flight." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 535-544. New York and London: Academic Press, 1965.

E5,498/65

Detailed report on changes in the urinary excretion and blood levels of various steroids (corticoids, estrogens, androgens and so on) in chimpanzees during actual or simulated space flights. "Interpretation of the above data is difficult due to the varying degrees of time-lapse from the point of termination of the stress to the time of sampling."

Jovy, D., Brüner, H., Klein, K. E., Wegmann, H. M.: "Adaptive responses of adrenal cortex to some environmental stressors, exercise and acceleration." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 545-553. New York and London: Academic Press, 1965. E5,499/65

Plasma corticoid and eosinophil determinations in healthy young men exposed to several stressors encountered during space flights (hypoxia, cold, heat, acceleration, muscular work). The results of exposure to these stressors, alone or in various combinations, are taken as an expression of individual sensitivity to stress, and offer a criterion of practical importance.

Ulvedal, F., Roberts, J. J.: "Study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. VI. Excretion of steroids and catecholamines." *Aerosp. Med.* 37: 572-578 (1966). F93,442/66

Men kept in a double-walled space cabin simulator in an oxygen-helium atmosphere showed no significant disturbance in glucocorticoid or catecholamine elimination. A reversal of the corticoid excretion rhythm was noted in subjects who slept during the day and worked at night (22 refs.).

Colehour, J. K., Graybiel, A.: "Biochemical changes occurring with adaptation to accelerative forces during rotation." *Aerosp. Med.* 37: 1205-1207 (1966). F95,358/66

Bourne, P. G., Rose, R. M., Mason, J. W.: "Urinary 17-OHCS levels. Data on seven helicopter ambulance medics in combat." *Arch. Gen. Psychiatry* 17: 104-110 (1967). G63,035/67

In seven helicopter ambulance physicians in Vietnam, "the variation in the level of 24-hour urinary 17-OHCS excretion deviates very little from the overall mean, and bears no direct relationship to whether the subjects were flying combat missions or not." It is assumed that "stress can only be defined in terms of the individual's interaction with the environment, and that man is able to make

a satisfactory psychological and physiological adaptation even to the most threatening situations."

"Stress in helicopter personnel." *J.A.M.A.* 201: 320-321 (1967). F85,752/67

Studies on helicopter ambulance crews showed that the usual stress-induced increase in urinary corticoid excretion can be remarkably well controlled by certain psychologic adjustments minimizing the reality of the danger to be faced on combat missions and exaggerating the dangers already dealt with "in order to enhance... feelings of omnipotence and invincibility."

Lafontaine, E., Lavernhe, J., Courillon, J., Medvedeff, M., Ghata, J.: "Influence of air travel east-west and vice-versa on circadian rhythms of urinary elimination of potassium and 17-hydroxycorticosteroids." *Aerosp. Med.* 38: 944-947 (1967). H3,611/67

Studies on transatlantic flight crews show that, among various metabolic parameters, 17-OHCS exhibits the clearest circadian variations. After a quick roundtrip, with twenty hours of exposure to a negative time zone change of eleven hours, the circadian rhythm of potassium and 17-OHCS immediately re-establishes concordance with the preexisting reference rhythm. With five days of exposure to a similar time zone change, the circadian eliminatory rhythm of 17-OHCS begins to adapt itself to local time on the third day and becomes complete by the fifth day, by then being the antithesis of the preestablished reference rhythm.

Lafontaine, E., Ghata, J., Lavernhe, J., Courillon, J., Bellanger, G., Laplane, R.: "Rythmes biologiques et décalages horaires. Etude expérimentale au cours de vols commerciaux long-courriers" (Biologic rhythm and time zone differences. Experimental study during long commercial flights). *Concours Méd.* 89: 3731-3746; 3963-3976 (1967). G47,151/67

On flights from Paris to Anchorage, with an eleven-hour time zone difference, there occurred a decrease in diuresis followed by a "rebound," and a disruption in the circadian rhythm of catecholamine and corticoid elimination.

Wegmann, H. M., Klein, K. E., Brüner, H.: "Die Auswirkung fliegerischer Belastung auf einige Blutkomponenten" (Effects of flying stress on certain components of the blood). *Int. Z. Angew. Physiol.* 23: 293-304 (1967). G45,957/67

Among the indicators examined in jet pilots training for Starfighter F-104 G flights, corticoids and certain enzyme activities in the blood proved most sensitive to stress, whereas other enzyme and blood sugar variations were unreliable (24 refs.).

Hale, H. B., Williams, E. W.: "Endocrine-metabolic response to sequential decompression during simulated orbital flight." *Aerosp. Med.* **39**: 1175-1177 (1968). H22,180/68

In men exposed to sequential decompression during simulated orbital flights, "non-specific stress was evident, as there were decompression-induced elevations (which were progressive with time) in creatinine, urine volume, sodium, norepinephrine, and urea. Epinephrine was also elevated, but the peak effect came at an early time. As a late effect, 17-OHCS excretion became elevated."

Miller, R. G.: "Secretion of 17-hydroxycorticosteroids (17-OHCS) in military aviators as an index of response to stress: a review." *Aerosp. Med.* **39**: 498-501 (1968).

J22,567/68

Rubin, R. T., Miller, R. G., Arthur, R. J., Clark, B. R.: "Differential adrenocortical stress responses in naval aviators during aircraft carrier landing practice." *Psychol. Rep.* **26**: 71-74 (1970).

J15,627/70

Miller, R. G., Rubin, R. T., Clark, B. R., Crawford, W. R., Arthur, R. J.: "The stress of aircraft carrier landings. I. Corticosteroid responses in naval aviators." *Psychosom. Med.* **32**: 581-588 (1970). G80,363/70

During aircraft carrier landing practice of two-man F-4B jets, U.S. Navy pilots showed considerable "adrenal cortical stress" (17-OHCS excretion), while their flight officers did not. "The complex and dangerous task of carrier landing appears to be a greater stress on the pilot in control of the aircraft than on his passive partner" (25 refs.).

Leach, C. S., Alexander, W. C., Johnson, P. C.: "Adrenal and pituitary response of the Apollo 15 crew members." *J. Clin. Endocrinol. Metab.* **35**: 642-645 (1972).

H61,627/72

"Inflight studies during the 14-day Gemini 7 mission showed increased urinary aldosterone excretion." Inflight specimens were not collected during the Apollo 15 mission, but when pre- and postflight levels were compared, the elimination of urinary aldosterone was again manifest. "Increased secretion of this hormone could be one of man's adaptations to the weightless environment."

Glusskaya, I. G., Vinogradov, L. A., Noskov, V. B., Balakhovskiy, I. S.: "Effect of hypodynamia and other spaceflight factors on the excretion of 17-hydroxycorticosteroids and aldosterone." *Kosm. Biol. Med.* **7** No. 3: 43-48 (1973).

J14,652/73

Hale, H. B., Storm, W. F., Goldzieher, J. W., Hartman, B. O., Miranda, R. E., Hosenfeld, J. M.: "Physiological cost in 36 and 48 hour simulated flights." *Aerosp. Med.* **44**: 871-881 (1973).

H95,634/73

"Physiologic cost was assessed by use of a battery of urinary techniques, including potassium, sodium, urea, 17-OHCS, and, in some cases, individual 17-ketosteroids. Comparison was made of responses to (a) uncomplicated flight, (b) flight complicated by environmental dryness, (c) flight complicated by 8,000-ft pressure altitude, and (d) flight complicated by dryness and altitude. The prolonged psychomotor effort (and attendant sleep deprivation) acted as a nonspecific stressor. Altitude had intensifying influence, but dryness tended to counteract some phases of the stress response."

Hale, H. B., Hartman, B. O., Harris, D. A., Miranda, R. E., Williams, E. W.: "Physiologic cost of prolonged double-crew flights in C-5 aircraft." *Aerosp. Med.* **44**: 999-1008 (1973).

J11,333/73

The changes in urinary elimination of EP, NEP, 17-OHCS, potassium, nitrogen, urea and creatinine on double-crew transpacific missions in C-5 military aircraft essentially confirmed earlier observations made under similar conditions in C-141 aircraft. "Recovery from these long missions (average duration = 65 hrs) involved differential reversal among the flight-affected endocrine-metabolic functions. Extrapolations of post-flight data suggest that the time for complete recovery exceeded the flight time."

Leach, C. S., Rambaut, P. C., Johnson, P. C.: "Adrenocortical responses of the Apollo 17 crew members." *Aerosp. Med.* **45**: 529-534 (1974).

J13,390/74

In Apollo 17 astronauts during their first thirteen days in space, "aldosterone excretion was normal early and elevated later in the mission, probably causing a loss in total body exchangeable potassium. There was decreased 17-hydroxycorticosteroid excretion only during the early mission days for the two moon landers and throughout the mission for the other astronaut. Cortisol excretion was elevated on physically stressful mission days.

At recovery, plasma ACTH was elevated without a similar increase in plasma cortisol."

Arslan, M., D'Amelio, G., Marchiori, C.: "Clinical and endocrinological effects of coriolis accelerations and their behavior under drug treatment." *Acta Otolaryngol.* (Stockh.) **77**: 155-158 (1974).

J12,116/74

In subjects who make head movements during a body rotation at constant angular speed, coriolis accelerations occur by provoking a flow of endolymph in the semicircular canals. This is associated with nausea, dizziness, pallor, sweating, vomiting, variations in pulse rate and arterial pressure and a considerable rise in urinary catecholamine, 17-KS and 17-OHCS elimination. The authors conclude that "for normal subjects, exposure to Coriolis accelerations represents a stress which affects the adrenergic but not the hypophysial-cortical system. This stress is consistently related to the emotional tension originated by the test itself. The possibility of preventing the adrenergic hyperactivity of emotional origin by diazepam is discussed."

Pinter, E. J.: "Metabolic and endocrine changes in aerobic flight." *Aerospace Med.* **45**: 1159-1163 (1974).

J17,132/74

→Epinephrine and Norepinephrine. Euler, U. S. von, Lundberg, U.: "Effect of flying on the epinephrine excretion in air personnel." *J. Appl. Physiol.* **6**: 551-555 (1954).

C1,706/54

In military pilots, EP excretion was about four times less during ground activity than during flight, and was lower still during sleep. Corresponding variations in NEP output were slight or nonexistent.

Klepping, J., Buisson, O., Guerrin, J., Escousse, A., Didier, J. P.: "Evaluation de l'élimination urinaire des catécholamines chez des pilotes d'avions à réaction" (Evaluation of the urinary excretion of catecholamines in jet pilots). *C.R. Soc. Biol.* (Paris) **157**: 1727-1729 (1963).

G9,483/63

In jet pilots, urinary excretion of catecholamines after a brief flight at 50,000 ft. is considerably increased. More marked augmentation alternates between EP and NEP concentrations. The response is ascribed to psychic rather than physical stressor effects.

Klepping, J., Truchot, R., Mounie, J., Eygonnet, J. P.: "Evaluation de l'élimination urinaire de l'acide 3-méthoxy-4-hydroxymandélique (VMA) chez les pilotes d'avions à

réaction au cours de vols d'entraînement de différents types" (Evaluation of the urinary elimination of 3-methoxy-4-hydroxymandelic acid [VMA] in jet pilots during different types of training flights). *C.R. Soc. Biol.* (Paris) **158**: 1815-1817 (1964).

E35,277/64

Euler, U. S. von: "Quantitation of stress by catecholamine analysis." *Clin. Pharmacol. Ther.* **5**: 398-404 (1964).

G18,238/64

Review of the literature and personal observations on man suggest that "gravitational stress and exposure to cold are mainly associated with an increase in the norepinephrine excretion, indicating the importance of this hormone in circulatory and temperature controlling homeostatic mechanisms. Mental stress involving exhilarating or aggressive reactions is also associated with an increase in the norepinephrine excretion. The types of emotional stress which are mainly characterized by apprehension, anxiety, pain, or general discomfort are regularly accompanied by an increase in the epinephrine excretion." Special sections are devoted to catecholamine excretion associated with flying, mental work and exposure to cold.

McKenzie, J. M., Fiorica, V.: *Physiological Responses of Pilots to Severe Weather Flying*. Federal Aviation Administration, Aviation Med. pamphlet, p. 8. Washington, D.C., 1966.

G44,104/66

Among the physiologic responses examined in pilots flying under very bad weather conditions, an increase in total urinary catecholamine excretion was most constant.

Melton, C. E., Wicks, M., Saldivar, J. T. Jr., Morgan, J., Vance, F. P.: *Physiological Studies on Air Tanker Pilots Flying Forest Fire Retardant Missions*. Federal Aviation Administration, Aviation Med. pamphlet, p. 10. Washington, D.C., 1968.

G67,527/68

In air tanker pilots flying forest fire retardant missions of limited length, urinary catecholamine and corticoid excretion, heart rate and ECG were used to appraise stress. "None of the measurements indicated that a significant amount of stress was involved, nor was fatigue evident. Heart rates correspond to those of sedentary workers, though doubling of heart rate occurred during two emergencies (hydraulic line failure). Heart rate followed a consistent pattern during flights with the minimums occurring on route to and from fires and maximums during retardant drops."

Hale, H. B., Anderson, C. A., Williams, E. W., Tanne, E.: "Endocrine-metabolic effects of unusually long or frequent flying missions in C-130E or C-135B aircraft." *Aerosp. Med.* **39**: 561-570 (1968). G63,855/68

"Flight-stress appraisal was made by means of a battery of urinary determinations (epinephrine, norepinephrine, 17-OHCS, urea, uric acid, phosphorus, magnesium, sodium, and potassium) for flyers who participated in (a) 20-hour missions in C-130E aircraft (flights from New Zealand to Antarctica, and back), (b) 6-day missions in C-135B aircraft (earth-circling missions) or (c) 7-week missions in C-135B aircraft (overfrequent transoceanic and transcontinental flying). The adrenal medulla (judging by urinary epinephrine) consistently showed flight-sensitivity, but other endocrine-metabolic functions varied in ways indicative of adaptation." East- and westbound earth-circling missions did not elicit essentially different degrees of flight stress, as demonstrated by the above mentioned indices.

Hale, H. B., Williams, E. W., Buckley, C. J.: "Aeromedical aspects of the first nonstop transatlantic helicopter flight: III. Endocrine-metabolic effects." *Aerosp. Med.* **40**: 718-723 (1969). G75,913/69

In the crew of the first nonstop transatlantic helicopter flight, "nonspecific stress was evident, as flight caused a 143 percent gain in epinephrine, a 25 percent gain in urea and a 51 percent reduction in the norepinephrine/epinephrine ratio. It also modified the circadian trends for 17-OHCS and phosphorus."

Debijadji, R., Perovic, L., Varagic, V.: "Evaluation of the sympatho-adrenals activity in pilots by determination of urinary catecholamines during supersonic flight." *Aerosp. Med.* **41**: 677-679 (1970). J21,924/70

Observations on supersonic pilots "indicate that stress reactions to flight conform to the General Adaptation Syndrome pattern."

Rubin, R. T., Miller, R. G., Clark, B. R., Poland, R. E., Arthur, R. J.: "The stress of aircraft carrier landings. II. 3-Methoxy-4-hydroxyphenylglycol excretion in naval aviators." *Psychosom. Med.* **32**: 589-597 (1970). G80,364/70

In naval aviators practicing landing on aircraft carriers (which causes considerable stress), the urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG), a catechol-

amine metabolite, increased considerably. "These findings suggest that there may be an accelerated metabolism of brain norepinephrine under conditions of heightened arousal and concentration compared to the normal waking state."

Melton, C. E., Fiorica, V.: *Physiological Responses of Low-Time Private Pilots to Cross-Country Flying*. Federal Aviation Administration, Aviation Med. pamphlet, p. 6. Washington, D.C., 1971. G85,171/71

In inexperienced private pilots, each of whom made three cross-country flights, heart rate and urinary excretion of EP and NEP did not change in proportion to the length of the flight. "However, the level of stress was high when compared to other types of flying activities. The total stress of such flights must, therefore, be considered to be in direct proportion to the length of the flights." Terminal procedures at unfamiliar airports caused the greatest increase in catecholamine excretion and "acted as rather powerful stressors of short duration compared to the duration of the entire flight."

Hale, H. B., Hartman, B. O., Harris, D. A., Williams, E. W., Miranda, R. E., Hosenfeld, J. M.: "Time zone entrainment and flight stressors as interactants." *Aerosp. Med.* **43**: 1089-1094 (1972). J2,017/72

In flight crews on fifty-four-hour bi- or tri-directional transmeridian missions, urinary corticoid and catecholamine excretion showed rhythmic variability that corresponded to the crews' home base, even after several time zones had been crossed. Corticoid and catecholamine responses to flight stressors were least pronounced at 22:00 and most marked at 06:00 Eastern Standard Time, which corresponded to home base. Essentially similar findings were obtained on fifty-hour missions.

→**5-HT and Histamine.** Parin, V. V., Antipov, V. V., Raushenbakh, M. O., Saksonov, P. P., Shashkov, V. S., Chernov, G. A.: "Changes in blood serotonin level in animals exposed to ionizing radiation and dynamic factors of space flight." *Fed. Proc.* **25**: T103-T106 (1966). F60,935/66

In various species of animals travelling in satellite-spaceships, exposure to x-rays, acceleration and vibration considerably diminished the blood 5-HT content.

Vaysfel'd, I. L., Il'icheva, R. F.: "Diurnal rhythm of the content of biogenous amines

(histamine, serotonin) in human blood under normal conditions and during altered work-sleep cycles." *Kosm. Biol. Med.* **6** No. 5: 56-62 (1972) (English translation of Russian original). H79,765/72

The histamine-diaminoxidase system shows considerable circadian variations in healthy subjects. The blood 5-HT content tends to decrease at night. Changes in the work-sleep cycle cause fluctuations in these parameters "related not only to the stressor applied, but also to the initial state of the organism." These findings are especially important in space medicine.

→**Metabolites.** Persky, H.: "Response to a life stress: evaluation of some biochemical indices." *J. Appl. Physiol.* **6**: 369-374 (1953). J11,917/53

Pilots under training were subjected to various stressors (parachute jumps, physical exercise and so on) which caused a significant diminution in blood eosinophil and *glutathione* levels, but which did not affect the synthesis of *hippuric acid* from administered sodium benzoate. "These findings are taken to indicate that airborne training focal stresses are of intermediate severity on a scale whose poles are fear of failure and fear of bodily injury."

Beischer, D. E.: "Effect of simulated flight stresses on the concentration of serum *cholesterol*, *phospholipid* and *lipoprotein*." *J. Aviat. Med.* **27**: 260-266 (1956) (24 refs.). J13,199/56

Marchbanks, V. H. Jr., Hale, H. B., Ellis, J. P. Jr.: "Stress responses of pilots flying 6-hour overwater missions in F-100 and F-104 aircraft." *Aerosp. Med.* **34**: 15-18 (1963). G2,360/63

In navy pilots flying six-hour overwater missions in F-100 and F-104 aircraft, corticoid levels were increased in the plasma but not in urine. Urinary EP and NEP values were considerably above normal, as was the excretion rate of *urea* and *uric acid*, while phosphate levels were not altered. The total reaction depended very much upon airplane characteristics and pilot experience.

Tabusse, L., Pannier, R., Gourves, P.: "Hypoglycémie et malaises chez l'aviateur" (Hypoglycemia and malaise in pilots). *Rev. Cps. Santé Armées* **6**: 623-637 (1965). G35,120/65

Hypoglycemia with malaise and hyper-

sensitivity to insulin may sometimes occur in pilots, but its relationship to stress remains in doubt.

Austin, F. H. Jr.: "A review of stress and fatigue monitoring of naval aviators during aircraft carrier combat operations: blood and urine biochemical studies." In: Bourne, P. G., *The Psychology and Physiology of Stress: With Reference to Special Studies of the Viet Nam War*, pp. 197-218. New York and London: Academic Press, 1969.

E8,568/69

Review on stress and fatigue-monitoring in naval aviators during combat operations on a U.S. Navy aircraft carrier in North Vietnam. Plasma phospholipid fractions behaved unlike those of normal individuals or those exposed to other stressors. "The *phosphatidylglycerol* responded to this type of stress more markedly and consistently than the other fractions. A discriminant functions formula has been developed which may facilitate identification of the stress type and degree of subject response up to and including psychophysiological exhaustion and collapse." Variations in typical stress hormone levels are also reported.

Lutwak, L., Whedon, G. D., Lachance, P. A., Reid, J. M., Lipscomb, H. S.: "Mineral, electrolyte and nitrogen balance studies of the Gemini-VII fourteen-day orbital space flight." *J. Clin. Endocrinol. Metab.* **29**: 1140-1156 (1969). H16,831/69

Metabolic studies on two astronauts during two weeks of orbital space flight (NASA Gemini VII) revealed considerable individual variations in metabolic responses. "In one man, significant increases in urinary *calcium* occurred during the second week of flight, and persisted during the recovery phase; calcium balance became less positive in flight in both subjects. Urinary *phosphate* excretion increased substantially in flight in both subjects despite reduction in phosphate intake. Urinary *nitrogen* and *sulfate* excretion decreased in flight but less than would be expected from the reduction in intake. Patterns of excretion of *magnesium*, *sodium*, *potassium* and *chloride* were different for each subject and could in part be correlated with changes in adrenocortical steroid production. The principal hormonal change was a striking decrease during flight in the urinary excretion of 17-hydroxycorticosteroids."

Pichler, H. J.: "Über ein interessantes Phänomen bei Schwerelosigkeit" (An interest-

ing phenomenon caused by weightlessness). *Arch. Klin. Exp. Ohren. Nasen-Kehlkopftheilk.* **202**: 543-548 (1972). H80,799/72

As soon as astronauts reach weightlessness after takeoff, they develop the illusion of standing on their heads because of increased blood supply to the brain. At the same time, *polyuria* sets in. [Stress is not specifically discussed (H.S.).]

Raichle, M. E., King, W. H.: "Functional hypoglycemia: a potential cause of unconsciousness in flight." *Aerosp. Med.* **43**: 76-78 (1972). J20,017/72

In a student pilot, functional *hypoglycemia* with unconsciousness developed during acceleration a few hours after a high carbohydrate meal.

→**Blood Count.** Pincus, G.: "Studies of the role of the adrenal cortex in the stress of human subjects." *Recent Prog. Horm. Res.* **1**: 123-145 (1947). 98,426/47

Excellent review on the biochemical changes characteristic of the G.A.S. in man, with special reference to 17-KS excretion and blood count as influenced by circadian variations, the stresses of daily life, operating a Hoagland-Werthessen pursuit meter, flying and exposure to heat. The response of schizophrenics is abnormal in many respects, and the question is raised whether adrenal malfunction may play a pathogenic role in mental disease (20 refs.).

Domanski, T. J., Nuttall, J. B.: "The physiological recognition of strain associated with flying." *J. Aviat. Med.* **24** Sect. 2, Supp.: 441-445 (1953). B96,198/53

Stress associated with flying causes definite eosinopenia in man.

Murphy, C. W., Gofton, J. P., Cleghorn, R. A.: "Effect of long-range flights on eosinophil level and corticoid excretion." *J. Aviat. Med.* **25**: 242-248 (1954). C5,680/54

Murphy, C. W., Cleghorn, R. A.: "Study of adrenocortical physiology in jet flying." *Can. J. Biochem.* **34**: 534-542 (1956).

C16,203/56

Flying a jet aircraft caused pronounced eosinopenia but only moderate increases in corticoid excretion and no alteration in salivary electrolyte concentration.

Domanski, T. J.: "Human stress response in contrasting aircraft operations." *Fed. Proc.* **15**: 51 (1956). C14,056/56

On training missions in B-47 and B-29 type aircraft, pre- and postflight eosinopenia was essentially similar in student and instructor pilots.

→**Cardiovascular System.** Morris, D. P.: "Blood pressure and pulse changes in normal individuals under emotional stress; their relationship to emotional instability." *Psychosom. Med.* **3**: 389-398 (1941).

B26,186/41

In student nurses undergoing examinations and student pilots performing different flying exercises for the first time, a rise in blood pressure was quite constant, while pulse rate was more variable and sometimes actually decreased during the stress. Pallor, tremor, flushing, excessive sweating, restlessness and apprehensive facial expression were also studied as possible indicators of stress, but the results proved more difficult to interpret.

Eliasch, H., Rosen, A., Scott, H. M.: "Systemic circulatory response to stress of simulated flight and to physical exercise before and after propranolol blockade." *Br. Heart J.* **29**: 671-683 (1967).

G50,658/67

Heart rate, blood pressure and cardiac output all increased in pilots during a Link trainer simulated flight, as well as after physical exercise on a bicycle ergometer. Comparisons with similar tests after propranolol administration "indicate that beta adrenergic receptor activity is extensively involved in the circulatory reaction to emotional stress. In contrast, this activity appears to be involved but less essential in the achievement of the circulatory adjustments during moderate physical exercise."

Scheinman, H. Z.: "Coronary atherosclerosis in military pilots: I. Relationship to flying and aviation accidents." *Aerosp. Med.* **39**: 1348-1351 (1968).

G85,445/68

Autopsies on 206 military pilots "demonstrate that the amount of flying time (when the age factor is considered) and type of aircraft are neither statistically related nor contributory to the severity of coronary atherosclerosis." It is concluded that drastic elimination of older aircrew will not significantly reduce aviation accidents.

Benetato, G., Adamache, A., Vrâncianu, R., Ionescu, V.: "Cercetari asupra asemnificării variatiilor telereogramei cardiotoracice în condiții de solicitare la aviatori" (The sig-

nificance of variations in the cardiothoracic telerheogram in airmen under conditions of stress). *Fiziol. Norm. Patol.* **18**: 385-394 (1972) (Roumanian). J20,500/72

Billings, C. E., Gerke, R. J., Chase, R. C., Eggspuehler, J. J.: "Stress and strain in student helicopter pilots." *Aerosp. Med.* **44**: 1031-1035 (1973). J11,332/73

Comparative studies on the tachycardia noted in student helicopter pilots under various conditions.

→ **Varia.** Jenson, R. L.: "Diabetes in flying personnel." *Aerosp. Med.* **32**: 1127-1134 (1961). D16,277/61

Stress associated with flying, especially combat missions, may lead to aggravation of preexistent diabetes.

Preston, F. S., Bateman, S. C., Short,

R. V., Wilkinson, R. T.: "Effects of flying and of time changes on menstrual cycle length and on performance in airline stewardesses." *Aerosp. Med.* **44**: 438-443 (1973) (21 refs.). J14,835/73

Ilin, E. A., Serova, L. V., Portugalov, V. V., Tigranian, R. A., Savina, E. A., Gaievskaya, M. S., Kondratiev, I. I., Noskin, A. D., Miliavski, V. I.: Iurov, B. N.: "Preliminary results of examinations of rats after a 22-day flight aboard the Cosmos-605 biostation." *Aviat. Space Environ. Med.* **46**: 319-321 (1975). J22,154/75

In rats under simulated weightless conditions in the Salyut and Skylab orbital stations, organ changes were not conspicuous, "except the weight of the spleen and the thymus which was lower in the experimental animals, and that of the adrenals and kidneys which was higher in the experimental rats."

Parachute Jumping

Parachute jumping produces definite indicators of stress, especially among beginners. The associated free anxiety enhances hippuric acid output following administration of sodium benzoate. There is also a rise in EP, NEP and corticoid excretion, as well as eosinopenia, and an increased GSR. Plasma 17-OHCS, EP, NEP, VMA, FFA and blood sugar elevations are less pronounced in experienced, competent parachute jumpers than in beginners.

Parachute Jumping

(See also our earlier stress monographs, p. xiii)

Korchin, S. J., Basowitz, H.: "Perceptual adequacy in a life stress." *J. Psychol.* **38**: 495-502 (1954). J13,189/54

Earlier observations have shown that stress with free anxiety elevates hippuric acid excretion following administration of a standard dose of sodium benzoate. During paratroop training, men with low hippuric acid excretion prior to the test are uniformly superior in performance, and proneness to stress responses is reflected in the prestress hippuric acid elimination rate.

Persky, H.: "Glutathione metabolism in men under psychological stress." *Psychosom. Med.* **16**: 489-495 (1954). J13,307/54

In man, blood-reduced glutathione is considerably lowered five to ten hours after parachute jumping but not after severe physical exercise. Despite this apparent lack of nonspecificity, "it is postulated that severe psychological stress operating over long periods may produce irreversible depression of the blood glutathione level and its associated metabolic dysfunctions."

Bloom, G., Euler, U. S. von, Frankenhaeuser, M.: "Catecholamine excretion and personality traits in paratroop trainees." *Acta Physiol. Scand.* **58**: 77-89 (1963). E20,130/63

In paratroop trainees, EP and NEP excretion rose during jumps as compared to rest periods. Increased pulse rate and eosinopenia were noted even during procedures preceding the jump.

Fenz, W. D.: "Conflict and stress as related to physiological activation and sensory, perceptual, and cognitive functioning." *Psychol. Monogr.* **78**: 1-33 (1964).

J7,687/64

Monograph on the relationship between real life stress (parachute jumping) created by an approach-avoidance conflict situation and physiologic activation (GSR) and performance. "Parachutists produced increasingly steep gradients of GSR to parachute-relevant and anxiety words with increasing proximity to a jump." They also became more reactive on the day of a jump, and showed a corresponding deficit in general performance which was measured by various sensory and cognitive parameters.

Landorenko, L. G., Kuz'mich, I. S., Mozzhukhin, A. S.: "Haematological characteristics of emotional stress induced by a parachute jump." *Fiziol. Zh. SSSR* **57**: 1140-1144 (1971) (Russian). J20,892/71

Fenz, W. D., Jones, G. B.: "Individual differences in physiologic arousal and performance in sport parachutists." *Psychosom. Med.* **34**: 1-8 (1972). G98,011/72

Arousal and performance studies in sport parachutists show that "while repeated exposure to a stressor is an important variable, there are also other variables not related to experience which are responsible for differ-

ences between subjects in their ability to deal effectively with stress."

Daniel, J., Mikulaj, L., Vrazda, L.: "Correlations between certain emotional and endocrine stress indicators in man." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 255-258. Bratislava: Slovak Academy of Sciences, 1973. E10,473/73

Such chemical indicators of stress as plasma 17-OHCS, EP, NEP, VMA, FFA and blood sugar were less elevated in experienced parachute jumpers, whose performance was good, than in novices.

Fenz, W. D., Jones, G. B.: "Cardiac conditioning in a reaction time task and heart rate control during real life stress." *J. Psychosom. Res.* **18**: 199-203 (1974).

J15,137/74

In man, conditioned cardiac response to a task involves the gradual adaptive control of an involuntary reaction in anticipation of a stressor. This can be shown for a number of real-life stressors, particularly parachute jumping.

Deroanne, R., Cession-Fossion, A., Juchmes, J., Servais, J. C., Petit, J. M.: "Telemetric control of heart adaptation during automatic and free-fall parachute jumps." *Aviat. Space Environ. Med.* **46**: 128-131 (1975). J22,136/75

Air-Traffic Control

Despite their sedentary occupation and their agreeable working conditions (usually pleasant, air-conditioned rooms), air traffic controllers (ATCs) experience considerable stress, especially during busy work periods, presumably because they have to concentrate continuously and are personally responsible for the lives of many people. The longer they are in their profession the more they develop subjective feelings of disease. They also show objective indicators of stress, such as tachycardia, increased GSR, plasma phospholipids, phosphatidylglycerol and so on. Catecholamine excretion is roughly proportional to the number of aircraft operations supervised, and the morning rise in corticoid elimination does not tend to subside during the day or even when the ATCs are off-duty. Night shifts are particularly stressful.

Among ATCs, peptic ulcers, hypertension and probably also CHD are especially common. In one study, 32.5 percent of the ATCs suffered from peptic ulcers. In another group, the incidence was even higher.

Whereas there can be no doubt about predisposition to hypertension and peptic ulcers, the evidence for proneness to diabetes has yet to be confirmed.

Air-Traffic Control

(See also our earlier stress monographs, p. xiii)

Kozarovitskii, L. B.: "Dynamics of skin-galvanic reactions in control panel operators during their work of regulating airplane traffic." *Zh. Vyssh. Nerv. Deiat.* **14**: 387-396 (1964) (Russian). J23,845/64

Dougherty, J. D., Trites, D. K., Dille, J. R.: "Self-reported stress-related symptoms among air traffic control specialists (ATCS) and non-ATCS personnel." *Aerosp. Med.* **36**: 956-960 (1965). G34,323/65

On the basis of self-reported stress-related symptoms, "it is safe to conclude that as an Air Traffic Control Specialist progresses through his career the sicker he thinks himself to be in comparison with non-Air Traffic Control Specialists having similar years of experience, occupational status, and location." However, the authors admit that without confirmation by more objective medical indices, the true health status of ATCs remains in doubt.

Dougherty, J. D.: "Cardiovascular findings in air traffic controllers." *Aerosp. Med.* **38**: 26-30 (1967). J22,615/67

Schaad, R., Gilgen, A., Grandjean, E.: "Die Ausscheidung von Katecholaminen beim Personal des Flugsicherungsdienstes" (Excretion of catecholamines in air traffic control personnel). *Schweiz. Med. Wochenschr.* **99**: 889-892 (1969). G68,034/69

Rosenbrock, F.: "Hardware problems in ergonomics measurements." *Ergonomics* **14**: 617-623 (1971). J19,713/71

Multichannel automatic data acquisition and processing instruments are described for the objective measurement of work loads on ATCs, using physiologic variables such as ECG, EMG, EOG (electro-oculogram), respiration and so on. "To correlate these variables with factors of stress and strain a coding is described, which renders the evaluation of a multi-dimensional work process study automatically and synchronously with the physiological data."

Grandjean, E. P., Wotzka, G., Schaad, R., Gilgen, A.: "Fatigue and stress in air traffic controllers." *Ergonomics* **14**: 159-165 (1971). J20,014/71

Kalsbeek, J. W. H.: "Standards of accept-

able load in ATC tasks." *Ergonomics* **14**: 641-650 (1971). J20,015/71

Reiche, D., Kirchner, J. H., Laurig, W.: "Evaluation of stress factors by analysis of radio-telecommunication in ATC." *Ergonomics* **14**: 603-609 (1971). J19,714/71

Laurig, W., Becker-Biskaborn, G. U., Reiche, D.: "Software problems in analysing physiological and work study data." *Ergonomics* **14**: 625-631 (1971). J19,718/71

Philipp, U., Reiche, D., Kirchner, J. H.: "The use of subjective rating." *Ergonomics* **14**: 611-616 (1971). J19,716/71

Both subjective and objective methods are used to evaluate stress in ATCs.

Rohmert, W.: "An international symposium on objective assessment of work load in air traffic control tasks." *Ergonomics* **14**: 545-547 (1971). J19,715/71

Report on the first International Symposium on Objective Assessment of Work Load in Air Traffic Control Tasks arranged by the Stress in Air Traffic Control Research Association—SATCRA.

Melton, C. E. Jr., McKenzie, J. M., Polis, B. D., Funkhouser, G. E., Iampietro, P. F.: *Physiological Responses in Air Traffic Control Personnel: O'Hare Tower*. Federal Aviation Administration, Aviation Med. pamphlet, p. 11. Washington, D.C., 1971. G83,666/71

Among ATCs at O'Hare Tower, Chicago, pulse rates were higher on the busy evening shift than during the light morning shift. GSR tests indicated that adaptation to the morning shift was incomplete in five days. Blood fibrinogen was not elevated, but plasma phospholipids and phosphatidylglycerol did increase. Catecholamine excretion was related to the number of aircraft operations, and corticoid elimination rose late in the morning and failed to recover completely during the following off-duty rest period.

Smith, R. C., Melton, C. E., McKenzie, J. M.: *Affect Adjective Check List Assessment of Mood Variations in Air Traffic Controllers*, p. 8. Washington, D.C.: Department of Transportation, Federal Aviation Administration, 1971. G86,726/71

Description of Malmstrom's Composite Mood Adjective Check List (CMACL) which evaluates stress in ATCs by eliciting their own subjective assessment of eighty

adjectives (relating to aggression, anxiety, concentration, depression, distrust, dizziness, fatigue and so on). Night shifts prove to be especially fatiguing.

Hale, H. B., Williams, E. W., Smith, B. N., Melton, C. E. Jr.: "Excretion patterns of air traffic controllers." *Aerosp. Med.* **42**: 127-138 (1971). G81,175/71

Studies on ATCs at O'Hare Airport, Chicago, revealed increased catecholamine and corticoid excretion roughly proportionate to work stress during the day, with a return to normal after rest. "In many respects the stress of O'Hare tower work exceeded the stress induced by long or difficult flying operations, a 10-hour test in a flight-simulator (inexperienced subjects), or prolonged decompression."

Gee, B. M.: *Stress and Testing in Air Traffic Control*, p. 6. Report of the Canadian Ministry of Transport. Ottawa, 1972.

G98,569/72

Report prepared for the Canadian Ministry of Transport on ways of testing stress induced by the activities of ATCs.

Smith, R. C., Cobb, B. B., Collins, W. E.: "Attitudes and motivations of air traffic controllers in terminal areas." *Aerosp. Med.* **43**: 1-5 (1972). J8,605/72

ATCs at seventeen high-density airports answered questionnaires asking what they liked best or least about their jobs. The responses from the various facilities were very similar. In general, job challenge was the most-liked aspect, and management the least.

Grayson, R. R.: "Air controllers syndrome: peptic ulcer in air traffic controllers." *Illinois Med. J.* **142**: 111-115 (1972).

G99,015/72

In a large group of ATCs examined, 32.5 percent suffered from duodenal or gastric ulcers. "Peptic ulcer in this series is concluded to be a stress-related disease, the stress being occupational."

Wehrmacher, W. H.: "Seminar on stress." *Curr. Med. Dialogue* **39**: 1102-1105 (1972).

J7,675/72

Among 111 ATCs who sought medical advice, eighty-six showed x-ray evidence of intestinal lesions, and thirty-six of these had duodenal ulcers.

Grandjean, E.: "Ergonomie" (Ergonomics). *Rev. Méd. Suisse Rom.* **92**: 201-210 (1972). J19,073/72

As judged by blood EP and clinical obser-

vations, ATCs exhibit considerably stronger manifestations of stress than do telegraphists.

Klimmer, F., Aulmann, H. M., Rutenfranz, J.: "Katecholaminausscheidung im Urin bei emotional und mental belastenden Tätigkeiten im Flugverkehrskontrolldienst" (Catecholamine excretion in urine during mental work load in the air traffic control service). *Int. Arch. Arbeitsmed.* **30**: 65-80 (1972). J22,753/72

Rohmert, W.: *Psycho-physische Belastung und Beanspruchung von Fluglotsen* (Psychophysical stress and strain in air traffic controllers), p. 273. Berlin, Köln and Frankfurt/M: Beuth-Vertrieb, 1973.

E10,905/73

Smith, R. C., Melton, C. E. Jr.: *Susceptibility to Anxiety and Shift Difficulty as Determinants of State Anxiety in Air Traffic Controllers*. Federal Aviation Administration, Aviation Med. pamphlet, p. 3. Washington, D.C., 1973.

J17,246/73

The anxiety proneness scores as determined by the STAI "were predictive of the general A-state level of controllers, but were not predictive of the degree of anxiety experienced under the stress of difficult shifts."

"Happy landing." *Br. Med. J.* August 25, 1973, p. 421.

H75,451/73

Catecholamine excretion in ATCs was raised during periods of arduous work. It was also suggested that "certain so-called stress diseases, which could include coronary heart disease, though this condition was not amenable to analysis in the study, may be related to the controllers' work." These men are also predisposed to the development of peptic ulcers and hypertension.

Melton, C. E., McKenzie, J. M., Smith, R. C., Polis, B. D., Higgins, E. A., Hoffmann, S. M., Funkhouser, G. E., Saldivar, J. T.: *Physiological, Biochemical, and Psychological Responses in Air Traffic Control Personnel: Comparison of the 5-Day and 2-2-1 Shift Rotation Patterns*. Federal Aviation Administration, Aviation Med. pamphlet, p. 15. Washington, D.C., 1973. J15,362/73

At the Houston Intercontinental Tower, a two-two-one sequence (two evening shifts, two day shifts, one mid-shift) was compared with the straight five-day shift (five consecutive days on the same shift). "Physiological and psychological assessments showed no significant stress differences on the two schedules. On neither of the schedules did the con-

trollers' stress levels differ from the general population."

Melton, C. E., McKenzie, J. M., Polis, B. D., Hoffmann, M., Saldivar, J. T. Jr.: *Physiological Responses in Air Traffic Control Personnel: Houston Intercontinental Tower*. Federal Aviation Administration, Aviation Med. pamphlet, p. 19. Washington, D.C., 1973. J15,363/73

Studies on ATCs showed that "day work (heavy traffic load) at Houston was characterized by elevated levels of all stress indicators as compared with the mid-shift (light traffic); epinephrine excretion increased significantly during the last half of the mid-shift as compared with the first half. Urinary stress indicators (17-ketogenic steroids, epinephrine, norepinephrine) were all significantly elevated during day sleep as compared with night sleep, indicating less effective rest during day sleep."

Various authors: "First annual seminar on stress, Chicago." *Stress* (Am. Acad. Air Traffic Control Medicine) Spring, 1973.

G99,023/73

Report on a meeting of the American Academy of Air Traffic Control Medicine at which various speakers discussed the stress problems related to this type of occupation.

Cobb, S., Rose, R. M.: "Hypertension, peptic ulcer, and diabetes in air traffic controllers." *J.A.M.A.* **224**: 489-492 (1973).

H68,557/73

Statistical studies on several thousand ATCs showed that they are predisposed to certain stress diseases. "Quite compelling evidence has been adduced to support the hypothesis with regard to hypertension; on peptic ulcer the evidence is moderately strong and for diabetes it is slight but suggestive."

Margolis, B. L.: "Stress is a work hazard, too." *Ind. Med. Surg.* **42**: 20-23 (1973).

J7,424/73

Popularized summary on occupational stress as a work hazard with special refer-

ence to policemen, ATCs and shift workers.

Thackray, R. I., Jones, K. N., Touchstone, R. M.: *Personality and Physiological Correlates of Performance Decrement on a Monotonous Task Requiring Sustained Attention*. Federal Aviation Administration, Aviation Med. pamphlet, p. 13. Washington, D.C., 1973. J15,364/73

"Reductions in task load resulting from the increasing automation of air traffic control may actually increase the requirement for controllers to maintain high levels of sustained attention in order to detect infrequent system malfunctions. A previous study indicated that individuals scoring high on a distractibility scale found it difficult to maintain sustained attention on a monotonous, but perceptually demanding, task."

Mathews, J. J., Collins, W. E., Cobb, B. B.: *A Sex Comparison of Reasons for Attrition of Non-Journeyman FAA Air Traffic Controllers*. Federal Aviation Administration, Aviation Med. pamphlet, p. 12. Washington, D.C., 1974 (16 refs.). J15,073/74

Melton, C. E., McKenzie, J. M., Saldivar, J. T. Jr., Hoffmann, S. M.: *Comparison of Opa Locka Tower with other ATC Facilities by Means of a Biochemical Stress Index*. Federal Aviation Administration, Aviation Med. pamphlet, p. 11. Washington, D.C., 1974.

J22,333/74

Among ATCs, catecholamine excretion is greatest at airports with the heaviest traffic.

Cobb, S.: "Role responsibility: the differentiation of a concept." In: McLean, A., *Occupational Stress*, pp. 62-69. Springfield, Ill.: Charles C Thomas, 1974. E10,888/74

Nolland, R., Erfmann, R. K. L., Masson, J. M., Moline, J., Martin, A.: "Réactions végétatives observées chez 40 contrôleurs d'écho-radar" (Autonomic reactions observed in 40 radar operators). *Nouv. Presse Méd.* **3**: 1543-1545 (1974). J21,226/74

Navy, Marine, Submarine

Very few studies have been published on the stressor effect of service in the Navy or Marine Corps, but the relationship between life in submarines and the G.A.S. has been explored extensively. Even training in tanks for submarine work produces such typical manifestations of stress as an increase in 17-KS and creatinine output; these

changes are still more evident on prolonged submarine trips. In submarine personnel on twenty-four hour sleep-wake schedules, the circadian cycles of urinary, testoid and corticoid elimination shifted their peaks, but available data are insufficient to establish a definite pattern.

Navy, Marine, Submarine

(See also our earlier stress monographs, p. xiii)

Haggard, E. A.: "Psychological causes and results of stress." In: Lindsley, D. B. et al., *Human Factors in Undersea Warfare*, pp. 441-461. Washington, D.C.: National Research Council, 1949. B23,076/49

Darrow, C. W., Henry, C. E.: "Psychophysiology of stress." In: Lindsley, D. B. et al., *Human Factors in Undersea Warfare*, pp. 417-439. Washington, D.C.: National Research Council, 1949. B47,919/49

Review on the relationships between psychologic factors and organic manifestations of the G.A.S. Special attention is given to undersea warfare (102 refs.).

Cook, E. B., Wherry, R. J.: "The urinary 17-ketosteroid output of naval submarine enlisted candidates during two stressful situations." *Human Biol.* **22**: 104-124 (1950). B48,615/50

In submarine enlisted candidates, stress-producing training in tanks evokes typical manifestations of the G.A.S., including an increase in 17-KS and creatinine output, although the two parameters are not strictly related.

Weybrew, B. B.: "Psychological problems of prolonged marine submergence." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 87-125. Glencoe, Ill.: Free Press, 1963. E10,427/63

Brief review on psychologic disturbances during prolonged underwater voyages, particularly in relation to the concept of stress as applied to the closed ecology of submarines.

Crafts, R., Llerena, L. A., Guevara, A., Lobotsky, J., Lloyd, C. W.: "Plasma androgens and 17-hydroxycorticosteroids through-

out the day in submarine personnel." *Steroids* **12**: 151-163 (1968). G60,445/68

In submarine personnel on a twenty-four-hour sleep-wake schedule, the testosterone and androstenedione excretion rates were highest at 07:00 and lowest at night. The 17-OHCS peak shifted from 07:00 to 13:00 or 19:00 during an eighteen-hour day. The androgens also changed their peaks, although there was no correlation between these steroids and plasma LH. In males, therefore, androstenedione shows the same pattern and magnitude of circadian variations as 17-OHCS, "suggesting that it is primarily of adrenal origin."

Solodkov, A. S., Berdyshev, V. V.: "Development of states of physiologic stress in sailors during cruises in low latitudes." *Voen. Med. Zh.* **7** No. 7: 86-90 (1972) (Russian). J19,876/72

Nakamura, F.: "Health status of ocean-going oil tanker seamen." *Bull. Tokyo Med. Dent. Univ.* **20**: 221-244 (1973).

H85,587/73

Extensive study of the stressors encountered by tanker seamen (48 refs.).

Milton-Thompson, G. J.: "The problem of duodenal ulcer in the Royal Navy." *J. R. Nav. Med. Serv.* **60**: 45-48 (1974). J20,068/74

Davies, D. M.: "Physiological response to the submarine environment." *J. R. Nav. Med. Serv.* **60**: 28-33 (1974).

J20,065/74

Halliday, J. J., Rivers, J. F.: "Stress and myocardial infarction." *J. R. Nav. Med. Serv.* **60**: 52-54 (1974). J20,070/74

A statistical study of every naval rank from sub-lieutenant to vice-admiral indicated that "the stress of a naval environment does not appear to affect the incidence of myocardial infarction."

Diving

The stressor effect of diving, especially in relation to underwater demolition work, has been well established. Serum urate and cholesterol levels rise concomitantly with

the anticipated psychologic stress, whereas serum urate concentrations fall during the actual stress period.

In U.S. Navy underwater demolition teams, serum cortisol rose particularly during difficult training, and this may be associated with an elevation of serum uric acid and cholesterol.

In scuba divers practicing in cold water, heat loss added to the effects of anxiety, increased barometric pressure, and other stressors inherent in diving as such. In another group of scuba divers reaching depths of 30 meters or more, plasma cortisol levels and urinary EP excretion were high, although rectal temperature dropped only 0.33°C. Here, cold did not appear to add considerably to the stress of the situation.

The psychologic response, especially the motivation of the divers, seems to have a considerable effect upon the biochemical indicators of stress. In oxygen-helium dives, thiamine excretion was decreased, presumably because thiamine requirements are directly related to energy expenditure, and in such a situation "hyperbaric stress exacerbates exercise and cold stress, thereby creating a greater thiamine demand." In one of these divers, the changes persisted even after decompression.

Underwater task performance indicated that, in divers, sentence comprehension, aptitude at arithmetic, and manual dexterity did not appear to be considerably influenced at a depth of 30 meters, but memory was markedly diminished.

Diving

(See also our earlier stress monographs, p. xiii)

Sciarli, R.: "La plongée libre et ses dangers" (Free diving and its dangers). *Arch. Med. Gen. Trop.* **42**: 297-316 (1965).

G37,313/65

Review on diving as a stressor agent capable of eliciting the G.A.S., as indicated by its metabolic and hormonal consequences. Probably one important factor is hypoxia.

Baddeley, A. D.: "Diver performance and the interaction of stresses." *Underwater Assoc. Rep.* 1966-67, pp. 35-38.

J11.915/66-67

Rahe, R. H., Arthur, R. J.: "Stressful underwater demolition training. Serum urate and cholesterol variability." *J.A.M.A.* **202**: 1052-1054 (1967). F91,967/67

In men training for underwater demolition work, the serum urate concentration was elevated during anticipation of a demanding task, and "cholesterol levels rose concomitant with a period of particular psychological stress. Serum urate concentration demonstrated a significant fall during a period of quite intense psychological stress."

Skreslet, S., Aarefjord, F.: "Acclimatization to cold in man induced by frequent scuba diving in cold water." *J. Appl. Physiol.* **24**: 177-181 (1968). G55,183/68

Scuba divers practicing in cold water go through the: "1) unacclimatized stage: cold stress is met with by an elevated metabolic rate compensating heat loss. 2) intermediate stage: there is a fall in the rectal (core) temperature as heat loss is not fully compensated for by metabolism, believed to be caused by habituation of the CNS. 3) acclimatized stage: a constant rectal temperature is maintained, although minor metabolic heat is produced. Conservation of heat is attributed to lowered heat transfer with the blood to the body surface." [It is difficult to establish to what extent these reactions are truly non-specific and hence characteristic of stress as such, rather than of cold (H.S.).]

Rahe, R. H., Rubin, R. T., Arthur, R. J., Clark, B. R.: "Serum uric acid and cholesterol variability. A comprehensive view of Underwater Demolition Team Training." *J.A.M.A.* **206**: 2875-2880 (1968).

G63,836/68

Rubin, R. T., Rahe, R. H., Arthur, R. J., Clark, B. R.: "Adrenal cortical activity changes during underwater demolition team training." *Psychosom. Med.* **31**: 553-564 (1969). G72,049/69

Serum cortisol levels rise in U.S. Navy underwater demolition teams undergoing difficult training. Considerable literature is cited to show that this kind of occupation elicits subjective indicators of stress (27 refs.).

Rubin, R. T., Rahe, R. H., Clark, B. R., Arthur, R. J.: "Serum uric acid, cholesterol and cortisol levels. Interrelationships in normal men under stress." *Arch. Intern. Med.* **125**: 815-819 (1970). G74,760/70

In healthy young U.S. Navy men undergoing underwater demolition training, the physical and psychologic stress is accompanied by increases in serum uric acid, cholesterol and cortisol (34 refs.).

Capel, W. C., Youngblood, D., Stewart, G. T.: "Note on stress, anxiety and related defenses in a controlled situation." *Psychol. Rep.* **27**: 351-355 (1970). J22,040/70

Gunderson, E. K. E., Rahe, R. H., Arthur, R. J.: "Prediction of performance in stressful underwater demolition training." *J. Appl. Psychol.* **56**: 430-432 (1972). J19,381/72

Rahe, R. H., Biersner, R. J., Ryman, D. H., Arthur, R. J.: "Psychosocial predictors of illness behavior and failure in stressful training." *J. Health Soc. Behav.* **13**: 393-397 (1972). J19,655/72

"A new unit scoring method was used to delineate recent life-change events from the Schedule of Recent Experience (SRE) questionnaire which correlated significantly with U.S. Navy Underwater Demolition Team (UDT) trainees' dispensary visits."

Davis, F. M., Charlier, R., Saumarez, R., Muller, V.: "Some physiological responses to the stress of aqualung diving." *Aerosp. Med.* **43**: 1083-1088 (1972). G95,712/72

Scuba (aqualung) diving in 12°C British coastal waters caused hormonal changes characteristic of stress. "Plasma cortisol levels were significantly raised before and after 30-meter dives when compared with 3-meter dives. Raised urinary levels of adrenalin, with high adrenalin to noradrenalin excretion ratios, were seen in several divers. The average decrease in rectal temperature was 0.33°C and mean skin temperatures remained approximately 16°C above ambient water temperature. Cold stress was considered unlikely to contribute to the hormonal changes seen. These changes are probably due to anxiety over deep open water diving in a 'stressful' diving situation" (22 refs.).

Russell, C. J., McNeill, A., Evonuk, E.: "Some cardiorespiratory and metabolic responses of scuba divers to increased pressure and cold." *Aerosp. Med.* **43**: 998-1001 (1972). H79,362/72

Rahe, R. H., Rubin, R. T., Gunderson, E. K. E.: "Measures of subjects' motivation and affect correlated with their serum uric acid, cholesterol, and cortisol." *Arch. Gen. Psychiatry* **26**: 357-359 (1972).

G90,674/72

Among trainees in a U.S. Navy underwater demolition team, "predominantly positive correlations were seen between the subjects' serum uric acid levels and their estimates of their own motivation. Their serum cholesterol concentrations demonstrated consistently negative correlations with their motivational and pleasant affect scores. Highest correlations were positive ones found between the subjects' serum cholesterol levels and their unpleasant affect scores. Serum cortisol correlations with the three psychological criteria demonstrated wide variability around a zero correlation baseline."

Davis, F. M., Osborne, J. P., Baddeley, A. D., Graham, I.M.F.: "Diver performance: nitrogen narcosis and anxiety." *Aerosp. Med.* **43**: 1079-1082 (1972). G99,706/72

Without being told that they were participating in a stress test, divers were asked to perform four tasks underwater at 3 m. and again at 30 m. These comprised a sentence comprehension test, a memory test, a simple arithmetic test and a manual dexterity test. All but the memory test showed a significant drop in efficiency at depth.

Rahe, R. H., McHugh, W., Kaplan, N., Rimon, R., Arthur, R. J.: "Serum lactic acid variability in subjects experiencing stressful training." *Dis. Nerv. Syst.* **33**: 403-408 (1972). H79,743/72

In a U.S. Navy underwater demolition team undergoing a psychologically and physically stressful training swim, serum lactic acid rose considerably. "In contrast to reports by other authors, no significant correlation was seen between subjects' serum lactic acid levels and a psychological questionnaire's indices of psychoneurotic symptomatology. A significant correlation was seen between a measure of physical fitness of the men and their serum lactic acid concentrations."

Frattali, V., Robertson, R.: "Nutritional evaluation of humans during an oxygen-helium dive to a simulated depth of 1000 feet." *Aerosp. Med.* **44**: 14-21 (1973).

H79,775/73

In man, oxygen-helium dives to a simu-

lated depth of 1000 ft. decreased thiamine excretion and erythrocyte transketolase activity. In one diver, these changes persisted to the end of the decompression phase. "Since thiamin requirement is directly related to energy expenditure, it is possible that hyperbaric stress exacerbates exercise and cold stress, thereby creating a greater thiamin demand."

Rubin, R. T., Rahe, R. H.: "U.S. Navy underwater demolition team training: bio-

chemical studies." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 208-226. Springfield, Ill.: Charles C Thomas, 1974.

E10,692/74

Scaglione, G. C., Gattuso, C.: "Lo stress nella fisiopatologia subacquea" (Stress in underwater physiopathology). *Minerva Med.* **65**: 4505-4523 (1974).

J21,680/74

Rawlins, J. S. P.: "Psychological reactions in divers." *J. R. Nav. Med. Serv.* **60**: 34-38 (1974).

J20,066/74

Military Life, including Combat

(See also Concentration Camps, POWs; Catastrophe, Accidents; Aerospace, Navy, Marine, Submarine, Diving, Underwater Demolition Work, Driving and other special activities practiced by the Armed Forces)

Generalities. Many review articles deal with the various stressors encountered in military life at peace or war; these will serve as a general introduction to such problems.

→**Hormones.** Evidence of increased corticoid production in U.S. soldiers under combat conditions has been obtained in various theaters of war, including Korea, Japan and Vietnam. The reactions differ, depending upon the intensity and duration of the stress situation, and are generally associated with increased catecholamine excretion, but they are essentially the same in infantry men, bomber pilots and helicopter crews, and are accompanied by characteristic mental responses which will be discussed later.

Similar evidence of stress has also been noted under simulated combat conditions (taped sounds of real combat, shooting at targets, sleeplessness) which likewise result in increased catecholamine elimination.

Even in recruits during basic training, psychologic evidence of stress was correlated with 17-OHCS production. Measurements of both these parameters are considered to be more accurate tests of probable behavior during combat than are determinations of either alone.

Among Special Forces recruits, anticipation of imminent combat caused a drop in various testoids and their metabolites, conjointly with a rise in 17-OHCS.

→**Nonhormonal Metabolites.** Comparatively little is known about nonhormonal biochemical changes during military activities. However, allegedly, in naval aviators during combat, the phosphatidylglycerol response is more pronounced and consistent than during other types of stress.

→**Nervous System.** Of course, the most important neuropsychologic reactions to combat conditions are the so-called "war neuroses." Their development, like that of neuroses in peacetime, depends very largely upon both endogenous and exogenous con-

ditioning factors, such as hereditary predisposition, preparatory indoctrination to boost morale, interpersonal relations within the fighting group, and motivation.

The articles briefly summarized in the following pages contain valuable data not only on these factors, but also on the various classes of war neuroses, and their prophylaxis and treatment, as well as the associated metabolic (particularly endocrine) changes.

Some attention has also been given to the neuropsychiatric effects of military life during peacetime, especially among men not used to life under disciplined, strictly supervised conditions. Change in command appears to be a particularly stressful experience, both in peace and in war.

→**Peptic Ulcers.** Peptic ulcers of the stomach and duodenum are very common among combat casualties, as they are following burns, severe psychic insults, anxiety, and other severe stress situations in civilian life. They are even relatively frequent in peacetime soldiers who are undergoing particularly strict training and are subject to especially severe discipline.

→**Other Diseases.** Comparatively few investigators have reported data on general disease susceptibility in military life, especially during battle. It is known that dermatologic, respiratory and gastrointestinal diseases were particularly common on a U.S. Navy aircraft carrier in Vietnam, mostly among a small proportion of predisposed men who performed physically demanding or hazardous tasks during combat conditions. Illness was highest among younger men preoccupied with health.

Military Life, including Combat

Generalities. (See also our earlier stress monographs, p. xiii and cf. Concentration Camps, POWs, Catastrophe, Accidents, Bombing, Trauma, Aerospace, Navy, Marine, Submarine, Diving, Underwater Demolition Work, Driving, and other special activities practiced by the Armed Forces).

Wright, D. G.: *Notes on Men and Groups Under Stress of Combat: For the Use of Flight Surgeons in Operational Units*, pp. 1-19. Report to the Air Surgeon, U.S. Army Air Forces by The Josiah Macy, Jr. Foundation. New York, 1945. B40,065/45

Gramlich, F. W.: "A psychological study of stress in service." *J. Gen. Psychol.* 41: 273-296 (1949). B26,793/49

Discussion of stress manifestations in the U.S. Navy and Marines under combat and noncombat conditions.

Funkenstein, D. H., King, S. H., Drolette, M.: "The experimental evocation of stress", pp. 304-322. *Symposium on Stress*. Washington, D.C.: Army Medical Service Graduate School, 1953. B89,539/53

Review on combat stress with special emphasis on the development of laboratory stress-inducing situations for man.

Taylor, J. G.: *Symposium on the Role of Stress in Military Operations*, p. 56. Chevy Chase, Md.: Operations Res. Off., Johns Hopkins Univ., 1953. J13,726/53

Report on a conference at which numerous experts reported their experiences concerning the stressor effect of military life, particularly combat.

Caudill, W.: "Cultural perspectives on stress." *Symposium on Stress*, pp. 194-208. Washington, D.C.: Army Medical Service Graduate School, 1953. B89,530/53

The stressor effects of epidemics, wars, drastic technologic changes and economic or physiologic deprivation are very different in people of distinct cultural and ethnic backgrounds.

Pace, N., Schaffer, F. L., Elmadjian, F., Minard, D., Davis, S. W., Kilbuck, J. D., Walker, E. L., Johnston, M. E., Zilinsky, A., Gerard, R. W., Fosham, P. H., Taylor, J. G.: "Physiological studies on infantry men in

combat." *Univ. Calif. Publ. Physiol.* **10**: 1-47 (1956). J12,692/56

Sells, S. B.: *Military Small Group Performance Under Isolation and Stress. Critical Review*. Technical Report No. 62-31, Project No. 8243-11, Vol. 2. Fort Worth: Dept. of Psychology, Texas Christian University, 1962. J13,020/62

Berkun, M. M.: "Performance decrement under psychological stress." *Hum. Factors* **6**: 21-30 (1964). J18,097/64

Studies using the SSS, as well as corticoid excretion, eosinopenia and so on, to estimate performance under stress situations simulating those encountered in warfare.

Archibald, H. C., Tuddenham, R. D.: "Persistent stress reaction after combat. A 20-year follow-up." *Arch. Gen. Psychiatry* **12**: 475-481 (1965). J23,735/65

Weitz, J.: *Stress*, p. 1-39. Research paper P-251 (IDA/HQ 66-4672) Institute Defense Analyses (IDA), Research and Engineering Support Div. Washington, D.C.: 1966.

J13,888/66

Review on stress research, particularly in relation to military medicine, with a section criticizing various currently used definitions of the term stress (16 refs.).

Joy, R. J. T.: "Heat stress in army pilots flying combat missions in the Mohawk aircraft in Vietnam." *Aerosp. Med.* **38**: 895-900 (1967). J22,616/67

Lewis, C. E. Jr., Jones, W. L. Jr., Austin, F., Roman, J.: "Flight research program: IX. Medical monitoring of carrier pilots in combat—II." *Aerosp. Med.* **38**: 581-592 (1967). J22,617/67

Bourne, P. G.: *The Psychology and Physiology of Stress: With Reference to Special Studies of the Viet Nam War*, p. 242. New York and London: Academic Press, 1969.

E8,563/69

A symposium on the psychology and physiology of stress, based mainly on experiences in the Vietnam war.

Stevens, A.: "Psychiatric rejects from military service and their employability in civilian life." *Ind. Med. Surg.* **39**: 522-528 (1970). J14,859/70

Neshev, G.: "Problem of stress in military medicine (Review of the literature)." *Voen. Med. Zh.* No. 10: 42-44 (1972) (Russian). J24,133/72

A review of stress in military life in relation to the G.A.S.

Borus, J. F.: "Reentry: II. 'Making it' back in the States." *Am. J. Psychiatry* **130**: 850-854 (1973). J19,549/73

"The author defines the differential characteristics, adjustment stresses, and coping methods of three groups of successful and unsuccessful Viet Nam veterans attempting to 'make it' back in the States."

Renbourn, E. T.: *Psycho-Physiological Stress and the Soldier With a Review of the Literature*. Rep. No. 118. Clothing and Equipment Physiol. Res. Establishment, Great Britain, June 1961. Abstracted in: *Staff Century Res. Corp. Pamphlet* (1128th abstract), Vol. 2. Arlington, Va., 1973.

J16,132/73

→Hormones. Elmadjian, F.: "Adrenocortical function of combat infantrymen in Korea." In: *Ciba Found. Coll. Endocrinol.* **8**: 627-642 (1955). C3,666/55

Detailed studies on the physiologic, psychologic and psychiatric aspects of combat stress in U.S. infantrymen fighting in Korea and Japan. Extensive data on urinary steroid determinations and nitrogen metabolism during chronic and acute stress situations are compared.

Howard, J. M., Olney, J. M., Frawley, J. P., Peterson, R. E., Smith, L. H., Davis, J. H., Guerra, S., Dibrell, W. H.: "Studies of adrenal function in combat and wounded soldiers. A study in the Korean theatre." *Ann. Surg.* **141**: 314-320 (1955).

C20,630/55

In soldiers, there was no evidence of adrenal exhaustion as manifested by corticosteroid excretion, after prolonged exposure to combat situations in the Korean war.

Davis, S. W.: "Stress in combat." *Sci. Am.* **194**: 31-35 (1956). B28,532/56

Semipopular description of changes in urinary corticoids, 17-KS, electrolytes and blood count during combat in Korea. The responses differed according to the intensity and length of stress. After combat the men "were impassive, lethargic, uncommunicative, almost antisocial, where before being sent into combat they had been exuberant—telling stories, laughing and back-slapping. Yet our psychological tests failed to show any evidence of changes matching those in physiology." The reported alterations and their

chronologic development corresponded with projections based on the G.A.S. concept.

Artiss, K. L.: "Human behavior under stress—from combat to social psychiatry." *Milit. Med.* **128**: 1011-1015 (1963).

E31,186/63

Review of the literature on corticoid and EP excretion in soldiers under combat conditions.

"Stress in helicopter personnel." *J.A.M.A.* **201**: 320-321 (1967). F85,752/67

Studies on helicopter ambulance crews showed that the usual stress-induced increase in urinary corticoid excretion can be remarkably well controlled by certain psychologic adjustments minimizing the reality of the danger to be faced on combat missions and exaggerating the dangers already dealt with "in order to enhance... feelings of omnipotence and invincibility."

Rose, R. M., Poe, R. O., Mason, J. W.: "Psychological state and body size as determinants of 17-OHCS excretion." *Arch. Intern. Med.* **121**: 406-413 (1968). G57,520/68

In recruits undergoing basic combat training, both psychologic state and body size correlated significantly with 17-OHCS excretion. Combined use of both variables was most helpful in predicting performance (28 refs.).

Bourne, P. G., Rose, R. M., Mason, J. W.: "17-OHCS levels in combat. Special Forces 'A' team under threat of attack." *Arch. Gen. Psychiatry* **19**: 135-140 (1968).

G60,245/68

In a Special Forces team living in anticipation of attack on the Vietnam border, an officer and radio operator showed a rise in urinary 17-OHCS while the enlisted men showed a drop. Presumably, "assigned role in the group plays a major part in determining the effect of stress as measured by 17-OHCS excretion, and...when the opportunities for handling the stress are limited, group influences minimize the significance of individual differences."

Rose, R. M., Bourne, P. G., Poe, R. O., Mougey, E. H., Collins, D. R., Mason, J. W.: "Androgen responses to stress. II. Excretion of testosterone, epitestosterone, androsterone and etiocholanolone during basic combat training and under threat of attack." *Psychosom. Med.* **31**: 418-436 (1969).

G70,683/69

Among Special Forces recruits anticipating

imminent combat in Vietnam, testosterone, epitestosterone, androsterone and etiocholanolone excretion dropped, whereas 17-OHCS elimination rose. Although marked individual differences make the interpretation of data difficult, it appears that decreased 17-KS persisted but was associated with a parallel fall in 17-OHCS (39 refs.).

Poe, R. O., Rose, R. M., Mason, J. W.: "Multiple determinants of 17-hydroxycorticosteroid excretion in recruits during basic training." *Psychosom. Med.* **32**: 369-378 (1970). G77,861/70

In recruits during basic training, psychologic ratings and weight were correlated with, and together predicted, 17-OHCS levels more accurately than did either alone. In twelve of fourteen men who lost a parent, 17-OHCS values were extremely high. The results "suggested that an individual's 17-OHCS level is influenced by psychologic, biologic, historic and environmental variables" (27 refs.).

→**Metabolites.** Austin, F. H. Jr.: "A review of stress and fatigue monitoring of naval aviators during aircraft carrier combat operations: blood and urine biochemical studies." In: Bourne, P. G., *The Psychology and Physiology of Stress: With Reference to Special Studies of the Viet Nam War*, pp. 197-218. New York and London: Academic Press, 1969. E8,568/69

Review on stress and fatigue-monitoring in naval aviators during combat operations on a U.S. Navy aircraft carrier in North Vietnam. Plasma *phospholipid* fractions behaved unlike those of normal individuals or those exposed to other stressors. "The phosphatidylglycerol responded to this type of stress more markedly and consistently than the other fractions. A discriminant functions formula has been developed which may facilitate identification of the stress type and degree of subject response up to and including psychophysiological exhaustion and collapse." Variations in typical stress hormone levels are also reported.

→**Nervous System.** Simmel, E.: "War neuroses." In: Lorand, S., *Psychoanalysis Today*, pp. 227-248. New York: International Univ. Press, 1944. E85,797/44

A psychologic study of stress-induced war neuroses.

Bleckwenn, W. J.: "Neuroses in the com-

bat zone." *Ann. Intern. Med.* **23**: 177-183 (1945). B26,425/45

Bartemeier, L. H., Kubie, L. S., Menninger, K. A., Romano, J., Whitehorn, J. C.: "Combat exhaustion." *J. Nerv. Ment. Dis.* **104**: 358-389; 489-525 (1946).

B26,509/46

Review on combat fatigue among American troops in the European Theater at the end of World War II with principal emphasis on psychiatric considerations.

Lidz, T.: "Psychiatric casualties from Guadalcanal. A study of reactions to extreme stress." *Psychiatry* **9**: 193-213 (1946).

B26,649/46

Phillips, E. L.: "War neurosis: I. A preliminary study of clinical and control groups." *J. Clin. Psychol.* **3**: 148-154 (1947).

B40,644/47

Kardiner, A.: *War Stress and Neurotic Illness*, p. 428. New York and London: Paul B Hoeber, 2nd ed., 1947. E8,327/47

Monograph concerned mainly with the psychosomatic aspects of war neuroses (112 refs.).

Moran, Lord: "Wear and tear." *Lancet* June 17, 1950, pp. 1099-1101. D78,877/50

Lecture on the relationship between the G.A.S. and battle fatigue.

Various authors: *Symposium on Stress*, p. 332. Washington, D.C.: Army Medical Service Graduate School, 1953. B87,548/53

A conference on stress sponsored by the Division of Medical Sciences, National Research Council, and the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C. Numerous papers on the hormonal and nervous regulation of stress responses, with special reference to combat situations, interpersonal relationships, nutrition and adaptation to catastrophic events.

Sells, S. B.: *Military Small Group Performance Under Isolation and Stress. An Annotated Bibliography*. Technical Report No. 61-19, Project No. 8243-11, Vol. 1. Fort Worth: Dept. of Psychology, Texas Christian University, 1961. J13,019/61

Berkun, M. M., Bialek, H. M., Kern, R. P., Yagi, K.: "Experimental studies of psychological stress in man." *Psychol. Monogr.* **76**: 1-39 (1962). J2,509/62

In examining the well known phenomenon of degradation of behavior in combat, ex-

tensive psychologic studies have been carried out on the reactions of soldiers to simulated events such as aircraft emergencies, disruption of military exercise by misdirected artillery shells, forest fires and radioactive fallout. The associated stress effects were measured by the intensity of eosinopenia and corticoid excretion. Situations in which subjects thought themselves responsible for an explosion that was believed to have seriously injured other soldiers, produced the most extreme results according to all criteria used, including mental problem solving activities.

Grinker, R. R., Spiegel, J. P.: *Men Under Stress*, p. 484. New York, Toronto and London: McGraw-Hill, 1963. B18,363/63

Extensive monograph on the stressor effects of combat upon U.S. troops during World War II. There are sections dealing with genetic predisposing factors, the combat environment, morale, reactions after combat and applications to civilian psychiatry.

Levi, L.: "Physical and mental stress reactions during experimental conditions simulating combat." *Försvarsmedicin* **2**: 3-8 (1966). G35,833/66

Soldiers in the Swedish Army were exposed to a seventy-two-hour vigil which included being subjected to stressors (taped sounds of real combat, shooting at targets, sleeplessness) simulating battle conditions. Nervous (alertness, ECG) and physical (EP excretion, urine analysis) reactions were examined in relation to the resulting stress effect.

Levi, L. (ed.): *Emotional Stress. Physiological and Psychological Reactions. Medical, Industrial and Military Implications*, p. 280. Stockholm: Kungl. Boktryckeriet P. A. Norstedt and Söner, 1967. E7,006/67

International Symposium arranged by the Swedish Delegation for Applied Medical Defense Research. A large number of speakers presented papers on the relationship between the G.A.S. and various psychologic and biochemical (particularly hormonal) responses to emotional stressors of different kinds, especially those encountered in the armed forces.

Weybrew, B. B.: "Patterns of psychophysiological response to military stress." In: Appley, M. H. and Trumbull, R. T., *Psychological Stress. Issues in Research*, pp. 324-362. New York: Appleton-Century-Crofts, 1967. E10,339/67

Detailed review of the literature and per-

sonal observations on stress situations connected with military activities.

Bourne, P. G. (ed.): *The Psychology and Physiology of Stress*, p. 242. New York and London: Academic Press, 1969.

E8,563/69

Discussion of combat stress with special reference to observations made during the Vietnam war. Most of the contributors were army physicians who dealt with psychiatric problems of combat stress, heat stress in army pilots, stress and fatigue-monitoring of naval aviators. Interesting data are presented on corticoid and androgen excretion as influenced by combat situations.

Mayfield, D. G., Fowler, D. R.: "Combat plus twenty years. The effect of previous combat experience on psychiatric patients." *Milit. Med.* **134**: 1348-1354 (1969).

E55,698/69

A statistical study indicates that "service-connected disabilities were more common among combat veterans, suggesting that combat experience increases the probability of the presence of longstanding emotional illness." These may become manifest only years after a combat experience (11 refs.).

Crocq, L.: "Les névroses de guerre" (War neuroses). *Rév. Méd.* **10**: 57-62; 175-188 (1969).

G99,089/69

Review based principally on experiences in the French army between 1918 and 1962.

Grinker, R. R., Spiegel, J. P.: "Combat stress." In: Sahakian, W. S., *Psychopathology Today: Experimentation, Theory and Research*, pp. 197-202. Itasca, Ill.: F E Peacock, 1970.

E8,715/70

In a textbook on psychopathology, this chapter is devoted to the psychiatric manifestations of "combat stress" with special reference to narcoticsynthesis. Pentothal treatment can detect the relationship of a specific incident in combat to a conversion symptom.

Bey, D. R. Jr.: "Change of command in combat: a locus of stress." *Am. J. Psychiatry* **129**: 698-702 (1972).

G96,808/72

On the basis of purely psychologic indices, it is concluded that "in the military a change of command is particularly stressful for the members of the unit involved. A comparison of units, some of which showed few increases in the indices of organizational stress and some of which showed great increases, revealed a relationship between the administrative style of the departing com-

mander and the amount of stress experienced by the unit."

Schuckit, M. A., Gunderson, E.K.E.: "Job stress and psychiatric illness in the U.S. Navy." *J. Occup. Med.* **15**: 884-887 (1973).

J7,436/73

In the U.S. Navy, there appears to be some connection between job stress and psychiatric illness, but various other factors complicate interpretation of the data, which are much less clear-cut than the causal relationship between stress and physical illness.

→**Peptic Ulcers.** Sullivan, B. H., Hamilton, E. L.: "Peptic ulcer in military personnel. Incidence and management." *U.S. Armed Forces Med. J.* **6**: 1459-1468 (1955).

C8,406/55

Among U.S. Army personnel, the incidence of peptic ulcers has greatly increased in recent years as a consequence of intensive training and a tense international situation conducive to stress.

Stremple, J. F., Molot, M. D., McNamara, J. J., Mori, H., Glass, G. B. J.: "Posttraumatic gastric bleeding. Prospective gastric secretion composition." *Arch. Surg.* **105**: 177-185 (1972).

G93,305/72

In nine of fifty combat casualties, bleeding ulcers developed although steroid excretion remained within the normal range. Total gastric juice sialic acid output was independent of bleeding, but the total "leak" of plasma protein was greater in the gastric ulcer group. "Initial decreased acid output, accompanied by plasma protein 'leakage' into the gastric lumen, is consistent with back diffusion of H⁺ ions soon after trauma," as has been postulated for stress ulcers occurring in the G.A.S. (33 refs.).

Mori, H., Stremple, J., Glass, G.B.J.: "Stress ulcer following war wounds in Vietnam." *Clin. Res.* **21**: 723 (1973).

H69,455/73

Among soldiers wounded in Vietnam, gastric and duodenal ulcers were common.

Klettenhammer-Tischina, H. P.: "Die Ulkuskrankheit bei Soldaten des österreichischen Bundesheeres unter besonderer Berücksichtigung des Ulcus duodeni" (Peptic ulcers in soldiers of the Austrian army. Particular consideration is given to duodenal ulcers). *Wien. Med. Wochenschr.* **124**: 177-179 (1974).

H82,314/74

General discussion of factors involved in

the development of duodenal ulcers, with suggested therapeutic measures.

Crocq, L., Rabarihoela, O., Molinie, C., Essioux, H., Cristau, P., Laverdant, C.: "Etude psychosomatique des ulcères duodénaux chez le jeune adulte en milieu militaire" (Psychosomatic study of duodenal ulcer in young adults during military service). *Sem. Hôp. Paris* **51**: 465-469 (1975).

J23,316/75

→**Other Diseases.** Rubin, R. T., Gunderson, E. K. E., Doll, R. E.: "Life stress and illness patterns in the U.S. Navy. I. Environmental variables and illness onset in an attack carrier's crew." *Arch. Environ. Health* **19**: 740-747 (1969).

G70,058/69

Statistical studies on the occupations of enlisted men and the diseases they developed on board a U.S. Navy attack carrier during a six-month deployment in Vietnam. Dermatologic, respiratory and gastrointestinal disorders were most common. The majority of the illnesses occurred in a relatively small proportion of the population, with consistent elevations among men who performed physically demanding or hazardous tasks in hostile environments, that is, during combat periods.

Rubin, R. T., Gunderson, E. K. E., Arthur, R. J.: "Life stress and illness patterns in the U.S. Navy. IV. Environmental and demographic variables in relation to illness onset in a battleship's crew." *J. Psychosom. Res.* **15**: 277-288 (1971).

G99,748/71

On the battleship USS New Jersey during

a seven-month deployment in Vietnam, the illness rate was highest in combat periods particularly among men who performed hazardous jobs. The most common ailments were dermatologic and respiratory.

Rubin, R. T., Gunderson, E. K. E., Arthur, R. J.: "Life stress and illness patterns in the U.S. Navy. V. Prior life change and illness onset in a battleship's crew." *J. Psychosom. Res.* **15**: 89-94 (1971).

G82,945/71

Studies using the SRE questionnaire on the crew of the battleship USS New Jersey during combat in Vietnam revealed that "subjects with higher total life change scores based on the standard scoring system tended to have greater numbers of illnesses, but this scoring system was of little utility in predicting future illness for this sample. The life change scores based on the regression-derived scoring system did significantly discriminate future illness; the mean numbers of illnesses for the highest quartiles were about 50 per cent greater than those for the lowest quartiles."

Rubin, R. T., Gunderson, E. K. E., Arthur, R. J.: "Life stress and illness patterns in the U.S. Navy. VI. Environmental, demographic, and prior life change variables in relation to illness onset in naval aviators during a combat cruise." *Psychosom. Med.* **34**: 533-547 (1972).

G97,605/72

Among naval aviators flying combat missions from a U.S. aircraft carrier in Vietnam, illness rates were highest in the younger age groups and in those more preoccupied with health.

Automobile Driving

Because of the ever-increasing importance of automobile driving throughout the world, this stressor has received considerable attention. From a practical point of view, it is helpful to appraise its effects as if it were a single entity, but of course its stressor potentiality is due to a combination of factors: concentration (especially when driving at high speed in heavy traffic), anxiety, the physical discomfort of maintaining the same position, and boredom during prolonged trips. In addition, there is the concern of reaching one's destination on time, and—depending upon the construction of the vehicle—vibration, noise, and so on.

In general, it may be said that driving and other stressors elicit essentially the same physical and somatic manifestations, namely, eosinopenia, increased corticoid and catecholamine production, psychologic signs of nervous tension or exhaustion, elevated blood pressure, tachycardia and sweating.

These changes are most pronounced under dangerous conditions (for example, auto

races or very prolonged truck driving, especially if the cargo is flammable, explosive or particularly valuable).

β -Adrenergic blocking agents allegedly diminish the tachycardia, without affecting performance. In coronary candidates, S-T segment depression in the ECG or frequent premature ventricular contractions are readily induced by driving.

Increased plasma NEP levels may remain high even after an automobile race. The rise in urinary catecholamines is mainly a result of increased NEP excretion.

FFA levels are often elevated in race drivers, even before and after a race. This change, as well as the associated emotional stress, may likewise be diminished by β -blockade without interfering with performance.

A car simulator has been developed which can elicit reproducible degrees of stress under conditions suitable for the investigation of pharmacologic agents that may affect symptoms and performance.

In alcoholic drivers, subjective feelings of stress are significantly correlated with traffic accidents, but personality and demographic variables are not.

Automobile Driving

(See also our earlier stress monographs, p. xiii)

Fatigue and Hours of Service of Interstate Truck Drivers. Public Health Bull. No. 265. Washington, D.C.: GPO, 1941.

B27,815/41

Frost, J. W., Dryer, R. L., Kohlstaedt, K. G.: "Stress studies on auto race drivers." *J. Lab. Clin. Med.* 38: 523-525 (1951).

B26,147/51

Auto racing causes eosinopenia and increased excretion of 17-KS, but no consistent response in sodium, potassium, uric acid or creatinine elimination nor in blood levels.

Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., Parks, J. W.: "Coronary heart-disease and physical activity of work." *Lancet* November 21, 28, 1953, pp. 1053, 1111-1120.

D85,741/53

An extensive epidemiologic study on thirty-one thousand London men aged thirty-five to sixty-four years. The results indicate that physically active men have a lower incidence of CHD in middle age than those holding sedentary jobs. "Transport workers, postal workers, and Civil Service executive officers and clerks were observed during 1949-50. Bus conductors (on double-decker vehicles) were found to have less coronary heart-disease than bus drivers, and postmen less than telephonists, executive officers, and clerks."

McFarland, R. A., Moseley, A. L., Fisher, M. B.: "Age and the problems of profes-

sional truck drivers in highway transportation." *J. Gerontol.* 9: 338-348 (1954) (34 refs.).

D89,421/54

Hoffmann, H., Reygers, W.: [Title unavailable] *Zentralbl. Verkehrsmed.* 3: 131 (1960).

J11,881/60

General remarks on the stressor effect of automobile driving.

Crawford, A.: "Fatigue and driving." *Ergonomics* 4: 143-154 (1961).

E54,972/61

Review of the literature and personal observations lead to the conclusion that "stress is an important factor in the production of driving fatigue." Methods for assessing and preventing the effects of emotional arousal caused by driving are discussed.

Hoffmann, H.: [Title unavailable] *Heft Z. Unfallheilk.* 71: 127 (1962).

J11,883/62

[Title unavailable] *Verkehrssicherheit* 11: 145 (1965).

J11,882/65

Practical observations on the stressor effect of automobile driving.

Hoffmann, H.: "Herzkrank am Steuer von Kraftfahrzeugen. Untersuchungen über das Kreislaufverhalten im Fahrversuch an gesunden und kranken Kraftfahrzeugführern" (Car driving and cardiac patients. Examination of blood circulation during driving in healthy and sick drivers). *Münch. Med. Wochenschr.* 37: 1790-1796 (1963).

E28,340/63

In cardiac patients, driving tends to cause ECG anomalies and unusually marked increases in blood pressure. "This shows that at

least for the driver with angina pectoris the operation of a vehicle is an irresponsible stress."

Schmid, E., Meythaler, C.: "Untersuchungen über die sympathico-adrenale Reaktion bei Autofahrern mit Hilfe der Vanillinmandelsäure-Bestimmung im Harn" (Examination of the sympathetic-adrenal reaction in drivers. Urinary vanillylmandelic acid excretion). *Klin. Wochenschr.* **42**: 139-140 (1964). F2,669/64

In ordinary city drivers and even in their passengers, VMA excretion increases considerably, implying raised catecholamine production during stress.

Mast, T. M., Jones, H. V., Heimstra, N. W.: "Effects of fatigue on performance in a driving device." *Highway Res. Rec.* No. 122: 93 (1966). J15,854/66

Burns, N. M., Baker, C. A., Simonson, E., Keiper, C.: "Electrocardiogram changes in prolonged automobile driving." *Percept. Mot. Skills* **23**: 210 (1966). J23,665/66

Simonson, E., Baker, C., Burns, N., Keiper, C., Schmitt, O. H., Stackhouse, S.: "Cardiovascular stress (electrocardiographic changes) produced by driving an automobile." *Am. Heart J.* **75**: 125-135 (1968). F92,986/68

Driving produces marked changes in cardiovascular functions, especially those measured by the ECG (39 refs.).

Selzer, M. L., Rogers, J. E., Kern, S.: "Fatal accidents: the role of psychopathology, social stress, and acute disturbance." *Am. J. Psychiatry* **124**: 1028-1036 (1968). E84,312/68

"Significantly more psychopathology and social stress were present in 96 drivers causing fatal accidents than in a matched control group." Twenty percent of the drivers had acutely disturbing experiences within six hours before causing a fatal accident (20 refs.).

Tauber, J. B.: "Diabetes in an occupational group." *J. Occup. Med.* **10**: 65-66 (1968). J15,861/68

The incidence of diabetes mellitus in truck drivers was about ten times the national average. [In view of the small number of cases examined, confirmation on a larger scale will be necessary (H.S.).]

Bellet, S., Roman, L., Kostis, J.: "The effect of automobile driving on catecholamine

and adrenocortical excretion." *Am. J. Cardiol.* **24**: 365-368 (1969). H16,504/69

In patients with CHD and in controls, "excretion of both catecholamines and 11-OHCS was found to be significantly increased during a two hour period of driving compared with a two hour control period. These results suggest that automobile driving represents a mental stress.... The electrocardiographic changes (ischemic type of S-T segment depression or frequent premature ventricular contractions, or both) which occur during driving in subjects with coronary artery disease are induced by this stress."

Taggart, P., Gibbons, D., Somerville, W.: "Some effects of motor-car driving on the normal and abnormal heart." *Br. Med. J.* October 18, 1969, pp. 130-134. H18,098/69

"Little or no change in the plasma catecholamine levels was noted in three coronary subjects immediately after a city drive compared with resting levels. All the racing drivers showed a considerable increase in noradrenaline, and in one instance adrenaline, immediately after racing."

Mezzasalma, G., Severgnini, B.: "La radio-elettrocardiografia nei piloti di automobili su circuiti sperimentali. Esperienze preliminari" (First results of a radio-transmitted ECG study of car drivers on testing circuits). *Minnerva Cardioangiolog.* **17**: 447-452 (1969). J22,110/69

Ravina, A.: "Effets de la conduite automobile sur le coeur normal et pathologique sur l'excrétion des catécholamines et des 11-hydroxystéroïdes" (Effect of automobile driving on the normal and pathologic heart, and on catecholamine and 11-hydroxysteroid excretion). *Presse Méd.* **77**: 2063-2064 (1969). J22,013/69

Hoffmann, H.: "Untersuchungen zur Leistungsüberforderung im Straßenverkehr." (Studies on excessive demand on the driver in street traffic.) *Hefte Unfallheilkd.*, No. 99: 180-183 (1969). J20,842/69

McDonald, L., Baker, C., Bray, C., McDonald, A.: "Plasma-catecholamines after cardiac infarction." *Lancet* November 15, 1969, pp. 1021-1023. H18,916/69

In racing drivers, plasma NEP levels were greatly elevated immediately after the race. Following cardiac infarction, "patients with atrial dysrhythmias or early ventricular dysrhythmias had higher noradrenaline con-

centrations in their plasma. There was no such difference for patients with late ventricular dysrhythmias, and adrenaline levels were unremarkable. The raised noradrenaline levels are not thought to be related to stress because six other patients undergoing the stressful procedure of cardiac catheterisation had low levels."

Selzer, M. L.: "Alcoholism, mental illness, and stress in 96 drivers causing fatal accidents." *Behav. Sci.* **14**: 1-10 (1969).

J16,328/69

Goldman, V., Comerford, B., Hughes, D., Nyberg, G.: "Effect of β -adrenergic blockade and alcohol on simulated car driving." *Nature* **224**: 1175-1178 (1969). H19,740/69

The β -adrenergic-blocking agent alprenolol diminishes the tachycardia produced by an exciting ride in a fast roller coaster or a simulated car driving machine without significantly affecting driving performance.

Pramatorov, A., Balev, L.: "Menstrual anomalies and the influence of motor vehicle vibrations on conductors from the city transport." *Akush. Ginekol. (Mosk.)* **8**: 31 (1969) (Russian). J15,928/69

Heimstra, N. W.: "The effects of 'stress fatigue' on performance in a simulated driving situation." *Ergonomics* **13**: 209-218 (1970). E85,703/70

Andersson, A. L., Nilsson, A., Henriksson, N. G.: "Personality differences between accident-loaded and accident-free young car drivers." *Br. J. Psychol.* **61**: 409-421 (1970). J15,060/70

Sussman, E. D., Morris, D. F.: *An Investigation of Factors Affecting Driver Alertness*. Cornell Aeronautical Lab. Tech. Rep. VJ-2849-B-1. Ithaca, N.Y., 1970.

J16,201/70

Case, H. W., Hulbert, S.: *Effects of Fatigue on Skills Related to Driving*. UCLA, Dept. of Engineering Rep. 70-60. Los Angeles, 1970. J16,203/70

McGuire, F. L.: "A typology of accident proneness." *Behav. Res. Highway Safety* **1**: 26-32 (1970). J16,598/70

A review on the role of stress in accident proneness, particularly in relation to driving.

McMurray, L.: "Emotional stress and driving performance: the effect of divorce." *Behav. Res. Highway Safety* **1**: 100-114 (1970). J16,599/70

Platt, F. N.: "Heart rate measurements of drivers with the highway systems research car." *J. Med. Assoc. Ga.* **59**: 16-22 (1970). J23,107/70

Carruthers, M. O., Taggart, P.: "Study of plasma catecholamine and lipid responses to emotional stress." *Q. J. Med.* **40**: 578-579 (1971). J19,080/71

Public speaking raised the blood catecholamine and FFA values, as did the stress of racing driving.

Falkner, F.: "The stress of racing driving." *Lancet* March 27, 1971, p. 650.

J21,150/71

Taggart, P., Carruthers, M.: "Endogenous hyperlipidaemia induced by emotional stress of racing driving." *Lancet* February 20, 1971, pp. 363-366. H35,851/71

During racing driving, "the total catecholamine levels were grossly elevated, the increase being largely due to noradrenaline. The free-fatty-acid levels were also elevated one to three minutes before the start while the drivers were on the starting grid, and up to one hour after the race. The triglyceride levels were slightly elevated after the event, continued to increase, and reached a peak at one hour." Blood cholesterol showed no significant change.

Taggart, P., Gibbons, D.: "The motor-car and the normal and abnormal heart." *Triangle* **10**: 63-68 (1971). J16,979/71

ECG studies on ordinary and racing-car drivers "indicate strongly that emotionally induced angina, and borderline left ventricular failure, should be contraindications to holding a driving licence."

Ashton, H., Savage, R. D., Thompson, J. W., Watson, D. W.: "A method for measuring human behavioural and physiological responses at different stress levels in a driving simulator." *Br. J. Pharmacol.* **45**: 532-545 (1972). G92,253/72

Description of a car simulator with which it is possible to produce controlled and reproducible degrees of stress under conditions that are also suitable for the investigation of the effects of pharmacologic agents upon it. In this study, classic biochemical indicators of stress were not measured.

Ashton, H., Savage, R. D., Telford, R., Thompson, J. W., Watson, D. W.: "The effects of cigarette smoking on the response to stress in a driving simulator." *Br. J. Pharmacol.* **45**: 546-556 (1972). J14,838/72

Taggart, P., Carruthers, M.: "Suppression by oxprenolol of adrenergic response to stress." *Lancet* August 5, 1972, pp. 256-258.

H57,669/72

In racing drivers, oxprenolol given one hour before the race suppresses tachycardia, plasma FFA and plasma total catecholamine concentrations, as compared with values obtained on the same drivers on previous occasions. This β -blockade appears to diminish emotional stress without interfering with performance.

Harris, W., Mackie, R. R. et al.: *A Study of the Relationships among Fatigue, Hours of Service, and Safety of Operators of Bus and Truck Drivers*. Final Rep. No. DOT-FH-11-7777. Goliita, Cal.: Human Factors Res. Inc., 1972. Abstracted in: *Staff Century Res. Corp.* pamphlet (1199th abstract), Vol. 2. Arlington, Va., 1973.

J16,129/72

"Cannabis and driving skills." *Can. Med. Assoc. J.* **107**: 269-270 (1972).

J16,956/72

Rohmert, W.: "Abhängigkeit der Fahrtauglichkeit von der Gestaltung des Verkehrsarbeitsplatzes" (Dependence of driving ability on the configuration of traffic conditions). *Med. Welt* **23**: 1356-1360 (1972).

J16,957/72

Kaatzsch, H.: "Endogene Cholesterinbildung bei Kraftfahrern, Akkord-und Schichtarbeitern" (Endogenous cholesterol synthesis in truck drivers, piece-workers and shift-workers). *Med. Klin.* **67**: 262-266 (1972).

J16,980/72

In truck drivers and shiftworkers, the increase in blood cholesterol roughly paralleled the elevation of blood catecholamines, and reflected the severity of the stress associated with their work.

Rutley, K. S., Mace, D. G. W.: "Heart rate as a measure in road layout design." *Ergonomics* **15**: 165-173 (1972).

J17,214/72

Discussion of heart rate as an indicator of stress produced by driving, especially in relation to road junction design.

Taylor, S. H., Meeran, M. K.: "Different effects of adrenergic beta-receptor blockade on heart rate response to mental stress, catecholamines and exercise." *Br. Med. J.* November 3, 1973, pp. 257-259.

H77,497/73

A single oral tablet of oxprenolol relieves the tachycardia associated with automobile driving or with isoproterenol in normal peo-

ple, whereas exercise tachycardia is substantially less influenced. "Thus relatively small doses of beta-receptor antagonists will suppress the increase in heart rate induced by mental stress or catecholamines with relatively little effect on the response to everyday exercise. Possibly smaller doses of these drugs would relieve emotionally-induced anginal pain and tachycardia."

Hülemann, K. D., List, M.: "Fortlaufende EKG-Aufzeichnung bei Autorennfahrern" (Continuous EKG registration in racing-car drivers). *Med. Welt* **24**: 1360-1363 (1973).

J15,935/73

In racing-car drivers, training decreases tachycardia. Arrhythmias are seen only in inexperienced drivers, and usually they have pre-existent cardiac disease (20 refs.).

Matthews, G.: "Cardiological changes and car driving." *Br. Med. J.* June 30, 1973, pp. 779-780.

J16,958/73

Littler, W. A., Honour, A. J., Sleight, P.: "Direct arterial pressure and electrocardiogram during motor car driving." *Br. Med. J.* May 5, 1973, pp. 273-277.

J16,959/73

Baroody, N. B., Thomason, J. M., O'Bryan, E. C. Jr.: "The heart of the 500 mile race." *Am. Family Physician* **8**: 184-189 (1973).

J16,988/73

ECG studies on racing-car drivers often reveal sinus tachycardias which are attributed primarily to emotional stress.

Luff, K., Karger, J. von: "Zur Frage der Verhaltenskontrolle von Kraftfahrern nach Verkehrsunfällen unter Berücksichtigung des Schuldmaßes" (Behavioral self-control of drivers following road accidents with reference to the degree of guilt). *Beitr. Gerichtl. Med.* **31**: 18-21 (1973).

J17,717/73

The stressor effect of automobile accidents may lead to an immediate disturbance of decision making conducive to flight from the scene of an accident. The legal implications in German courts are described.

Somerville, W.: "Emotions, catecholamines and coronary heart disease." *Adv. Cardiol.* **8**: 162-173 (1973).

J16,987/73

A statistical study shows that "certain experienced motor-car drivers with a history of coronary heart disease when driving in busy traffic develop angina, sinus tachycardia, ectopic beats and various arrhythmias. Healthy racing drivers, stimulated by the emotions of competition and danger, develop high-grade sinus tachycardia, raised plasma catechol-

amines and free fatty acids immediately before and after a race. Public speaking induces in normal persons similar changes in heart rate and rhythm and elevations in plasma catecholamines and free fatty acids. In both drivers and public speakers, triglycerides show a peak elevation 1-2 h after the event. Oxprenolol inhibits the increase in heart rate, plasma catecholamines, free fatty acids and triglycerides."

Retterstøl, N.: "Cannabis og bilkjøring" (Cannabis and car driving). *T. Norske Laegeforen.* **93:** 2121-2122 (1973) (Swedish). J16,347/73

Rodstein, M.: "Accident proneness." *J.A.M.A.* **229:** 1495 (1974). H91,883/74

Concise summary of principal factors responsible for accident proneness under stressful conditions, with special reference to automobile accidents.

Klonoff, H.: "Marijuana and driving in real-life situations. The effect of marijuana on driving is bidirectional and dependent on compensatory ability and dose." *Science* **186:** 317-324 (1974). H93,920/74

Selzer, M. L., Vinokur, A.: "Life events, subjective stress and traffic accidents." *Am. J. Psychiatry.* **131:** 903-906 (1974).

J13,882/74

Replies to a questionnaire by 532 normal or alcoholic male drivers revealed that transitory, subjective stress experiences were significantly correlated with traffic accidents, but personality and demographic variables were not. The literature on stress-induced traffic accidents is reviewed (20 refs.).

Bugard, P.: *Stress, Fatigue et Dépression. (L'homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue and depression. Man and the aggressions of daily life), Vol. 1, p. 294; Vol. 2, p. 302. Paris: Doin Edit., 1974.

E10,487/74

Discussion on automobile driving within a two-volume monograph on stress, fatigue and depression.

Saario, I., Linnoila, M., Mäki, M.: "Interaction of drugs with alcohol on human psychomotor skills related to driving: effect of sleep deprivation or two weeks' treatment with hypnotics." *J. Clin. Pharmacol.* **15:** 52-59 (1975). H96,783/75

Industry, Labor, Business, Finance

(See also Social Factors, Neuropsychologic Factors, Sound, Vibration, Temperature and Various other sections dealing with stressors common in industry and business)

Some occupations (for example, executive work, the practice of law, police work, shift work, the telephone and telegraph system and others) have been arbitrarily separated from those generally implied by the title, and have been assigned special sections because a good deal of research has been devoted to their stressor effect. Also, many readers may wish to find pertinent data without having to search through the entire literature on careers related to business and industry.

This arbitrariness is especially evident with regard to the section on executive life, since at any but the lowest level, some executive responsibility is inherent in all business. Nevertheless, we decided to separate the relevant literature for the convenience of those who are particularly interested in this aspect of stress, irrespective of the type of executive work involved. Of course, the stressor effects in most occupations overlap to such an extent that an exhaustive appreciation of the topic would require consultation of all related sections.

Some excellent articles have been cited for an overview of the stressors encountered in modern business and technology. Particularly interesting observations have been made on accountants, whose serum cholesterol levels consistently rose during severe

occupational stress periods when income tax and other reports had to be prepared. This type of stress also predisposes to CHD.

Among invoicing clerks, subjective feelings of fatigue and urinary catecholamine excretion increased whenever remuneration was changed from fixed salaries to piece wages, presumably because of the extra motivation to accomplish as much as possible in the shortest period. The stress of harried, concentrated work also tends to cause fatigue, backache and pain in the arms and shoulders.

An extensive study on 270,000 male employees of the Bell Telephone and Telegraph Company led to the conclusion that the high management group did not run a greater risk of CHD than those at lower levels. It was concluded that high responsibility is not particularly stressful. However, the many differences in the daily tasks, social and economic backgrounds, eating habits and so on, of the two groups would also have to be taken into account before generalizations could be made.

In industrial occupations, job satisfaction was negatively related to death from CHD. Job pressure undoubtedly aggravates distress in lower level employees, as well as in management. Furthermore, a good deal of evidence has been compiled to show the "curative effect of work satisfaction" on mental stress, and there is much literature on the distress caused by overpromotion, underpromotion, or managerial indifference to the personal problems of employees.

Allegedly, severe distress in industrial work may even lead to impotence or decreased fertility.

Industry, Labor, Business, Finance

(See also our earlier stress monographs, p. xiii, and cf. Shift Work)

Skinner, E. F.: "Psychological stresses in industry." *Practitioner* 153: 37-44 (1944).

B26,973/44

Main, T. F.: "Industrial stress and psychiatric illness." In: Rees, J. R., *Modern Practice in Psychological Medicine*, pp. 397-413. New York and London: Paul B Hoeber, 1949.

E83,374/49

Thomson, A. G.: "The effect of temperature and humidity on the working efficiency of miners." *Mining J.* 240: 98-100 (1953).

E53,354/53

Neel, R. G.: "Nervous stress in the industrial situation." *Personnel Psychol.* 8: 405-415 (1955).

J13,198/55

Friedman, M., Rosenman, R. H., Carroll, V.: "Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress." *Circulation* 17: 852-861 (1958).

C56,083/58

In a large group of accountants, each subject's highest serum cholesterol consistently occurred during severe occupational or other stress, and his lowest at times of minimal

stress. The results could not be ascribed to any changes of weight, exercise or diet. Marked acceleration of blood clotting time consistently occurred when occupational stress was maximal, in contrast to normal blood clotting during periods of respite.

Rosenman, R. H., Friedman, M.: "The possible relationship of occupational stress to clinical coronary heart disease." *Calif. Med.* 89: 169-174 (1958).

C61,455/58

Review of the literature and personal observations show that all the predisposing factors for CHD (increased plasma lipids, intimal damage, altered hemodynamics, accelerated blood clotting) are affected by various types of stressors. It is suggested that "the increasing occupational stress unique to industrialized society plays a dominant role in the high incidence of clinical coronary heart disease."

Lipman, D. C.: "Stress factors in industry. An approach at the U.S. Naval Gun Factory." *Ind. Med. Surg.* 27: 295-297 (1958).

D87,097/58

Argyris, C.: "Organizational effectiveness under stress." *Harv. Business Rev.* 38: 137-146 (1960).

J15,729/60

"The policy of 'being nice' to employees is fine for the company that is coasting along,

but it breaks down when there is real pressure for growth, expansion, and efficiency."

Buell, P., Breslow, L.: "Mortality from coronary heart disease in California men who work long hours." *J. Chron. Dis.* **11**: 615-626 (1960). E84,336/60

Statistical studies on the registered mortality of men in California suggest that long working hours predispose different occupational groups to CHD. Farmers and farm laborers, however, seem to be relatively protected. In any event, it appears that stress "may be associated with thrombotic complications but not necessarily with progressive atherosclerosis of the coronary arteries." The correlation between long working hours and coronary accident is particularly obvious among men under forty-five years of age in occupations involving deadline pressures.

Selye, H.: "Stress of technology: can man adjust?" *Ind. Can.* **63**: 223-226 (1962). D26,080/62

General considerations on man's ability to adjust to the stress created by modern technology.

Gwózdz, B.: "The effect of thermal stress on the level of 17-hydroxycorticosteroids in the blood serum of man." *Endokrinol. Pol.* **13**: 275-286 (1962) (Polish). D31,024/62

Studies on miners exposed to dry heat (29 refs.).

Pell, S., D'Alonzo, C. A.: "Acute myocardial infarction in a large industrial population. Report of a 6-year study of 1,356 cases." *J.A.M.A.* **185**: 831-838 (1963). E26,954/63

The age-adjusted incidence of myocardial infarction among male employees was inversely proportional to their annual income. These results are difficult to interpret because "the demands of a top-management job may be no more stressful than situations commonly encountered by persons in lower job levels, at work and at home. Secondly, men chosen for advancement may be those whose personal qualities are characteristic of both executive talent and resistance to coronary disease. It is conceivable, for example, that in selecting persons to assume greater responsibilities, supervisors and managers, knowingly or unknowingly, may tend to choose the better adjusted individuals, who by virtue of their personality and psychic state are better able to cope with life's stresses in general."

Kahn, R. L., Wolfe, D. M., Quinn, R. P., Snoek, J. D.: *Organizational Stress: Studies in Role Conflict and Ambiguity*, p. 470. New York, London and Sydney: John Wiley & Sons, 1964. E10,438/64

A monograph on "organizational stress," particularly in diverse social and industrial groups. There are some highly interesting data on the roles of conflict and ambiguity as they affect various personalities, but the word stress is used essentially as a synonym for difficulties, and not in its now generally accepted medical meaning (about 125 refs.).

Selye, H.: "The stress of life: new focal point for understanding accidents." *Ind. Med. Surg.* **33**: 621-625 (1964).

G11,115/64

Concise summary of the stress concept in relation to industrial accidents.

Levi, L.: "The stress of everyday work as reflected in productiveness, subjective feelings and urinary output of adrenaline and noradrenaline under salaried and piece-work conditions." *J. Psychosom. Res.* **8**: 199-202 (1964). G24,076/64

In female invoicing clerks, productivity, subjective feelings of fatigue, and urinary catecholamine excretion were enhanced when remuneration was changed from fixed salaries to piece-wages. The percentage of miscalculations was not altered during the period of increased productivity, but half the group complained of feeling harried, and experiencing fatigue, backache and pain in their arms and shoulders.

Jonderko, G.: "Effect of work mechanization upon the improvement of working condition and the accident rate in coal mining." *Med. Pracy* **15**: 237-243 (1964) (Polish). J16,122/64

Russek, H. I.: "Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups." *J.A.M.A.* **192**: 189-194 (1965). F36,826/65

Statistical studies on twelve thousand professional men in fourteen occupational categories in the U.S. On the basis of questionnaires evaluated by specialists in each field, CHD was "strikingly related to the relative stressfulness of occupational activity" among physicians, lawyers, security analysts, and traders. In combination with emotional stress, high-fat diets and smoking were also associated with a high incidence of CHD. Smoking was most frequent in stressful occupations,

but unexpectedly, CHD was more common among nonsmokers than among persons who once smoked but gave it up. Possibly, "the ability to stop smoking may imply a resilient personality response to stress and diminished vulnerability to atherogenic influences."

Rogg, S. G., D'Alonzo, C. A.: *Emotions and the Job*, p. 192. Springfield, Ill.: Charles C Thomas, 1965. E10,661/65

Levi, L. (ed.): *Emotional Stress. Physiological and Psychological Reactions. Medical, Industrial and Military Implications*, p. 280. Stockholm: Kungl. Boktryckeriet P. A. Norstedt and Söner, 1967. E7,006/67

Symposium on stress responses, particularly those elicited by emotional factors in military and industrial personnel.

Hinkle, L. E., Jr., Whitney, L. H., Lehman, E. W., Dunn, J., Benjamin, B., King, R., Plakun, A., Flehinger, B.: "Occupation, education, and coronary heart disease. Risk is influenced more by education and background than by occupational experience, in the Bell System." *Science* **161**: 238-246 (1968). H1,311/68

A five-year statistical study on the relation between occupation, education and CHD among 270,000 male employees of the Bell Telephone and Telegraph Company showed that "men who attain the highest levels of management as a group do not have a higher risk of coronary heart disease than men who remain at lower levels. The findings provide no evidence that men who have high levels of responsibility, or who have been promoted rapidly, frequently, or recently, or men who are transferred to new departments or to new companies, have any added risk of coronary heart disease." The difference is not necessarily due to social and economic backgrounds but may result from eating habits, smoking and lifestyles.

Vitte, N. K.: "Objective evaluation of efforts and stress in work performance." *Gig. Tr. Prof. Zabol.* **12** No. 3: 3-7 (1968) (Russian). J23,986/68

Williams, M. K.: "Stress in industry." *Trans. Soc. Occup. Med.* **20**: 8-12 (1970). J21,699/70

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Conditions of work: psychological and endocrine stress reactions." *Arch. Environ. Health* **21**: 789-797 (1970). G79,762/70

Gross, E.: "Work, organization and stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 54-110. Chicago: Aldine, 1970. E10,714/70

Aldridge, J. F. L.: "Emotional illness and the working environment." *Ergonomics* **13**: 613-621 (1970). E86,568/70

Gass, G. Z.: "Hardcore personality and industrial illnesses and accidents." *Ind. Med. Surg.* **39**: 174-178 (1970). J13,408/70

Stevens, A.: "Psychiatric rejects from military service and their employability in civilian life." *Ind. Med. Surg.* **39**: 522-528 (1970). J14,859/70

Sales, S. M., House, J.: "Job dissatisfaction as a possible risk factor in coronary heart disease." *J. Chron. Dis.* **23**: 861-873 (1971). J10,970/71

Statistical studies show that "job satisfaction is negatively related to a group's rate of death from coronary heart disease."

Hall, S. A.: "Heat stress in outdoor manual workers in East Africa." *Ergonomics* **14**: 91-94 (1971). J19,719/71

Pelnar, P. V.: "L'influence des aspects physico-chimiques du lieu de travail sur l'équilibre mental du travailleur" (The influence of the physical and chemical aspects of place of employment upon the mental equilibrium of the worker). *Un. Méd. Can.* **100**: 1985-1989 (1971). H46,885/71

Siegrist, J.: "Belastungen der Arbeitssituation bei Angestellten" (Work situation stresses in employees). *Z. Allgemeinmed.* **47**: 1037-1040 (1971). J20,647/71

Cameron, C.: "Fatigue problems in modern industry." *Ergonomics* **14**: 713-720 (1971). J14,877/71

Study of the relation between stress and fatigue in modern industry, particularly in civil aviation.

Buck, V. E.: *Working Under Pressure*, p. 252. London: Staples Press, 1972. E10,628/72

Monograph on job pressure by a professor of organizational behavior and administrative theory. Written mainly from a behavioral science perspective, the volume deals not only with somatic problems, but also gives advice to management and lower level employees alike regarding job pressure and satisfaction. Interpretation of numerous questionnaires and statistics (over 150 refs.).

- Schäcke, G., Woitowitz, H. J., Rietschel, E., Havla, R.: "Radiotelemetrische Langzeituntersuchungen von Herzschlagfrequenz und Elektrokardiogramm bei Führungskräften der Industrie" (Radiotelemetric long-term studies on the heart rate and ECG of industrial managers). *Int. Arch. Arbeitsmed.* **29**: 142-158 (1972). *J20,338/72*
- Pincherle, G.: "Assessment of the relationship between stress and work performance." *Proc. R. Soc. Med.* **65**: 321-324 (1972). *J15,629/72*
- Kearns, J. L.: *Stress in Industry*, p. 160. London: Priory Press, 1973. *E10,573/73*
- Monograph on the workaday aspects of dealing with stress in industry, mainly from the standpoint of interpersonal relations. The terms stress and stressors are used but not defined, and the biologic basis of the G.A.S. is excluded from consideration. Even such words as adrenal, adrenaline corticoids, hypothalamus and nervous system are not to be found in the index. The book aims primarily at giving practical advice concerning behavior and, being illustrated by many humorous drawings, it is easy to read.
- Stauber, M.: "Männliche Fertilitätsstörungen durch beruflichen Stress" (Professional stress may cause male fertility disturbances). *Med. Monatsschr.* **27**: 108-110 (1973). *H69,981/73*
- Review of the literature with personal observations showing that the stress involved in professional life, particularly in industry, may lead to impotence or a decrease in fertility.
- Brook, A.: "Mental stress at work." *Practitioner* **210**: 500-506 (1973). *J1,772/73*
- Theoretical considerations and case reports illustrating the curative effects of work satisfaction on mental stress problems. Social factors connected with work such as overpromotion, underpromotion and managerial indifference to personal problems of employees are found to cause pathogenic stress.
- Various Authors: "Problems in occupational safety and health: a critical review of select physical and psychological factors." In: *Staff Century Res. Corp.* pamphlet, Vol. 2, p. 90. Arlington, Va., 1973. *J13,172/73*
- Annotated bibliography of 1,317 articles on occupational safety and accident proneness.
- Wilkins, W. L.: "Social stress and illness in industrial society." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 242-254. Springfield, Ill.: Charles C Thomas, 1974. *E10,694/74*
- Discussion of various definitions of stress. Special attention is given to "Stress (Selye)" but no definite recommendation is made (12 refs.).
- Cobb, S.: "Physiologic changes in men whose jobs were abolished." *J. Psychosom. Res.* **18**: 245-258 (1974). *J16,527/74*
- "There are meaningful changes in norepinephrine excretion and in serum creatinine, serum uric acid and serum cholesterol associated with the stress of job termination."
- Margolis, B. L., Kroes, W. H., Quinn, R. P.: "Job stress: an unlisted occupational hazard." *J. Occup. Med.* **16**: 659-661 (1974). *J17,654/74*
- Müller-Limmroth, W.: "Stress und Strain am Arbeitsplatz" (Stress and strain at the place of work). *Arbeitsmed. Sozialmed. Präventivmed.* **9**: 209 (1974). *J18,265/74*
- Levi, L.: "Was ist und bedeutet Stress?" (What is stress?). *Arbeitsmed. Sozialmed. Präventivmed.* **9**: 209-211 (1974). *J18,266/74*
- Diebschlag, W.: "Stress am modernen Arbeitsplatz" (Stress at the modern working place). *Arbeitsmed. Sozialmed. Präventivmed.* **9**: 217-222 (1974). *J18,268/74*
- Frankenhaeuser, M.: "Aspects of research on man in future society." *Rep. Psychol. Lab. Univ. of Stockholm*, Supp. 24: 31 (1974). *J18,270/74*
- Considerations on the dangers of over- and understimulation in relation to stress in industry.
- Bronner, R.: "Stressbewältigung durch Koordination. Ergebnisse experimenteller Organisationsforschung" (Overcoming of stress through coordination. Results of experiments in organizational research). *Z. Organis.* **43**: 450-455 (1974). *J19,051/74*
- Bronner, R.: "Stress und Leistung. Ergebnisse experimenteller Entscheidungsforschung" (Stress and performance. Results of experiments in decisional research). *Z. Organis.* **43**: 363-368 (1974). *J19,052/74*
- General outlines of a program for mastering stress in industrial and other social settings through better organization.
- Collins, R. T.: "Managing stress on the

job." In: Miller, E., *Stress. Blue Print for Health* 25, No. 1, pp. 48-53. Chicago: Blue Cross Association, 1974. E10,818/74

(IgG, IgA, IgM) of miners in uranium mines." *Z. Immunitaetsforsch.* 148: 356-365 (1975). J23,619/75

Wagner, V., Andrlíková, J., Pálek, V.: "Immunoglobulins under the influence of nonspecific factors. II. The influence of work-stress on levels of immunoglobulins

In miners, prolonged exposure to work stress caused "a significant decrease of all 3 classes of Ig. In the group exposed for a shorter time only the IgG decreased significantly."

Executive Life

A good deal has been written about the stressor effect of executive responsibilities in middle and top management, relative to that in subordinate employees merely following orders. Undoubtedly, executive responsibilities, if taken very seriously, produce severe distress, with somatic, psychic and often pathogenic consequences. However, here, as in all considerations of stress manifestations, conditioning factors cannot be neglected because whatever a person's position in the hierarchy of command, the stressor effect of his decision-making depends not only upon what he does or even what the consequences will be, but also upon the way he takes it. This explains the many contradictory statements about whether being the boss or being bossed about is more distressful or eustressful. Some people are leaders, others followers. The main problem each person must face squarely is to determine what he actually prefers to do, and behave accordingly. I know from personal experience that some highly intelligent and capable employees in our Institute repeatedly refused promotions (which would have resulted in increased status and salary) because they had the insight to realize that the higher level of responsibility would have brought with it too much frustration and job dissatisfaction.

However, the executive is also responsible for his employees, and hence must consider his organizational pattern in light of the fact that many of his subordinates will not be able to make these decisions for themselves.

It is a truism that the conscientious executive must make good rules and enforce them rigidly, but the real art is to know when to make exceptions. This is particularly true of promotion policies. It is common practice to promote personnel from a job in which they performed competently to a higher position. However, this process tends to go on until they have reached a level at which they are incompetent. To prevent this, the best technique I have been able to develop is to ask an employee temporarily to substitute for one in a higher position (to avoid disappointment, without revealing the wish to promote him); I then offer the higher post only after he has already shown his competence for it.

Executive Life

(See also our earlier stress monographs, p. xiii)

"Job stress and the executive: 6,000 managers report their experience." *Management Rev.* 47: 13-21 (1958). J14,312/58

Purely empirical but largely sound recommendations based on statistics concerning job satisfaction and interpersonal relationships.

"Stress stems from within the man himself, not from the outer forces of his living or working environment. In other words, their jobs aren't killing them—they are killing themselves."

Felton, J. S.: "How to live with executive stress." *Management Rev.* 47: 29-31 (1958). J14,313/58

Highly popularized brief comment.

Lee, R. E., Schneider, R. F.: "Hypertension and arteriosclerosis in executive and non-executive personnel." *J.A.M.A.* **167**: 1447-1450 (1958). C81,673/58

To the authors' surprise, among more than one thousand subjects in business, hypertension and cardiovascular disease (arteriosclerosis, CHD, myocardial infarction) were disproportionately low in the executive group. The authors note that "stress is a relative matter and that the disruption of the harmonious balance between a man and his environment can result from either the demands of the environment or the failure of the man to measure up to them. Success in a career goes hand in hand with good health. The executive, as part of his training, learns to judge the amount of occupational stress he can stand and to appreciate the value of outside avenues of expression."

Useem, J., Useem, R.: "Social stresses and resources among middle management men." In: Jaco, E. G., *Patients, Physicians and Illness. Sourcebook in Behavioral Science and Medicine*, pp. 74-91. Glencoe, Ill.: Free Press, 1958. J9,292/58

Analysis of the stress characteristics of middle management men, mainly regarding psychosocial factors.

Mortensen, J. M., Stevenson, T. T., Whitney, L. H.: "Mortality due to coronary disease analyzed by broad occupational groups." *Arch. Ind. Hyg.* **19**: 1-4 (1959).

E57,220/59

A statistical study shows that "in the Bell Telephone System there is no material difference in coronary mortality between the top management group and the craftsmen and laborers group but there is a marked difference between top management and middle management which is not explainable from presently available data. The popular notion that high executive positions are associated with high coronary mortality is likely due to the greater publicity connected with such deaths rather than to statistical facts."

Singer, H. A.: "The management of stress." *Adv. Management.* **25**: 11-13 (1960). J14,314/60

Popular review on stress, especially as it affects managers, with recommendations on the avoidance of distress.

Selye, H.: "Stress: its implications in everyday life." *Merit News* **13**: 1-4 (1961). C95,847/61

Popular article on the role of stress in executive and business life.

Dunn, J. P., Cobb, S.: "Frequency of peptic ulcer among executives, craftsmen, and foremen." *J. Occup. Med.* **4**: 343-348 (1962). J4,086/62

Statistical studies on several Pittsburgh companies showed that foremen suffered from peptic ulcer more frequently than craftsmen or executives. The data do not support the widely held notion that ulcer disease is unusually high among executives. "Though both the prevalence and the incidence of peptic ulcer within the several groups correlated well with the level of serum pepsinogen it remains an enigma that the mean pepsinogen levels should be lowest for the foremen and highest for the executives."

Ayers, A. W., Burr, H. B., Tuttle, W. B.: "Personality concomitants of peptic ulcer among managerial, supervisory, and presupervisory personnel." *J. Occup. Med.* **5**: 252-258 (1963) (26 refs.). E57,199/63

Webber, R. A.: "The roots of organizational stress." *Personnel* **43** No. 5: 32-39 (1966). J13,883/66

Discussion (with case reports) of the stress induced by poor organization in industry, particularly among managers.

Jaques, E.: "Executive organization and individual adjustment." *J. Psychosom. Res.* **10**: 77-82 (1966). J23,664/66

Lesse, S.: "Psychodynamic mechanisms of emotional illness in executives." *Int. J. Soc. Psychiatry* **12**: 24-28 (1966). J23,116/66

Warshaw, L. J.: "The industrial physician and executive stress." In: McLean, A., *To Work is Human. Mental Health and the Business Community*, pp. 161-167. New York: Macmillan, 1967. J19,153/67

Taylor, G. C.: "Executive stress." In: McLean, A., *To Work is Human. Mental Health and the Business Community*, pp. 153-160. New York: Macmillan, 1967. J19,131/67

Page, R. C.: *How to Lick Executive Stress*, p. 176. New York: An Essandess Special Edition, 1967. E109/67

A medical consultant to various governmental and industrial management groups, and former Chairman of the Board of the Occupational Health Institute gives advice in simple language on how to apply the stress theory to problems of executives in overcoming the constant pressures of their occupa-

tions. No reference is made to the technical literature.

Eaton, M. T.: "Detecting executive stress in time." *Ind. Med. Surg.* **36**: 115-118 (1967). J9,677/67

Wright, H. B.: "Executive stress in Great Britain." In: McLean, A., *To Work is Human: Mental Health and the Business Community*, pp. 168-189. New York: Macmillan, 1967. J13,884/67

Weiss, J. M.: "Effects of coping responses on stress." *J. Comp. Physiol. Psychol.* **65**: 251-260 (1968). G56,996/68

Observations on rats comparable to the "executive monkey" experiments in which electric shock either could or could not be prevented by the animal. Conditions determining gastric ulcer formation are examined.

Lundberg, U., Lundberg, G.: "Stress och administrationen" (Stress and administration). *Nord. Med.* **80**: 1581-1587 (1968) (Swedish). H10,248/68

Speculative survey of stress among industrial personnel, particularly executives. For prevention of distress, the authors emphasize the importance of correct choice of managers at all levels especially those possessing the ability to cooperate.

Taylor, G. C.: "Executive stress." *Int. Psychiatry Clin.* **6**: 307-316 (1969). J21,638/69

Levinson, H.: *Executive Stress*, p. 289. New York, Evanston, Ill., and London: Harper and Row, 1970. E10,572/70

Monograph describing the social stress situations characteristic of executive work. No attempt is made to correlate these with confirmed data on the physiologic and particu-

larly the somatic mechanisms regulating stress responses.

French, J. R. P. Jr., Caplan, R. D.: "Organizational stress and individual strain." In: Marrow, A. J., *The Failure of Success*, pp. 30-66. New York: AMACOM, 1972.

J19,039/72

Appleton, W. S.: "Psychiatric dangers in running for political office." *Perspect. Biol. Med.* **16**: 188-198 (1973). J19,726/73

Chin, A., Mandel, H.: "The two faces of stress: a new look at the enemy." *Impetus* November, 1973, pp. 16-19; 53-59.

H62,174/73

Popular review on the stress concept, with special reference to its applicability to the problems of executives.

"L'homme d'affaires peut éviter le stress" (The businessman can avoid stress). *Québec ind.* **28**: 29-31 (1973). H70,346/73

Popular review on stress among executives.

Kiev, A.: *A Strategy for Handling Executive Stress*, p. 178. Chicago: Nelson-Hall, 1974. E10,800/74

The author uses as a motto for this monograph these words from Emerson's essay on self-reliance: "It is easy in the world to live after the world's opinion; it is easy in solitude to live after our own; but the great man is he who in the midst of the crowd keeps with perfect sweetness the independence of solitude." The book is replete with useful practical advice which can be characterized by a few quotations: "Every communication holds a stress. Business is a battle.... Stress and the drives of life are inseparable." The bodily manifestations of stress and its biochemical mechanism are given little attention.

Medicine, Dentistry, Nursing

(See also Diseases of Adaptation—where problems of veterinarians will be discussed conjointly with the spontaneous diseases of animals)

Medicine. A statistical study on more than twenty-five hundred physicians suggested that the incidence of CHD is higher among general practitioners and anesthesiologists than among dermatologists and pathologists, allegedly because the former two groups have a higher stress level.

In many U.S. hospitals where medical interns have particularly strenuous work shifts, their performance as well as their health is endangered because of excess

stress. Radiotelemetric observations on physicians and medical students performing stressful tasks almost invariably revealed tachycardia, which roughly paralleled urinary catecholamine excretion. This was particularly evident in surgical personnel encountering operative difficulties.

Patients admitted to hospital emergency wards frequently suffered such intense psychosocial stresses that the routine presence of a psychiatrist was recommended.

A statistical study on British physicians revealed a special predisposition to drug addiction, suicide and mental disease.

Obviously, considerable attention should be given to stress factors both among physicians and among their patients. Careful additional studies along these lines would be of considerable value in making definite recommendations for preventive measures.

Dentistry. Here we shall deal mainly with stress in the dentist and his patient. The role of stress in the development of dental disease will be discussed under the morphologic characteristics of stress.

Several investigators have studied the objective manifestations of stress in dental practice and have found that such typical indicators as increased corticoid and catecholamine production, as well as the typical psychic signs of distress, are readily detectable in both patients and the dentist, especially during complex and painful interventions. In several cases, the use of tranquilizers has been found to be justified and effective in combatting most of these complications, at least to a considerable degree.

Nursing. Among nurses, as among physicians, stress is undoubtedly most severe during work in intensive care units. Of course, temporary stress situations also arise during any unexpected crisis or in dealing with particularly difficult patients, especially in psychiatric wards. It is important to give due consideration to this stress factor because—as one author put it—many nurses are too much in need of support to give any, and obviously, their performance declines under such conditions.

Medicine, Dentistry, Nursing

(See also our earlier stress monographs, p. xiii)

Medicine. Holzknecht, F.: "Die Überlastung des Klinikarztes" (The overloading of the hospital physician). *Med. Klin.* **54:** 1789–1790 (1959). J23,201/59

Newesely, W.: "Die Überbelastung der Ärzte und des Pflegepersonals. Die Überbelastung des praktischen Ärztes" (The overloading of the physician and nursing personnel. The overloading of the general practitioners). *Med. Klin.* **54:** 1787–1788 (1959). J23,204/59

Charvat, J.: "Stress reaction during operation." *Pol. Tyg. Lek.* **15:** 1647–1650 (1960) (Polish). J24,147/60

Discussion of the stressor effect of performing surgical operations in terms of the G.A.S.

Russek, H. I.: "Emotional stress and coronary heart disease in American physicians." *Am. J. Med. Sci.* **240:** 711–721 (1960). C97,308/60

On the basis of a questionnaire to which 2,587 physicians replied, general practitioners and anesthesiologists had a distinctly higher CHD rate than dermatologists and pathologists. The former two groups were rated as "high stress," the latter as "low stress" occupations. It is concluded that "emotional stress of occupational origin is one of the more important etiologic factors in the genesis of coronary artery disease among persons subsisting on a relatively high-fat diet."

Master, A. M.: "The role of effort and occupation (including physicians) in coronary occlusion." *J.A.M.A.* **174:** 942–948 (1960). J7,796/60

A general review of epidemiologic data does not convince the author that the fre-

quency of CHD has reached epidemic proportions, or that it is elicited by the stress of modern life. He believes that the apparently increased incidence of CHD is due to a rise in the mean age of the population and to improved diagnostic techniques.

Martin, H. W.: "Structural sources of strain in a small psychiatric hospital." *Psychiatry* **25**: 347-353 (1962). J23,456/62

Russek, H. I.: "Emotional stress and coronary heart disease in American physicians, dentists and lawyers." *Am. J. Med. Sci.* **243**: 716-725 (1962). D34,808/62

Questionnaires sent to ten thousand physicians, dentists and attorneys, aged forty to sixty-nine, revealed a definite positive correlation between occupational stress and CHD. "General practitioners in each field showed coronary heart disease prevalence rates 2 to 3 times those of the specialists selected for survey. No consistent relationship was found for prevalence rates of reported hypertension and occupational stress." Correlations of the data with the diets of these subjects "lend support to clinical and experimental studies which suggest that emotional stress is an important accelerating factor in atherogenesis when the diet is relatively high in animal fat" (28 refs.).

Ira, G. H., Whalen, R. E., Bogdonoff, M. D.: "Heart rate changes in physicians during daily 'stressful' tasks." *J. Psychosom. Res.* **7**: 147-150 (1963). E37,679/63

Radio-telemetric observations on the ECG of physicians and medical students showed that, during stressful tasks, tachycardia occurred in virtually all subjects though it was usually of short duration. Urinary catecholamine excretion roughly paralleled the tachycardia.

Russek, H. I.: "Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups." *J.A.M.A.* **192**: 189-194 (1965). F36,826/65

Statistical studies on twelve thousand professional men in fourteen occupational categories in the U.S. On the basis of questionnaires evaluated by specialists in each field, CHD was "strikingly related to the relative stressfulness of occupational activity" among physicians, lawyers, security analysts and traders. In combination with emotional stress, high-fat diets and smoking were also associated with a high incidence of CHD. Smoking was most frequent in stressful occu-

pations, but unexpectedly, CHD was more common among nonsmokers than among persons who once smoked but gave it up. Possibly, "the ability to stop smoking may imply a resilient personality response to stress and diminished vulnerability to atherogenic influences."

Chertok, L.: "Tensions among psychotherapists" (abstracted). *Am. J. Psychiatry* **121**: 1106-1108 (1965). J22,979/65

Chertok, L.: "An introduction to the study of tensions among psychotherapists." *Br. J. Med. Psychol.* **39**: 237-243 (1966). J22,886/66

DeSole, D. E., Singer, P., Aronson, S.: "Suicide and role strain among physicians." *Int. J. Soc. Psychiatry* **15**: 294-301 (1969). J21,639/69

Solomon, J.: "Physician, heal thyself. Does the venerable tradition of long, irregular hours for medical interns damage these young physicians, and endanger the lives of their patients?" *Sciences* **11**: 6-7; 29-31 (1971). H45,901/71

Semipopular review on stress in medical interns due to their strenuous work shifts.

Satin, D. G.: "(Help:) Life stresses and psycho-social problems in the hospital emergency unit." *Soc. Psychiatry* **7**: 119-126 (1972). G99,171/72

Patients admitted to a hospital emergency unit often suffer from severe psychosocial stresses, and the presence of a psychiatrist is recommended.

Goldman, L. I., McDonough, M. T., Rosemond, G. P.: "Stresses affecting surgical performance and learning. I. Correlation of heart rate, electrocardiogram, and operation simultaneously recorded on videotapes." *J. Surg. Res.* **12**: 83-86 (1972). H73,783/72

"Fatigue and operative difficulty were associated with tachycardia in susceptible surgical personnel. Operative performance was impaired during the former with probable impaired learning."

Gerber, L. A.: "Coping with stress as a theme in teaching psychopathology to medical students." *Psychiatr. Q.* **46**: 273-283 (1972). J19,663/72

Zimmerly, J. G., Oleniewski, W. A.: "Mental anguish as an element of damages in malpractice cases." *Maryland Med. J.* **22**: 37-39 (1973). J20,207/73

- Medico-legal aspects of malpractice as they affect physician and patient.
- Oleniewski, W. A., Zimmerly, J. G.: "Mental anguish claims in medical malpractice cases." *Postgrad. Med.* **53**: 131-132 (1973). *J19,728/73*
- "Emotional stresses of patient-physician encounters." *J.A.M.A.* **223**: 1037-1038 (1973). *H65,585/73*
- Adams, P. E.: "Psychiatric residents in blurred roles: adaptation." *Psychosomatics* **15**: 157-159 (1974). *H96,178/74*
- "The stress of a blurred role which includes a change in a trained hierachial expectation by the psychiatric resident physician as he comes on the service of a therapeutic milieu program with a team approach is added to the recognized stress of encountering psychiatric patients."
- Fielding, J. M., Grounds, A. D., Mellspor, G.: "Psychiatrists' roles and staff stresses in a renal homotransplantation unit." *Med. J. Austr.* **1**: 66-67 (1974). *J23,825/74*
- Maddison, D.: "Stress on the doctor and his family." *Med. J. Austr.* **2**: 315-318 (1974). *J19,463/74*
- Murray, R. M.: "Psychiatric illness in doctors." *Lancet* June 15, 1974, pp. 1211-1212. *H87,575/74*
- A statistical study on British physicians revealed that they are particularly susceptible to drug addiction and suicide, but a special proneness to mental illness was not otherwise detectable (24 refs.).
- Dentistry.** Selye, H.: "The alarm reaction, the general adaptation syndrome, and the role of stress and of the adaptive hormones in dental medicine." *Oral Surg., Oral Med., and Oral Pathol.* **7**: 355-367 (1954). *B88,779/54*
- A brief lecture on the role of the G.A.S. in dentistry.
- Shannon, I. L., Prigmore, J. R., Hester, W. R., McCall, C. M. Jr., Isbell, G. M.: "Stress patterns in dental patients: I. Serum free 17-hydroxycorticosteroids, sodium and potassium in subjects undergoing local anesthesia and simple exodontic procedures." *J. Oral Surg. Anesth.* **19**: 486-491 (1961). *J11,143/61*
- Shannon, I. L., Isbell, G. M., Hester, W. R.: "Stress in dental patients." *School of Aerosp. Medicine Report No. 62-58* (1962). *J11,879/62*
- Schmid, E., Süss, G., Zicha, L., Süss, E., Weiss, P.: "Über den Einfluss der emotionellen Belastung zahnärztlicher Behandlungsmassnahmen auf die Reaktion des Sympathico-adrenalen Systems" (The influence of the emotional stress of dental interventions on the sympathetic-adrenal system). *Arzneim. Forsch.* **14**: 852-855 (1964). *F20,699/64*
- Weiss, P., Schmid, E., Zicha, L., Süss, G., Süss, E.: "Untersuchungen über die emotionelle Belastung verschiedener zahnärztlicher Eingriffe an Hand der Nebennierenmark- und Nebennierenrindenfunktion" (The effect of the emotional stress of various adrenal interventions on the function of the adrenal medulla and adrenal cortex). *Dtsch. Zahnaerztl.* **20**: 638-641 (1965). *G25,229/65*
- In patients undergoing dental work, urinary steroid and VMA excretion rises despite local anesthesia, but tranquilizers appear to diminish the sympatho-adrenergic stimulation.
- Zicha, L., Schmid, E., Süss, E., Süss, G., Weiss, P., Bergner, D.: "Über das Verhalten der Nebennierenrinden-Steroidausscheidung im Harn und ihre Beziehung zur Vanillinmandelsäure bei emotioneller Belastung durch zahnärztliche Behandlungsmassnahmen" (Urinary adrenocortical steroid excretion and its relation to vanillylmandelic acid during the emotional stress of dental interventions). *Endokrinologie* **47**: 281-289 (1965). *F43,836/65*
- Studies on steroid and VMA levels in the urine of patients submitted to the emotional stress of various dental interventions. Local anesthetics do not influence these responses, but central depressants inhibit them. Increased hormone and hormone-metabolite excretion is ascribed to the emotional stress associated with surgery.
- Dyce, J. M., Dow, J. A.: "F.D.I. special commission on dentists' health diagnosis and stress in dentistry. A study of stress." *Int. Dent. J.* **15**: 405-416 (1965). *J23,131/65*
- Dyce, J. M., Dow, J. A.: "Further studies of stress factor in dentistry." *Dent. Pract. Dent. Rec.* **15**: 326-331 (1965). *J23,132/65*

Detailed discussion of the G.A.S. in dentistry.

Lazarus, R. S.: "Some principles of psychological stress and their relation to dentistry." *J. Dent. Res.* **45** Supp. 6: 1620-1626 (1966). J22,584/66

Fox, J. G., Jones, J. M.: "Occupational stress in dental practice." *Br. Dent. J.* **123**: 465-473 (1967). J22,690/67

Train, G. J.: "The dentist's emotional reaction to the troublesome patient." *Psychosomatics* **10**: 176-180 (1969).

J21,951/69

Paul, E.: "The elimination of stress and fatigue in operative dentistry." *Br. Dent. J.* **127**: 37-41 (1969). J22,673/69

Fredericks, M. A., Mundy, P.: "Relations between social class, stress-anxiety responses, academic achievement, and professional attitudes of dental students." *J. Dent. Educ.* **33**: 377-384 (1969). J22,712/69

Krotky, H.: "Untersuchungen über akute Lärmschäden des Gehörs durch Einwirkung von Turbinenschall hoher Frequenz in der zahnärztlichen Praxis" (Investigation of acute hearing defects caused by high frequency turbine sound in dental practice). Doctoral thesis, University of Berlin, 1971, p. 108. J15,035/71

Edmondson, H. D., Roscoe, B., Vickers, M. D.: "Biochemical evidence of anxiety in dental patients." *Br. Med. J.* October 7, 1972, pp. 7-9. H60,527/72

"Plasma adrenaline, noradrenaline, and free fatty acids were estimated before treatment, immediately after sedation with diazepam 0.2 mg/kg body weight in the phobic patients, during induction of oral anaesthesia, and during and after surgery. Patients with dental phobia had significantly higher levels of adrenaline, which were only temporarily lowered by sedation, and which during treatment remained consistently higher than those of control patients."

Sakai, S.: "Effect of protein content of rat diet on amount of corticosterone in tooth extraction." *Folia Pharmacol. Jap.* **68**: 66-72 (1972) (Japanese). H79,322/72

In rats on a low-protein diet the adrenals are comparatively small but show a pronounced increase in size during the stress of tooth extraction, which is ineffective in this

respect in controls given normal amounts of protein.

Howard, J. H., Cunningham, D. A., Rechnitzer, P. A., Goode, R. C.: "Some patterns of stress in the job and career of a dentist." *Ontario Dent.* **52**: 14-25 (1975). J21,942/75

"Time pressure is a universal source of stress...there is a significant relationship between exercise behaviour and stress symptoms."

Nursing. Mayer, M.: "Die Überlastung im Schwesternberuf" (The overload in the nursing profession). *Med. Klin.* **54**: 1790-1791 (1959). J23,205/59

Cleland, V. S.: "The effect of stress on performance. A study of the effect of situational stressors on performance of nurses—modified by need for social approval." *Nurs. Res.* **14**: 292-298 (1965) (18 refs.). J23,649/65

Cleland, V. S.: "Effects of stress on thinking." *Am. J. Nurs.* **67**: 108-111 (1967). J23,677/67

McBride, M.A.B.: "Nursing approach, pain, and relief: an exploratory experiment." *Nurs. Res.* **16**: 337-341 (1967). J23,672/67

Pride, L. F.: "An adrenal stress index as a criterion measure for nursing." *Nurs. Res.* **17**: 292-303 (1968). J23,742/68

Gardam, J. E. D.: "Nursing stresses in the intensive care unit." *J.A.M.A.* **208**: 2337-2338 (1969). J22,287/69

Davitz, L. J., Pendleton, S. H.: "Nurses' inferences of suffering." *Nurs. Res.* **18**: 100-107 (1969). J23,691/69

Vreeland, R., Ellis, G. L.: "Stresses on the nurse in an intensive-care unit." *J.A.M.A.* **208**: 332-334 (1969). J21,952/69

Arndt, C., Laeger, E.: "Role strain in a diversified role set—the director of nursing service, Part I." *Nurs. Res.* **19**: 253-259 (1970). J12,700/70

Arndt, C., Laeger, E.: "Part II. Sources of stress." *Nurs. Res.* **19**: 495-501 (1970). J12,703/70

Graffam, S. R.: "Nurse response to the

- patient in distress. Development of an instrument." *Nurs. Res.* **19**: 331-336 (1970). J12,701/70
- Michaels, D. R.: "Too much in need of support to give any?" *Am. J. Nurs.* **71**: 1932-1935 (1971). J20,895/71
- Rogers, P. J.: "Design for patient care." *Int. Nurs. Rev.* **19**: 267-282 (1972). J22,043/72
- Quinlan, D. M., Blatt, S. J.: "Field articulation and performance under stress: differential predictions in surgical and psychiatric nursing training." *J. Cons. Clin. Psychol.* **39**: 517 (1972). J20,503/72
- Cassem, N. H., Hackett, T. P.: "Sources of tension for the CCU nurse." *Am. J. Nurs.* **72**: 1426-1430 (1972). J20,910/72
- Davitz, L. J.: "Identification of stressful situations in a Nigerian school of nursing." *Nurs. Res.* **21**: 352-357 (1972). J19,895/72
- Hay, D., Oken, D.: "The psychological stresses of intensive care unit nursing." *Psychosom. Med.* **34**: 109-118 (1972). G89,730/72
- Description of psychologic stresses among nurses in an intensive care unit. Recommendations for improvements are made.
- Davidhizar, R. H.: "Stress patients: a new dimension in psychiatric nursing education." *Perspect. Psychiatr. Care* **11**: 129-131 (1973). J21,584/73
- Oberst, M. T.: "The crisis-prone staff nurse." *Am. J. Nurs.* **73**: 1917-1921 (1973). J22,603/73

Law

Among lawyers, too, CHD has been claimed to be particularly frequent if their work is associated with considerable stress. On the other hand, based on a questionnaire answered by almost two thousand attorneys in the Cleveland area, CHD was correlated with law school quality but not with the stress-ranking of their legal specialties. These observations, as well as serum cholesterol determinations, did not supply sufficient evidence to show that the practice of law is especially likely to predispose to stress-induced disturbances.

Law

(See also our earlier stress monographs, p. xiii)

Russek, H. I.: "Emotional stress and coronary heart disease in American physicians, dentists and lawyers." *Am. J. Med. Sci.* **243**: 716-725 (1962). D34,808/62

Questionnaires sent to ten thousand physicians, dentists and attorneys, aged forty to sixty-nine, revealed a definite positive correlation between occupational stress and CHD. "General practitioners in each field showed coronary heart disease prevalence rates 2 to 3 times those of the specialists selected for survey. No consistent relationship was found for prevalence rates of reported hypertension and occupational stress." Correlations of the data with the diets of these subjects "lend support to clinical and experimental studies which suggest that

emotional stress is an important accelerating factor in atherogenesis when the diet is relatively high in animal fat" (28 refs.).

Russek, H. I.: "Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups." *J.A.M.A.* **192**: 189-194 (1965). F36,826/65

Statistical studies on twelve thousand professional men in fourteen occupational categories in the U.S. On the basis of questionnaires evaluated by specialists in each field, CHD was "strikingly related to the relative stressfulness of occupational activity" among physicians, lawyers, security analysts and traders. In combination with emotional stress, high-fat diets and smoking were also associated with a high incidence of CHD. Smoking was most frequent in stressful occupations, but unexpectedly, CHD was more common among nonsmokers than among per-

sons who once smoked but gave it up. Possibly, "the ability to stop smoking may imply a resilient personality response to stress and diminished vulnerability to atherogenic influences."

Friedman, E. H., Hellerstein, H. K.: "Occupational stress, law school hierarchy, and coronary artery disease in Cleveland attorneys" (abstracted). *Circulation* 32: II-89 (1965). F59,156/65

As indicated by questionnaires answered by almost two thousand attorneys in Cleveland, "coronary prevalence correlated with

law school quality, but not with stress-ranking of legal specialties."

Friedman, E. H., Hellerstein, H. K., Jones, S. E., Eastwood, G. L.: "Behavior patterns and serum cholesterol in patent attorneys (P)." *Circulation* 32: II-89-II-90 (1965).

J2,902/65

On the basis of interviews, 107 male patent attorneys were divided into types A and B according to the personality classification criteria of Rosenman and Friedman. Differences in serum cholesterol were not significant between the two groups.

Police Work

Although policemen undoubtedly have to cope with many stressors, comparatively little attention has been paid to their problems from this point of view. Of course, working only night shifts, particularly variable day and night shifts or unusually long hours, as well as meeting extraordinary dangers in dealing with criminals, are undoubtedly sources of distress frequently encountered in typical police work. Yet a statistical study on a large number of Cincinnati policemen somewhat surprisingly revealed, in reply to questionnaires, that they themselves assessed as their most important stressors those circumstances which threatened their sense of professionalism. It must be kept in mind that even off the job the policeman must accept prejudice, suspicion, and hostility from a large segment of the population, all of which causes considerable job dissatisfaction. This, in turn, leads to a good deal of disappointment, especially when the policeman compares his work to the closely related activities of military personnel, who face similar dangers only in times of war, yet are generally held in high esteem.

Police Work

(See also our earlier stress monographs, p. xiii)

Drabek, T. E., Haas, J. E.: "Laboratory simulation of organizational stress." *Am. Sociol. Rev.* 34: 223-238 (1969).

J23,820/69

Observations on police teams during simulated disaster situations. "Changes in team performance patterns under stress appeared related to strains existent in the system prior to stress and to incompatibilities between system structure and emergent system demands. Among the most important changes in group structure which increased system capacity was the gradual emergence of a display mechanism whereby intra-team activity became more shared."

Symonds, M.: "Emotional hazards of

police work." *Am. J. Psychoanal.* 30: 155-160 (1970).

J20,843/70

Margolis, B. L.: "Stress is a work hazard, too." *Ind. Med. Surg.* 42: 20-23 (1973).

J7,424/73

Popularized summary of occupational stress as a work hazard, with special reference to policemen, ATCs and shift workers.

Kroes, W. H., Margolis, B. L., Hurrell, J. J. Jr.: "Job stress in policemen." *J. Police Sci. Admin.* 2: 145-155 (1974).

J10,489/74

This statistical study on one hundred Cincinnati policeman revealed through questionnaires that their most significant stressors were those circumstances which threatened their sense of professionalism. "In fact, these stressors were more frequently mentioned and more heavily emphasized than were directly life-threatening stressors." Even off

the job, the policeman must accept prejudice, fear, suspicion and hostility from a large segment of society. In addition, there are physical dangers inherent in the occupation. There is much interesting material on the stressors that cause greatest job dissatisfaction among policemen, but adequate statistical evaluation of their predisposition to stress diseases is still lacking.

Kirkham, G. L.: "From professor to patrolman: a fresh perspective on the police." *J. Police Sci. Admin.* **2**: 127-137 (1974).

J10,534/74

General considerations on the stressors encountered in police work.

Kroes, W. M., Hurrell, J. J. Jr., Margolis, B.: "Job stress in police administrators." *J. Police Sci. Admin.* **2**: 381-387 (1974).

J19,592/74

Studies on administrators of the Cincinnati Police Department suggested that "the most significant stressors seemed to be a result of the administrator's being in the position of the 'man in the middle' while complex demands were being made upon him from the community, his superiors, and subordinates."

Shift Work

The stressor effect of work on prolonged, and particularly on varying, night shifts, or merely that of unusually long hours, has generated much attention. Yet the circadian rhythm of plasma corticoids appears to remain unaltered in both night workers and blind persons, which would suggest that at least this change is not considerably affected by light.

On the other hand, working long hours predisposes various occupational groups to CHD, except farmers and farm laborers, who would appear to tolerate long working hours unusually well. The association between long working hours and CHD is especially striking in men under forty-five years of age who work under pressure trying to meet deadlines.

In one study, reference is made to the comparatively high incidence of peptic ulcers and gastritis among shift workers, but the causative role of stress has not been clearly established here; questionnaires merely suggested that night shifts are particularly fatiguing and conducive to psychologic manifestations of distress.

Night work causes least alteration in adrenocortical rhythm in people adapted to it and who work in a community in which this sort of life is universal and generally accepted so that it does not provoke social problems. Rotating shift work, on the other hand, appears to produce the greatest disturbances in corticoid and catecholamine secretion indicative of stress.

Measurements on machine operators in a Swedish paper mill showed that EP and NEP excretion was lowest on the night shift, although fatigue ratings were highest.

In any event, all investigators agree that shift work becomes less stressful in proportion to habituation and that being "excluded from society" is perhaps the most prominent complaint among night shift workers.

Shift Work

(See also our earlier stress monographs, p. xiii)

"Making night work pay." *Mod. Ind.* **20**: 40-45 (1948).

B64,574/48

Wyatt, S., Marriott, R.: "Night work and shift changes." *Br. J. Ind. Med.* **10**: 164-172 (1953).

D54,869/53

Migeon, C. J., Tyler, F. H., Mahoney, J. P., Florentin, A. A., Castle, H., Bliss, E. L., Samuels, L. T.: "The diurnal variation of plasma levels and urinary excretion of 17-hydroxycorticosteroids in normal subjects, night workers and blind subjects." *J. Clin. Endocrinol. Metab.* **16**: 622-633 (1956).

C15,075/56

The circadian rhythm in plasma 17-OHCS

levels reached a peak at about 06:00 and a nadir around 24:00. A similar rhythm in 17-OHCS excretion followed the same pattern, but with a delay of approximately two hours. This periodicity was not changed in night workers and blind persons.

Mott, P. E., Mann, F. C., McLoughlin, Q., Warwick, D. P.: *Shift Work. The Social, Psychological, and Physical Consequences*, p. 351. Ann Arbor, Mich.: University of Michigan Press, 1965. E10,439/65

A psychosocial analysis of occupations necessitating shift work. Some reference is made to peptic ulcers and gastritis due to the stress of shift work, but the term stress as used here is not clearly defined.

Matthews, G.: "Shift work: a review of present knowledge." *Med. Bull. Stand. Oil Co.* **25**: 37-44 (1965). J16,326/65

Blakelock, E. H.: "A Study of Some Social and Psychological Effects of rotating Shift Work." Thesis, University of Michigan, 1967. Abstracted in: *Staff Century Res. Corp.* pamphlet (151st abstract), Vol. 2, Arlington, Va., 1973. J16,127/67

Colquhoun, W. P., Blake, M. J. F., Edwards, R. S.: "Experimental studies of shift-work. III: Stabilized 12-hour shift systems." *Ergonomics* **12**: 865-882 (1969).

J13,917/69

Lesniok, A., Bajdur, M., Sośnierz, D.: "Role of some etiopathogenetic factors of gastric and duodenal peptic ulcer in miners." *Med. Pracy* **21**: 202-208 (1970) (Polish).

J16,123/70

In miners, hereditary predisposition and night shift work were found to increase the incidence of peptic ulcers.

Colquhoun, W. P.: "Circadian rhythms, mental efficiency and shift work." *Ergonomics* **13**: 558-560 (1970). E85,744/70

Conroy, R. T. W. L., Elliott, A. L., Mills, J. N.: "Circadian rhythms in plasma concentration of 11-hydroxycorticosteroids in men working on night shift and in permanent night workers." *Br. J. Ind. Med.* **27**: 170-174 (1970). H24,017/70

Comparative studies of plasma corticoid levels were made in newspaper printing shop employees who regularly worked at night, and in engineering factory workers on monthly rotation shifts. Among the newspaper workers, maximal concentrations were noted around 14:00 when they awoke, whereas the

pattern was much more irregular in the engineering shift employees. "It appears that the adrenal cortical rhythm can be adapted to night work in a community in which this is universal, accepted and lifelong, but that such adjustment is unusual in men on night shift work for limited periods, and whose associates are mainly following a usual nyctohemeral existence."

Colquhoun, W. P., Edwards, R. S.: "Circadian rhythms of body temperature in shift-workers at a coalface." *Br. J. Ind. Med.* **27**: 266-272 (1970). J12,866/70

Hale, H. B., Williams, E. W., Smith, B. N., Melton, C. E. Jr.: "Neuroendocrine and metabolic responses to intermittent night shift work." *Aerosp. Med.* **42**: 156-162 (1971). G81,174/71

In six men studied nightly during cycles of unaccustomed alternating shift work, "evidence was obtained of work-associated neuroendocrine and metabolic hyperactivity (nonspecific stress) which was most distinct during the first week of morning work. Relatively high values of urinary epinephrine and 17-OHCS were found during morning periods in the weeks in which there was no morning work, indicating that the rotating shift schedule itself, not just the night work, acted as a stressor. An adaptive change was evident, since there was a lessening of the physiologic disturbance with each return to morning duty, as judged by urinary epinephrine, norepinephrine, 17-OHCS, and urea."

Smith, R. C., Melton, C. E., McKenzie, J. M.: *Affect Adjective Check List Assessment of Mood Variations in Air Traffic Controllers*, p. 8. Washington, D.C.: Department of Transportation, Federal Aviation Administration, 1971. G86,726/71

Description of Malmstrom's Composite Mood Adjective Check List (CMACL) which evaluates stress in ATCs by their subjective assessment of eighty adjectives (relating to aggression, anxiety, concentration, depression, distrust, dizziness, fatigue and so on). Night shifts prove to be especially fatiguing.

Aschoff, J.: "Eigenschaften der menschlichen Tagesperiodik" (Characteristics of circadian rhythm in man). *Schriftenr. Arb.-med. Soz.-med. Arb.-hyg.* **38**: 21-43 (1971). J10,472/71

Review on the influence of night or shift work upon the well-being and productivity of packers, in relation to natural circadian rhythm.

Sobczyk, W., Markiewicz, L.: "Catecholamine excretion in the urine during work with a high emotional load." *Acta Physiol. Pol.* **23**: 65-72 (1972) (Polish).

H55,094/72

At a thermal-electric power plant, in control room workers who worked in three shifts (06:00-14:00, 14:00-22:00, and 22:00-06:00) at tasks demanding constant attention, the highest EP and 17-OHCS elimination values were found in first-shift and the highest NEP excretion rates in third-shift employees. However, the authors claim that "the excretion of catecholamines and 17-OHCS is markedly below normal values. The results point to a low emotional load during the work performed; this is the result of a practice of long standing."

Vaisfel'd, I. L., Il'icheva, R. F.: "Diurnal rhythm of the content of biogenous amines (histamine, serotonin) in human blood under normal conditions and during altered work-sleep cycles." *Kosm. Biol. Med.* **6** No. 5: 56-62 (1972) (English translation of Russian original).

H79,765/72

The histamine-diaminoxidase system shows considerable circadian variations in healthy subjects. The blood 5-HT content tends to decrease at night. Changes in the work-sleep cycle cause fluctuations in these parameters "related not only to the stressor applied, but also to the initial state of the organism." These findings are especially important in space medicine.

Fröberg, J., Karlsson, C. G., Levi, L.: "Shift work: a study of catecholamine excretion, self-ratings and attitudes." In: Swenson, A., *Night and Shift Work*, Rep. No. 11, pp. 10-20. Studia Laboris et Salutis, 1972.

J4,858/72

Correlation between catecholamine excretion and shift work among operators of machinery in a Swedish paper mill. Fatigue ratings increased sharply within the afternoon and night shifts; EP and NEP elimination was lowest on the night shift.

Ehrenstein, W., Schaffler, K., Müller-Limmroth, W.: "Die Wirkung von Oxazepam auf den gestörten Tagschlaf nach Nachschichtarbeit" (The effect of oxazepam on day sleep disturbed due to night work). *Arzneim. Forsch.* **22**: 421-427 (1972).

J15,868/72

In nurses doing night shift work, oxazepam aided adjustment to sleeping during the day. "In oxazepam day sleep, the sleep of stage 3

and 4 and the REM sleep were increased to the values registered in night sleep. In oxazepam day sleep the share of waking periods remained clearly below the reference values of normal day and night sleep. Stages 1 and 2 of orthodox sleep were increased in oxazepam day sleep as compared to normal day sleep but did not reach the values of night sleep."

Kaatzsch, H.: "Endogene Cholesterinbildung bei Kraftfahrern, Akkord- und Schichtarbeitern" (Endogenous cholesterol synthesis in truck drivers, piece-workers and shift-workers). *Med. Klin.* **67**: 262-266 (1972).

J16,980/72

In truck drivers and shift-workers, increases in blood cholesterol roughly paralleled the elevation of blood catecholamines, and reflected the severity of the stress associated with their work.

Östberg, O.: "Interindividual differences in circadian fatigue patterns of shift workers." *Br. J. Ind. Med.* **30**: 341-351 (1973).

H79,224/73

Data from computer operators working on different shifts show individual differences in circadian fatigue patterns. "By means of a questionnaire on preferences and habits of activity and time of day, three subgroups of five subjects each were selected—'morning,' 'middle,' and 'evening' groups. Significant differences were found between the groups and between the shifts. Most interesting was the significant interaction of group x shift, on the basis of which it could be concluded that the 'morning' type of subjects had the most pronounced difficulty in adapting to the shift system practised."

Margolis, B. L.: "Stress is a work hazard, too." *Ind. Med. Surg.* **42**: 20-23 (1973).

J7,424/73

Popularized summary of occupational stress as a work hazard with special reference to policemen, ATCs and shift-workers.

Melton, C. E., McKenzie, J. M., Smith, C. C., Polis, B. D., Higgins, E. A., Hoffmann, S. M., Funkhouser, G. E., Saldivar, J. T.: *Physiological, Biochemical, and Psychological Responses in Air Traffic Control Personnel: Comparison of the 5-day and 2-2-1 Shift Rotation Patterns*. Federal Aviation Administration, Aviation Med. pamphlet, p. 16. Washington, D.C., 1973.

J15,362/73

At the Houston Intercontinental Tower, the two-two-one sequence (two evening shifts, two day shifts, one mid-shift) was compared with the straight five-day shift

(five consecutive days on the same shift). "Physiological and psychological assessments showed no significant stress differences on the two schedules. On neither of the schedules did the controllers' stress levels differ from the general population."

Melton, C. E., McKenzie, J. M., Polis, B. D., Hoffmann, M., Saldivar, J. T. Jr.: *Physiological Responses in Air Traffic Control Personnel: Houston Intercontinental Tower*. Federal Aviation Administration, Aviation Med. pamphlet, p. 19. Washington, D.C. 1973.

J15,363/73

Studies on ATCs showed that "day work (heavy traffic load) at Houston was characterized by elevated levels of all stress indicators as compared with the mid-shift (light traffic); epinephrine excretion increased significantly during the last half of the mid-shift as compared with the first half. Urinary stress indicators (17-ketogenic steroids, epinephrine, norepinephrine) were all significantly elevated during day sleep as compared with night sleep, indicating less effective rest during day sleep."

Hockey, R.: "Changes in information-selection patterns in multisource monitoring as a function of induced arousal shifts." *J. Exp. Psychol.* **101**: 35-42 (1973).

J17,213/73

Review on the stressor effects of shift work and sleep deprivation.

Fröberg, J. E., Åkerstedt, T.: "Auswirkungen der Nacht- und Schichtarbeit auf die Gesundheit" (Night- and shift-work and health). *Arbeitsmed. Sozialmed. Präventivmed.* **9**: 223-226 (1974).

J18,283/74

Rutenfranz, J.: "Risikofaktor Nacht- und Schichtarbeit" (Risk factors of night and shift work). *Med. Klin.* **69**: 12-16 (1974).

H81,515/74

In West Germany alone, more than two million people (three hundred thousand of

them women) are engaged in occupations demanding shift work, usually at night and on weekends and holidays. The resulting modifications of various circadian rhythms, as well as the detrimental effects of being "excluded from society" or deprived of normal sleep, are surveyed (33 refs.).

Davies, J. A., Navaratnam, V., Redfern, P. H.: "The effect of phase-shift on the passive avoidance response in rats and the modifying action of chlordiazepoxide." *Br. J. Pharmacol.* **51**: 447-451 (1974).

H92,485/74

"In rats trained to a 12 h light-12 h dark cycle, advancing the phase by 6 h produced a resynchronization of the 24 h variation in passive avoidance response (PAR) which was completed after 10 days." Chlordiazepoxide lessened the disruptive effect of phase-shift. The clinical implications of this work are discussed.

Boucher, M. C.: "Les horaires de travail" (The working hours). *Méd. Qué.* **9**: 34-36 (1974).

H93,450/74

Brief review on the stressor effect of shift work.

Elias, R., Mateescu, R., Zotovici, L., Popescu, G., Cristescu, M., Branescu, R.: "Stress du temps, rotation irrégulière des horaires et fatigue des techniciens des émissions radiodiffusées" (Time stress, irregular schedule rotation and fatigue of broadcasting technicians). *Arch. Mal. Prof.* **35**: 525-532 (1974).

J17,147/74

Taub, J. M., Berger, R. J.: "Acute shifts in the sleep-wakefulness cycle; effects on performance and mood." *Psychosom. Med.* **36**: 164-173 (1974).

J18,920/74

Belova, T. A., Vassiliev, V. N.: "The adrenal cortex function in man during intense shift labour." *Fiziol. Zh. SSSR* **60**: 329-333 (1974) (Russian).

J23,372/74

Telephone and Telegraph Operators

Several statistical studies have been performed on stress in telephone and telegraph operators because they have to be constantly alert. It was found that, in women, mere operation of a telephone switchboard sufficed to produce eosinopenia. The high rate of absenteeism among them was likewise considered to be a result of their stressful occupation.

In Australia, neurosis was studied comparatively in several occupational groups.

A correlation with the typical stress diseases was not particularly evident, although bronchial and gastrointestinal disturbances and absenteeism were common. In any event, neurotic complaints and absenteeism were decreasingly frequent among telegraphists, clerks and mechanics. The most common complaints (rigid job supervision, noise, drug and drinking habits) were not so much due to the work itself as to the response of the workers to their tasks.

Telephone and Telegraph Operators

(See also our earlier stress monographs, p. xiii)

Tatai, K., Mori, Y., Ito, K.: "Response of the pituitary-adrenocortical system to mental strain in healthy women." *Jap. J. Physiol.* **1**: 316-319 (1951). B59,995/51

In women, the stressor effect of calculating or of operating a telephone switchboard sufficed to produce pronounced eosinopenia.

Hinkle, L. E. Jr., Plummer, N.: "Life stress and industrial absenteeism. The concentration of illness and absenteeism in one segment of a working population." *Ind. Med. Surg.* **21**: 363-375 (1952). B29,097/52

Among 1,297 telephone operators, it was found that a high rate of absenteeism was common in those "exposed throughout their period of employment to life situations and experiences which were to them stressful."

Solovieva, V. P., Podoba, E. V.: "Physiological evaluation of the stress borne by operators at control desks." *Gig. Tr. Prof. Zabol.* **12** No. 10: 3-7 (1968) (Russian).

J23,985/68

Podoba, E. V., Prosekin, A. M.: "Some cardiovascular changes in female telegraph operators of the central telegraph office in the course of their work day." *Gig. Tr. Prof. Zabol.* **14** No. 6: 4-7 (1970) (Russian).

J22,116/70

Grandjean, E.: "Ergonomie" (Ergonomics). *Rev. Méd. Suisse Rom.* **92**: 201-210 (1972). J19,073/72

As indicated by blood EP and clinical observations, ATCs exhibit considerably

stronger manifestations of stress than do telegraphists.

Ferguson, D.: "A study of neurosis and occupation." *Br. J. Ind. Med.* **30**: 187-198 (1973). H69,794/73

In Sydney, Melbourne and Brisbane, neurosis was much more frequent among telegraphists than among those in other occupations. "An increase in indices of mental stress was noted but some disorders commonly attributed to stress were not unduly prevalent in neurotics." Yet absenteeism ascribed to bronchial and dyspeptic ailments or injury appeared to be especially persistent.

Ferguson, D.: "A study of occupational stress and health." *Ergonomics* **16**: 649-663 (1973). J8,265/73

Systematic studies, undertaken because of claims by telegraphists' unions in various cities of Australia, showed that the proportion of neurotic absentees was greater in telegraphists than in clerks, and greater in clerks than in mechanics. "The only occupational characteristics that could be identified strongly with neurosis were the negative attitudes to job supervision, and noise in the workplace, though the drug habits of smoking, drinking and analgesic-taking (all strongly associated with neurosis) were also work-related." The most common complaints were due not so much to the work itself but to the response of the workers to their tasks. No clear association was found between neuroses and such disorders as hypertension, CHD, asthma, nasal allergy and migraine. Remedial measures are suggested.

Various Other Occupations

Apart from a few comparative publications on the stressor effects of diverse occupations, the special studies cited here have been carried out on students, musicians, train dispatchers, heat and power station workers, rickshaw pullers, fishermen, workers in Israeli kibbutzim, personnel of research and teaching institutions, and others.

Various Other Occupations

(See also our earlier stress monographs, p. xiii)

McCord, C. P.: "Life and death by the minute." *Ind. Med.* **17**: 377-382 (1948).

B61,006/48

General remarks on the stressors involved in the lives of *train dispatchers*. Their life expectancy is comparatively low and they often suffer from psychosomatic disorders and CHD.

Wolfenden, J.: "Students' strains and stresses." *Br. J. Psychiatry* **116**: 577-585 (1970).

G75,655/70

More philosophic than medical considerations on the "strains and stresses" imposed by today's *student* life.

Schilling, R. S. F.: "Hazards of deep-sea fishing." *Br. J. Ind. Med.* **28**: 27-35 (1971).

J13,787/71

Singh, A., Krishan, I., Singh, N.: "The effect of occupational stress on the electrocardiogram of *Rickshaw pullers*." *Indian Heart J.* **24**: 266-270 (1972).

H79,369/72

Sobczyk, W., Markiewicz, L.: "Catecholamines excretion in urine during work with high emotional load." *Acta Physiol. Pol.* **23**: 59-65 (1972).

J6,003/72

In control room employees at a *heat and power station*, three-shift work did not change the circadian rhythm of catecholamine and 17-OHCS excretion. The urinary catecholamine and steroid levels were comparatively low although EP elimination increased in proportion to physical activity.

Jatho, K., Hellmann, H.: "Zur Frage des Lärm- und Klangtraumas des Orchestermusikers" (The problem of acoustic trauma in orchestra musicians). *H.N.O.* (Berlin) **20**: 21-29 (1972).

J17,046/72

Effect of audiogenic stress upon professional *musicians*.

Butler, H. F.: "Education for the professions. *Student* role stress." *Am. J. Occup. Ther.* **26**: 399-405 (1972).

J19,654/72

Åstrand, I., Fugelli, P., Karlsson, C. G., Rodahl, K., Vokac, Z.: "Energy output and work stress in coastal fishing." *Scand. J. Clin. Lab. Invest.* **31**: 105-113 (1973).

H65,774/73

Among *fishermen*, "about a tenfold increase in epinephrine and a fourfold increase in norepinephrine excretion were observed

during work as compared to resting night values."

Shirom, A., Eden, D., Silberwasser, S., Kellermann, J. J.: "Job stresses and risk factors in coronary heart disease among five occupational categories in kibbutzim." *Soc. Sci. Med.* **7**: 875-892 (1973).

J8,517/73

Among 762 adult male *kibbutz* members in Israel, agricultural workers were most likely to experience stress associated with CHD. Yet, such cardiac lesions and acknowledged predisposing risk factors "did not significantly differ among managerial and professional workers, clerical workers, craftsmen, factory workers, and agricultural workers."

Ramprasad, G.: "Evaluation of stress in non-manual work: an empirical investigation." *Indian J. Med. Res.* **61**: 1714-1721 (1973).

J12,450/73

Description of a questionnaire designed to test stress and work satisfaction among the personnel of *research* and *teaching* institutions.

Elias, R., Mateescu, R., Zotovici, L., Popescu, G., Cristescu, M., Branescu, R.: "Stress du temps, rotation irrégulière des horaires et fatigue des techniciens des émissions radiodiffusées" (Time stress, irregular schedule rotation and fatigue of *broadcasting technicians*). *Arch. Mal. Prof.* **35**: 525-532 (1974).

J17,147/74

Vasiliev, V. N., Kikolov, A. I., Brodskaya, T. A., Matlina, E. A.: "Excretion of catecholamines and of their precursor Dopa in the daytime and at night during performance of *dispatcher's* work." *Gig. Tr. Prof. Zabol.* **18** No. 2: 6-11 (1974) (Russian).

J22,004/74

Barnard, R. J., Duncan, H. W.: "Heart rate and ECG responses of *fire fighters*." *J. Occup. Med.* **47**: 247-250 (1975) (17 refs.).

J23,896/75

Unemployment, RetirementGiffen, M. B., McNeil, J. S.: "Effect of military retirement on dependents." *Arch. Gen. Psychiatry* **17**: 717-722 (1967).

J22,507/67

"Retirement from the military service may be perceived as a time of crisis by the career servicemen, as well as by members of his family" (10 refs.).

PHYSIOLOGIC STATES

(In this section we will discuss such physiologic conditions as age, sex, pregnancy, and lactation only inasmuch as they can influence susceptibility to stressors. The changes that occur in the sex organs during stress have been arbitrarily listed under Morphologic Changes, since it is virtually impossible to separate structural variations in the gonads and mammary glands from the associated functional alterations. Data on pertinent hormone determinations will also be found under Chemical Changes. The effect of stress upon aging has been considered under Theories—Adaptation Energy and the Triphasic Nature of the G.A.S.)

Age

. The response to stressors is considerably influenced by age, and numerous investigators have analyzed its course from fetal life to senility. In general, young animals are more adaptable to the stressor effect of various agents, a fact that has been ascribed to their greater supply of "adaptation energy." The latter is admittedly a rather vague, though an indispensable concept; the well-known loss of adaptability becomes increasingly evident as an organism ages, and is one of the outstanding characteristics of senility.

On the basis of various function tests, it had been suggested that people who survive to a very advanced age in good health can "preserve a relatively intact pituitary-adrenal mechanism involved in response to acute stress."

Forced exercise on a treadmill during the first few weeks of life initially inhibited the growth of rats, but later they grew better and became much more resistant to exhaustion than controls. "It is not known whether improved treadmill performance is indicative of a general increased resistance to stress or is a specific effect of the early treadmill experience."

Data concerning the role of stress in producing normal or premature aging will be discussed in the sections on Theories in relation to Triphasic Nature of the G.A.S. There we shall list the many similarities between the stage of exhaustion (produced by intense stress applied during a short period) and the exhaustion of vitality as a consequence of aging.

A careful review of the entire literature led us to the conclusion that actually very little has been learned to date, or is likely to be elucidated in the immediate future, concerning the basic mechanism of aging. However, considerable progress is under way with regard to the prolongation of life as more and more is learned about the prevention and cure of those specific diseases (peptic ulcers, cardiovascular lesions, metabolic and nervous changes) that result in the phenomena characteristic of old age.

Many investigators have studied the early morphologic and functional development of the hypothalamus-pituitary-adrenocortical axis, as well as its behavior later in life in animals and man, because of its manifest importance for stress resistance. Considerable work has also been done on the effects of perinatal stress upon the development of this system. This will be discussed here, whereas other consequences of early

exposure to stress will receive attention in separate subsections later (see Pre- and Perinatal Stress, including Malformations).

→**CRF.** Apparently, the adrenals of the neonatal rat can respond to various stressors by corticoid discharge, presumably because CRF release is possible during the fetal and early postnatal stages of maturation. Allegedly, however, at about seven days of age, the rat develops an ACTH deficiency due to the failure of CRF to reach the hypophysis. In the newborn guinea pig, deafferentation of the hypothalamus interferes more seriously with growth and gonadal function than with corticoid secretion, especially in males. Allegedly, the STH- and gonadotropin-releasing factors are more dependent upon neural input than are those factors responsible for ACTH secretion.

It was known long before the development of the stress concept that anencephalic human fetuses tend to have atrophic suprarenal glands. This shows the importance of corticotropic stimulation, even for the prenatal development of the cortex. Furthermore, destruction of the hypothalamus during late fetal life interferes with the development of the hypophyseal-adrenal system. Yet, even after removal of the brain, the adrenal cortices of encephalectomized rat fetuses can be maintained at or near normal by the administration of CRF-containing extracts. The latter must act through the pituitary, since they have no effect upon the adrenal after decapitation, which removes the pituitary.

The circadian variations in the hypothalamic CRF of rats become manifest only when they are about three weeks of age. However, responses to stress occur much earlier. Even the fetal hypothalamus shows an immediate increment in CRF activity after stress, although the corresponding plasma cortisone rise may be delayed because of immaturity of the portal vessels. Allegedly, capillaries penetrate into the ME of the rat only on the fifth day after birth, but a capillary plexus between the ME and the pars tuberalis of the adenohypophysis is demonstrable on the eighteenth to twentieth day of fetal life in the rat, and apparently suffices to take up CRF, although this process is subsequently facilitated through invasion of the capillaries into the ME substance proper. In any event, when viewed under the EM, the ME of the newborn rat is very similar to that of an adult and contains a well-developed Golgi region and RES as well as some dense-core vesicles. Finally, ACTH-producing cells have been demonstrated by an immunohistochemical technique on the sixteenth day of fetal life in the rat. Thus, all morphologic and functional data are in agreement with the assumption that the elements for the neurohumoral control of ACTH discharge are efficacious even before birth.

Additional pertinent data which shed some light upon the maturation of CRF production will be found in the next sections which deal with the hypothalamus-pituitary-adrenal system and with pre- and perinatal stress.

→**Hypothalamus-Pituitary-Adrenal System.** Probably the first observation on the activity of this system was made in 1888 when Stilling found that, after removal of one adrenal, the contralateral gland undergoes compensatory hypertrophy in young but not in old rabbits. The next observation in this domain was made more than half a century later when we found that in immature, unlike in adult rats, large doses of estradiol cause considerable adrenocortical and pituitary hypertrophy.

There can be no doubt today that age influences the responsiveness of the cortico-

tropic mechanism, although the results obtained are variable and probably largely dependent upon the species and experimental conditions used.

The fetal rat's pituitary reacts to stressors, even after hypophysectomy of the mother. Furthermore, fetuses delivered by Cesarean section likewise respond to stressors; hence, it is not maternal ACTH that causes adrenocortical stimulation in the embryo. Allegedly, in neonatal rats, the adrenal ascorbic acid-depleting property of EP or cold is negligible, although ACTH is effective in this respect even during the first week. Yet, newborn infants appeared to excrete glucocorticoids in response to severe trauma soon after birth, and some investigators did observe adrenal ascorbic acid depletion following laparotomy in rats less than one week old.

Others claimed that electroshock (unlike vasopressin) fails to cause ascorbic acid depletion or increased corticosterone formation in the adrenal cortex during the first eight days of life in rats. They ascribed this "stress-non-responsive period" to immaturity of hypothalamic regulating centers; yet, in the same laboratory, compensatory adrenal hypertrophy was observed in newborn rats subjected to unilateral adrenalectomy. One reason why the findings of different authors appear to be so contradictory may be neglect of the considerable perinatal variations in adrenal weight. These occur during the first days of life, even without exposure to any experimental stimulus, and presumably reflect adaptation to extrauterine conditions. In any event, the results obtained differ so widely that no definitive generalizations are possible, and the individual data must be consulted in the original publications abstracted at the end of this section.

In some experiments, the pituitaries of newborn animals appeared to be irresponsible to stimulation by stressors; yet, there can be no doubt that, under appropriate conditions, stress is associated with increased adrenocortical activity not only immediately after birth, but even in fetal rats after the twentieth day of gestation.

→**STH.** In newborn infants, heel-pricks decreased plasma STH concentrations, contrary to the response of adults. In certain strains of dwarf mice predisposed to premature aging, indirect evidence suggested lower STH production before death, but this might have been due to stress.

→**Catecholamines.** In premature babies, urinary NEP excretion, unlike EP excretion, was subnormal after exposure to cold, possibly because in the newborn, cold rapidly exhausts NEP stores and thereby causes inability to stimulate and utilize chemical thermogenesis.

→**Metabolites.** The metabolic response of various animal species to stressors likewise depends upon their age. For example, in some premature, unlike in mature newborn mammals, cooling is generally not accompanied by significant glycogenolysis because of insufficient EP secretion. Furthermore, in malnourished children, cooling decreased rectal temperature more readily than in well-nourished controls. Plasma FFA in the human fetus is controlled by the same mechanism as in adults, but unlike the pregnant woman, the fetus is unable to respond to high plasma glucose concentration with a fall in plasma FFA. This difference may be due to a limited fetal insulin supply or to the inadequacy of the lipid-synthesizing enzyme systems.

→**Organ Lesions.** Almost every functional or structural change resulting from stress is age-dependent to some extent, but it would be futile to describe all of them in detail here. A few interesting examples will suffice. Young rats and babies are especially sensitive to the induction of peptic ulcers by stress. In menopausal women, flushes can be elicited by emotional stress.

→**Nervous System.** The psychologic reactions to virtually any stressor are naturally quite different in man and animals of different age groups, and relocation to relatives' or old folks' homes is one of the most important stressors for the elderly. Noise has less pronounced effects upon the sleep pattern of twenty-five-year-olds than upon that of aged people.

It has even been claimed that rats whose grandmothers were exposed to avoidance conditioning before mating, or to conditioned stress during pregnancy, were more active in a common open test field than were normal controls. Hence, it was concluded that "stress before or during pregnancy, like infantile handling, can influence the behavior of future generations beyond the immediate offspring of the manipulated females." However, this extraordinary result requires confirmation.

Several review articles deal with the stressors most commonly affecting children or aged people and with the delayed mental reactions caused in children by maternal stress during gestation, but these can be consulted in the abstract section.

Pre- and Perinatal Stress. So much research has been done on the effects of stress during embryonic and early postnatal life that we shall discuss this work conjointly here, irrespective of the stressors used or the organs affected.

For example, gentling and caressing rats during the first three weeks of life make them more resistant to restraint in adulthood, as indicated by various objective manifestations of stress. However, in such experiments, temperature variations must also be kept in mind, since it has been claimed that, at room temperature, handling of two-day-old rats increases their plasma corticosterone levels but if they are placed in handling cans maintained at 35.5°C, a similar reaction will not occur.

Among the most common results of prenatal stress are decreases in fertility, interruption of pregnancy and the development of malformations in the offspring.

A statistical study on a small group of mongoloid children suggested that emotional stress during pregnancy predisposes babies to this disease, but the evidence is not entirely convincing.

Age

(See also our earlier stress monographs, p. xiii)

Generalities. Selye, H.: "Studies on adaptation." *Endocrinology* 21: 169-188 (1937).

38,798/37

Experiments on rats showed that age and sex can noticeably influence resistance to stressors. "Old animals react more readily than young ones, possibly because much of their adaptation energy has already been used to meet the incidental demands of life.

This probably explains also why resistance against almost any alarming stimulus is more difficult to obtain in fully adult rats, a fact which led to the use of animals 2 to 3 months of age in preference to older ones for the purposes of the present experimental series. Females show a more marked involution of the lymphatic organs after exposure to alarming stimuli than males. This may find its explanation in the fact that the adrenals are larger in the female rat than they are in the male."

Thomson, A. P.: "Response of the aged to stress." *J. Gerontol.* **6** Supp. 3: 157 (1951).
J18,632/51

Grad, B., Kral, V. A.: "The effect of senescence on resistance to stress: I. Response of young and old mice to cold." *J. Gerontol.* **12**: 172-181 (1957). C33,287/57

Adaptation to cold is less effective in old than in young mice. "The fatal failure of old mice to adapt to cold generally occurred early in the stress period, that is, in the alarm phase of Selye's adaptation syndrome."

Yoon, Y. H.: "Pathological studies on the baby pig with hypoglycemia." *J. Kor. Vet. Med. Assoc.* **6**: 1222-1232 (1962) (Korean with English summary). G16,777/62

In baby pigs, stress induced by exposure to cold or starvation caused changes typical of the G.A.S., such as loss of adrenal lipids, hypoglycemia and eosinopenia (24 refs.).

Mysliveček, J., Reinis, S., Sobotka, P., Zahalva, J.: "Reaction of rats exposed to thermal stress in relation to age and to perinatal brain damage." *Čas. Lék. Česk.* **101**: 768-773 (1962) (Czech). J24,369/62

Frolkis, V. V., Svechnikova, N. V., Verzhikovskaya, N. V., Verkhratskii, N. S.: "Peculiarities of the course of the general adaptation syndrome in old and young animals under the effect of nervous and humoral stimulation." *Fiziol. Zh.* **9**: 336-337 (1963) (Russian). E20,419/63

Denenberg, V. H.: "Some relationships between strong ('stressful') stimulation in infancy and adult performance." *Symp. Medical Aspects of Stress in the Military Climate*, Washington, D.C., pp. 297-310 (1964).

B43,377/64

Rapaport, A., Allaire, Y., Bourlière, F., Girard, F.: "Réactivité au 'stress' et capacité d'adaptation à une situation inhabituelle chez le rat jeune, adulte et âgé" (Reaction to 'stress' and capacity of adaptation to an unusual situation in young, adult and aged rats). *Gerontologia* (Basel) **10**: 20-30 (1964/65). F37,689/64-65

Levitt, R. A., Webb, W. B.: "Effect of infantile treadmill experience on body-weight and resistance to exhaustion in the rat." *Nature* **208**: 1128-1129 (1965).

F58,465/65

Rats forced to run in a treadmill during the first few weeks of life initially lost weight but then grew better than the controls and

became much more resistant to exhaustion. "It appears that the treadmill acted as a stressor and that this 'acute stress' during infancy was responsible for the increased growth of muscle and other tissue. It is not known whether the improved treadmill performance is indicative of a general increased resistance to stress or is a specific effect of the early treadmill experience."

Gray, R. M., Baker, J. M., Kesler, J. P., Newman, W. R. E.: "Stress and health in later maturity." *J. Gerontol.* **20**: 65-68 (1965). F31,165/65

Statistical studies showed that among elderly people, those "who had experienced the most stress during the past ten years also had the poorest health scores. In addition, the data revealed that the severely disabled persons had significantly higher stress scores than did non-disabled older persons, which indicated that they had experienced more stress than the non-disabled."

Levine, S.: "Infantile stimulation and adaptation to stress." *Res. Publ. Assoc. Nerv. Ment. Dis.* **43**: 280-291 (1966).

J23,725/66

Geber, W. F., Anderson, T. A., Dyne, B. van: "Age factor in the response of the albino rat to emotional and muscular stresses." *Growth* **30**: 87-97 (1966). G39,247/66

Selye, H.: "The future for aging research." In: Shock, N. W., *Perspectives in Experimental Gerontology*, pp. 375-385. Springfield, Ill.: Charles C Thomas, 1966. G19,438/66

Final chapter of a jubilee volume in honor of Professor Fritz Verzár, based on a congress held in Vienna with the participation of numerous outstanding gerontologists. One of the principal conclusions is that aging may not have a single cause but represents the sum of the many morphologic and chemical scars accumulated during a lifetime of facing the most varied stressors. The speaker concluded by stating that "what I have said is not intended to dissuade creative minds from continuing their search for an all-embracing theory which might lead to the prophylaxis or even the cure of the aging process itself. My purpose was only to point out that, at present, we have no objective basis for suspecting that such endeavors could be fruitful, while we do have many reliable techniques (and good reasons to assume that even better ones could be developed) for the study of individual morbid lesions which decrease life expectancy."

- Kral, V. A.: "Stress reactions in old age." *Laval Méd.* **38**: 561-566 (1967). G59,772/67
- Troyer, W. G. Jr., Eisdorfer, C., Bogdonoff, M. D., Wilkie, F.: "Experimental stress and learning in the aged." *J. Abnorm. Psychol.* **72**: 65-70 (1967). J24,051/67
- Horrocks, J. E., Mussman, M. C.: "Mid-dlescence: age related stress periods during adult years." *Genet. Psychol. Monogr.* **82**: 120-159 (1970) (56 refs.). J20,758/70
- Blichert-Toft, M., Jensen, H. K.: "Stressaksens funktion i den postoperative fase med speciel interesse for udtrætning hos ældre" (The function of the stress axis in the post-operative phase with special regard to fatigue in elderly people). *Nord. Med.* **86**: 1393-1394 (1971) (Danish). J20,176/71
- Coddington, R. D.: "The significance of life events as etiologic factors in the diseases of children. I. A survey of professional workers." *J. Psychosom. Res.* **16**: 7-18 (1972). J20,342/72
- Studies on the stressor effect of numerous life events upon children of various age groups, using modified types of the SRSS (8 refs.).
- Tzankoff, S. P., Robinson, S., Pyke, F. S., Brawn, C. A.: "Physiological adjustments to work in older men as affected by physical training." *J. Appl. Physiol.* **33**: 346-350 (1972). J14,820/72
- Wagner, J. A., Robinson, S., Tzankoff, S. P., Marino, R. P.: "Heat tolerance and acclimatization to work in the heat in relation to age." *J. Appl. Physiol.* **33**: 616-622 (1972). H79,771/72
- Males aged eleven to sixty-seven years were compared in standard work heat stress (walking on a treadmill in dry heat). "The older men had lower coefficients of heat conductance and finger blood flow in the heat than the young men. During work in the heat the older men and preadolescent boys were more limited in the sensitivity and secretory capacity of the sweating mechanism than the young men and the older boys."
- Golden, H. M.: "The dysfunctional effects of modern technology on the adaptability of the aging." *Gerontologist* **13**: 136-143 (1973). J16,963/73
- General review on the stressor effects related to the life of the aging population.
- Mazzei, E. S.: "El envejecimiento y la vejez: recientes progresos sobre su conocimiento" (Aging and old age: recent progress on their understanding). *Prensa Méd. Argent.* 60th Anniversary issue 1974, pp. 1-16. H88,851/74
- Review on various factors influencing the aging process with special emphasis upon the importance of stress (62 refs.).
- Prinz, A. F.: "Alt werden wie Methusalem. Modelldenken und Bedenken für die Menschen von morgen" (To be as old as Methuselah. Model-thinking and reflection for the man of tomorrow). *Eur. Med. Mag.* **14**: 22-26 (1974). J14,317/74
- Popular review on the relationship between stress and aging.
- Gersten, J. C., Langner, T. S., Eisenberg, J. G., Orzeck, L.: "Child behavior and life events: undesirable change or change per se?" In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 159-170. New York, London and Sydney: John Wiley & Sons, 1974. E10,788/74
- Coles, R. M.: "Mastering adolescence." *Stress. Blue Print for Health* **25** No. 1: 26-33 (1974). E10,815/74
- Birren, J. E.: "Weathering the years." *Stress. Blue Print for Health* **25** No. 1: 35-41 (1974). E10,816/74
- Bennett, A. N.: "Children under stress." *J. R. Nav. Med. Serv.* **60**: 83-87 (1974). J20,075/74
- Review of the "battered baby syndrome" and other types of cruelty to infants and children.
- Tuchweber, B., Salas, M.: "Experimental pathology of aging." In: *Methods and Achievements in Experimental Pathology*. Basel: S Karger (in press). J4,285/
- Review on the various theories of aging, with a special section devoted to stress and hormones (296 refs.).
- CRF. Rinne, U. K., Kivalo, E.: "Maturation of hypothalamic neurosecretion in rat, with special reference to the neurosecretory material passing into the hypophysial portal system." *Acta Neuroveg.* **27**: 166-183 (1965). G28,269/65
- Zarrow, M. X., Philpott, J. E., Denenberg, V. H.: "Postnatal changes in the pituitary-adrenal axis of the rat." *Proc. Soc. Exp. Biol. Med.* **128**: 269-272 (1968). F99,833/68

Review of earlier literature showing that the adrenal glands of the neonatal rat respond to various stressors in a normal manner, whereas at about seven days of age a period of comparative nonresponsiveness sets in. The present experiments reveal similar age-dependent variations in the adrenal reaction to ACTH or to partial adrenalectomy. "The fetal and early postnatal maintenance of the pituitary levels of ACTH could be the result of a diffusion of CRF to the pituitary which becomes more difficult and fails with the growth and development of the rat. Thus the 7-day-old rat is showing signs of ACTH deficiency due to a failure of CRF to get to the pituitary gland." [The postulates concerning the role of CRF are purely hypothetical (H.S.).]

Joseph, S. A., Knigge, K. M., Voloschin, L.: "Effects of isolation of the hypothalamo-pituitary unit in newborn guinea pigs." *Neuroendocrinology* 4: 42-50 (1969).

H8,974/69

In newborn guinea pigs, deafferentation of the hypothalamus with a modified Halász-knife showed that within about three months "growth and gonadal function were most seriously impaired; development of thyroid and adrenal function was unaffected in male animals and only moderately affected in females. The results indicate that those RF-producing neurons associated with growth hormone and the gonadotrophins may require afferent neural connections for their normal maturation, while RF-producing neurons associated with thyrotrophin and corticotrophin may develop normally in the isolated hypothalamo-pituitary unit."

Jost, A., Dupouy, J. P., Geloso-Meyer, A.: "Hypothalamo-hypophyseal relationships in the fetus." In: Martini, L., Motta, M. et al., *The Hypothalamus*, pp. 605-615. New York and London: Academic Press, 1970.

J4,841/70

Experiments on various species as well as observations on anencephalic human fetuses indicate that mammalian ACTH activity is more strictly dependent upon the hypothalamus than is TTH function during prenatal life.

Fujita, T., Eguchi, Y., Morikawa, Y., Hashimoto, Y.: "Hypothalamic-hypophyseal adrenal and thyroid systems: observations in fetal rats subjected to hypothalamic destruction, brain compression and hypervitaminosis A." *Anat. Rec.* 166: 659-672 (1970).

G74,197/70

Observations suggest that "in the late period of fetal life in rats, the hypophysial-adrenal system is regulated largely by the hypothalamus," but that the hypophyseal-thyroid system is not fully under its control.

Hiroshige, T., Sato, T.: "Postnatal development of circadian rhythm of corticotropin-releasing activity in the rat hypothalamus." *Endocrinol. Jap.* 17: 1-6 (1970).

H27,251/70

In rats, the circadian rhythm of plasma corticosterone (with a peak in the evening and a nadir in the morning) as well as the concurrent circadian variations in hypothalamic CRF content, become detectable only when they are about three weeks of age.

Hiroshige, T., Sato, T.: "Circadian rhythm and stress-induced changes in hypothalamic content of corticotropin-releasing activity during postnatal development in the rat." *Endocrinology* 86: 1184-1186 (1970).

H25,238/70

In rats, development of a circadian rhythm in CRF activity becomes evident between the 14th and 21st day of postnatal life, whereas responsiveness to stressors is manifest by the 7th day. "The hypothalamic CRF may at least be one of the rate-limiting phases in the mechanism of stress nonresponsiveness during the first few days of postnatal life in the rat."

Hiroshige, T., Sato, T.: "Changes in hypothalamic content of corticotropin-releasing activity following stress during neonatal maturation in the rat." *Neuroendocrinology* 7: 257-270 (1971).

H42,531/71

Even fetal hypothalamic tissue exhibited an immediate increment of CRF after stress, but the plasma corticosterone rise was delayed, perhaps because of immaturity of the portal vessels. "Since the pituitary glands of the 2-day-old neonates contained ACTH, to which their own adrenals were quite responsive, it is most likely that inability of CRF release from the hypothalamus may be a cause of non-responsiveness to stress during this specific period. Furthermore, since a fetal response to stress as well as a day-1 neonatal responsiveness was clearly observed, it is probable that the day-2 neonatal non-responsiveness is a result of the previous activity associated with delivery and not a developmental rate limitation as suggested by others."

Hiroshige, T., Sato, T., Abe, K.: "Dynamic changes in the hypothalamic content

of corticotropin-releasing factor following noxious stimuli: delayed response in early neonates in comparison with biphasic response in adult rats." *Endocrinology* **89**: 1287-1294 (1971). H48,432/71

Hiroshige, T., Abe, K.: "Dynamics of activity of hypothalamic corticotropin releasing factor in the rat." *J. Physiol. Soc. Jap.* **34**: 529-530 (1972). H79,788/72

In rats, the circadian rhythm in hypothalamic CRF content (with a peak in the afternoon and a nadir in the morning) develops after two to three weeks of postnatal life, whereas responses to stress occur as early as the seventh day. The circadian rhythm persists in the absence of circulating corticosterone and hence appears to be dependent only upon nervous regulation, not upon negative feedback.

Skebelskaia, I. B.: "A possible participation of the hypothalamus of a pregnant rat in the reaction of fetuses to stress." *Probl. Endocrinol.* **20** No. 2: 62-65 (1974) (Russian).

H92,517/74

Various experiments on rats suggest that the maternal hypothalamus participates in the fetal reaction to stress.

→**Hypothalamus-Pituitary-Adrenal System.** Stilling, H. H.: "Note sur l'hypertrophie compensatrice des capsules surrénales" (Note on compensatory hypertrophy of the adrenal glands). *Rev. Méd.* **8**: 459-461 (1888).

35,886/1888

In old but not in young rabbits, removal of one adrenal does not lead to compensatory hypertrophy of the other.

Pincus, G.: "Measures of stress responsiveness in younger and older men." *Psychosom. Med.* **12**: 225-228 (1950). B51,621/50

On the basis of various function tests, "it is suggested that men surviving to old age without overt ill health or infirmity may preserve a relatively intact pituitary-adrenal mechanism involved in response to acute stress."

Engle, E. T., Pincus, G. (eds.): *Hormones and the Aging Process*, p. 323. New York and London: Academic Press, 1956.

C29,609/56

Proceedings of a conference. Many experts discussed the literature on hormones and aging in fairly technical language. The discussions are well-documented by references. One section (by D. J. Ingle) is specifically de-

voted to the role of stress in aging and the hormones produced during the G.A.S.

Eskin, I. A., Mikhailova, N. V.: "The functional condition of hypophysis and adrenal cortex under 'stress' in young and old rats." *Probl. Endokrinol.* **6** No. 3: 3-8 (1960) (Russian). D51,490/60

Comparative studies on the G.A.S., particularly the pituitary-adrenocortical axis, in various age groups.

Milković, S., Milković, K.: "Reactivity of fetal pituitary to stressful stimuli. Does the maternal ACTH cross the placenta?" *Proc. Soc. Exp. Biol. Med.* **107**: 47-49 (1961). D7,489/61

Chisci, R., Bellora, M.: "Alcuni aspetti della funzione corticosurrenale del neonato in relazione allo stress della nascita" (Various aspects of adrenal cortex function in the newborn infant in relation to the stress of birth). *Minerva Ginecol.* **13**: 1236-1240 (1961). J24,544/61

Milković, K., Milković, S.: "Studies of the pituitary-adrenocortical system in the fetal rat." *Endocrinology* **71**: 799-802 (1962).

D40,017/62

"Adrenal ascorbic acid depletion caused by stressful stimuli was the same in the fetuses of hypophysectomized rats as in those of normal rats." However, hypophysectomy of the fetus itself (for example, by decapitation) prevents a stress-induced adrenal ascorbic acid discharge. "These data show that at term the adrenals of fetuses are stimulated by the fetal pituitary."

Schapiro, S.: "Neonatal cortisol administration: effect on growth, the adrenal gland and pituitary-adrenal response to stress." *Proc. Soc. Exp. Biol. Med.* **120**: 771-774 (1965). F59,453/65

Eguchi, Y., Wells, L. J.: "Response of the hypothalamic-hypophyseal-adrenal axis to stress: observations in fetal and Caesarean newborn rats." *Proc. Soc. Exp. Biol. Med.* **120**: 675-678 (1965). F59,425/65

EP caused depletion of adrenal ascorbic acid in normal but not in decapitated fetal rats or in premature newborns obtained by Caesarean section. It is presumed that "in the rat the hypothalamic-hypophyseal-adrenal axis begins to function before birth and that after delivery this axis temporarily becomes refractory to stimulation by injected epinephrine."

Verzár, F.: "Anterior pituitary function in age." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 444-459. London: Butterworths, 1966. E10,528/66

Jost, A.: "Anterior pituitary function in foetal life." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 299-323. London: Butterworths, 1966.

G44,491/66

Werff ten Bosch, J. J. van der: "Anterior pituitary function in infancy and puberty." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 324-345. London: Butterworths, 1966. E10,527/66

Milković, K., Milković, S.: "Adrenocorticotrophic hormone secretion in the fetus and infant." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 1, pp. 371-405. New York and London: Academic Press, 1966. E6,489/66

Review and personal observations on the responsiveness of the fetal and neonatal adrenal to stress. The fetal adrenal cortex reacts to stressors with a slight but significant ascorbic acid depletion which is associated with a rise in plasma corticosterone in the rat. Such a result is also seen in fetuses delivered by Cesarean section; hence it is not dependent upon maternal or placental ACTH. Only decapitation of the fetus makes it unresponsive to stress. It is assumed that the stress of delivery and adaptation to extrauterine life causes an initial hyperfunction of the pituitary-adrenocortical system at birth, which manifests itself by low adrenal ascorbic acid and high plasma corticosterone in the newborn. It is further assumed that this hyperfunction limits the adrenocortical reserve, which is only about one-fifth that of the adult, and induces a relative nonresponsiveness to stressors during the first days of life (several hundred refs.).

Zarrow, M. X., Philpott, J. E., Denenberg, V. H.: "Postnatal changes in the pituitary-adrenal axis of the rat." *Proc. Soc. Exp. Biol. Med.* **128**: 269-272 (1968). F99,833/68

Review of earlier literature showing that the adrenal glands of the neonatal rat respond to various stressors in a normal manner, whereas at about seven days of age a period of comparative nonresponsiveness sets in. The present experiments reveal similar age-dependent variations in the adrenal reaction to ACTH or to partial adrenalectomy. "The fetal and early postnatal maintenance of the pituitary levels of ACTH could be the

result of a diffusion of CRF to the pituitary which becomes more difficult and fails with the growth and development of the rat. Thus the 7-day-old rat is showing signs of ACTH deficiency due to a failure of CRF to get to the pituitary gland." [The postulates concerning the role of CRF are purely hypothetical (H.S.).]

Dilman, V. M.: "Age-associated elevation of hypothalamic threshold to feedback control, and its role in development, ageing, and disease." *Lancet* June 12, 1971, pp. 1211-1219. H41,351/71

"It is suggested that the key process in the genetic programme of development and ageing is a gradual elevation of the threshold of sensitivity of the hypothalamus to feedback suppression." [Based mainly on speculative considerations (H.S.).]

Hromadová, M., Macho, L., Alexandrová, M., Šudová, K., Stukovský, R.: "The effect of premature weaning on the response of rat adrenals to stress and ACTH." *Physiol. Bohemoslov.* **21**: 329-335 (1972).

J2,286/72

Nvota, J., Lamošová, D., Fáberová, A.: "Critical periods in the development of chicks." *Physiol. Bohemoslov.* **22**: 337-343 (1973).

J21,555/73

The stress of restraint during a critical period of about 3 to 4 weeks after hatching produced a maximal decrease in thyroid activity in adulthood and a significant drop in the BMR of the chick. "The critical phase for regulation of the function of the pituitary-adrenal and pituitary-gonad axis was found to be the period between the 15th and 21st day after hatching. Exposure to stress in this phase caused a significantly greater reaction of the adrenals to stress situations in the adult hens and significantly stimulated sexual maturation (egg-laying)."

Goldman, L., Winget, C., Hollingshead, G. W., Levine, S.: "Postweaning development of negative feedback in the pituitary-adrenal system of the rat." *Neuroendocrinology* **12**: 199-211 (1973).

H74,726/73

Given before ether or electroshock, "pretreatment with peripherally injected dexamethasone completely blocked a plasma corticosterone increase, in response to an ether and blood sampling stress in adults, but only partially reduced this response in weanlings. The failure of basal hypothalamic implants of corticoids to differentiate between ages in their ability to inhibit this stress response

supported the suggestion of extra-hypothalamic inhibitory systems as the loci of the deficit in weanlings."

Alexander, D. P., Britton, H. G., Nixon, D. A., Ratcliffe, J. G., Redstone, D.: "Corticotrophin and cortisol concentrations in the plasma of the chronically catheterised sheep fetus." *Biol. Neonate* **23**: 184-192 (1973).

J10,051/73

In chronically catheterized sheep fetuses, plasma ACTH levels were unusually high. Plasma cortisol was not strictly related to ACTH in individual samples but showed a high correlation in pooled data. The process of catheterization may have acted as a stressor.

Kral, V. A.: "Stress and senile psychosis." Proc. 5th World Congr. of Psychiatry, Mexico, D. F., 1971. *Int. Congr. Ser. No. 274*, pp. 331-337 (1973). J17,514/73

Resistance to stress decreases with age. Hormonal studies indicate, "firstly, that there is a decline in adrenocortical function with aging; and secondly, that patients suffering from organic psychoses of the senium, particularly senile dementia, show a tendency to a delayed adrenocortical overactivity, to ACTH stimulation as well as in stressful situations. It would appear, therefore, that cerebral pathology modifies the function of the adrenal cortex."

Wise, P. M., Frye, B. E.: "Functional development of the hypothalamo-hypophyseal-adrenal cortex axis in the chick embryo, *Gallus domesticus*." *J. Exp. Zool.* **185**: 277-291 (1973). J7,865/73

Studies on chick embryos, based mainly on plasma corticosterone determinations after stress produced by opening the shell and breaking one shank. "The adrenal exhibits significant autonomous functional capability prior to day 14, and the pituitary becomes important in maintaining both the resting level of hormone and the stress response between days 14 and 16 of incubation. The hypothalamus does not appear to control normal resting levels of corticosterone, but is essential for the stress response." The initial autonomy of the adrenal is demonstrated by the persistence of significant plasma corticosterone levels after decapitation of the embryo.

Dunn, J. D.: "Pituitary-adrenal function in adult androgenized female rats." *Proc. Soc. Exp. Biol. Med.* **146**: 75-77 (1974).

H87,171/74

Neonatal treatment with testosterone did not markedly affect the pituitary-adrenal response of female rats to ether stress in adult life.

Cote, T. E., Yasumura, S.: "Fluctuations in adrenal cyclic AMP levels in immature rats in response to ACTH and histamine stress." *Fed. Proc.* **33**: 205 (1974).

H83,812/74

Adrenal cyclic AMP levels were studied in six-day-old rats "subjected to treatment with either ACTH (50 mU/rat) or histamine dihydrochloride (0.2 mg/g body wt.). Untreated rats were used as controls in order to preclude the stress of vehicle injections. In 6-day-old rats, the values for adrenal cyclic AMP were: 3.35 pmol/mg in the untreated group; 4.35 pmol/mg in the histamine-treated group; and 37.03 pmol/mg 25 min. after injection of ACTH. The corresponding plasma corticosterone levels were 4.55 µg/100 ml in the untreated group; 5.13 µg/100 ml in the histamine-treated group; and 7.27 µg/100 ml in the ACTH-treated group. In 15-day-old rats, the values for adrenal cyclic AMP were: 4.60 pmol/mg in the untreated group; 45.1 pmol/mg in the histamine-stressed group; and 47.3 pmol/mg in the ACTH-treated group. The corresponding plasma corticosterone levels were: 4.58 µg/100 ml in the untreated group; 14.25 µg/100 ml in the histamine-stressed group; and 14.05 µg/100 ml in the ACTH-treated group." Apparently, the functional ACTH-sensitive adenyl cyclase system is present in rats by the sixth day after birth, but the presumably hypothalamic mechanism that controls stress-induced ACTH release is inoperative until the fifteenth day.

Müller, H. F., Grad, B.: "Clinical-psychological, electroencephalographic, and adrenocortical relationships in elderly psychiatric patients." *J. Gerontol.* **29**: 28-38 (1974).

J9,661/74

Cohen, A., Negellen, E.: "Changes in adrenal glands during stress in foetal rats." *Gen. Comp. Endocrinol.* **22**: 400-401 (1974).

H83,308/74

In fetal rats, subcutaneous formalin produces adrenal ascorbic acid depletion through stimulation of the hypothalamo-hypophyseal system, but only after the twentieth day of gestation. Ether anesthesia of adrenalectomized pregnant rats on the twentieth day of pregnancy increases the corticosterone content of fetal adrenals, but this can be pre-

vented by decapitation of the fetus, and by encephalectomy (ablation of the brain and hypothalamus, leaving the pituitary intact). "Ether acts as a stressor agent for the 20-day-old rat foetus."

→**STH.** Stubbe, P., Wolf, H.: "The effect of stress on growth hormone, glucose and glycerol levels in newborn infants." *Horm. Metab. Res.* **3**: 175-179 (1971).

H42,368/71

In full-term newborn infants, the stress of heel-pricks causes a decrease in blood STH whereas glucose and glycerol concentrations are increased, presumably as a consequence of catecholamine release. "The failure of the newborn infant to increase growth hormone concentration as do individuals during later life is evidence that adaptation of metabolic and hormonal reactions occurs during the postnatal period."

Fekete, M., Milner, R. D. G., Soltész, G., Assan, R., Mestyán, J.: "Plasma glucagon, thyrotropin, growth hormone and insulin response to cold exposure in the human newborn." *Acta Paediatr. Scand.* **61**: 435-441 (1972).

G92,222/72

In full-term and premature babies, exposure to cold caused no significant change in plasma insulin, glucagon, STH or TTH concentrations.

Shire, J. G. M.: "Growth hormone and premature ageing." *Nature* **245**: 215-216 (1973).

H78,587/73

In certain strains of dwarf mice, premature aging is associated with decreased STH production and depressed ^3H -thymidine uptake by several tissues, including the thymus. These dwarf mice are also deficient in other hormones, and not all strains show premature aging. Hence, "the altered uptake of thymidine in dwarf mice close to death could be caused by stress rather than by premature ageing."

→**Corticoids.** Selye, H., Albert, S.: "Age factor in responsiveness of pituitary and adrenals to folliculoids." *Proc. Soc. Exp. Biol. Med.* **50**: 159-161 (1942).

A37,751/42

In adult but not in immature rats, large doses of estradiol fail to cause pituitary or adrenal cortical hypertrophy.

Jailer, J. W.: "The maturation of the pituitary-adrenal axis in the newborn rat." *Endocrinology* **46**: 420-425 (1950).

B48,333/50

Adrenal ascorbic acid does not fall under the influence of EP in rats less than eight days old, nor in those exposed to cold before the age of sixteen days. However, ACTH causes adrenal ascorbic acid depletion even in rats aged four to six days. Earlier clinical observations have shown that human infants excrete glucocorticoids in response to severe trauma soon after birth, but the rat adrenal matures less rapidly than that of man.

Rinfret, A. P., Hane, S.: "Depletion of adrenal ascorbic acid following stress in the infant rat." *Endocrinology* **57**: 497-499 (1955).

B29,292/55

In four- to seven-day-old rats, adrenal ascorbic acid depletion in response to a stressor (laparotomy) is the same as in more mature animals, and occurs between two and six hours following initiation of stress.

Grad, B., Kral, V. A.: "Adrenal cortical stress effects in senility. II. The response to heat stimulation produced by the Hardy-Wolff-Goodell dolorimeter." *Can. Psychiatr. Assoc. J.* **6**: 66-74 (1961).

J10,361/61

Hockman, C. H.: "Prenatal maternal stress in the rat: its effects on emotional behavior in the offspring." *J. Comp. Physiol. Psychol.* **54**: 679-684 (1961).

J23,011/61

Biochemical changes produced in the offspring of rats exposed to psychogenic stress during pregnancy are explained tentatively in terms of increased secretion of endocrine substances.

Schapiro, S.: "Pituitary ACTH and compensatory adrenal hypertrophy in stress-non-responsive infant rats." *Endocrinology* **71**: 986-989 (1962).

D45,372/62

In newborn rats, adrenal ascorbic acid depletion and corticosterone synthesis fail to occur under the influence of stressors, but unilateral adrenalectomy causes pronounced compensatory hypertrophy of the contralateral gland.

Schapiro, S., Geller, E., Eiduson, S.: "Neonatal adrenal cortical response to stress and vasopressin." *Proc. Soc. Exp. Biol. Med.* **109**: 937-941 (1962).

D24,932/62

In rats, electroshock (unlike natural or synthetic vasopressin) fails to elicit the usual ascorbic acid depletion and increase the corticosterone concentration of the adrenal cortex during the first eight days of life. This "stress-non-responsive period" is ascribed to "immaturity of the hypothalamic osmoreceptor mechanism which underlies adjustments in vasopressin secretion."

Cuny, G., Duheille, J., Guerci, O., Tenette, M.: "Elimination des 17 O.H. et stress chirurgical chez les vieillards" (Elimination of 17-hydroxycorticosteroids and surgical stress in the aged). *Rev. Franç. Gérontol.* 8: 391-399 (1962). J24,006/62

Milković, K., Milković, S.: "Functioning of the pituitary-adrenocortical axis in rats at and after birth." *Endocrinology* 73: 535-539 (1963). E31,802/63

The ascorbic acid content of the adrenals fell in rats at birth, but returned to embryonic levels on the first or second day of life. Subsequently there was a precipitous decrease followed by a secondary rise by the tenth day. Plasma corticosterone levels dropped slightly after birth. Intravenous EP, used as a stressor in newborn rats immediately after birth, did not deplete adrenal ascorbic acid. However, stress increased plasma corticosterone prenatally and at birth, but then not again until the fourteenth postnatal day.

Schapiro, S., Geller, E.: "Fetal-maternal adrenal cortical response to stress in the intact and hypophysectomized rat." *Endocrinology* 74: 737-741 (1964). F9,485/64

Histamine or surgical trauma applied to pregnant hypophysectomized rats produced no adrenal corticosterone or ascorbic acid depletion such as was found in intact controls. The fetuses revealed no evidence of adrenocortical stimulation, irrespective of whether the mother was intact or hypophysectomized when exposed to the stressors.

Daikoku, S., Saijo, S.: "Volumetrical observation on the influence of maternal sham hypophysectomy on the fetal adrenal gland." *Endocrinol. Jap.* 11: 55-61 (1964).

F12,069/64

Sham hypophysectomy in pregnant rats increases corticoid secretion, and the latter crosses the placental barrier, inhibiting the development of the fetal adrenal.

Bowman, R. E., Wolf, R. C.: "Plasma 17-OHCS response of the infant rhesus monkey to a noninjurious, noxious stimulus." *Proc. Soc. Exp. Biol. Med.* 119: 133-135 (1965).

F42,116/65

In two-day-old rhesus monkeys, centrifugation caused elevations in the nonconjugated 17-OHCS content of the plasma, but this effect was not as marked as that obtained with ACTH, "suggesting either that the restraint and rotation was not sufficiently

stressful or that the infant CNS-hypophyseal axis was not sufficiently developed to stimulate fully the adrenal cortex."

Baca, Z. V., Chiodi, H.: "Developmental changes in the size and ascorbic acid content of the adrenals of white rats." *Endocrinology* 76: 1208-1212 (1965). F41,308/65

In rats, the adrenal weight per 100 gm. body weight decreases during the last few days of prenatal and the first days of postnatal life, reaching a maximum by the twentieth day and then declining to the adult level which remains stable until old age. The vitamin C content of the fetal adrenal increases in the last days of pregnancy, showing an abrupt fall in the four days after birth, and then remaining low until the twelfth day. Adult values are reached around the seventieth day of life. The perinatal changes are ascribed to the stress of adaptation to extrauterine life.

Schapiro, S.: "Androgen treatment in early infancy: effect upon adult adrenal cortical response to stress and adrenal and ovarian compensatory hypertrophy." *Endocrinology* 77: 585-587 (1965). F49,822/65

One-day-old female rats given 1 mg. testosterone subsequently developed the expected persistent estrus syndrome. The response to stress (ether) was normal in both sexes although the extent of compensatory adrenal hypertrophy appeared to be less after testosterone pretreatment. An addendum notes that "neonatal treatment with 1 mg cortisol has been subsequently observed to produce a fertile 'corticoid runt' with a normal adrenal cortical response to stress."

Haltmeyer, G. C., Denenberg, V. H., Thatcher, J., Zarrow, M. X.: "Response of the neonatal rat after subjection to stress." *Nature* 212: 1371-1373 (1966).

F74,906/66

During the first five days of life, the stress of heat or electric shock raises the adrenal and plasma concentration of corticosterone in the rat. Manifestly, the neonatal rat adrenal can respond normally to stressors by increased synthesis and release of corticoids. These data contradict earlier reports of a "stress-non-responsive period" in this species. With adrenal ascorbic acid depletion used as an indicator, the situation appears to be different, and reactivity also depends upon the stressor (20 refs.).

Grad, B., Kral, V. A., Payne, R. C., Berenson, J.: "Adrenal cortical function in the psy-

chooses of later life." *Laval Méd.* **37**: 126-134 (1966). G37,699/66

There were no significant differences in plasma cortisol and corticosterone levels between male and female, normal and senile psychotic patients. However, normal men showed significantly higher urinary corticoid excretion than psychotics. This difference was less obvious in women.

Mozhaev, V. I.: "The glucocorticoid function of the adrenal cortex in the postoperative period in aged patients." *Vestn. Khir.* **97** No. 8: 55-62 (1966) (Russian).

J23,733/66

In aged patients, surgical stress produces a subnormal discharge of glucocorticoids.

Levine, S.: "Maternal and environmental influences on the adrenocortical response to stress in weanling rats." *Science* **156**: 258-260 (1967). F82,015/67

Adrenocortical steroids in the plasma of newborn rats were reduced at weaning after the pups "were exposed to novel stimuli as compared with controls that were not handled."

Zarrow, M. X., Denenberg, V. H., Halmeyer, G. C., Brumaghim, J. T.: "Plasma and adrenal corticosterone levels following exposure of the two-day-old rat to various stressors." *Proc. Soc. Exp. Biol. Med.* **125**: 113-116 (1967). F80,161/67

Even in two-day-old rats, ACTH, histamine, electroshock, heat and cold increase the plasma and adrenal corticosterone levels of both sexes. Only tight ligature above the knee joint is ineffective at this age, perhaps as Fortier suggested, because neural stressors (pain) act through a different pathway. Presumably the pituitary-adrenal axis is operative in the two-day-old rat but "the neural component in the system is not active as yet." Contradictions in the earlier literature on the responsiveness of the neonatal pituitary are analyzed.

Schäfer, K. H.: "Das reife Neugeborene" (The mature newborn infant). *Arch. Gynäekol.* **204**: 137-151 (1967). F80,470/67

The blood corticoid level in newborn infants rises sharply during the first two days, and this is associated with other manifestations of "birth stress" which are most intense in cases of difficult deliveries.

Denenberg, V. H., Brumaghim, J. T., Halmeyer, G. C., Zarrow, M. X.: "Increased

adrenocortical activity in the neonatal rat following handling." *Endocrinology* **81**: 1047-1052 (1967). F89,864/67

Handling two-day-old rats increased their plasma corticosterone levels within half an hour after they were returned to their mothers. However, this response could be prevented if the pups were placed in handling cans maintained at 35.5°C.

Kral, V. A., Grad, B., Payne, R. C., Berenson, J.: "The effect of ACTH on the plasma and urinary corticoids in normal elderly persons and in patients with senile psychosis." *Am. J. Psychiatry* **123**: 1260-1269 (1967).

G45,322/67

In patients with senile psychosis, the rise in plasma cortisol and corticosterone levels following exposure to physical and psychologic stressors was excessive, but their response to ACTH remained within normal limits. This "might have its cause in a dysfunction of either the pituitary or the hypothalamus or both."

Ader, R., Friedman, S. B., Grota, L. J., Schaefer, A.: "Attenuation of the plasma corticosterone response to handling and electric shock stimulation in the infant rat." *Physiol. Behav.* **3**: 327-331 (1968).

H5,148/68

In rats eight, fifteen and twenty-one days old, stressor-induced elevations of plasma corticosterone were first seen at fifteen days, at which time the responses to handling and electric shock were similar. Twenty-one-day-old unmanipulated rats showed a greater reaction to electric shock than to handling. Previously shocked animals displayed little adaptation, whereas repeated handling diminished the plasma corticosterone response.

Cathro, D. M., Forsyth, C. C., Cameron, J.: "Adrenocortical response to stress in newborn infants." *Arch. Dis. Child.* **44**: 88-95 (1969). G65,468/69

In both full-term and premature newborn infants, various incidental stressors (asphyxia, respiratory distress) generally produced the expected increase in urinary corticoid excretion. This relationship was not significant, however, in dysmature (light-for-dates) infants. The somewhat contradictory pertinent literature is reviewed.

Grad, B., Kral, V. A.: "The delayed effect of ACTH administration on the plasma corticoid level of normal elderly persons and pa-

tients with chronic brain syndrome." *J. Am. Geriatr. Soc.* **17**: 15-24 (1969).

H6,490/69

Patients with senile or arteriosclerotic brain syndrome are more reactive to stress than are normal aged subjects. Their adrenal cortices are more responsive to ACTH.

Hess, G. D., Riegle, G. D.: "Adrenocortical responsiveness to stress and ACTH in aging rats." *J. Gerontol.* **25**: 354-358 (1970).

G78,322/70

Following exposure to ether vapors or exogenous ACTH, old rats showed significantly lower plasma corticosterone levels than young controls.

Fulker, D. W.: "Maternal buffering of rodent genotypic responses to stress: a complex genotype-environment interaction." *Behav. Genet.* **1**: 119-124 (1970).

J19,543/70

"The effects of prenatal stress on open-field exploration in rats and mice and the 11-hydroxy-corticosteroid response to stress in mice were re-analysed by biometrical methods."

Adlard, B. P. F., Smart, J. L.: "Plasma 11-hydroxy corticosteroid concentrations in stressed adult rats after undernutrition in early life." *Biochem. J.* **125**: 12P-13P (1971).

J20,013/71

Jensen, H. K., Blichert-Toft, M.: "Investigation of pituitary-adrenocortical function in the elderly during standardized operations and postoperative intravenous metyrapone test assessed by plasma cortisol, plasma compound S and eosinophil cell determinations." *Acta Endocrinol. (Kbh.)* **67**: 495-507 (1971).

H42,510/71

During the postoperative stage, elderly patients show a significantly stronger response to intravenous metyrapone than do young persons.

Gutai, J., George, R., Koeff, S., Bacon, G. E.: "Adrenal response to physical stress and the effect of adrenocorticotrophic hormone in newborn infants." *J. Pediatr.* **81**: 719-725 (1972).

G93,968/72

In newborn infants exposed to various stressors, blood cortisol levels failed to rise. However, since injection of ACTH caused the usual elevation of blood cortisol, their insensitivity could not have resulted from the primary unresponsiveness of their adrenals.

Riegle, G. D., Hess, G. D.: "Chronic and acute dexamethasone suppression of stress

activation of the adrenal cortex in young and aged rats." *Neuroendocrinology* **9**: 175-187 (1972).

H54,322/72

The corticoid feedback mechanism is much less effective in old than in young rats exposed to ether vapor.

Meyer, J. S., Bowman, R. E.: "Rearing experience, stress and adrenocorticosteroids in the rhesus monkey." *Physiol. Behav.* **8**: 339-343 (1972).

H68,304/72

Nyakas, C., Endrőczi, E.: "Effect of neonatal corticosterone administration on behavioural and pituitary-adrenocortical responses in the rat." *Acta Physiol. Acad. Sci. Hung.* **42**: 231-241 (1972).

J6,600/72

Neonatal corticosterone administration can have persistent effects on behavioral and pituitary-adrenocortical responses in the rat.

Franks, R. C.: "Urinary 17-hydroxycorticosteroid and cortisol excretion in childhood." *J. Clin. Endocrinol. Metab.* **36**: 702-705 (1973).

H68,183/73

The increase in urinary corticoid excretion is approximately the same in both adults and children exposed to various stressors, such as cardiac catheterization.

Pokoly, T. B.: "The role of cortisol in human parturition." *Am. J. Obstet. Gynecol.* **117**: 549-553 (1973).

J6,868/73

In human newborns, plasma cortisol rises as a consequence of the stress of labor. Babies born by Cesarean section show significantly less cortisol. In contrast, fetal lambs experience a pronounced increase in cortisol levels preceding birth. This is thought to be essential for the onset of labor.

Ader, R., Grotta, L. J.: "Adrenocortical mediation of the effects of early life experiences." *Prog. Brain Res.* **39**: 395-406 (1973).

H93,701/73

Tennes, K., Carter, D.: "Plasma cortisol levels and behavioral states in early infancy." *Psychosom. Med.* **35**: 121-128 (1973).

J2,627/73

In newborn infants, blood cortisol levels usually varied in relation to behavioral states.

Riegle, G. D.: "Chronic stress effects on adrenocortical responsiveness in young and aged rats." *Neuroendocrinology* **11**: 1-10 (1973).

H67,112/73

Young and old rats were subjected to repeated restraint for twenty days. The decrease in stress responsiveness was greater in the former than in the latter groups.

- Butte, J. C., Kakihana, R., Farnham, M. L., Noble, E. P.: "The relationship between brain and plasma corticosterone stress response in developing rats." *Endocrinology* **92**: 1775-1779 (1973). H71,519/73
- Dalle, M., Delost, P.: "Changes in the concentrations of cortisol and corticosterone in the plasma and adrenal glands of the guinea-pig from birth to weaning." *J. Endocrinol.* **63**: 483-488 (1974). H98,345/74
- Ogle, T. F., Kitay, J. I.: "Effects of premature weaning on adrenal function in intact and gonadectomized rats." *J. Endocrinol.* **63**: 489-496 (1974). H98,346/74
- Barlow, S., McElhatton, P., Morrison, P., Sullivan, F. M.: "Effects of stress during pregnancy on plasma corticosterone levels and foetal development in the mouse." *J. Physiol. (Lond.)* **239**: 55P-56P (1974). J21,234/74
- Takacs, I., Balogh, A., Borsos, A., Smid, I., Misz, M.: "Veränderung der Hypophysen-Nebennierenrindenfunktion im Klimakterium" (Changes of the hypophysis-adrenal cortex function during the menopause). *Zentralbl. Gynäekol.* **96**: 1057-1063 (1974). J17,037/74
- Kraus, M., Erdösova, R.: "Effect of early weaning on in vitro adrenal gland activity in young male rats." *Gen. Comp. Endocrinol.* **22**: 399 (1974). H83,304/74
- In rats early weaning on the fifteenth day decreases aldosterone and corticosterone production as well as responsiveness to stressors. [The brief abstract does not lend itself to critical evaluation (H.S.).]
- Erdösová, R., Jakoubek, B., Kraus, M.: "Effect of preweaning stress and its suppression by diazepam on androgenic and adrenocortical activity in adult males" (abstracted). *Physiol. Bohemoslov.* **24**: 51 (1975). J22,934/75
- Catecholamines.** Kärki, N. T.: "The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it." *Acta Physiol. Scand.* **39** Supp. 132: 1-96 (1956). C26,120/56
- Monograph on human catecholamine excretion as influenced by circadian variations, age, muscular work, emotional stress and sex (160 refs.).
- Huttunen, M. O.: "Persistent alteration of turnover of brain noradrenaline in the off-spring of rats subjected to stress during pregnancy." *Nature* **230**: 53-55 (1971). H36,187/71
- Stanton, H. C., Mueller, R. L., Bailey, C. L.: "Adrenal catecholamine levels and synthesizing enzyme activities in newborn swine exposed to cold and 6-hydroxydopamine." *Proc. Soc. Exp. Biol. Med.* **141**: 991-995 (1972). H64,032/72
- Hucklebridge, F. H., Nowell, N. W.: "Effect of infantile handling upon plasma catecholamine response to acute noxious stimulation in adulthood." *Behav. Biol.* **9**: 563-579 (1973). J22,755/73
- Shoemaker, W. J., Wurtman, R. J.: "Effect of perinatal undernutrition on the metabolism of catecholamines in the rat brain." *J. Nutr.* **103**: 1537-1547 (1973). J7,704/73
- Anagnostakis, D., Economou-Mavrou, C., Agathopoulos, A., Matsaniotis, N.: "Neonatal cold injury: evidence of defective thermogenesis due to impaired norepinephrine release." *Pediatrics* **53**: 24-28 (1974). J9,386/74
- In preterm newborn babies exposed to cold, urinary excretion of NEP was considerably lower than after recovery. Urinary excretion of EP was unaffected by cold stress. Possibly, exposure of the newborn to cold exhausts the NEP stores and thereby causes inability to stimulate and utilize chemical thermogenesis.
- Metabolites.** Cooke, R. E., Pratt, E. L., Darrow, D. C.: "The metabolic response of infants to heat stress." *Yale J. Biol. Med.* **22**: 227-249 (1950) (52 refs.). B30,242/50
- Roux, J. F., Romney, S. L.: "Plasma free fatty acids and glucose concentrations in the human fetus and newborn exposed to various environmental conditions." *Am. J. Obstet. Gynecol.* **97**: 268-276 (1967). J22,838/67
- Observations on women exposed to various stressors show that "the regulation of fetal plasma FFA is controlled by the same mechanisms as those of the pregnant adult. The fetus is however, unable to respond to a high plasma glucose concentration as the pregnant woman does (i.e., by a decrease in plasma FFA concentration). This difference is probably due to a limited supply of fetal insulin and/or to the saturation of the en-

zyme systems synthesizing lipids in fetal tissues. Pathologic conditions of gestation and stresses in utero have no effect on the fetal plasma FFA concentrations. This is considered as an expression of fetomaternal homeostatic ability. Increase in fetal plasma FFA concentrations takes place after birth."

Danilova, L. Y.: "The role of adrenal glands in the regulation of carbohydrate metabolism of undercooled animals having different degrees of thermoregulation." *Acta Biol. Med. Ger.* **21**: 625-634 (1968) (Russian). H7,143/68

In various premature but not in mature newborn mammals, cooling is not accompanied by glycogenolysis owing to insufficient EP secretion. Glucocorticoids raise the hepatic glycogen reserves in newborns, but fail to increase their resistance to hypothermia.

Groza, P., Buzoianu, V., Ionescu, S., Bogatu, D.: "Uropepsinogen reaction in surgical stress in terms of age." *Rev. Roum. Physiol.* **6**: 203-206 (1969). H18,402/69

In elderly patients, operative stress causes a fall in uropepsinuria which is not obvious in younger subjects. "Uropepsin assay may represent a functional test for post-traumatic reactivity."

Almeida, P. A. M., Kulay, L. Jr., Camano, L.: "Histochemical study of the monoamine oxidase (MAO) in the placenta of rats (*Rattus norvegicus albinus*, Rodentia mammalia) which were submitted to acute stress on the 15th and 18th days of pregnancy." *Ann. Histochim.* **16**: 265-272 (1971).

G88,359/71

Lee, C. J., Dubos, R.: "Lasting biological effects of early environmental influences. VII. Metabolism of adenosine 3'-5'-monophosphate in mice exposed to early environmental stress." *J. Exp. Med.* **135**: 220-234 (1972). H50,727/72

Holden, K. R., Young, R. B., Piland, J. H., Hurt, W. G.: "Plasma pressors in the normal and stressed newborn infant." *Pediatrics* **49**: 495-503 (1972). G90,865/72

Kudriashov, B. A., Bazazian, G. G., Liapina, L. A., Sytina, N. P.: "Restriction of complex formation of heparin in the blood of aged animals under stress conditions against the background of natural diet." *Kardiologiya* **13** No. 11: 118-120 (1973) (Russian). J23,976/73

Davison, T. F.: "Metabolite changes in the neonate fowl in response to cold stress." *Comp. Biochem. Physiol. [A]* **44**: 979-989 (1973). H64,678/73

Good, W., Cochran, T. E., MacDonald, H. N., Cumberbatch, K. N.: "Seromucoid and albumin levels in maternal and cord serum in relation to obstetric stress." *J. Obstet. Gynaecol. Brit. Commonw.* **80**: 704-707 (1973). J12,911/73

Yuwiler, A., Geller, E., Schapiro, S.: "Effect of neonatal corticoids on tryptophan pyrrolase and brain serotonin." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 215-228. Bratislava: Slovak Academy of Sciences, 1973. E10,470/73

In newborn rats, a single injection of cortisol induces tryptophan pyrrolase and diminishes both body growth and the 5-HT content of the brain. These results are discussed in relation to the function of tryptophan in stress.

Brooke, O. G., Harris, M., Salvosa, C. B.: "The response of malnourished babies to cold." *J. Physiol. (Lond.)* **233**: 75-91 (1973). J5,659/73

Malnourished Jamaican children failed to raise their heat production and their rectal temperatures fell, when the ambient temperature decreased from 28° to 25°C.

Clapp, J. F., Patel, N., Abrams, R. M.: "Fetal metabolic response to surgical stress" (abstracted). *Physiologist* **17**: 196 (1974). H89,878/74

In lamb fetuses, surgical stress elicits changes in oxygen and glucose utilization, lactate production and amino acid uptake.

→**Morphology.** Hoagland, H., Bergen, J. R., Bloch, E., Elmadjian, F., Gibree, N. R.: "Adrenal stress responses in normal men." *J. Appl. Physiol.* **8**: 149-154 (1955). C12,916/55

Manipulation of the Hoagland-Werthessen pursuit meter was used as a stress test. Young men (sixteen to twenty years) "appear to call very little on adrenal cortical mechanisms to meet stresses which enhance adrenocortical responses of older men." Eosinopenia correlates better with urinary excretion of EP than with 17-KS excretion, regarded as indicators of adrenocortical activity.

Brodie, D. A., Hanson, H. M.: "A study of the factors involved in the production of

gastric ulcers by the restraint technique." *Gastroenterology* **38**: 353-360 (1960).

C87,271/60

Young rats are more predisposed to stress-induced gastric ulcers than are old rats.

Wilson, T. R.: "Age and susceptibility to gastric ulceration in male and female rats." *Gerontologia* (Basel) **12**: 226-230 (1966).

F78,288/66

Young rats are much more susceptible to restraint-induced gastric ulcers than adults.

Krakowski, A. J.: "Psychophysiologic gastrointestinal disorders in children." *Psychosomatics* **8**: 326-330 (1967). F91,348/67

The most common stress-induced gastrointestinal disorders in children are gastritis, peptic ulcer, ulcerative colitis and diarrhea.

Heim, T., Kellermayer, M.: "The effect of environmental temperature on brown and white adipose tissue in the starving newborn rabbit." *Acta Physiol. Acad. Sci. Hung.* **31**: 339-346 (1967). G50,688/67

The effect of stress upon fat mobilization was studied in newborn rabbits starved to death at different environmental temperatures. "Brown fat is mobilized in response to cold but not during starvation in a thermoneutral environment, whereas white fat apparently serves as a general metabolic reserve and is used during starvation both in the absence and the presence of a cold-induced increase in heat production."

Rassaert, C. L., Steinert, B. G.: "Influence of inanition and cold exposure on biological age of rat tail tendon collagen." *Proc. Soc. Exp. Biol. Med.* **128**: 789-793 (1968).

H2,015/68

In rats, reduction of food supply caused changes typical of the G.A.S., as well as increases in isometric tail tendon contraction indicative of premature aging. However, exposure to cold elicited no such alterations in collagen contractility.

Sultz, H. A., Schlesinger, E. R., Feldman, J. G., Mosher, W. E.: "The epidemiology of peptic ulcer in childhood." *Am. J. Public Health* **60**: 492-498 (1970).

J8,025/70

Peptic ulcers are far more common during childhood than had been suspected. Often, marital difficulties between parents are the cause of this stress reaction.

Grezicka-Filus, B., Socha, J., Bittner, K.:

"Psychological aspects of peptic ulcer in children." *Pediatr. Pol.* **45**: 821-826 (1970).

J23,785/70

Schaefer, G. J., Darbes, A.: "The effects of preweaning handling and postweaning housing on behavior and resistance to deprivation induced stress in the rat." *Dev. Psychobiol.* **5**: 231-238 (1972). J19,601/72

In rats, preweaning handling reduced starvation-induced gastric ulcerogenesis.

Yuwiler, A., Geller, E., Schapiro, S.: "Effect of neonatal corticoids on tryptophan pyrolase and brain serotonin." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 215-228. Bratislava: Slovak Academy of Sciences, 1973. E10,470/73

In newborn rats, a single injection of cortisol induces tryptophan pyrolase and diminishes both body growth and the 5-HT content of the brain. These results are discussed in relation to the function of tryptophan in stress.

Spada, A., Damilano, C.: "Ulcere da stress in neonati immaturi" (Stress ulcers in premature neonates). *Minerva Med.* **64**: 3676-3682 (1973) (42 refs.). H66,649/73

Siegel, M. I., Smookler, H. H.: "Fluctuating dental asymmetry and audiogenic stress." *Growth* **37**: 35-39 (1973).

J8,473/73

Dental asymmetry has been ascribed to environmental stress. In this study, pregnant rats were exposed to intermittent audiogenic stress. "The degree of fluctuating asymmetry of mandibular molar width and length was determined for stressed litters and shown to be significantly greater than for controls reared under normal laboratory conditions."

Skála, J. P., Hahn, P.: "Changes in interscapular brown adipose tissue of the rat during perinatal and early postnatal development and after cold acclimation. VI. Effect of hormones and ambient temperature." *Int. J. Biochem.* **5**: 95-106 (1974) (28 refs.). J13,050/74

→ **Cardiovascular System.** Malmo, R. B., Shagass, C.: "Variability of heart rate in relation to age, sex and stress." *J. Appl. Physiol.* **2**: 181-184 (1949). B26,775/49

Clemmer, T. P., Telford, I. R.: "Abnormal development of the rat heart during prenatal hypoxic stress." *Proc. Soc. Exp. Biol. Med.* **121**: 800-803 (1966). F64,073/66

Fennell, W. H., Moore, R. E.: "Peripheral vascular responses to heat stress in elderly men." *Int. J. Biometeorol.* **15**: 325-329 (1971). J20,332/71

Assali, N. S., Brinkman, C. R. III: "The role of circulatory buffers in fetal tolerance to stress." *Am. J. Obstet. Gynecol.* **117**: 643-653 (1973). J7,057/73

Clayden, J. R., Bell, J. W., Pollard, P.: "Menopausal flushing: double-blind trial of a non-hormonal medication." *Br. Med. J.* March 9, 1974, pp. 409-412. H85,394/74

Attention is called to the frequency of menopausal flushes elicited by emotional stress; in this study simple reassurance sufficed to alleviate the vasomotor symptoms.

Hofer, M. A., Weiner, H.: "Physiological mechanisms for cardiac control by nutritional intake after early maternal separation in the young rat." *Psychosom. Med.* **37**: 8-24 (1975). J23,312/75

→**Nervous System.** Klopfer, W. G.: "Psychologic stresses of old age." *Geriatrics* **13**: 529-531 (1958). J7,968/58

Psychoanalytic studies on the stressor effect of aging.

Ader, R.: "The effects of early experience on subsequent emotionality and resistance to stress." *Psychol. Monogr.* **73**: 1-31 (1959). D88,458/59

Gauron, E. F., Becker, W. C.: "The effects of early sensory deprivation on adult rat behavior under competition stress: an attempt at replication of a study by Alexander Wolf." *J. Comp. Physiol. Psychol.* **52**: 689-693 (1959). J23,322/59

Abramson, J. H., Singh, A. R., Mbambo, V.: "Antenatal stress and the baby's development." *Arch. Dis. Child.* **36**: 42-49 (1961). D4,534/61

A study of Indian expectant mothers in Durban "revealed a relationship between emotional stress during pregnancy and a low level of motor development in the infant."

Thompson, W. R., Watson, J., Charlesworth, W. R.: "The effects of prenatal maternal stress on offspring behavior in rats." *Psychol. Monogr.* **76**: 1-26 (1962). J24,212/62

Kral, V. A.: "Stress and mental disorders of the senium." *Med. Serv. J. Can.* **18**: 363-370 (1962). D25,424/62

Review of the author's work suggesting that "the lowered stress resistance of the aged may be one of the determining factors of, at least, some of the mental disorders encountered in the aged. On the other hand, stress endured in the past may play a role in the aetiology of the psychoses of the senium." However, "the mental disorders of the senium *per se* may be so stressful to the aging organism as to accelerate senescent decline or even precipitate death."

Keeley, K.: "Prenatal influence on behavior of offspring of crowded mice." *Science* **135**: 44-45 (1962). D16,058/62

Hunt, H. F., Otis, L. S.: "Early 'experience' and its effects on later behavioral processes in rats: I. Initial experiments." *Trans. N.Y. Acad. Sci.* **25**: 858-870 (1963).

J23,588/63

Schaefer, T. Jr.: "Early 'experience' and its effects on later behavioral processes in rats: II. A critical factor in the early handling phenomenon." *Trans. N.Y. Acad. Sci.* **25**: 871-889 (1963). J23,586/63

Handling is effective in reducing later emotionality in the life of a rat, but only if applied very early. This study implies that "handling is ineffective unless it is accompanied by a temperature change." In fact, lowering the ambient temperature at the same early period of life produces an equal effect.

Lieberman, M. W.: "Early developmental stress and later behavior." *Science* **141**: 824-825 (1963). E24,883/63

"The effects of behavioral stress on mice during pregnancy on the behavior of offspring are mimicked by epinephrine injection of mice during pregnancy; hydrocortisone and norepinephrine injection also produce behavioral changes in the offspring. Similar results were obtained in chicks hatched from injected eggs." Presumably, "injection of stress-syndrome hormones into pregnant mice and into chicken eggs produce changes similar to those produced by subjecting pregnant mice to a behavioral stressor."

Hutchings, D. E.: "Early 'experience' and its effects on later behavioral processes in rats: III. Effects of infantile handling and body temperature reduction on later emotionality." *Trans. N.Y. Acad. Sci.* **25**: 890-901 (1963). J23,587/63

Confirmatory evidence that handling during the immediate postnatal period decreases

emotionality in rats only because of the associated drop in temperature.

Goldman, J. R.: "The effects of handling and shocking in infancy upon adult behavior in the albino rat." *J. Genet. Psychol.* **104**: 301-310 (1964). *J22,967/64*

DeFries, J. C.: "Prenatal maternal stress in mice. Differential effects on behavior." *J. Hered.* **55**: 289-295 (1964). *G25,880/64*

Fries, J. L., Weir, M. W.: "Open field behavior of C57BL/6 mice as a function of age, experience, and prenatal maternal stress." *Psychon. Sci.* **1**: 389-390 (1964). *J23,783/64*

Thompson, W. R., Quinby, S.: "Prenatal maternal anxiety and offspring behavior: parental activity and level of anxiety." *J. Genet. Psychol.* **106**: 359-371 (1964). *J22,969/64*

Joffe, J. M.: "Effect of foster-mothers' strain and pre-natal experience on adult behaviour in rats." *Nature* **208**: 815-816 (1965). *F56,774/65*

"Subjecting female rats to stress in maturity affected the adult avoidance conditioning but not the emotionality of the foster-offspring which they reared." Apparently, exposure of a mother to stressors can modify the behavior of the foster offspring.

Joffe, J. M.: "Genotype and prenatal and premating stress interact to affect adult behavior in rats." *Science* **150**: 1844-1845 (1965). *F59,236/65*

"Open-field ambulation scores of rats were affected by stress received by their mothers prior to mating, whereas avoidance-conditioning scores were affected only by gestational stress."

Joffe, J. M.: "Emotionality and intelligence of offspring in relation to prenatal maternal conflict in albino rats." *J. Gen. Psychol.* **73**: 1-11 (1965). *J23,415/65*

Goldman, P. S.: "Conditioned emotionality in the rat as a function of stress in infancy." *Anim. Behav.* **13**: 434-442 (1965). *J23,414/65*

Fox, M. W., Stelzner, D.: "Behavioural effects of differential early experience in the dog." *Anim. Behav.* **14**: 273-281 (1966). *J23,426/66*

Gauron, E. F.: "Effects of mother's shock traumatization in infancy upon offspring be-

havior." *J. Genet. Psychol.* **108**: 221-224 (1966). *J23,564/66*

Henderson, N. D.: "Effects of preweaning noxious stimulation on later behavior of rats: role of experimenter contact and spacing of stimulation." *Psychol. Rep.* **21**: 97-104 (1967). *G55,670/67*

Vernon, D. T. A., Foley, J. M., Schulman, J. L.: "Effect of mother-child separation and birth order on young children's responses to two potentially stressful experiences." *J. Pers. Soc. Psychol.* **5**: 162-174 (1967). *J23,853/67*

Terigi, A. T.: *Longevita' e Vitalita'* (Longevity and vitality), p. 213. Bologna: Casa Editrice Prof. Riccardo Patron, 1967.

E666/67

A monograph on the traumatic and psychic problems of senility with special reference to the G.A.S.

Kral, V. A., Grad, B., Berenson, J.: "Stress reactions resulting from the relocation of an aged population." *Can. Psychiatr. Assoc. J.* **13**: 201-209 (1968). *G58,342/68*

In subjects relocated to homes for the aged, plasma corticoids increased, especially among men who developed organic signs of disease. Of the normal men, 25 percent died within six months of relocation, while all normal women survived. More psychotics died than normal subjects.

Chapouthier, G., Legrain, D., Spitz, S.: "Stress' de la mère gravide et capacités d'apprentissage des jeunes souris" ("Stress" in the pregnant mother and learning capacity of young mice). *C.R. Acad. Sci. (Paris)* **269**: 504-506 (1969). *J21,283/69*

Porter, R. H., Wehmer, F.: "Maternal and infantile influences upon exploratory behavior and emotional reactivity in the albino rat." *Dev. Psychobiol.* **2**: 19-25 (1969).

J19,542/69

In rats, "1. both offspring infantile handling and maternal pregnancy stress tend to increase adult exploratory behavior; 2. adult weight was lower for subjects whose mother had undergone stress during pregnancy than for offspring of non-stress females; 3. several 2-way interactions were found to significantly influence open-field exploration; 4. when offspring infantile handling was combined with maternal pregnancy stress, emotional reactivity (i.e., defecation) was found to increase

significantly over that following either type of stimulation alone."

Tallmer, M., Kutner, B.: "Disengagement and the stresses of aging." *J. Gerontol.* **24**: 70-75 (1969). G65,232/69

Stressors associated with aging, such as ill health, widowhood and retirement, produce "disengagement" which is a gradual withdrawal from society.

Moore, T.: "Stress in normal childhood." *Hum. Relat.* **22** No. 3: 235-250 (1969). E67,152/69

Effects of psychologic stressors upon the mentality of children, including neonates.

Wehmer, F., Porter, R. H., Scales, B.: "Pre-mating and pregnancy stress in rats affects behaviour of grandpups." *Nature* **227**: 622 (1970). H27,899/70

Rats whose grandmothers were exposed to avoidance conditioning before mating or to conditioned stress during pregnancy were more active in the common open test field than were the descendants of nondisturbed control grandmothers. Apparently, "stress before or during pregnancy, like infantile handling, can influence the behaviour of future generations, beyond the immediate offspring of the manipulated females."

Markus, E., Blenkner, M., Bloom, M., Downs, T.: "Relocation stress and the aged." In: Blumenthal, H. T., *The Regulatory Role of the Nervous System in Aging*, pp. 60-71. Basel, München, and New York: S. Karger, 1970. E8,832/70

Relocation of aged persons from an accustomed to an unknown environment increases morbidity and mortality because it "generates stress and discomfort which call forth coping responses from the relocated person beyond those required by familiar routines." Relocation is particularly damaging to males, especially those with severe mental dysfunctions.

Simon, A.: "Physical and socio-psychologic stress in the geriatric mentally ill." *Compr. Psychiatry* **11**: 242-247 (1970).

J21,325/70

Archer, J. E., Blackman, D. E.: "Prenatal psychological stress and offspring behavior in rats and mice." *Dev. Psychobiol.* **4**: 193-248 (1971). J3,039/71

Extensive review of the literature and many interesting personal observations on the effects upon the offspring of stress ap-

plied to the mother. The results permit few conclusions except that some change in activity-reactivity may be thus induced (numerous refs.).

Fink, G., Smith, G. C.: "Ultrastructural features of the developing hypothalamo-hypophyseal axis in the rat. A correlative study." *Z. Zellforsch. Mikrosk. Anat.* **119**: 208-226 (1971). G85,999/71

EM studies on the fetal ME of the rat. The finding that "the development of granular vesicles precedes that of agranular vesicles is discussed with reference to the times at which neurosecretory materials and monoamines become detectable in the region."

Steen, R. E.: "Stress disorders in childhood. Part I." *J. Ir. Med. Assoc.* **65**: 607-614 (1972). G99,557/72

Extensive review on diseases and behavioral patterns ascribed to stress in children.

Roth, T., Kramer, M., Trinder, J.: "The effect of noise during sleep on the sleep patterns of different age groups." *Can. Psychiatr. Assoc. J.* **17**: SS197-SS201 (1972).

H79,724/72

EEG, EMG and EOG recordings indicate that noise of moderate intensity has little effect upon the sleep pattern of twenty-five-year-old subjects, but causes increasing disturbance with progressing age.

Balcerzak, W., Friedrich, D., Rodewald, H. K.: "Effects of dimensionality, pacing, and sex on oddity problem performance of kindergarten students." *Psychol. Rep.* **31**: 779-782 (1972). J19,723/72

Studies on the effect of stress on oddity-problem performance in kindergarten children.

Joffe, J. M.: "Postnatal experience and the detection of the effects of prenatal stress on behavior: a reply to Archer and Blackman." *Dev. Psychobiol.* **5**: 389-390 (1972).

J23,560/72

Lorenz, R. J.: "Effects of differential pre-weaning social isolation on emotional reactivity and stress tolerance in the rat." *Dev. Psychobiol.* **5**: 201-213 (1972).

J19,379/72

Ward, I. L.: "Prenatal stress feminizes and demasculinizes the behavior of males." *Science* **175**: 82-84 (1972). H49,615/72

Restraint of pregnant rats "causes an increase in the weak adrenal androgen, an-

drostenedione, from the maternal or fetal adrenal cortices, or from both, and a concurrent decrease in the potent gonadal androgen, testosterone."

Jolley, A., Dreesman, H.: "Increased illumination level during gestation and offspring emotionality in the rat." *Anim. Behav.* **21**: 660-664 (1973). J24,110/73

Young, L. D., Suomi, S. S., Harlow, H. F., McKinney, W. T. Jr.: "Early stress and later response to separation in rhesus monkeys." *Am. J. Psychiatry* **130**: 400-405 (1973). J1,204/73

Howard, E.: "Increased reactivity and impaired adaptability in operant behavior of adult mice given corticosterone in infancy." *J. Comp. Physiol. Psychol.* **85**: 211-220 (1973). J6,970/73

"Intensive corticosterone treatment given to mice in the first postnatal week irreversibly decreases growth and DNA synthesis in the brain." After early hypercorticism, adult mice become hyperresponsive when working for food and show impaired ability to adapt to schedule changes.

Ressler, R. H., Anderson, L. T.: "Avoidance conditioning in mice as a function of their mothers' exposure to shock." *Dev. Psychobiol.* **6**: 105-111 (1973).

H80,110/73

Kral, V. A.: "Psychiatric problems in the aged: a reconsideration." *Can. Med. Assoc. J.* **108**: 584-590 (1973). H65,964/73

Among the numerous mental disorders found in senile people, "only two direct relationships are seen: the acute confusional states due to the age-linked decline in stress resistance; and the neurotic reactions due to the diminished capacity for rapid and adequate adjustment to the more subtle but chronic sociopsychological changes the aged individual is so frequently exposed to in our society."

Johnston, R. E., Miya, T. S., Paolino, R. M.: "Facilitated avoidance learning and stress-induced corticosterone levels as a function of age in rats." *Physiol. Behav.* **12**: 305-308 (1974). J11,624/74

"Older animals acquired the conditioned avoidance response (CAR) faster and required a longer time to extinguish, than the younger animals. The enhanced CAR performance of the older animals could not be attributed to an altered pain threshold but

was correlated with a significantly higher plasma corticosterone response to ether-stress. The data are interpreted as being consistent with the notion of a positive relationship between pituitary-adrenal activity and facilitated avoidance learning."

←**Pre- and Perinatal Stress in General**
(excluding Handling, Retirement and specific changes previously mentioned). Weininger, O.: "Mortality of albino rats under stress as a function of early handling." *Can. J. Psychol.* **7**: 111-114 (1953). B93,807/53

None of the rats gentled ten minutes daily for about ten days after weaning died when exposed to a complex stressor situation (cold, starvation and water deprivation) in adulthood, but the same procedure applied at the same time in adulthood to nongentled controls caused adrenal enlargement, bleeding gastric erosions and other manifestations of the alarm reaction, as well as a high mortality rate.

Weininger, O.: "Physiological damage under emotional stress as a function of early experience." *Science* **119**: 285-286 (1954). B91,063/54

Recently weaned rats were gentled by mild handling and caressing for three weeks. When later exposed to restraint, they were more resistant as indicated by body weight, manifestations of fear, gastrointestinal and cardiovascular lesions and by reduced adrenal hypertrophy.

Christian, J. J.: "A review of the endocrine responses in rats and mice to increasing population size including delayed effects on offspring." *Naval Med. Res. Inst.* August 6, 1957, pp. 443-462. C53,409/57

Rats and mice living under crowded conditions show many manifestations of stress, including a decrease in fertility which may act as a regulator of population density to maintain an optimal level. Crowding can also cause lasting changes in the offspring of surviving females, probably due to lactational deficiencies.

Soiva, K., Grönroos, M., Aho, A. J.: "Effect of audiogenic-visual stimuli on pregnant rats." *Ann. Med. Exp. Fenn.* **37**: 464-470 (1959). C97,217/59

In the offspring of rats exposed to audio-visual stress during pregnancy, the average weight of the body as a whole and of the adrenals, pituitary, ovaries and heart was essentially unchanged, but there was some

renal enlargement and a slight increase in blood pressure.

Linneweh, F.: "Über Anpassungskrankheiten nach der Geburt" (On adaptation diseases after birth). *Klin. Wochenschr.* **39**: 1041-1044 (1961). D75,664/61

Becker, R. F., Boneau, A., King, J. E., Marsh, R., Brown, E.: "Responses of animal fetuses and neonates to intra-uterine stress." *J.A.M.A.* **178**: 819-820 (1961).

E91,882/61

Schnürer, L. B.: "Maternal and foetal responses to chronic stress in pregnancy. A study in albino rats." *Acta Endocrinol. (Kbh.)* **43** Supp. 80: 1-96 (1963).

D67,319/63

Hale, J. F.: "On the interaction effect between early experience, later response to a terminal stressor, and the presence or absence of an intervening stressor." *J. Comp. Physiol. Psychol.* **57**: 451-452 (1964).

J22,974/64

Gauron, E.: "Infantile shock traumatization and subsequent adaptability to stress." *J. Genet. Psychol.* **104**: 167-178 (1964).

J22,968/64

In rats, "previous experience with shock produced decremental performance on a stressful test involving the repetition of shock, but not on a stressful test not involving shock nor on a nonstressful test."

Meyers, W. J.: "Effects of different intensities of postweaning shock and handling on the albino rat." *J. Genet. Psychol.* **106**: 51-58 (1965). J23,572/65

McIver, A. H.: "Reactivity to stress in rats as a function of infantile experience." *Proc. Soc. Exp. Biol. Med.* **119**: 757-759 (1965).

F46,123/65

Ader, R., Friedman, S. B.: "Differential early experiences and susceptibility to transplanted tumor in the rat." *J. Comp. Physiol. Psychol.* **59**: 361-364 (1965).

G32,592/65

Castellion, A. W., Swinyard, E. A., Goodman, L. S.: "Effect of maturation on the development and reproducibility of audiogenic and electroshock seizures in mice." *Exp. Neurol.* **13**: 206-217 (1965). J22,995/65

Roubicek, C. B.: "Stress adaptation in the rat as measured by postweaning growth." *Growth* **30**: 79-85 (1966). G39,305/66

"The detrimental effects of high tempera-

ture on animal weight are due to the difference in the slope of the growth curve, rather than to a longer adjustment period."

Campbell, B. A., Riccio, D. C.: "Cold-induced stress in rats as a function of age." *J. Comp. Physiol. Psychol.* **64**: 234-239 (1966). G39,214/66

Comparative studies in animals of different age groups exposed to cold showed that "initial colonic temperatures were lower and behavioral recovery times slower in weanling rats, whereas colonic temperature-recovery times did not vary with age."

Riccio, D. C., Campbell, B. A.: "Adaptation and persistence of adaptation to a cold stressor in weanling and adult rats." *J. Comp. Physiol. Psychol.* **61**: 406-410 (1966).

F76,331/66

No major difference in adaptability to cold was observed between weanling and adult rats "when severity of the stressor was equated on the basis of previously reported behavioral and physiological measures."

Zarrow, M. X., Haltmeyer, G. C., Denenberg, V. H., Thatcher, J.: "Response of the infantile rat to stress." *Endocrinology* **79**: 631-634 (1966). F70,599/66

Klatskin, E. H., McGarry, M. E., Steward, M. S.: "Variability in developmental test patterns as a sequel of neonatal stress." *Child Dev.* **37**: 819-826 (1966).

J22,682/66

Heider, G. M.: "Vulnerability in infants and young children: a pilot study." *Genet. Psychol. Monogr.* **73**: 1-216 (1966).

G41,942/66

Monograph on the use of various tests to evaluate stress susceptibility in infants (57 refs.).

DeFries, J. C., Weir, M. W., Hegmann, J. P.: "Differential effects of prenatal maternal stress on offspring behavior in mice as a function of genotype and stress." *J. Comp. Physiol. Psychol.* **63**: 332-334 (1967).

G45,513/67

Comparative studies on the effect of prenatal maternal stress on the offspring of mice as influenced by genetic factors.

Noël, V.: *Syndrome de Transmission* (Syndrome of transmission), p. 36. Port-Au-Prince, Haiti: Imprimerie Theodore, 1967.

G46,108/67

The term syndrome of transmission is suggested for the development of anomalies in

embryos whose mothers were exposed to stressors during gestation.

Talbert, J. L., Karmen, A., Graystone, J. E., Haller, J. A. Jr., Cheek, D. B.: "Assessment of the infant's response to stress." *Surgery* **61**: 626-633 (1967). G45,548/67

Geber, W. F., Anderson, T. A.: "Abnormal fetal growth in the albino rat and rabbit induced by maternal stress." *Biol. Neonate* **11**: 209-215 (1967). J23,432/67

Morra, M.: "Ethanol and maternal stress on rat offspring behaviors." *J. Genet. Psychol.* **114**: 77-83 (1969). J22,650/69

A review of the literature concerning the effect of stress during pregnancy upon the offspring of rats. Administration of ethanol to the mother significantly diminished the influence of stress upon her young.

Corson, J. A., Hesseltine, G. F. D., Smith, D. J.: "Psychological stress during pregnancy, effects on mothers and offspring." *Br. J. Pharmacol.* **38**: 457P-458P (1970). J23,168/70

Billinson, M. R.: "Prematurity and low birth weight litters: a mechanism elicited by thermal stress." *Am. J. Obstet. Gynecol.* **108**: 970-974 (1970). H45,391/70

In rats, "thermal stress" increases 5-HT excretion which may be accompanied by premature delivery or low birth weight of the litters.

Bloch, S.: "Beobachtungen über den Einfluss einiger vor der Gravidität applizierter emotioneller Traumata auf die nachfolgende Trächtigkeit und die postnatale Entwicklung der Jungen der auf das Trauma folgenden Trächtigkeit bei der Laboratoriums-Maus. Teil I-II" (Effect of various emotional traumas applied before pregnancy on the subsequent pregnancy and the postnatal development of offspring of the laboratory mouse. Parts 1 and 2). *Z. Psychosom. Med. Psychoanal.* **16**: 360-373 (1970). G80,665/70

Emde, R. N., Harmon, R. J., Metcalf, D., Koenig, K. L., Wagonfeld, S.: "Stress and neonatal sleep." *Psychosom. Med.* **33**: 491-497 (1971). G87,978/71

Ermolov, V. I.: "Effects of disturbance of the normal course of pregnancy in dogs on development of natural immunity in the progeny." *Biull. Éksp. Biol. Med.* **71** No. 3: 64-66 (1971) (Russian). Engl. transl.: *Bull. Exp. Biol. Med.* **71** No. 3: 285-287 (1971). J21,617/71

In dogs exposed to stressors during pregnancy, "the immunologic properties of the blood of the fetuses and newborn puppies were appreciably weakened. The phagocytic response was depressed most sharply, and this was accompanied by a decrease in the digestive power of the leukocytes. Weakening of the immunobiological properties led to the appearance of inflammation in the lungs and intestine by the action of the automicroflora and was responsible for death of a large proportion of the newly born animals."

Elliott, D. S., Ulberg, L. C.: "Early embryo development in the mammal. I. Effects of experimental alterations during first cell division in the mouse zygote." *J. Anim. Sci.* **33**: 86-95 (1971). J20,902/71

Hensleigh, P. A., Johnson, D. C.: "Heat stress effects during pregnancy. I. Retardation of fetal rat growth." *Fertil. Steril.* **22**: 522-527 (1971). G85,938/71

Hensleigh, P. A., Johnson, D. C.: "Heat stress effects during pregnancy. II. Pituitary gonadotropins in intact, adrenalectomized and ovariectomized rats." *Fertil. Steril.* **22**: 528-535 (1971). G85,939/71

Albrecht, H., Stemmann, E. A., Waltke, A. J., Seidemann, U.: "Die Bewertung perinataler Belastungsfaktoren für die Weiterentwicklung Neugeborener mit einer schweren Anpassungsstörung" (The evaluation of perinatal stress factors in the continuing development of newborn infants with a severe adaptation disorder). *Geburtshilfe Frauenheilkol.* **32**: 650-656 (1972). J19,422/72

Dottke, R. B.: "Intrapartaler Blutverlust und Stress Syndrom" (Hemorrhage during delivery and the stress syndrome), p. 63. Thesis, University of Berlin, 1972. J16,430/72

Petropoulos, E. A., Lau, C., Liao, C. L.: "Neurochemical changes in the offspring of rats subjected to stressful conditions during gestation." *Exp. Neurol.* **37**: 86-99 (1972). G96,023/72

The progeny of rats exposed during pregnancy to various stressors or ACTH developed characteristic chemical changes in the hypothalamus, cerebral cortex and cerebellum.

Lyle, J. G., Jonson, K. M., Edwards, M. J., Penny, R. H.: "Effect of prenatal heat stress at mid- and late gestation on the learning of mature guinea-pigs." *Dev. Psy-*

- chobiol.* **6**: 483-494 (1973). J8,629/73
 In guinea pigs subjected to "heat stress" during certain stages of gestation, black-white serial discrimination was impeded and morphologic evidence of brain damage often became detectable.
- Stott, D. H.: "Follow-up study from birth of the effects of prenatal stresses." *Dev. Med. Child. Neurol.* **15**: 770-787 (1973). J8,860/73
 "No relationship was found between the children's health and physical illness, accidents, work stresses or dental operations in the [pregnant] mothers. Situational stresses such as the death or severe illness of a family member, or shocks and frights, experienced by the expectant mother were also not significant. On the other hand, stresses involving severe, continuing personal tensions (in particular marital discord) were closely associated with child morbidity in the form of ill-health, neurological dysfunction, developmental lag and behaviour disturbance."
- Organ, L. W., Milligan, J. E., Goodwin, J. W., Bain, M. J. C.: "The pre-ejection period of the fetal heart: response to stress in the term fetal lamb." *Am. J. Obstet. Gynecol.* **115**: 377-386 (1973). G99,511/73
 Lipkowitz, M. H.: "The child of two survivors. A report of an unsuccessful therapy." *Isr. Ann. Psychiatry* **11**: 141-155 (1973). J21,854/73
 Description of the morbid changes that may occur in the children of concentration camp survivors.
- Lane, E. A., Hyde, T. S.: "Effect of maternal stress on fertility and sex ratio: a pilot study with rats." *J. Abnorm. Psychol.* **82**: 78-80 (1973). H94,829/73
 Female rats repeatedly restrained one week before conception gave birth to significantly fewer males and smaller litters than did unstressed controls.
- Curtis, S. E.: "Responses of the piglet to perinatal stressors." *J. Anim. Sci.* **38**: 1031-1036 (1974). J21,586/74
 Evidence reviewed suggests that stress from the prenatal respiratory-gas environment is directly related to intrapartal stillbirth and reduced neonatal survivability and that stress from the postnatal thermal environment is very likely related directly and indirectly to neonatal mortality in the piglet."
- Krauss, A. N., Auld, P. A. M.: "Intrauterine stress and pulmonary maturation." *J. Pediatr.* **85**: 880 (1974). J22,675/74
 Phelps, D. L.: "Intrauterine stress and pulmonary maturation." *J. Pediatr.* **85**: 879-880 (1974). J22,674/74
 "The data do not support the hypothesis that intrauterine stress leads to increased lung maturity."
- Gorsuch, R. L., Key, M. K.: "Abnormalities of pregnancy as a function of anxiety and life stress." *Psychosom. Med.* **36**: 352-362 (1974). J19,154/74
 Studies on 118 women at a low-income clinic "indicated that anxiety around the first trimester was related to abnormalities of pregnancy, parturition and infant status. Life stress during the second and third trimesters was similarly associated with the same measure of abnormalities" (23 refs.).
- Smith, D. J., Joffe, J. M., Heseltine, G. F. D.: "Modification of prenatal stress effects in rats by adrenalectomy, dexamethasone and chlorpromazine." *Fed. Proc.* **33**: 223 (1974). H83,859/74
 Adrenalectomy and treatment of pregnant rats with chlorpromazine or dexamethasone can prevent or modify the prenatal effects produced by stress in the offspring. [The brief abstract is difficult to evaluate (H.S.).]
- Bell, R. W., Nitschke, W., Bell, N. J., Zachman, T. A.: "Early experience, ultrasonic vocalizations, and maternal responsiveness in rats." *Dev. Psychobiol.* **7**: 235-242 (1974). J12,730/74
 In neonatal rats, exposure to cold and several other stressors induces ultrasonic vocalization and agitation of their mothers. "If the pup is mildly stressed he displays a pattern of ultrasonic signaling which elicits adaptive maternal responsiveness. If the pup is too severely stressed he displays persistent signaling which agitates the mother, preventing an adaptive pattern of behavior, and resulting in a prolonged response to stress in the pup."
- Trojan, S., Jilek, L., Staudacherova, D., Travníčkova, E.: "Adaptation of rats to repeated aerogenic hypoxia in early postnatal ontogenesis and adulthood." *Physiol. Bohemoslov.* **23**: 199-209 (1974). J14,696/74
 Comparative observations on adaptation to hypoxia in newborn and adult rats, with special reference to the G.A.S.

Genazzani, A. R., Cocola, F., Nasi, A., Neri, P., Fioretti, P.: "Endocrinological monitoring of late pregnancy: HCS plasma levels and chronic fetal distress." *J. Nucl. Biol. Med.* **18**: 60-66 (1974). J16,740/74

In human embryos, pre-eclampsia, severe eclampsia, feto-placental dystrophy, multiple placental infarcts and prolonged pregnancy allegedly produce "chronic fetal distress" with a diminution of human chorionic STH in the mother's blood. The manifestations of this condition are that the baby is small, shows fetal dystrophy and/or marked skin dryness at delivery.

←Prenatal Stress Conducive to Malformations or Stillbirths. Yokobori, K.: "Experimental studies of noise stimulation effects on congenital malformation." *J. Otolaryngol. Jap.* **62**: 69-81 (1956). J24,385/56

Strean, L. P., Peer, L. A.: "Stress as an etiologic factor in the development of cleft palate." *Plast. Reconstr. Surg.* **18**: 1-8 (1956). D7,329/56

Among 232 cases of cleft palate, the maternal case histories revealed a high incidence of stress (emotional, traumatic, infectious) at the time when the maxillae of the embryo are expected to fuse. This phenomenon is ascribed to increased cortisol production around the sixtieth day of pregnancy and is discussed in terms of the G.A.S. concept.

Ingalls, T. H.: "Causes and prevention of developmental defects." *J.A.M.A.* **161**: 1047-1051 (1956). C27,896/56

In mice, hypoxia applied as a standard stressor during pregnancy leads to a variety of malformations in the offspring. There is evidence that a similar situation exists in women.

Runner, M. N.: "Embryocidal effect of handling pregnant mice and its prevention with progesterone" (abstracted). *Anat. Rec.* **133**: 330-331 (1959). D98,022/59

Ishii, H., Yokobori, K.: "Experimental studies on teratogenic activity of noise stimulation." *Gunma J. Med. Sci.* **9**: 153-167 (1960). G98,756/60

Mice exposed to noise during early pregnancy give birth to an increased number of malformed newborns.

Härtel, A., Härtel, G.: "Experimental study of teratogenic effect of emotional stress in rats." *Science* **132**: 1483-1484 (1960). J22,939/60

In rats, although restraint during the ninth to twelfth days of pregnancy produced no malformations, it increased the teratogenic effect of vitamin A.

Warkany, J., Kalter, H.: "Maternal impressions and congenital malformations." *Plast. Reconstr. Surg.* **30**: 628-637 (1962). J23,642/62

In mice, audiogenic stress applied during pregnancy, unlike cortisone, does not produce cleft palate or other malformations in the offspring.

Caldwell, D. F.: "Stillbirths from adrenal demedullated mice subjected to chronic stress throughout gestation." *J. Embryol. Exp. Morphol.* **10**: 471-475 (1962). J23,452/62

In mice, psychogenic stress applied during pregnancy increases the incidence of stillbirth, but this effect is largely prevented by demedullation of the adrenals.

Goldman, A. S., Yakovac, W. C.: "The enhancement of salicylate teratogenicity by maternal immobilization in the rat." *J. Pharmacol. Exp. Ther.* **142**: 351-357 (1963). E35,710/63

Fraser, F. C., Warburton, D.: "No association of emotional stress or vitamin supplement during pregnancy to cleft lip or palate in man." *Plast. Reconstr. Surg.* **33**: 395-399 (1964) (16 refs.). G13,856/64

Nemets, N. M.: "Analysis of the characteristics and significance of changes in internal environment of the body during pregnancy." *Biull. Éksp. Biol. Med.* **55** No. 2: 45-49 (1963) (Russian). Eng. transl.: *Fed. Proc.* **23**: 401-403 (1964). F5,962/64

Pregnant rabbits with experimental neuroses often aborted or gave birth to immature progeny (23 refs.).

Ishii, H., Kimura, K., Harada, O.: "Stress and auditory characteristics of the rat." *Ann. Otol. Rhinol. Laryngol.* **73**: 948-956 (1964). G27,159/64

Studies on the teratogenic effect of noise applied during pregnancy in various species.

Jaworska, M., Reszke, S., Kawiak, H.: "Attempted analysis of the etiology of cleft-palate, based on 438 cases." *Pol. Tyg. Lek.* **19**: 1517-1519 (1964) (Polish). J24,122/64

The mothers of children born with cleft palate are frequently undernourished and have been exposed simultaneously to psychic

or somatic injuries. "These two factors (i.e. undernourishment and psychic or physical trauma) are still not definitely proved to be teratogenic for the human embryo. It seems however, that they should be treated as such, and ought to be included into the problem of general prophylaxis in the pregnant woman."

Drillien, C. M., Wilkinson, E. M.: "Emotional stress and mongoloid births." *Dev. Med. Child Neurol.* **6**: 140-143 (1964).
J23,843/64

Cizkova, J.: "Prenatal endocrine influences on the foetus and their relation to late behaviour." *Clin. Dev. Med.* No. 19: 10-13 (1965). G66,783/65

A statistical study on a small sample of mongoloid children in Prague suggests that emotional stress during pregnancy predisposes the embryo to this disease.

Rosenzweig, S.: "Psychological stress in cleft palate etiology." *J. Dent. Res.* **45** Supp. 6: 1585-1593 (1966). J22,586/66

Geber, W. F.: "Developmental effects of chronic maternal audiovisual stress on the rat fetus." *J. Embryol. Exp. Morphol.* **16**: 1-16 (1966). G40,642/66

When pregnant rats were exposed to audiovisual stress, many of their litters were absorbed, while others exhibited developmental abnormalities which "included interparietal meningocele, abdominal hernia (omphalocele), spina bifida, and defects of the eye, tail, hind- and forefoot. Hematomas, varying in size and location, were found throughout the cranial area. Localized hematomas were found in the sublingual areas. Osteogenic effects, ranging from partial to complete inhibition, were widespread." These changes may be due to an "imbalance of the maternal autonomic neurohormone and hypothalamic-pituitary-adrenal relationships."

Kosmachevskaia, E. A., Chebotar, N. A.: "Damaging action of 4-methyluracil upon the embryogenesis of rats under stress to which the maternal organism is exposed." *Bull. Éksp. Biol. Med.* **66** No. 12: 89-92 (1968) (Russian). H34,247/68

Bloch, S.: "Beobachtungen über den Einfluss einiger vor der Gravidität applizierter Traumata auf die nachfolgende Trächtigkeit bei der Laboratoriums-Maus. I. Mitteilung" (Observations on the effect of various traumas applied before pregnancy on subsequent pregnancy in the laboratory mouse. Report

I). *Gynaecologia* (Basel) **166**: 361-368 (1968). H5,092/68

Various stressors (crowding, restraint), applied to female mice just before impregnation, "resulted partly in death of the animals, abortion and stillbirths," and in impaired growth and development of the young of the following gestation.

Bloch, S., Rippmann, E. T.: "Untersuchungen über den Einfluss verschiedener Traumata auf die Gravidität bei der Laboratoriums-Maus" (Studies on the influence of various psychic traumas on pregnancy in the laboratory mouse). *Z. Psychosom. Med.* **14**: 33-45 (1968). G57,334/68

Various stressors applied during pregnancy interfere with the development of the embryo.

Clifford, E.: "Parental ratings of cleft palate infants." *Cleft Palate J.* **6**: 235-244 (1969). J21,604/69

Peters, S., Strassburg, M.: "Stress als teratogener Faktor. Tierexperimentelle Untersuchungen zur Erzeugung von Gaumenspalten" (Stress as a teratogenic factor. Experimental animal studies on the induction of cleft palate). *Arzneim. Forsch.* **19**: 1106-1111 (1969). H16,043/69

James, W. H.: "The effect of maternal psychological stress on the foetus." *Br. J. Psychiatry* **115**: 811-825 (1969).

G67,988/69

"There is good evidence that severe emotional stress and strong sensory stimuli cause embryonic resorption and stillbirth in some mammals." The risk of stillbirth or death within the first month is above normal in illegitimate infants, and those whose father is absent through death, divorce, desertion, etc. There is no firm proof that anencephaly or mongolism is caused by maternal psychogenic stress.

Rosenzweig, S., Blaustein, F. M.: "Cleft palate in A/J mice resulting from restraint and deprivation of food and water." *Teratology* **3**: 47-52 (1970). J21,404/70

In mice, food and water deprivation during certain stages of pregnancy increases the incidence of cleft palate formation as a consequence of stress.

Thwaites, C. J.: "Embryo mortality in the heat stressed ewe. III. The role of the corpus luteum, thyroid and adrenal glands." *J. Reprod. Fertil.* **21**: 95-107 (1970).

H21,604/70

Increased embryo mortality in ewes stressed during pregnancy is ascribed to the G.A.S.

Hutchings, D. E., Gibbon, J.: "Preliminary study of behavioral and teratogenic effects of two 'stress' procedures administered during different periods of gestation in the rat." *Psychol. Rep.* **26**: 239-246 (1970).

J22,038/70

Shabana, E. H., Tricomi, V., Suarez, J. R.: "Stress and its influence on gestation." *Obstet. Gynecol.* **37**: 574-579 (1971).

G82,307/71

Observations on rats exposed to electroshock during pregnancy led to the conclusion that "stress and severe emotions during pregnancy may have an adverse effect on the products of conception, especially in the sensitive organism."

Brown, K. S., Johnston, M. C., Niswander, J. D.: "Isolated cleft palate in mice after transportation during gestation." *Teratology* **5**: 119-124 (1972).

G94,787/72

Euker, J. S., Riegle, G. D.: "Effects of stress on pregnancy in the rat." *J. Reprod. Fertil.* **34**: 343-346 (1973). H74,642/73

In rats exposed to restraint or surgical trauma during pregnancy, embryonic mortality is increased.

Hamburgh, M., Lang, A., Rader, M., Silverstein, H., Hoffman, K., Miller, D., Lynch, B.: "Teratogenesis in offspring of stress mice." *Acta Univ. Carol. Med. (Praha)* **56-57**: 235-237 (1973). H91,749/73

Geber, W. F.: "Inhibition of fetal osteogenesis by maternal noise stress." *Fed. Proc.* **32**: 2101-2104 (1973). H78,365/73

Endl, J., Schaller, A.: "Missbildungshäufigkeit unter Neugeborenen von Gastarbeiterinnen" (Frequency of malformation in newborn infants of foreign women working in Germany). *Wien Klin. Wochenschr.* **85**: 718-720 (1973). H78,590/73

There appears to be a comparatively high malformation rate in newborn infants of foreign women working in Germany. Arguments are discussed which suggest this to be a consequence of various stressors related to relocation.

Bellvé, A. R.: "Development of mouse embryos with abnormalities induced by parental heat stress." *J. Reprod. Fertil.* **35**: 393-403 (1973). H80,601/73

Exposure of pregnant mice to heat (34.5°C) caused abnormalities and high mortality among their embryos, presumably as a consequence of stress.

Zakem, H. B., Alliston, C. W.: "The effects of noise level and elevated ambient temperatures upon selected reproductive traits in female Swiss-Webster mice." *Lab. Anim. Sci.* **24**: 469-475 (1974).

J13,928/74

Exposure to noise or heat on the fifth day of gestation significantly reduced the number, size and weight of embryos in mice, but combined treatment with these stressors was not uniformly additive (17 refs.).

Saxén, I.: "Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors." *Int. J. Epidemiol.* **3**: 263-270 (1974). J20,848/74

Hamburgh, M., Mendoza, L. A., Rader, M., Lang, A., Silverstein, H., Hoffman, K.: "Malformations induced in offspring of crowded and parabiotically stressed mice." *Teratology* **10**: 31-37 (1974). J15,934/74

Malformations were induced in fetuses of mice kept under crowded conditions or parabiotically joined during pregnancy. "The abnormalities included amputation of peripheral limb structures, open neural folds, exencephaly, blisters, head, face, and tail malformation, and generalized growth retardation. The hypothesis that the teratogenic and other effects were consequences of prolonged prenatal stress induced by the experimental conditions is supported by the observation that both procedures led in a short time to significant increases in mean maternal adrenal weight."

Boyd, I. E., Chamberlain, G. V. P., Ferguson, I. L. C.: "The oxytocin stress test and the isoxsuprime placental transfer test in the management of suspected placental insufficiency." *J. Obstet. Gynaecol. Br. Commonw.* **81**: 120-125 (1974). J14,783/74

Of women who had an "oxytocin stress test" during pregnancy, several gave birth to babies with various functional or morphologic defects, whereas others had normal babies. Clearly, the oxytocin stress test does not adequately measure placental sufficiency.

Bal'magiiia, T. A., Surovtseva, Z. F.: "Growth pattern of rabbit fetuses during normal pregnancy and with inhibition of the 'gestation dominant.'" *Bull. Éksp. Biol. Med.* **77**: No. 4: 44-47 (1974) (Russian). Engl.

transl.: *Bull. Exp. Biol. Med.* **77**: 384-387 (1974). J24,300/74

In rabbits, exposure to stress (sound, electroshock) "in the embryonic period and also to some extent in the embryonic-fetal periods thus gives rise to death of the fetuses, whereas exposure in the early stages of the fetal period leads to their delayed growth. Exposure to stress on the 25th-27th day of pregnancy evidently leads to strengthening of the gestation dominant, as is reflected, in particular, in the increased size of the placenta. In addition, the fetuses respond in this period with an adaptive reaction of their own to stress, resulting in an increase in their rate of growth."

+Varia. Newton, G., Heimstra, N.: "Effects of early experience on the response to whole-body x-irradiation." *Can. J. Psychol.* **14**: 111-120 (1960). D84,835/60

Weanling rats which have been previously handled lose less weight following x-irradiation than do controls.

Trujillo, T. T., Spalding, J. F., Langham, W. H.: "A study of radiation-induced aging: response of irradiated and nonirradiated mice to cold stress." *Radiation Res.* **16**: 144-150 (1962). D24, 525/62

In mice, resistance to standard "cold stress" showed a linear decrease with age. The same reaction was obtained after x-irradiation. "The radiation-induced effect was considered similar to life shortening by natural aging."

Gauron, E. F., Rowley, V. N.: "Infantile shock traumatization and the mitigating effects of tranquilizing drugs." *J. Genet. Psychol.* **111**: 263-270 (1967). J22,350/67

Atherton, R. W., Ramm, G. M.: "General observations, erythrocyte counts and hemoglobin concentration in chick embryos subjected to centrifugal stress." *Aerosp. Med.* **40**: 389-391 (1969). J22,401/69

Norton, L., Nolan, P., Sales, J. E. L., Eise-

man, B.: "A swine stress ulcer model." *Ann. Surg.* **176**: 133-138 (1972). G93,135/72

Adult pigs are unusually resistant to the production of gastric ulcers by the stress of hemorrhage, whereas young piglets are particularly sensitive (19 refs.).

Upshall, D. G.: "Effects of o-chlorobenzylidene malononitrile (CS) and the stress of aerosol inhalation upon rat and rabbit embryonic development." *Toxicol. Appl. Pharmacol.* **24**: 45-59 (1973). J435/73

Meserve, L. A., Leathem, J. H.: "Neonatal hyperthyroidism and maturation of the rat hypothalamo-hypophyseal-adrenals axis." *Proc. Soc. Exp. Biol. Med.* **147**: 510-512 (1974). H97,672/74

In rats, thyroid feeding during pregnancy does not change the basal level of corticosterone in their pups but accelerates the maturation of the hypothalamo-hypophyseal-adrenal axis, as indicated by the response to ether stress or ACTH (30 refs.).

Thor, D. H., Ghiselli, W. B., Ward, T. B.: "Infantile handling and sex differences in shock-elicited aggressive responding of hooded rats." *Dev. Psychobiol.* **7**: 273-279 (1974). J12,750/74

Handling during infancy caused only minor changes in the aggressive response of male and female rats exposed to electric footshock in adulthood.

Mos, L., Vriend, J., Poley, W.: "Effects of light environment on emotionality and the endocrine system of inbred mice." *Physiol. Behav.* **12**: 981-989 (1974). J13,743/74

Mice of different strains were reared in either a dark or a light environment. "Strain and sex affected all organ weights, light rearing affected adrenal, spleen and ovary weight, and emotionality testing affected pituitary and adrenal weight. The results were interpreted that light rearing affects maturation of the hypothalamic-pituitary-adrenal axis and response to stress."

Sex (*Including the Sexual Cycle*)

Here, we shall discuss sex only as a stressor or conditioning agent; data on the effect of stress upon sexual activities, including the menstrual cycle, pregnancy, lactation and the structure of the sex organs, will be considered in the section Morphologic Changes.

Even in the first detailed paper on the G.A.S., it was pointed out that, following

exposure to stressors, female rats develop more marked thymicolumphatic involution than males, perhaps because their adrenals are larger to start with. However, there are many sex differences in responsiveness to various agents and certainly not all of them can be attributed to nonspecific mechanisms. Thus, it is well known that the sex hormones have a definite effect upon various specific detoxifying systems, including drug metabolism and clearance.

Sexual arousal is a typical stressor agent. In repeatedly bred rats, the incidence of arteriosclerosis and mild hypertension is increased, although it is not clear what part the different aspects of breeding (sexual intercourse, pregnancy, lactation) play in this response.

Under crowded urban conditions, men tend to become more competitive and aggressive, whereas women seem to assume a more lenient attitude toward each other. Women are increasingly entering occupations previously reserved for men, and their longevity appears to be decreasing gradually to the normal male level. Now they are more commonly subject to stress-induced diseases than has previously been the case, at least in Western societies.

Undoubtedly, the sexual cycle, especially its anomalies and premenstrual tension, can act as a stressor in females during the reproductive period of life.

In the Pacific salmon, during its spawning migration which lasts several months, the adrenals are considerably enlarged, and there is evidence of increased corticoid secretion as a consequence of this severely stressful activity.

When films that cause sexual arousal were viewed, catecholamine excretion was raised more markedly in male than in female students. There can be no doubt that many sex-dependent factors affect stress resistance but, despite the ample data published, it is still impossible to make any generalizations concerning the sex differences, because the subject is markedly complicated by the many specific elements, both somatic and psychosocial, that influence this phenomenon.

Sex (including the Sexual Cycle)

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* 21: 169-188 (1937). 38,798/37

Experiments on rats showed that age and sex can noticeably influence resistance to stressors. "Old animals react more readily than young ones, possibly because much of their adaptation energy has already been used to meet the incidental demands of life. This probably explains also why resistance against almost any alarming stimulus is more difficult to obtain in fully adult rats, a fact which led to the use of animals 2 to 3 months of age in preference to older ones for the purposes of the present experimental series. Females show a more marked involution of the lymphatic organs after exposure to alarming stimuli than males. This may find its explanation in the fact that the adrenals are larger in the female rat than they are in the male."

Lacey, J. I.: "Sex differences in somatic reactions to stress" (abstracted). *Am. Psychol.* 2: 343 (1947). B26,687/47

Gantt, W. H.: "Disturbances in sexual functions during periods of stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 1030-1050. Baltimore: Williams & Wilkins, 1950.

B51,958/50

Discussion of sexual arousal as a stressor agent and conversely as a functional variable readily influenced by stress.

Kärki, N. T.: "The urinary excretion of noradrenaline and adrenaline in different age groups, its diurnal variation and the effect of muscular work on it." *Acta Physiol. Scand.* 39 Supp. 132: 1-96 (1956). C26,120/56

Monograph on catecholamine excretion in man as influenced by circadian variations, age, muscular work, emotional stress and sex (160 refs.).

Qureshi, M. S.: *Current Medicine—1957*, p. 212. Karachi, Pakistan: Q Publications, 1957.

C40,033/57

Premenstrual tension is designated "premenstrual stress," and a special section is devoted to its possible relation to the G.A.S. Reduction of sodium intake and ammonium chloride treatment before the expected menstrual period allegedly provide relief.

O'Neill, D.: "Stress and the female role." *J. Obstet. Gynaecol. Br. Commonw.* **66**: 762-768 (1959).

J23,253/59

Mialhe-Voloss, C., Stutinsky, F.: "Influence du sexe sur la sensibilité aux agressions 'neurotropes' chez le rat blanc" (Influence of sex on the sensitivity to 'neurotropic' aggressions in the white rat). *C.R. Soc. Biol. (Paris)* **153**: 1848-1851 (1959).

E55,168/59

Soiva, K., Grönroos, M., Aho, A. J., Rinne, U.: "Über die Einwirkung von 'Stress' auf die Geschlechtsorgane und -funktionen der schwangeren und nicht-schwangeren Ratten" (On the effect of "stress" on the sexual organs and functions of the pregnant and non-pregnant rat). *Geburtshilfe Frauenheilkd.* **20**: 505-508 (1960).

G97,218/60

"Auditory and visual stress of 2-4 weeks' duration produced a decrease or a complete cessation in the activity of the genital system of non-pregnant rats." However, gestation failed to protect against the usual consequences of stress.

Toivanen, P., Hulkko, S., Näätänen, E.: "Effect of psychic stress and certain hormone factors on the healing of wounds in rats." *Ann. Med. Exp. Fenn.* **38**: 343-349 (1960).

D89,254/60

Allegedly, psychogenic stress retards wound healing in male but not in female rats.

Robertson, O. H., Krupp, M. A., Favour, C. B., Hane, S., Thomas, S. F.: "Physiological changes occurring in the blood of the Pacific salmon (*Oncorhynchus tshawytscha*) accompanying sexual maturation and spawning." *J. Endocrinol.* **68**: 733-746 (1961).

D4,921/61

During its spawning migration, the Pacific salmon begins a fast which lasts for several months and apparently acts as a potent stressor, in that the adrenals are enlarged and the 17-OHCS concentration of the plasma rises to very high levels.

Kitay, J. I.: "Sex differences in adrenal

cortical secretion in the rat." *Endocrinology* **68**: 818-824 (1961).

D4,930/61

The stress of ether anesthesia increased plasma corticosterone levels more markedly in female than in male rats. The same sex difference was noted after ACTH injections.

Selye, H.: "Stress and sex." In: Ellis, A. and Abarbanel, A., *Encyclopedia of Sexual Behavior*, pp. 1010-1011. New York: Hawthorn Books, 1961.

C58,332/61

Brief summary on stress in relation to sexual activity and sexual disorders.

Meier, R. M., Greenhoot, J. H., Shonley, I., Goodman, J. R., Porter, R. W.: "Sex differences in the serum cholesterol response to stress in monkeys." *Nature* **199**: 812-813 (1963).

E24,291/63

Stress caused by restraint decreased serum cholesterol in rhesus monkeys of both sexes, but particularly in males. A review of earlier data shows that some researchers found an increase, others a decrease, in plasma cholesterol levels in both animals and man, but the reasons for these discrepancies are not investigated (11 refs.).

Schell, R. E., Elliott, R.: "Note on sex differences in response to stress in rats." *Psychol. Rep.* **20**: 1201-1202 (1967).

J23,606/67

Experiments "showed males to be more emotional to relatively mild stress but more resistant than females to more stressful experiences."

Morimoto, T., Slabochova, Z., Naman, R. K., Sargent, F.: "Sex differences in physiological reactions to thermal stress." *J. Appl. Physiol.* **22**: 526-532 (1967).

G45,267/67

Williams, I.: "Some psychological stresses on women." *Med. J. Aust.* **2**: 97-100 (1968).

J10,827/68

Sociologic factors create a need for psychologic counselling among the "surprisingly small number of women who break down under stress of work and domesticity (very much in the field of marriage guidance), in dealing with worried parents and the girl who is difficult at school or in training for her career, and in all our contacts with education and personality training. I would put in the strongest possible plea to consider the whole aptitude of a girl before pushing her or allowing her to push herself into any occupation."

Levi, L.: "Sympatho-adrenomedullary activity, diuresis, and emotional reactions dur-

ing visual sexual stimulation in females and males." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 3: 1-33 (1968). G63,782/68

The viewing of films causing sexual arousal elicited more pronounced EP and NEP excretion in male than in female students. This difference paralleled self-rating scores in emotional reactions.

Gilbert, F. F., Bailey, E. D.: "Visual isolation and stress in female ranch mink particularly during the reproductive season." *Can. J. Zool.* **47**: 209-212 (1969).

J20,525/69

"Visual isolation is apparently more stressful to female mink during the anoestrous period but reduces stress during oestrus and pregnancy. The increased adrenal steroid output of control mink as part of the stress syndrome during the critical reproductive period might be responsible for increased *in utero* losses. But increased adrenocortical output associated with the stress of long term visual isolation might result in insufficient gonadal stimulation resulting in fewer pregnancies."

Hodges, W. F., Felling, J. P.: "Types of stressful situations and their relation to trait anxiety and sex." *J. Consult. Clin. Psychol.* **34**: 333-337 (1970). J20,483/70

Jégo, P., Lescoat, G., Beraud, G., Maniey, J.: "Etude des modalités de réponse du complexe hypothalamo-hypophysio-surrénalien à l'agression par l'éther chez le rat: cas d'une injection intrapéritonéale" (Study on the responsiveness of the hypothalamo-hypophysio-adrenal axis to stress by ether in the rat: effects of intraperitoneal injection). *C. R. Soc. Biol. (Paris)* **164**: 2117-2121 (1970).

H41,303/70

The increase in blood corticosterone produced in rats by ether is diminished by previous pentobarbital anesthesia. However, intraperitoneal injection of ether causes marked rises in blood corticosterone in pentobarbital-anesthetized females, but not in males.

Lescoat, G., Jégo, P., Beraud, G., Maniey, J.: "Influence du sexe sur les modalités de réponse de l'axe hypothalamo-hypophysio-surrénalien aux agressions émotionnelles et somatiques chez le rat" (Sex influences on the response of the hypothalamo-hypophysio-adrenal axis to emotional and systemic stress in the rat). *C. R. Soc. Biol. (Paris)* **164**: 2106-2113 (1970). H41,302/70

Hertig, B. A.: "Human physiological responses to heat stress: males and females

compared." *J. Physiol. (Paris)* **63**: 270-273 (1971). J19,855/71

Ehrlich, P., Freedman, J.: "Population, crowding and human behaviour." *New Scientist, Sci. J.* **50**: 10-14 (1971).

J13,725/71

Studies in urban areas led to the conclusion that, "under crowded conditions, men become more competitive, somewhat more severe, and like each other less, whereas women become more cooperative and lenient and like each other more."

Tanaka, M.: "Experimental studies on human reaction to cold—with reference to differences between males and females." *Bull. Tokyo Med. Dent. Univ.* **19**: 1-18 (1972).

H56,898/72

Upon exposure to cold, heat production was lower in women than in men, but the decrease in skin temperature was more pronounced in males. Urinary 17-KS concentrations increased in the male but not in the female.

Senay, L. C. Jr.: "Body fluids and temperature responses of heat-exposed women before and after ovulation with and without rehydration." *J. Physiol. (Lond.)* **232**: 209-219 (1973). J4,529/73

Personal observations and review of the literature on sex differences in the response of men and women to "heat stress." No special mention is made of any typical stress phenomena.

Wells, C. L., Horvath, S. M.: "Heat stress responses related to the menstrual cycle." *J. Appl. Physiol.* **35**: 1-5 (1973). J4,516/73

The few differences occurring during the menstrual cycle phase had a minimal influence upon the ability of normal women "to regulate body temperature when exposed to environmental heat stress."

Szuchtmann, H., Lambrou, P. J., Caggiula, A. R., Redgate, E. S.: "Plasma corticosterone levels during sexual behavior in male rats." *Horm. Behav.* **5**: 191-200 (1974).

J13,637/74

In male rats, plasma corticosterone levels are often but not invariably elevated during copulation.

Machtey, I., Meer, A.: "In certain physiological stress conditions on the problem of hyperuricemia." *Adv. Exp. Med. Biol.* **41**: 419-421 (1974). J24,476/74

Blood levels of uric acid remained essentially constant during menstruation and ovu-

lation but rose considerably during labor and following delivery. "It is therefore an attractive assumption, that the marked stress connected with labour is the possible cause of the hyperuricemia found in the reported cases."

Neufeld, R. W. J., Davidson, P. O.: "Sex differences in stress response: a multivariate analysis." *J. Abnorm. Psychol.* **83**: 178-185 (1974). J21,175/74

Halevy, S., Altura, B. M.: "Sex and genetics as factors influencing resistance to traumatic shock." *Fed. Proc.* **33**: 298 (1974). H84,061/74

Certain "strains of mice could be used as models to explore further the roles of sex and genetics in resistance to traumatic shock."

Wexler, B. C.: "Adrenocortical changes associated with methylandrostenediol-induced hypertension and isoproterenol-induced myocardial infarction in arteriosclerotic versus nonarteriosclerotic rats." *Lab. Invest.* **30**: 251-259 (1974). J12,177/74

Repeatedly bred rats had naturally-occurring arteriosclerosis and mild hyperten-

sion. If they were treated with isoproterenol, their mortality was high, serum triglycerides and cholesterol were greatly elevated and the repair of drug-induced cardiac necroses was impeded by the formation of aneurysms. It is concluded that "preexisting, chronic, severe hypertension plays a key role in the pathogenesis of left ventricular aneurysm formation during acute myocardial infarction and that severe hypertension combined with arteriosclerosis portends a poor prognosis toward survival" (42 refs.).

Eliot, R. S.: *Stress and The Heart*, Vol. 1, p. 415. Mount Kisco, N.Y.: Futura, 1974.

E10,556/74

Monograph containing many articles by numerous experts on the role of stress in the production of cardiovascular disease, with special reference to hypertension and myocardial infarction. There are chapters dealing with the role of occupation, homeostasis, environmental influences, sex, athletics, emotions and stress tests as well as the therapeutic value of various techniques for relaxation, including Transcendental Meditation, Yoga, Zen, sentic cycles, hypnosis and related practices.

Pregnancy and Lactation

Urinary corticoid excretion is increased during certain periods of gestation in women, and undoubtedly pregnancy, childbirth and lactation represent important sources of stress in females. Yet, curiously, in general, women with peptic ulcers tend to be free of symptoms during pregnancy.

Pregnancy, Lactation

(See also our earlier stress monographs, p. xiii)

Cope, C. L., Boysen, X., McCrae, S.: "Some observations on endogenous cortisone excretion in man." *Br. Med. J.* September 29, 1951, pp. 762-767. B64,531/51

Urinary corticoid excretion (assayed by eosinopenia in adrenalectomized mice) is increased in a variety of diseases (status asthmaticus, coronary infarct, bronchopneumonia, carcinoma of pancreas, pneumococcal meningitis, congestive cardiac failure, diabetic ketosis) as well as in late pregnancy.

Soiva, K., Grönroos, M., Aho, A. J., Rinne, U.: "Über die Einwirkung von 'Stress' auf die Geschlechtsorgane und -funktionen der

schwangeren und nicht-schwangeren Ratten" (On the effect of "stress" on the sexual organs and functions of the pregnant and non-pregnant rat). *Geburtshilfe Frauenheilkd.* **20**: 505-508 (1960). G97,218/60

"Auditory and visual stress of 2-4 weeks' duration produced a decrease or a complete cessation in the activity of the genital system of non-pregnant rats." However, gestation failed to protect against the usual consequences of stress.

Nicoll, C. S., Talwalker, P. K., Meites, J.: "Initiation of lactation in rats by non-specific stresses." *Am. J. Physiol.* **198**: 1103-1106 (1960). C87,153/60

In estradiol-pretreated rats, various stressors (cold, restraint, formaldehyde) initiated

lactation. "It is concluded that non-specific stresses can promote the secretion of prolactin and ACTH from the anterior pituitary in amounts adequate to induce lactation in estrogen-primed rats."

Hytten, F. E., Thomson, A. M.: "Pregnancy, childbirth and lactation." In: Edholm, O. G., and Bachrach, A., *The Physiology of Human Survival*, pp. 327-350. New York and London: Academic Press, 1965.

E6,288/65

Review on the effects of pregnancy upon nonspecific resistance and on stress manifestations during gestation. "Pregnancy is the most common physiological stress to which women are exposed. The study of the adaptations that occur during pregnancy is not only of interest in itself, but also may help to increase understanding of the nature of responses to other forms of stress."

Fries, J. C. de, Weir, M. W., Hegmann, J. P.: "Blocking of pregnancy in mice as a function of stress: supplementary note." *Psychol. Rep.* **17**: 96-98 (1965).

J23,378/65

Larsen, V. L.: "Stresses of the childbearing year." *Am. J. Public Health* **56**: 32-36 (1966).

E73,778/66

Gottfried, I., Lewenthal, H., Goldberg, S.: "Free 11-hydroxycorticosteroids in plasma and urine in pregnancy and in cases of stress." *Am. J. Obstet. Gynecol.* **102**: 924-927 (1968).

G62,921/68

The free plasma and urinary 11-OHCS levels were measured in normal nonpregnant and normal pregnant women, those with a suspected fetal death, and in female patients after surgical stress.

Helper, M. M., Cohen, R. L., Beitenman, E. T., Eaton, L. F.: "Life-events and acceptance of pregnancy." *J. Psychosom. Res.* **12**: 183-188 (1968).

J22,198/68

Hanford, J. M.: "Pregnancy as a state of conflict." *Psychol. Rep.* **22**: 1313-1342 (1968).

J24,486/68

Discussion of pregnancy in relation to the G.A.S. concept (118 refs.).

Corson, J. A., Heseltine, G. F. D., Smith, D. J.: "Psychological stress during pregnancy, effects on mothers and offspring." *Br. J. Pharmacol.* **38**: 457P-458P (1970).

J23,168/70

Jégo, P., Lescoat, G., Maniey, J.: "Influence de la gestation sur la réponse du

complexe hypothalamo-hypophysio-surrénalien aux agressions" (Influence of pregnancy on the response of the hypothalamo-hypophysio-adrenal complex to stressors). *C. R. Acad. Sci. (Paris)* **272**: 1133-1136 (1971).

G82,173/71

In pregnant rats, there is a mathematical correlation between the initial blood corticosterone level and the rise produced by psychogenic stressors.

Thieme, R., Theisinger, W.: "Stressulkus im Wochenbett (Ein kasuistischer Beitrag)" (Stress ulcers after delivery. A case report). *Zentralbl. Gynaekol.* **93**: 894-897 (1971).

G84,873/71

In general, patients with peptic ulcers tend to be free of symptoms during pregnancy. In one woman however, a perforating duodenal ulcer developed after delivery.

Boyne, R., Fell, B. F.: "Observations on the alkaline phosphatase content of the neutrophil granulocytes of some laboratory and farm animals, with particular reference to the effects of intensive management and reproduction." *Res. Vet. Sci.* **13**: 347-355 (1972).

J19,597/72

Alkaline phosphatase activity in circulating polymorphonuclear leukocytes was raised under relatively mild conditions of stress in cattle, pigs and rats. Marked increases occurred in association with pregnancy in pigs, sheep and rabbits." The effect is presumably caused by enhanced corticoid secretion.

Wilson, S. P., Doolittle, D. P., Dunn, T. G., Malven, P. V.: "Effect of temperature stress on growth, reproduction, and adrenocortical function of mice." *J. Hered.* **63**: 324-330 (1972).

G99,980/72

Nadelson, C.: "'Normal' and 'special' aspects of pregnancy." *Obstet. Gynecol.* **41**: 611-620 (1973).

J19,682/73

Paris, A. L., Ramaley, J. A.: "Effects of short-term stress upon fertility. I. Before puberty." *Fertil. Steril.* **24**: 540-545 (1973).

J4,325/73

Paris, A., Kelly, P., Ramaley, J. A.: "Effects of short-term stress upon fertility. II. After puberty." *Fertil. Steril.* **24**: 546-552 (1973).

J4,326/73

Meikle, S., Gerritse, R.: "A comparison of husband-wife responses to pregnancy." *J. Psychol.* **83**: 17-23 (1973).

J19,604/73

Stern, J. M., Goldman, L., Levine, S.: "Pituitary-adrenal responsiveness during lac-

tation in rats." *Neuroendocrinology* **12**: 179-191 (1973). H74,724/73

In rats, suckling itself induced ACTH discharge, and the elevated basal plasma corticosterone level during lactation was diminished by ether stress. "After dexamethasone treatment, the corticosterone output to exogenous ACTH was lower in the plasma and higher in the adrenal" of lactating than of non-lactating rats.

Machtey, I., Meer, A.: "In certain physiological stress conditions on the problem of hyperuricemia." *Adv. Exp. Med. Biol.* **41**: 419-421 (1974). J24,476/74

Blood levels of uric acid remained essentially constant during menstruation and ovulation but rose considerably during labor and following delivery. "It is therefore an attractive assumption, that the marked stress connected with labour is the possible cause of the hyperuricemia found in the reported cases."

Schlein, P. A., Zarrow, M. X., Denenberg, V. H.: "The role of prolactin in the depressed or 'buffered' adrenocorticosteroid response of the rat." *J. Endocrinol.* **62**: 93-99 (1974). H90,051/74

The diminished corticosterone secretion of lactating rats under stress is due to a blockade produced by an increased LTH level.

Hamburg, M., Mendoza, L. A., Rader, M., Lang, A., Silverstein, H., Hoffman, K.: "Malformations induced in offspring of crowded and parabiotically stressed mice." *Teratology* **10**: 31-37 (1974). J15,934/74

Malformations were induced in fetuses of mice kept under crowded conditions or parabiotically joined during pregnancy. "The abnormalities included amputation of peripheral limb structures, open neural folds, exencephaly, blisters, head, face, and tail malformation, and generalized growth retardation. The hypothesis that the teratogenic and other effects were consequences of prolonged prenatal stress induced by the experimental conditions is supported by the observation that both procedures led in a short time to significant increases in mean maternal adrenal weight."

Cohler, B. J., Grunebaum, H. U., Weiss, J. L., Gallant, D. H., Abernethy, V.: "Social relations, stress, and psychiatric hospitalization among mothers of young children." *Soc. Psychiatr.* **9**: 7-12 (1974). J15,145/74

Hospitalization for psychiatric disturbances of mothers of young children is associated with psychogenic stress; it "is believed to be related both to impairment in a woman's performance of her role as housewife and mother, as well as to life stress experienced prior to hospitalization."

GENETICS, RACE, CONSTITUTION

(See also Diseases of Adaptation in man—particularly in relation to urbanization, demographic factors, social and cultural stressors)

Undoubtedly, genetic factors are among the most important endogenous conditioning agents which predispose certain individuals, species and races to respond in a particular manner to identical stressors. Consequently, as we shall see, some species of animals genetically predisposed to hypertension, audiogenic seizures, aggressive behavior, or even stress as such, have furnished investigators with especially useful test objects for the study of various types of stress reactions.

Generalities

(See also our earlier stress monographs, p. xiii)

Garren, H. W., Shaffner, C. S.: "How the period of exposure to different stress stimuli affects the endocrine and lymphatic gland weights of young chickens." *Poultry Sci.* **35**: 266-272 (1956). C43,626/56

Chansky, N. M.: "Stress, personality and visual closure." *J. Psychol.* **57**: 289-301 (1964). J23,594/64

A modified Rorschach test with a questionnaire is used to show what personality traits are connected with defects in "visual closure," the ability to fill gaps in incomplete patterns during stress.

Shire, J. G. M.: "Endocrine genetics of

the adrenal gland." *J. Endocrinol.* **62**: 173-207 (1974). H90,064/74

Detailed review of the genetic factors that can influence the adrenals, particularly in their response to stressors (about 200 refs.).

Valtin, H., Stewart, J., Sokol, H. W.: "Genetic control of the production of posterior

pituitary principles." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 1, pp. 131-171. Washington, D.C.: American Physiological Society, 1974. E10,727/74

Review on vasopressin and oxytocin secretion during stress in various species (215 refs.).

Vertebrates

Man. In the many studies on the effect of racial and other genetic factors upon the stress resistance of people with different genetic backgrounds, it has been particularly difficult to distinguish the role of heredity as such from the associated differences in cultural, climatic socioeconomic and other demographic conditions which influence diverse populations. There is no doubt, however, that even in our Western civilization, certain individuals are genetically predisposed to respond very differently to the common stressors of pleasant and unpleasant events, interpersonal relationships in the family and at work, wars and other emergency situations, economic problems, disease and so on.

Extensive studies on primitive, rural or nomadic populations—as well as on Jews, the Irish, Mexicans, Negroes, Japanese, Eskimos, American Indians, and other races—have shown wide differences in their susceptibility to certain stressors, including the development of hypertension, peptic ulcers, mental illness, diabetes, ulcerative colitis and other diseases of adaptation. Among typical Caucasians, several investigators claim to have observed variations in stress resistance, depending upon physique and personality types.

Bat. In the bat, captivity during hibernation did not influence adrenal ascorbic acid content, but arousal of noncaptive hibernating bats caused a rise in the blood corticosterone level. ACTH and EP elicit similar effects, but these are definitely diminished during hibernation. *

The EM changes in the adrenals of bats have been carefully examined during hibernation. In this species, two types of medullary cells can be differentiated, one producing EP, the other NEP. The secretory activity of the cortex is diminished during hibernation and rises rapidly upon arousal.

Cat. Comparatively few investigators have performed studies on stress using the cat as an experimental animal. Yet it is noteworthy that in the cat the adenohypophysis receives no arterial blood and is supplied only by portal vessels descending from the stalk. Consequently, transection of the latter causes pituitary necrosis and renders the species unsuitable for studies on severance of the pituitary from the hypothalamus.

Unilateral adrenalectomy elicits ascorbic acid depletion in the contralateral gland of the cat, and this effect can be blocked by cortisol. Yet, compensatory hypertrophy of the adrenal is not as obvious here as in most other species.

Cattle. In cattle, various diseases are associated with histologic signs of adrenocortical hyperactivity, presumably as a consequence of their stressor action. "Heat

stress" adversely affects the spermatogenesis and fertility of bulls. It must be remembered, however, that heat has a known specific damaging influence on testicular tissue. In calves, aldosterone excretion is allegedly increased by shipping.

Donkey. Presumably because of a particularly efficient sweating and rehydration mechanism elicited by EP secretion, donkeys are extremely resistant to "desert heat stress." Interdermal injection of EP causes local sweating in the donkey and horse.

Gerbil. Certain genetically predisposed gerbils respond to stressors (electroshock, photic or auditory stimulation) with typical epileptoid seizures.

Goat. In goats, extensive investigations have confirmed that transection of the pituitary stalk (with prevention of anastomosis formation by a plate) causes infarction and/or atrophy of the adenohypophysis and infundibular process, but the intermediate lobe undergoes considerable hypertrophy. This finding may help in learning more about the hypothalamus-pituitary pathways, which play an important role in the mediation of stress responses.

Guinea Pig. In guinea pigs, prolonged exposure to noise or cold produces typical histologic changes in the adrenal cortex, which follow the three stages of the G.A.S. Pretreatment with ascorbic acid allegedly reverses the eosinophil response and virtually blocks the loss of ascorbic acid from the adrenals of guinea pigs exposed to cold.

In newborn guinea pigs, deafferentation of the hypothalamus impairs growth and gonadal function, but leaves thyroid and adrenal activity unaffected in males and only moderately diminishes it in females.

Hamster. Hamsters are also quite commonly used in experiments on stress. Allegedly, Syrian hamsters show little evidence of adrenal enlargement during exposure to cold, either during hibernation or at other times, yet the hamster adrenal is normally sensitive to other stressors.

No special seasonal variations in catecholamine excretion were noted in hamsters, although the elimination of these compounds is actually diminished during adaptation to cold. On the other hand, urinary glucocorticoid and aldosterone excretion is subject to definite seasonal fluctuations. At the time of awakening from hibernation, there appear signs of hyperactivity in both the cortex and medulla of the hamster adrenal.

Chinese hamsters unfamiliar with each other immediately start fighting when placed in the same cage. This results in glycosuria with a catecholamine and corticoid discharge characteristic of stress. It has been pointed out that such a response may help in our explorations of stress-induced diabetes.

Horse. In ponies, neither handling, repeated venipuncture, nor EP-induced hyperglycemia elicited eosinopenia, but injections of ACTH, insulin or histamine did bring about this response.

Adaptation to cold and muscular training increased thyroxine secretion in the horse, and exposure to various stressors caused singular pancreatic lesions whose pathogenesis has not yet been clarified.

Surgical trauma and induced hypoglycemia raise plasma cortisol levels, whereas exercise is much less effective in this respect. It is concluded that the mechanisms con-

trolling adrenocortical functions in the horse are similar to those in other mammals, although, curiously, here the plasma cortisol variations are not necessarily associated with corresponding changes in eosinophil count.

Monkey, Ape. As far as their hypothalamus-pituitary-adrenocortical and catecholaminergic responses are concerned, monkeys and apes appear to react to stressors essentially like human beings. This is true also of many other stress parameters. For example, in squirrel monkeys captured in Colombia, serum cholesterol rose significantly after transportation to North Carolina, presumably because of the stressor effect of translocation; this effect has also been demonstrated in man and many other species. Curiously, restraint has been claimed to decrease blood cholesterol in rhesus monkeys, at least under certain conditions. The major steroid produced during stress in monkeys and apes appears to be cortisol. In addition, capture, restraint and aversive conditioning also increase the plasma STH of the squirrel monkey.

In rhesus monkeys, electric stimulation of various hypothalamic areas results essentially in the same hormone reactions as in other species, including, presumably, man.

Mouse, Garden Doormouse. Certain strains of mice are particularly susceptible to audiogenic seizures, during which they exhibit typical manifestations of the G.A.S. such as eosinopenia, increased corticoid and catecholamine secretion. The brain levels of NEP and 5-HT are especially high in these seizure-susceptible strains. However, in the mouse—as in the rat—the genetically determined sensitivity to sound appears to be quite specific, and the manifestations of stress are secondary to the convulsive response. There is no definite evidence of hypersensitivity to other stressors.

In extremely seizure-susceptible mice, reserpine and MAO inhibitors diminish the lethality of convulsions. In conjunction with the observation that brain NEP is depleted during lethal seizures, it was assumed that NEP deprivation of nervous centers may be the cause of mortality. Yet, in mice rendered resistant to seizures by repeated exposure to sound, the brain NEP concentration also drops. Perhaps, lethality depends upon a particularly rapid catecholamine loss.

Allegedly, in mice, hypoglycemia and exposure to cold did not stimulate STH secretion, whereas fasting caused a slight depletion of the STH level in the pituitary and an increase in the plasma. Perhaps because of the high metabolic rate of this species, STH secretion is already near-maximal under basal conditions and hence cannot readily be raised further.

In hairless strains of mice, immobilization and exposure of the skin surface to intense sound vibrations can act as potent stressors, presumably because of impaired temperature regulation resulting from the absence of fur.

No definite difference in endurance was noted between wild and domestic mice swimming in cold water.

In mice with a "lethargic" mutant recessive gene, forced swimming causes especially pronounced manifestations of stress.

Pig. As judged by adrenal ascorbic acid determinations, chlorpromazine diminishes ACTH secretion in pigs exposed to high temperatures.

In baby pigs, cold or starvation causes typical G.A.S. changes with adrenal lipid loss, hypoglycemia and eosinopenia.

Stress may also elicit aggressive behavior, infarctoid cardiac necrosis and peptic ulcers in the stomach of pigs.

It has been possible to produce stress-susceptible and stress-resistant strains of pigs, by selective breeding.

Rabbit, Hare. Certain strains of wild rabbits react to frightening stimuli (for example, fear of a chasing dog) with a singular response designated by one group of investigators as "stress thyrotoxicosis." Here, thyroid hyperthyroidism and exophthalmus, due to increased TTH secretion, are associated with adrenocortical enlargement and are sometimes conducive to sudden death. The response can be prevented by hypophysectomy or methylthiouracil. There appears to be some ambiguity concerning the corticotrophic response, since in another publication the same investigators state that "the symptomatology and the cause of fear thyrotoxicosis can be classified in terms of the phases of the alarm reaction, resistance and exhaustion (Selye). Increased thyrotropic function causes inhibition of ACTH secretion." This latter finding might be explained by the "shift in hypophyseal hormone production," yet at other times both TTH and ACTH discharge may apparently be enhanced simultaneously.

In most strains of rabbits, stressors elicit only the usual response of the hypophysis-adrenocortical system. Both corticosterone and cortisol show a circadian rhythm with a peak during the day and a drop at the end of the night.

In captive hares, the presence of a hunting dog may elicit testicular atrophy as a result of fear. This finding agrees with the well-known tendency of stressors to cause gonadal involution.

Rat. Since the rat is the most common laboratory animal used in experiments on stress, there are ample data concerning strain differences in the nonspecific resistance of this species.

Comparative studies on wild and domesticated rats showed that the former have larger adrenals and a smaller thymicolympathic apparatus, since they are much more frequently exposed to stressors than are the sheltered laboratory variety. Also, in contrast to the domesticated type, wild rats cannot be indefinitely maintained on sodium chloride after adrenalectomy. Furthermore, the adrenals of wild Norway rats are less sensitive to intestinal trauma, hemorrhage, ether anesthesia, unilateral adrenalectomy, or even ACTH administration than are those of domesticated individuals of the same strain, as indicated by ascorbic acid depletion.

In the Brattleboro strain of rats, a hypothalamic diabetes insipidus tends to develop, which can be corrected by vasopressin. In these animals, stress caused by ether anesthesia or bleeding still raised plasma corticosterone, but to a significantly lesser extent than in normal controls. The CRF activity in the ME and the ACTH concentration in the pituitary were essentially the same in both strains. Hence, it was concluded that, although vasopressin is not identical with CRF, it may play a minor role in the adrenocortical response to stress.

In vitro observations suggest that, in the Brattleboro rat, the adrenal glands themselves are relatively insensitive to ACTH. It has been postulated that perhaps the absence of vasopressin in the internal milieu during early life may permanently influence adrenal sensitivity.

Another strain of rats is particularly susceptible to audiogenic seizures; they re-

spond very strongly to what has been called "auditory stress," which elicits pronounced adrenocortical hypertrophy and thymus involution.

Yet another strain of rats is congenitally predisposed to the spontaneous development of hypertension, and this tendency is aggravated by stress.

Sheep. A good deal of work has been done on sheep to verify the localization of the hypothalamic centers responsible for different types of adenohypophyseal activity. According to some investigators, transection of the stalk sometimes prevents the ACTH-induced corticoid discharge (presumably when no vascular anastomoses develop). Others, who inserted a plate between the cut ends of the stalk, found that most of the pituitary actually undergoes infarction in this species.

Various stressors, such as cold, EP and NEP, elicit the usual biochemical changes in lambs, that is, an increase in FFA, lactic acid and glucose with a decrease in muscle glycogen and body temperature. In accordance with observations on other species, repeated exposure to stressors induces resistance.

Tupaia. The tree shrew (*Tupaia belangeri*) lends itself particularly well to certain experiments on stress, because the hairs on the tail normally lie flat, but they become erect and bushy upon the slightest stimulation, thereby offering a readily visible indicator of increased sympathetic activity. This response is especially evident during sexual arousal of *Tupaias* or aggressive confrontation of two males. The phenomenon has been regarded as part of the G.A.S.

Male *Tupaias*, after being defeated by a trained fighter, become terrified upon seeing him, even if protected by a separating wire mesh. If the fight is repeated every one or two days, the defeated *Tupaia* dies in less than three weeks due to "psychosocial stress," even without suffering any mortal wounds. This response is characterized by adrenal enlargement and an increased ascorbic acid concentration, in contrast to a decrease in most other species. The blood glucocorticoids rise, and at the same time there is a loss of liver glycogen and body weight associated with an eventually fatal uremia due to kidney damage.

Although these experiments were all conducted under essentially identical conditions by the same investigator, they suggest that the *Tupaia* is particularly sensitive to psychogenic stress and in some respects responds to it in an unusual manner.

Various Other Mammals. Among other mammals, special attention has been given to the *hedgehog*, in which the changes induced by hibernation were similar to those of the G.A.S. However, presumably this is true only during arousal, since in deep hibernation the function of the adrenals is greatly diminished, although the mitochondria retain their EM characteristics.

Additional data on stress responses in the *beaver*, *deer*, *dolphin*, *ferret*, *giraffe*, *marsupials* (*kangaroo*, *wallabies*), *mink*, *mongoose*, *opossum*, *squirrel*, *vole*, *woodchuck* (*Marmota monax*) and others will be found in the abstract section in alphabetic order.

It appears that, in the lowest order of mammals (*Monotremata*), adrenal function is not very well developed. Still, their resistance to cold is diminished by adrenalectomy, and adrenal hypertrophy in *echidnas* shows the importance of these glands for resistance to stressors, such as fasting and cold.

Birds. Many stress studies have been performed on birds. In laying *chickens*, crowding causes adrenal hypertrophy and diminishes egg production, presumably as a consequence of stress.

Young chicks imprinted to surrogate mothers allegedly showed increased resistance to the stressor effect of a door bell, both in the presence and in the absence of their substitute mothers.

By moving cockerels into cages with other birds, it is possible to produce typical stress phenomena, such as adrenal hypertrophy, a loss of cholesterol, involution of the bursa, changes in blood count, decreased resistance to infection and even a rise of plasma corticosterone.

In chick embryos, breaking one shank (after opening the shell) elevates plasma corticosterone concentrations to some extent. However, the pituitary becomes important after two weeks of incubation in maintaining both the resting level of the hormone and the stress response. At this early age, the hypothalamus does not appear to control resting blood levels of corticosterone, although it is essential for the stress response. The initial autonomy of the adrenal cortex is demonstrated by persistent plasma corticosterone concentrations after decapitation of the embryo.

In the *pigeon*—as in most birds—the cortical and medullary cells of the adrenals are intermixed. Hypophysectomy causes only a slight decrease in adrenal weight, due mainly to atrophy of the interrenal (cortical) cells near the center of the gland, but various stressors (formaldehyde, insulin) induce hypertrophy of both interrenal and chromaffin cells, even in hypophysectomized pigeons. Allegedly, very large lesions in the ME and ventral hypothalamus produced adrenal hypertrophy rather than atrophy, even after total hypophysectomy, and did not prevent the response to formaldehyde. It was concluded from this that “the interrenal tissue of the pigeon responds to a humoral stimulus, not of hypophyseal origin in the absence of the hypophyseal hypothalamic system.” However, these findings do not agree with some later observations.

By means of localized hypothalamic lesions in pigeons, a well-defined adrenocorticotropic area could be demonstrated in the posterior medial and lateral hypothalamic regions whose destruction resulted in a fall of plasma corticosterone, similar to that obtained by adenohypophysectomy. Lesions in this area also suppressed the adrenocortical response to stressors. It remains to be seen whether the residual adrenocortical response of the hypophysectomized pigeon is due to partial autonomy of the gland or to some extrahypophyseal control system. In any event, the fact that destruction of the hypothalamic regulating center abolishes corticotrophic activity shows that even in this species the function of the adrenal cortex is not completely autonomous, as was previously suggested.

Deafferentation of the hypothalamus suppressed the circadian variations of plasma corticosterone in pigeons, but only diminished the response to ether stress.

Insulin and metyrapone induce hypertrophy and hyperplasia of the ACTH-producing “epsilon cells” in the adenohypophysis of the pigeon, with EM manifestations of hyperactivity and an increase in the ACTH content of the gland. Presumably, the epsilon cells of birds are the source of ACTH.

Stress reactions have also been studied in the *turkey*, *duck*, *black-headed gull*, *quail*, *parakeet* and *myna*. Comparative investigations on several avian species have shown that dexamethasone causes atrophy of the interrenal gland without any clearcut evidence of zonal differences.

According to a review of the literature, in several species of birds the hypothalamus can produce an extrahypophyseal ACTH-like polypeptide. In any event, the bird adrenal responds directly to ACTH by hypertrophy and increased corticoid secretion.

Reptiles. The adrenals of *lizards* consist of a dorsal medullary and a ventral interrenal (cortical) portion. In the Yucca night lizard, hypophysectomy, cortisone and DOC cause involution of the interrenal cells with lipid depletion. ACTH, which induces hypertrophy of this tissue, also depletes it of lipids. Similar changes indicative of interrenal hyperactivity are produced by the stress of starvation.

In the lizard *Anolis carolinensis*, a neuro-intermediate lobe grafted below the skin elicits a local small dark patch, owing to MTH discharge, and exposure to stressors results in a rapid release of MTH.

Turtles are especially adaptable to low or high oxygen tension, ultraviolet radiation and cold. This property makes them particularly suitable for certain types of stress research. Allegedly, they can long survive under anaerobic conditions, or at temperatures as high as 41°C. In this species, weight loss appears to be a better index of thermal stress than pulse rate.

Other reptiles used for stress research are *snakes*, *caimans* and *iguanas*.

Amphibians. The morphology and function of the pituitary-adrenal system have been carefully studied in frogs and toads.

In the *frog*, brief immobilization causes hyperactivity of the interrenal tissue, as indicated by increased plasma corticosterone levels and excess synthesis of corticoids in adrenal homogenates.

In the *toad*, the hypothalamus consists of a pars basalis, lamina terminalis and lobus infundibularis. The latter is attached to the hypophysis, and if lesioned, the gland becomes largely atrophic, with increased absorption of MTH (manifested by darkening of the animal) and other hormonal derangements. Under ordinary conditions, the toad responds to various stressors (cold, dehydration) and to ACTH with depletion of adrenocortical lipids, but in hibernation, allegedly, only dehydration is effective in this respect.

In the *newt*, hemorrhage caused neutrophilia followed by lymphopenia and eosinopenia. Since mere handling of the animals induced similar changes, these were ascribed to stress.

Fish. There exists considerable literature on the effect of stressors upon various types of fish, in some of which the chromaffin (medullary) and interrenal (cortical) tissues are intermixed, while in others they are completely separate. It was the latter type of arrangement that first permitted the demonstration that the interrenal gland is indispensable for the maintenance of life, since its selective removal caused muscular weakness and hyperpigmentation (similar to the manifestations of Addison's disease) which could be cured by interrenal extracts.

In the *goldfish*, in which the two cell types are intermixed, ACTH failed to alter the granulation of interrenal cells, but produced condensation of their cytoplasm as well as alterations in chromaffin cells. Similar changes were evoked by exposure to extremes of temperature. Evidence of increased corticoid and catecholamine secretion as well as other manifestations typical of stress have also been observed in numerous species of fish.

According to one group of investigators, the alarm reaction in fish is believed to be produced by a special substance, "pheromone," secreted by cells of the epidermis. A crude preparation of "alarm pheromone," dropped into an aquarium, causes fright and alarm behavior, withdrawal, and even enhancement of avoidance conditioning in fish. However, it is not quite clear whether this substance and the changes it produces are actually related to the alarm reaction, as described in mammals.

In goldfish, the blood cortisol levels show a clearcut circadian rhythm and a particularly pronounced rise following exposure to diverse stressors.

In various species of fish, the heart rate is also accelerated by hypoxia.

The stressors most often investigated in fish are changes in salinity, temperature variations, capture and restraint, muscular fatigue, hypoxia, hemorrhage and trauma. The most common indicators of stress are: increased catecholamine and corticoid secretion, characteristic changes in blood count, loss of body weight, variations in blood sugar, depletion of liver glycogen, high serum lactate and glucose as well as elevation of hepatic tyrosine aminotransferases.

Among *teleosts*, the prolonged swimming, without food intake, from Europe to the spawning grounds three thousand miles away represents a particularly potent stressor. In the migrating *Pacific salmon*, there is considerable hyperactivity of the interrenal body, and blood corticoid concentrations are increased. At the same time, the plasma EP level also rises.

In general, it may be said that the hypothalamus-pituitary-adrenocortical and catecholamine responses to stressors are essentially the same in fish as in mammals, whether their chromaffin and cortical tissue is separate or intermixed. However, it has not as yet been resolved with certainty that fish are equally, or less, dependent upon higher centers for their adrenal activity and for their stress responses in general.

Vertebrates

(See also our earlier stress monographs, p. xiii)

MAMMALS

Man. Funkenstein, D. H., King, S. H., Drolette, M. E.: "Personality correlates of two phases of stress reactions." *Arch. Neurol. Psychiatry* **74**: 222-223 (1955).

J12,442/55

Ames, M. M.: "Reaction to stress: a comparative study of nativism." *J. Anthropol.* **3**: 17-30 (1957). J2,333/57

Studies on four cultures—Manus (Mead, 1956), Klamath, Modoc, and Paviotso (Nash, 1937)—and their responses to the stress of culture contact which took various forms of nativistic reactions. An attempt was made "to show the importance of the cultural variable in an analysis of stress and its consequences, and to present an analytic scheme by which nativistic movements can be compared and classified."

Lazarus, R. S., Baker, R. W., Broverman, D. M., Mayer, J.: "Personality and psychological stress." *J. Pers.* **25**: 559-577 (1957).

B29,451/57

Personal observations and review of the literature on the role of personality in determining responses to psychogenic stressors (8 refs.).

Silverman, A. J., Cohen, S. I., Zuidema, G. D.: "Psychophysiological investigations in cardiovascular stress." *Am. J. Psychiatry* **113**: 691-693 (1957). C29,216/57

Personal aggressiveness was observed to be a significant factor in the gravity tolerance of men subjected to centrifugal stress; those individuals with outgoing and aggressive personalities proving definitely more resistant to centrifuge-induced black-out and loss of sight. Even among such better-adapted individuals, gravity tolerance varied in accordance with the immediate psychologic state, so that they experienced "highest black-out levels just after they had expressed some anger, or were relatively free from anxiety."

Lowest black-out levels were obtained when they were worried, depressed, anxious."

Caron, A. J., Wallach, M. A.: "Personality determinants of repressive and obsessive reactions to failure-stress." *J. Abnorm. Soc. Psychol.* **59**: 236-245 (1959). G82,249/59

Harvard freshmen received a complete battery of tests used in factor analysis either under normal conditions or when submitted to a failure stress. Their performance was related to their personality characteristics, particularly ego strength, need achievement and hysteria. The influence of these characteristics upon repressive and obsessive forms of defense is discussed.

Parkinson, L., Ghysot, E., Vlierberghe, R., van, Bone, G.: "Adrenocortical response of Bantus and Europeans to surgical stress." *Trans. R. Soc. Trop. Med. Hyg.* **54**: 366-372 (1960). J24,873/60

Sanua, V. D.: "Sociocultural factors in responses to stressful life situations: the behavior of aged amputees as an example." *J. Health Hum. Behav.* **1**: 17-24 (1960).

J10,962/60

Comparative studies on the psychic and behavioral changes in aged Jewish, "Old American," Irish and Negro male amputees. "Variations relating to types of reaction to stress are attributable to the family values and cultural conditioning of the respective ethnic and religious groups to which the patient belongs. The loss of a limb is much more serious to the Jewish patient than the non-Jewish. Crying and overt expression of emotion are more likely to be accepted in Jewish families without the loss of the 'masculine' status."

Scotch, N. A.: "A preliminary report on the relation of sociocultural factors to hypertension among the Zulu." *Ann. N.Y. Acad. Sci.* **84**: 1000-1009 (1960). B42,444/60

Studies on the influence of urbanization upon the incidence of hypertension in Zulus of two African communities.

Scotch, N. A.: "Sociocultural factors in the epidemiology of Zulu hypertension." *Am. J. Public Health* **53**: 1205-1213 (1963).

J10,864/63

The mean blood pressure of urban Zulu populations is significantly higher than that of rural ones. "There was a relationship between variables observed to be stressful and hypertension."

Kuttner, R. E., Mailander, J. C.: "Serum

pepsinogen in migrant Mexicans and stressed Caucasians." *J. Natl. Med. Assoc.* **57**: 109-111 (1965).

G28,384/65

Serum pepsinogen values are higher in Mexican men than in Caucasians. "This difference did not appear to be due to migrancy and its unsettling influences. A study of a presumably stressed female Caucasian population showed no influence on pepsin secretion. It was concluded that the Indian racial element in the Mexican sample was the responsible factor behind the pepsinogen elevation."

Schachter, J., Williams, T. A., Rowe, R., Schachter, J. S., Jameson, J.: "Personality correlates of physiological reactivity to stress: a study of forty-six college males." *Am. J. Psychiatry* **121**: xii-xxiv (1965).

J8,683/65

Review of the literature and personal observations on the relationship between personality and psychophysiological responses to psychogenic stress. Heart rate, skin resistance and blood pressure were used as indicators of stress. The interpretation of such studies is admittedly very difficult (27 refs.).

Kissel, S.: "Stress-reducing properties of social stimuli." *J. Pers. Soc. Psychol.* **2**: 378-384 (1965).

J8,704/65

Psychogenic stress, measured primarily by GSR, was induced by having subjects solve task problems in a laboratory setting. Such situations were less stressful in the presence of a friend than in that of a stranger. However, "the hypothesis that individuals with strong affiliative motives will show a greater reduction in stress responses than will individuals with weak affiliative motives in the presence of another person was not confirmed."

Frankenheuser, M., Patkai, P.: "Interindividual differences in catecholamine excretion during stress." *Scand. J. Psychol.* **6**: 117-123 (1965).

F72,211/65

Stewart, H.: "The relationship of physical illness to the IPAT 16 Personality Factors Test." *J. Clin. Psychol.* **21**: 264-266 (1965).

J23,269/65

Klein, R. F., Troyer, W. G., Back, K. W., Hood, T. C., Bogdonoff, M. D.: "Experimental stress and fat mobilization in lean and obese subjects." *Metabolism* **14**: 17-25 (1965).

F26,728/65

Plasma FFA values in obese persons exposed to two stressors (exercise on a sta-

tionary bicycle and a difficult perceptual judgment task) revealed lower initial levels and diminished variability as compared to nonobese subjects. "Insulin activity or adrenergic nervous system activity may be altered in obesity."

Lazarus, R. S., Tomita, M., Opton, E. Jr., Kodama, M.: "A cross-cultural study of stress-reaction patterns in Japan." *J. Pers. Soc. Psychol.* **4**: 622-633 (1966).

J15,487/66

Comparative studies on the response of Japanese students and middle-aged adults to stressful motion picture films. "The pattern of mood and the degree and timing of reported distress were similar, and the defensive orientations reduced stress reaction for both subjective and physiological measures. However, the hypothesized interaction between MMPI-scaled personality disposition and defensive orientations was not observed. Unlike Americans, Japanese Ss' skin conductance was almost as high during the benign film as during the stressful film, and their conductance during the stressful film was poorly correlated to the specific stressful scenes."

Masuda, M., Holmes, T. H.: "The social readjustment rating scale: a cross-cultural study of Japanese and Americans." *J. Psychosom. Res.* **11**: 227-237 (1967).

J13,504/67

Description of the SRRQ, designed to quantify the amount of change in life adjustment required by forty-three categories of life events. Some of these are socially desirable, others undesirable, but "each usually evokes or is associated with some adaptive or coping behavior on the part of the involved individual. The emphasis is on change from the existing steady state, and not on psychological meaning, emotion, or social desirability." Similarities and differences between American and Japanese population samples are discussed (22 refs.).

Henschel, A.: "Obesity as an occupational hazard." *Can. J. Public Health* **58**: 491-493 (1967) (15 refs.).

E71,837/67

Salem, S. N., Shubair, K. S.: "Non-specific ulcerative colitis in Bedouin Arabs." *Lancet* March 4, 1967, pp. 473-475.

F77,588/67

In Bedouins and other nomadic Arabs, ulcerative colitis has been noted after settlement in Kuwait city. Presumably, "the sudden shift from a simple life to a complicated one predisposes these people to the disease."

Jenkins, C. D., Rosenman, R. H., Friedman, M.: "Development of an objective psychological test for the determination of the coronary-prone behavior pattern in employed men." *J. Chron. Dis.* **20**: 371-379 (1967).

J5,580/67

"Coronary-prone behavior pattern, called Type A, is characterized primarily by excessive drive, aggressiveness, ambition, involvement in competitive activities, frequent vocational deadlines, pressure for vocational productivity, an enhanced sense of time urgency and restless motor mannerisms and staccato style of verbal response. The converse, low coronary-risk behavior pattern, called Type B, is characterized by the relative absence of this interplay of psychological traits and situational pressures. The Type B subject is relaxed and more easy going, seldom becomes impatient and takes more time to enjoy avocational pursuits. He is not easily irritated and works steadily, but without a feeling of being driven by a lack of time. He is not preoccupied with social achievement, and is less competitive in his occupational and avocational pursuits. He moves and speaks in a slower and more smoothly modulated style." Sir William Osler was one of the first to describe a typical behavior pattern in coronary-prone patients. The types presently outlined can be further divided into subtypes (23 refs.).

Opton, E. M. Jr., Lazarus, R. S.: "Personality determinants of psychophysiological response to stress: a theoretical analysis and an experiment." *J. Pers. Soc. Psychol.* **6**: 291-303 (1967).

J8,942/67

An effort was made to find connections between personality and individual differences in response to stressors. "A 795-item personality inventory revealed 131 discriminating items in an ipsative (intraindividual) design. Ss who responded relatively more strongly to a threatening motion-picture film than to threat of electric shock described themselves as lacking in impulse expression, socially inhibited, introverted, submissive, suggestible or obedient, insecure, passive, anxious, and not caring about friends. Ss who responded more strongly to threat of shock than to the movie attributed the opposite qualities to themselves. Normative (interindividual) analyses (high response to film compared to low response to film, high response to shock compared to low response to shock) found no more discriminating personality items than would be expected by

chance." The questionnaire included the five hundred items of the BPI, parts of the MMPI, the IES, the APQ, the SEI and other miscellanea.

Meloni, C., Torre, E.: "Stress, reazione neurovegetativa e tipo di personalità in soggetti normali e cardiopatici ischemici" (Stress, neuroautonomic reaction and type of personality in normal and ischemic cardiopathic subjects). *G. Ig. Med. Prev.* **9**: 3-20 (1968). J23,136/68

Bridges, P. K., Jones, M. T.: "Relationship of personality and physique to plasma cortisol levels in response to anxiety." *J. Neurol. Neurosurg. Psychiatry* **31**: 57-60 (1968). G56,652/68

During academic examinations, the plasma level of cortisol in medical students became considerably elevated as a consequence of anxiety. The degree of response was correlated with both the physical and the mental constitution of the candidates. "It is suggested that there is an intrinsic sensitivity in anxiety response to psychological stress that has an important association with physique."

Vallee, F. G.: "Stresses of change and mental health among the Canadian Eskimos." *Arch. Environ. Health* **17**: 565-570 (1968). G61,518/68

Study of the role of psychogenic stressors, as distinct from the stressor influence of the Arctic environment, in the genesis of mental disease among Canadian Eskimos. Special emphasis is placed upon the distinction between communal and personal stressors—the tendency among Eskimos to blame certain individuals or themselves for epidemics, starvation, drowning or getting lost—which are characteristic anxiety-producing situations among this population (12 refs.). [Somatic indicators of stress are not examined (H.S.).]

Morris, J. N., Gardner, M. J.: "Epidemiology of ischaemic heart disease." *Am. J. Med.* **46**: 674-683 (1969). G67,204/69

Extensive review on the social and medical implications of ischemic heart disease, which is particularly common among men "showing strong drive, competitiveness, time urgency and preoccupation with deadlines, and the frustrations attendant on these" (Type A). This is especially true in early middle age and results in particularly fatal disease. The incidence is twice that among Type B patients, who do not exhibit such personality traits.

Strydom, N. B., Williams, C. G.: "Effect

of physical conditioning on state of heat acclimatization of Bantu laborers." *J. Appl. Physiol.* **27**: 262-265 (1969) (15 refs.).

J14,803/69

Back, K. W., Wilson, S. R., Bogdonoff, M. D., Troyer, W. G.: "Racial environment, cohesion, conformity and stress." *J. Psychosom. Res.* **13**: 27-36 (1969). J22,201/69

Comparative studies on stress responses—especially the elevations of plasma FFA—in various groups, particularly blacks and whites.

Hoffman, H. E.: "Use of avoidance and vigilance by repressors and sensitizers." *J. Consult. Clin. Psychol.* **34**: 91-96 (1970).

J21,922/70

Re-evaluation of the concept according to which "repressors" and "sensitizers" (distinguished on the basis of a questionnaire) will respond differently to psychogenic stress situations. The sensitizer tends to confront threatening stimuli by intellectualization and isolation; the repressor by avoidance of the stressor.

Bailit, H. L., Workman, P. L., Niswander, J. D., MacLean, C. J.: "Dental assymmetry as an indicator of genetic and environmental conditions in human populations." *Hum. Biol.* **42**: 626-638 (1970). J20,565/70

Dental assymmetry may occur in various human populations as a consequence of genetic or environmental stress factors. "Genetic stress may result from inbreeding due to the finite size of the population or to a mating pattern involving consanguinity. This can lead to a reduction in population fitness because of the exposure of deleterious recessive genes in a homozygous state or, more importantly, because of a breakdown in the coadaptation of the genetic system. Indications of inbreeding stress are provided by estimates of the inbreeding coefficient, the effective population size, the amount of gene flow into the population, or by a comparison of the genetic variance of different quantitative characters with that observed in large random mating populations. Another genetic stress may result from a drastic diminution in population size, leaving too little genetic variation to adapt to a changing or extremely heterogeneous environment."

Dohrenwend, B. S., Dohrenwend, B. P.: "Class and race as status-related sources of stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 111-140. Chicago: Aldine, 1970.

B44,378/70

Bridges, P. K., Jones, M. T., Leak, D.: "A taxonomic study of physiological responses to a psychological stress." *J. Neurol. Neurosurg. Psychiatry* **33**: 180-187 (1970).

J11,245/70

In students, taxonomic studies were performed to establish the relationship between the stressor effect of examinations (plasma cortisol, catecholamine excretion, blood pressure and so on) and constitutional factors (body build, personality types).

Harburg, E., Schull, W. J., Erfurt, J. C., Schork, M. A.: "A family set method for estimating heredity and stress. I. A pilot survey of blood pressure among Negroes in high and low stress areas, Detroit, 1966-1967." *J. Chron. Dis.* **23**: 69-81 (1970).

G78,153/70

American blacks of both sexes have higher blood pressure and mortality from heart disease and strokes than do corresponding whites. A pilot study of blacks in low- and high-stress areas of Detroit suggested that "blood pressure levels were significantly correlated with different patterns of life stress for the essentially working class persons in the high stress area, and for the middle class persons in the low stress area. Briefly, working class persons in the high stress area with higher blood pressure levels (adjusted for sex, age and weight) reported greater economic frustration and more satisfaction (*sic*) with their marital life and their neighborhood than did their normotensive counterparts in the same tract. In contrast, middle class persons with higher blood pressure levels had higher occupational achievements and aspired to even more than did their normotensive neighbors."

Mendeloff, A. I., Monk, M., Siegel, C. I., Lilienfeld, A.: "Illness experience and life stresses in patients with irritable colon and with ulcerative colitis. An epidemiologic study of ulcerative colitis and regional enteritis in Baltimore, 1960-1964." *N. Engl. J. Med.* **282**: 14-17 (1970). H20,041/70

In the Baltimore area, "subjects with irritable colon had consistently higher scores for various social-cultural factors thought to represent life stresses than either the patients with ulcerative colitis or the general population. The group with ulcerative colitis resembled the general population in this respect, except for being significantly more Jewish." Specific stressor events preceding the outbreak of the disease could not be established, and hence these studies "fail to support the

thesis that ulcerative colitis is a paradigm of psychosomatic illness."

Matsumoto, Y. S.: "Social stress and coronary heart disease in Japan." *Milbank Mem. Fed. Q.* **48**: 9-36 (1970). G73,150/70

In Japan, the incidence of arteriosclerotic CHD is extremely low as compared to its incidence among white North Americans. "Although the diet factor remains dominant in current thinking, the stress hypothesis merits the most intensive probing as alternate or associated explanations of observed relations and differentiations" (87 refs.).

Beals, K. L.: "Head form and climatic stress." *Am. J. Phys. Anthropol.* **37**: 85-92 (1972). J20,343/72

"Based on a sample of 339 populations, the magnitude of the index is statistically different between zones of predominantly dry heat, wet heat, wet cold and dry cold. There is an inverse relationship between the mean cephalic index and temperature. It is argued that the occupation of cold climates is one of the circumstances increasing the frequency of brachycephaly through time," and that a relationship exists between climatic stress and head form.

Willett, E. A., Heilbronn, M.: "Repression-sensitization and discrepancy between self-report and official report of illness." *J. Psychol.* **81**: 161-166 (1972). J19,862/72

"The Repression-Sensitization (R-S) scale has been used to differentiate between two major defensive styles. Studies relating the R-S scale to measures of adjustment suggest that repressors are better adjusted than sensitizers."

Baldwin, B. A.: "Autonomic stress resolution in repressors and sensitizers following microcounseling." *Psychol. Rep.* **31**: 743-749 (1972). J19,724/72

Repressors tend to use avoidance mechanisms, such as withdrawal, denial, and rationalization in response to stress, whereas sensitizers, under the same conditions, typically overinterpret threat, and utilize approach mechanisms, such as obsessive rumination and intellectualization. Microcounseling based on this knowledge helps to resolve psychogenic stress.

Pagano, D. F.: "Effects of task familiarity on stress responses of repressors and sensitizers." *J. Consult. Clin. Psychol.* **40**: 22-26 (1973). J20,151/73

Comparison of the manner in which psy-

chogenic stressors affect repressors (characterized by the use of avoidance-denial techniques) and sensitizers (who use intellectual techniques of coping).

Bridges, P. K., Jones, M. T.: "Relationships between some psychological assessments, body-build, and physiological stress responses." *J. Neurol. Neurosurg. Psychiatry* **36**: 839-845 (1973). J7,429/73

During oral academic examination, constitutional factors greatly influenced the stress reaction. "Students of primarily linear physique had significantly higher plasma corticosteroid values than the predominantly muscular subjects at the time of the examination, as found previously. They also had significantly higher analogue measures of the degree of anxiety experienced at the examination (assessed both by the subject and by an observer.)"

Holmes, T. H., Masuda, M.: "Life change and illness susceptibility." In: Scott, J. P. and Seney, E., *Separation and Depression*, pp. 161-186. Washington, D.C.: Am. Assoc. Advancement Sci., 1973. J10,480/73

Among white and black Americans, Mexicans, Japanese, and various European ethnic groups, application of the SRRS revealed a "remarkable consensus about the common life events obtained when Americans, whose culture is embedded in the democratic Western ethic of internalized Christian moral values, are compared with Japanese, whose Eastern culture is embedded in a particularistic, hierarchical system emphasizing family-oriented, externally sanctioned rules of ethical conduct." On the other hand, it also showed certain cross-cultural quantitative and qualitative differences which are described in detail.

Harburg, E., Erfurt, J. C., Chape, C., Hauenstein, L. S., Schull, W. J., Schork, M. A., "Socioecological stressor areas and Black-White blood pressure: Detroit." *J. Chron. Dis.* **26**: 595-611 (1973). J8,243/73

Comparative studies in high- and low-stress areas of Detroit revealed that social and economic stress definitely predisposes to increased blood pressure, especially in blacks.

Harburg, E., Erfurt, J. C., Hauenstein, L. S., Chape, C., Schull, W. J., Schork, M. A.: "Socio-ecological stress, suppressed hostility, skin color, and Black-White male blood pressure: Detroit." *Psychosom. Med.* **35**: 276-296 (1973). J10,462/73

Comparative statistical studies on "socio-ecological stressor conditions" in various predominantly black or white areas of Detroit. Blood pressure levels were highest among male blacks in high-stress areas (47 refs.). [Characteristic G.A.S. manifestations were not examined (H.S.).]

Lumsden, D. P.: "Towards a systems model of stress: feedback from an anthropological study of the impact of Ghana's Volta River Project." In: Sarason, I. and Spielberger, C., *Dimensions of Anxiety and Stress—NATO Conference*, p. 40. House Publication, 1974. J15,030/74

An attempt to present a model of stress as an open system, based mainly on anthropologic studies of Ghana's Volta river project (125 refs.).

Win-May, M., Thin-Thin-Hlaing, Mya-Tu, M.: "Adrenocortical function in the Burmese." *Trop. Geogr. Med.* **26**: 126-132 (1974). J15,103/74

Adrenocortical function in the Burmese is essentially the same as in Europeans and Nigerians, both at rest and after treatment with ACTH or stressors.

Friedman, M., Byers, S. O., Diamant, J., Rosenman, R. H.: "Plasma catecholamine response of coronary-prone subjects (type-A) to a specific challenge." *Metabolism* **24**: 205-210 (1975). H98,918/75

The authors concisely summarize characteristics of CHD-prone (Type-A) and CHD-resistant (Type-B) persons as follows: "Type-A behavior pattern is an action-emotion complex shown by persons in chronic excessive struggle to achieve an unlimited number of things in the shortest possible time, perhaps against obstruction by other things or persons. The type-A individual does not despair of losing the struggle but confidently grapples with an endless succession of challenges. Type-A persons attempt to think, perform, communicate, and in general live more rapidly than do their peers.... Type-B subjects are the converse of type-A subjects. They tend to be introspective, less hostile or aggressive, and less concerned with time. Type-B subjects are concerned with quality rather than quantity of achievement; they pause to enjoy a goal attained rather than immediately setting out in pursuit of the next goal."

Bat. Krutzsch, P. H., Hess, M.: "Studies on the ascorbic acid content of the adrenal of

the bat (*Myotis lucifugus*)."
Endocrinology **69**: 664-666 (1961). D10,630/61

In the bat, captivity *per se* did not influence the vitamin C content of the adrenals during hibernation. "The most marked depletion of the adrenal vitamin occurred in the non-captive hibernating bats stressed by arousal, a finding well correlated with the blood corticosterone content reported for the hamster, another hibernating species, after similar treatment." Comparable though less pronounced effects were obtained with ACTH in hibernating animals, and with EP in active animals. Thus the bat responds to stress essentially as do most other species, at least with regard to the parameters examined.

Romita, G., Montesano, R.: "Aspetti istochimici ed ultrastrutturali delle ghiandole surrenali di Chiroterri durante l'ibernazione, il risveglio ed il periodo estivo" (Histochemical and ultrastructural aspects of adrenal glands in Chiroptera during hibernation, awakening and summer period). *Ateneo Parmense [Acta Biomed.]* **43**: 211-235 (1972). J1,213/72

Detailed description of the histochemical and EM changes in the adrenals of bats, especially with regard to the effect of hibernation. In the adrenal medulla, two types of cells have been differentiated, one synthesizing EP and the other NEP. "During the winter lethargy a depressed secretory activity has been noticed in the cells of the glomerulosa and moreover a remarkable secretion in the cells of both fasciculata and reticularis. Such activity increased after the awakening and became normal during the summer, demonstrating a tendency to store lipid droplets" (57 refs.).

Beaver. Smollich, A.: "Der Einfluss der DCA- und ACTH-Behandlung auf die Kerngrösse der Nebennierenrinde des Sumpfbibers" (The influence of DCA and ACTH treatment on nucleus size of the adrenal cortex in beavers). *Z. Mikrosk. Anat. Forsch.* **70**: 315-329 (1963). G2,544/63

In one beaver (*Myocastor coypus*), exposure to cold caused complete loss of lipids and doubly refractory substances, with other histologic changes which were ascribed to stress.

Cat. Merényi, D.: "Angioarchitektur der Katzenhypophyse. Morphologische Grundlagen zur experimentellen Forschung über das hypophyseo-diencephale System" (Angio-

architecture of the hypophysis in cats. Morphologic baseline for experimental investigations of the hypophyseal-diencephalic system). *Virchows Arch. [Pathol. Anat.]* **315**: 534-547 (1948). B27,100/48

Ink preparation injections indicate that in the cat the anterior lobe receives no arterial blood, and is supplied only by the portal vessels descending from the pars tuberalis and the stalk. Consequently, transection of the stalk causes pituitary necrosis; hence this species is unsuitable for studies concerning results of severing the pituitary from the hypothalamus.

Schwartz, N. B., Kling, A.: "Stress-induced adrenal ascorbic acid depletion in the cat." *Endocrinology* **66**: 308-310 (1960).

C80,679/60

In cats, unilateral adrenalectomy causes depletion of the ascorbic acid content of the remaining adrenal. This response can be blocked by cortisol, the blockade in turn being overcome by ACTH injection. Compensatory hypertrophy after unilateral adrenalectomy is not as obvious in the cat as in other species.

Cattle. Sybesma, W.: "Veranderingen in de bijnierschors van het zieke rund" (Changes in the adrenal cortex of the diseased dairy cow). *T. Diergeneesk.* **86**: 1129-1147 (1961) (Dutch). D42,897/61

Cattle exhibit an increase in the size of the adrenal cortex associated with histologic signs of hyperactivity and loss of vitamin C under the influence of a variety of diseases, particularly grass-tetany.

Shaw, K. E., Nichols, R. E.: "Plasma 17-hydroxycorticosteroids in calves—the effects of shipping." *Am. J. Vet. Res.* **25**: 252-254 (1964).

J24,154/64

Skinner, J. D., Louw, G. N.: "Heat stress and spermatogenesis in *Bos indicus* and *Bos taurus* cattle." *J. Appl. Physiol.* **21**: 1784-1790 (1966). G42,859/66

Even short-term exposure of bulls to "heat stress" can adversely affect spermatogenesis and fertility. [Since heat is known to have a specific damaging effect upon the testes, it remains to be shown that this is a nonspecific or stress action (H.S.).]

Rocco, A., Aguggini, G.: "Eliminazione urinaria degli 11-idrossi-corticosteroidi totali, dell'aldosterone e del testosterone nel vitello" (Urinary excretion of total 11-hydroxycorticosteroids, aldosterone and testosterone in

calves). *Boll. Soc. Ital. Biol. Sper.* **47**: 485-487 (1971). G88,973/71

In calves, aldosterone excretion is increased by the stress of travel. [The results do not lend themselves to statistical evaluation (H.S.).]

Wagnon, K. A., Rollins, W. C., Cupps, P. T., Carroll, F. D.: "Effects of stress factors on the estrous cycles of beef heifers." *J. Anim. Sci.* **34**: 1003-1010 (1972).

J20,504/72

Christison, G. I., Johnson, H. D.: "Cortisol turnover in heat-stressed cows." *J. Anim. Sci.* **35**: 1005-1010 (1972). J19,902/72

Wegner, T. N., Ray, D. E., Lox, C. D., Stott, G. H.: "Effect of stress on serum zinc and plasma corticoids in dairy cattle." *J. Dairy Sci.* **56**: 748-752 (1973).

J19,913/73

In cattle, various stressors produced inconsistent changes in serum zinc, which were not clearly related to the plasma corticoid levels.

Paape, M. J., Schultze, W. D., Miller, R. H., Smith, J. W.: "Thermal stress and circulating erythrocytes, leucocytes, and milk somatic cells." *J. Dairy Sci.* **56**: 84-91 (1973) (26 refs.). J19,911/73

Hartmann, H., Meyer, H., Steinbach, G., Deschner, F., Kreutzer, B.: "Allgemeines Adaptationssyndrom (Selye) beim Kalb. I. Mitteilung: Normalverhalten der Blutbildwerte sowie des Glukose- und 11-OHKS-Blutspiegels" (The general adaptation syndrome in calves. I. Normal behavior of the blood picture and the content of glucose and 11-hydroxycorticosteroids). *Arch. Exp. Vet. Med.* **27**: 811-823 (1973). J23,891/73

Deer. Tyler, C.: "The effect of prolonged emotional disturbance on the vasopressor and oxytocic activities contained in the posterior pituitary glands of fallow deer." *Arch. Int. Pharmacodyn. Ther.* **131**: 301-308 (1961).

D86,848/61

In deer harried before being shot, the ratio of vasopressin to oxytocin progressively increased in the posterior pituitary, probably owing to a fall in oxytocin.

Dog. Thorne, F. C.: "Differing reactions of friendly and fear-biting dogs to severe stress." *J. Clin. Psychol.* **24**: 181-184 (1968). J23,708/68

Corson, S. A.: "Physiologic responses to avoidable and unavoidable psychologic stress

in relation to genetic differences." *Ann. N.Y. Acad. Sci.* **164**: 526-534 (1969).

H19,312/69

Martínek, Z., Horák, F.: "Development of so-called 'genuine' epileptic seizures in dogs during emotional excitement." *Physiol. Bohemoslov.* **19**: 185-195 (1970).

J21,196/70

"Genuine" epileptic seizures are produced in isolated dogs of a special breed by exposure to the stressor effect of strong noise. These animals show a clear familial predisposition to epileptic seizures.

Courtney, G. A., Marotta, S. F.: "Adrenocortical steroids during acute exposure to environmental stresses: I. Disappearance of infused cortisol." *Aerosp. Med.* **43**: 46-51 (1972).

J20,019/72

Courtney, G. A., Marotta, S. F.: "II. Uptake and release of infused cortisol by the hind limb of dogs." *Aerosp. Med.* **43**: 52-55 (1972).

J20,018/72

In dogs, the disappearance rate of infused cortisol was not very consistently affected by a variety of stressors.

Dobsinska, E., Lehky, F.: "Effect of transportation as a stress factor on the blood picture of the German shepherd-dog." *Vet. Med. (Praha)* **18**: 499-506 (1973).

J24,388/73

Zike, W. L., Safae-Shirazi, S., Denbesten, L.: "The role of cholestyramine in the prevention of stress ulcers." *J. Surg. Res.* **17**: 315-319 (1974).

J19,651/74

In dogs, stress ulcers produced by hemorrhagic shock plus intragastric instillation of hydrochloric acid and bile salts can be prevented by cholestyramine.

Carmichael, S. W.: "Fluorescence microscopy of the adrenal medulla of the newborn puppy after asphyxia and hypothermia." *Acta Anat. (Basel)* **87**: 131-140 (1974).

J12,617/74

"Hypothermia reduces the release of catecholamines from the adrenal medulla to such a degree that there is little or no depletion of catecholamines during 32 min of total anoxia."

Dolphin. Maier, R. A.: "Effects of stress upon social distance in dolphins." *Percept. Mot. Skills* **27**: 862 (1968).

J22,143/68

"The reduced social distance, similar to the tight schooling observed in dolphins in the open ocean, is apparently a general reac-

tion to stress. This reaction may function to increase protection afforded to young or feeble members of the school when the group is attacked or stressed in some fashion."

Harrison, R. J., Boice, R. C., Brownell, R. L. Jr.: "Reproduction in wild and captive dolphins." *Nature* **222**: 1143-1147 (1969).

H13,797/69

Among various types of dolphins, ulceration of the forestomach occurred during captivity, while the number of pregnancies decreased considerably.

Medway, W., Geraci, J. R., Klein, L. V.: "Hematologic response to administration of a corticosteroid in the bottle-nosed dolphin (*Tursiops truncatus*)."
J. Am. Vet. Med. Assoc. **157**: 563-565 (1970). J23,086/70

Geraci, J. R., Medway, W.: "Simulated field blood studies in the bottle-nosed dolphin *Tursiops truncatus*. 2. Effects of stress on some hematologic and plasma chemical parameters."
J. Wildl. Dis. **9**: 29-33 (1973). J20,650/73

Donkey. Bullard, R. W., Dill, D. B., Yousef, M. K.: "Responses of the burro to desert heat stress."
J. Appl. Physiol. **29**: 159-167 (1970). G78,189/70

Donkeys are extremely resistant to "desert heat stress," presumably because of a particularly efficient sweating and rehydration mechanism which largely depends upon EP secretion. Intradermal injection of EP causes local sweating in this species.

Maloiy, G. M. O.: "The effect of dehydration and heat stress on intake and digestion of food in the Somali donkey."
Environ. Physiol. Biochem. **3**: 36-39 (1973).

H79,366/73

Ferret. Donovan, B. T., Harris, G. W.: "The effect of pituitary stalk section on light-induced oestrus in the ferret."
J. Physiol. (Lond.) **131**: 102-114 (1956).

J6,721/56

In the ferret—as in most other species examined—simple section of the pituitary stalk is followed by regeneration of the vessels, as a result of which the initially suppressed light-induced estrus response reappears. Permanent separation of the hypophysis from the hypothalamus by interposition of waxed paper between the cut ends of the stalk abolishes the light-induced estrus and causes a decrease in thyroid and adrenal weight.

Gerbil. Goldblatt, D.: "Seizure disorder in gerbils."
Neurology (Minneapolis) **18**: 303-304 (1968). J22,710/68

In genetically predisposed gerbils, stressors (electroshock, photic or auditory stimulation) can precipitate seizures which greatly resemble epilepsy in man.

Hughes, R. E., Nicholas, P.: "Effects of caging on the ascorbic acid content of the adrenal glands of the guinea-pig and gerbil."
Life Sci. [II] **10**: 53-55 (1971).

G84,434/71

Ascorbic acid determinations in the adrenals of guinea pigs and gerbils suggest that "individual caging would appear to 'stress' the animals less than group caging" (8 refs.).

Hull, E. M., Langan, C. J., Rosselli, L.: "Population density and social, territorial, and physiological measures in the gerbil (*Meriones unguiculatus*)."
J. Comp. Physiol. Psychol. **84**: 414-422 (1973). J5,208/73

Mongolian gerbils possess a ventral sebaceous gland which they rub against low objects in their environment to mark territorial claims. "Crowding depressed several social interaction measures as well as body, ventral gland, and testis weights. In the mixed-sex groups, paired males and females had heaviest adrenal glands, ventral glands, and marking scores, as well as the highest reproductive rate. Mixed-sex crowding did not depress either social or physiological measures as much as did same-sex crowding."

Giraffe. Weyrauch, D.: "Über das Vorkommen von Parenchymzellteilen im Sinusoidsystem, im subendothelialen und interstitiellen Raum der Nebennierenrinde der Masai giraffe (*Giraffa camelopardalis tippelskirchii*)" (Parenchyme cell fractions of sinusoids in the subendothelial and interstitial spaces of the adrenal cortex in Masai giraffes [*Giraffa camelopardalis tippelskirchii*.])
Anat. Anz. **135**: 267-276 (1974).

J13,520/74

EM studies on Masai giraffes showed that certain adrenocortical cells can be found free within the sinusoids. Such a holocrine type of secretion may be enhanced by exposure to stress, although this has not yet been definitely proven.

Goat. Daniel, P. M., Prichard, M. M. L.: "The effects of pituitary stalk section in the goat."
Am. J. Pathol. **34**: 433-469 (1958).

C54,157/58

In goats, insertion of a wax plate between the cut ends of the pituitary stalk led to massive infarction of the anterior lobe, but certain areas always survived and underwent regeneration with mitotic proliferation. The posterior lobe became atrophic and showed histologic signs of degeneration. The pars intermedia became hypertrophic (44 refs.).

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "Transection of the pituitary stalk in the goat, and its effect on the volume of the pituitary gland." *J. Pathol. Bacteriol.* **87**: 1-14 (1964). G2,581/64

In goats, a nonirritant plate was inserted between the cut ends of the pituitary stalk. This caused massive infarcts in the pars distalis with no substantial regeneration. The infundibular process became extremely small, whereas the pars intermedia underwent hypertrophy.

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "The long-term effect of transection of the pituitary stalk on the volume of the pituitary gland of the adult goat." *Acta Endocrinol. (Kbh.)* **51**: 377-390 (1966). F65,157/66

In goats, transection of the pituitary stalk with prevention of anastomosis formation by a resin plate caused atrophy of the anterior lobe and infundibular process whereas the intermediate lobe underwent substantial hypertrophy.

Bryant, G. D., Linzell, J. L., Greenwood, F. C.: "Plasma prolactin in goats measured by radioimmunoassay: the effects of teat stimulation, mating behavior, stress, fasting and of oxytocin, insulin and glucose injections." *Hormones* **1**: 26-35 (1970). G76,754/70

Plasma LTH in goats, measured by radioimmunoassay, showed considerable rises after copulation (in both males and females), oxytocin injections and mild restraint, as well as during lactation. Conversely, fasting and insulin caused a fall in serum LTH (19 refs.).

Johke, T.: "Factors affecting the plasma prolactin level in the cow and the goat as determined by radioimmunoassay." *Endocrinol. Jap.* **17**: 393-401 (1970). H39,458/70

Radioimmunologic determinations in cows and goats led to the conclusion that various stressors (venipuncture, pain, restraint, emotional disturbances) elevate the plasma LTH

level, but milking is most effective in eliciting this response.

Guinea Pig. Winkler, G., Blobel, R., Tonutti, E.: "17-OH-Corticoidausscheidung bei Meerschweinchen mit Läsionen im mittleren Hypothalamus" (The effect of lesions in the middle region of the hypothalamus on 17-OH-corticoid excretion in guinea pigs). *Acta Neuroveg.* **20**: 230-237 (1959).

C76,659/59

Jonek, J., Stanosek, J., Krauze, M., Wacławczyk, H.: "Histochemische Untersuchungen über das Verhalten einiger Enzyme in Nebennieren bei Meerschweinchen nach chronischer Lärmeinwirkung" (Histochemical examinations of various enzymes in the adrenals of guinea pigs after chronic exposure to noise). *Z. Mikrosk. Anat. Forsch.* **73**: 174-186 (1965). G38,514/65

Chronic exposure of guinea pigs to noise (kind not clearly described) produced characteristic histochemical changes in various enzyme activities which gradually tended to disappear, and were ascribed to the alarm and resistance stages of the G.A.S.

Marino, A., Jovino, R., Cotrufo, M.: "Preliminary research on the interference between psychological stress and experimental pharmacologic arteriopathies in the guinea pig." *Cazz. Int. Med. Chir.* **70**: 120-122 (1965). J23,770/65

Luparello, T. J.: "Restraint and hypothalamic lesions in the production of gastroduodenal erosions in the guinea pig." *J. Psychosom. Res.* **10**: 251-254 (1966).

G43,819/66

Pegelman, S. G., Kanarik, U. K.: "Adaptive responses in guinea pigs under conditions of a prolonged cooling." *Sechenov Physiol. J. U.S.S.R.* **53** No. 10: 1212-1217 (1967) (Russian). J13,141/67

In guinea pigs, exposure to cold causes marked adrenal hypertrophy and ascorbic acid depletion with eosinopenia. Pretreatment with ascorbic acid reverses the eosinophil response and virtually blocks the loss of ascorbic acid from the adrenals.

Schaefer, K. E., McCabe, N., Withers, J.: "Stress response in chronic hypercapnia." *Am. J. Physiol.* **214**: 543-548 (1968).

F96,116/68

In guinea pigs, the prolonged respiratory acidosis produced by exposure to 15 percent

carbon dioxide in 21 percent oxygen caused a rise in blood corticoids and plasma FFA, with a depletion of adrenal cholesterol and a reduction of lymphopenia.

Ludwig, W. M., Lipkin, M.: "Biochemical and cytological alterations in gastric mucosa of guinea pigs under restraint stress." *Gastroenterology* **56**: 895-902 (1969).

G66,300/69

Joseph, S. A., Knigge, K. M., Voloschin, L.: "Effects of isolation of the hypothalamo-pituitary unit in newborn guinea pigs." *Neuroendocrinology* **4**: 42-50 (1969).

H8,974/69

In newborn guinea pigs, deafferentation of the hypothalamus with a modified Halász knife showed that within about three months, "growth and gonadal function were most seriously impaired; development of thyroid and adrenal function was unaffected in male animals and only moderately affected in females. The results indicate that those RF-producing neurones associated with growth hormone and the gonadotrophins may require afferent neural connections for their normal maturation, while RF-producing neurones associated with thyrotrophin and corticotrophin may develop normally in the isolated hypothalamo-pituitary unit."

Hase, T., Scarborough, E. S.: "Development of stress ulcer in rats and guinea pigs by mechanical rotation." *J. Appl. Physiol.* **30**: 580-582 (1971).

G84,313/71

In guinea pigs and rats, stress ulcers of the stomach can be produced by mechanical rotation in a specially-designed chamber.

Hughes, R. E., Nicholas, P.: "Effects of caging on the ascorbic acid content of the adrenal glands of the guinea-pig and gerbil." *Life Sci. [II]* **10**: 53-55 (1971).

G84,434/71

Ascorbic acid determinations in the adrenals of guinea pigs and gerbils suggest that "individual caging would appear to 'stress' the animals less than group caging" (8 refs.).

Dalle, M., Delost, P.: "Changes in the concentrations of cortisol and corticosterone in the plasma and adrenal glands of the guinea-pig from birth to weaning." *J. Endocrinol.* **63**: 483-488 (1974).

H98,345/74

Hamsters. Deane, H. W., Lyman, C. P.: "Body temperature, thyroid and adrenal cortex of hamsters during cold exposure and

hibernation, with comparisons to rats." *Endocrinology* **55**: 300-315 (1954). B97,428/54

In both hibernating and nonhibernating Syrian hamsters, exposure to cold causes no significant adrenal enlargement or histologic evidence of hyperactivity similar to that produced in rats. However, the hamster adrenal is sensitive to other stressors.

Raths, P., Schulze, W.: "Die Nebennieren des Goldhamsters im Winterschlaf und bei anderen Aktivitätszuständen" (The adrenals of the golden hamster during hibernation and other activities). *Z. Biol.* **109**: 233-243 (1957).

C36,859/57

Detailed description of histologic changes in the adrenal medulla and cortex of the golden hamster during hibernation, upon awakening from hibernation and under anesthesia induced by cold.

Ehrentheil, O. F., Reyna, L. J., Yerganian, G., Chen, E. T.: "Studies in stress glycosuria. I. Prolonged glycosuria in Chinese hamsters after repeated stress." *Diabetes* **13**: 83-86 (1964).

F1,978/64

Chinese hamsters unfamiliar with each other started fighting when placed together. This resulted in glycosuria which continued for two weeks, after daily repeated fights. Both catecholamine and corticoid discharge during the G.A.S. may be of etiologic significance. The findings could be pertinent to the development of stress-induced diabetes.

Frenkel, J. K., Cook, K., Grady, H. J., Pendleton, S. K.: "Effects of hormones on adrenocortical secretion of golden hamsters." *Lab. Invest.* **14**: 142-156 (1965).

G26,921/65

Detailed description of the adrenal response to stress, ACTH, corticoids, metyrapone, amphenone and other conditioning agents in hamsters (34 refs.).

Canguilhem, B., Bloch, R.: "Evolution saisonnière de l'élimination des hormones surréaliennes chez un hibernant, *Cricetus cricetus*" (Seasonal evolution of adrenal hormone excretion in a hibernating animal, *Cricetus cricetus*). *Arch. Sci. Physiol.* **21**: 27-44 (1967).

G46,415/67

In the hamster (*Cricetus cricetus*), no seasonal variations in catecholamine output are noted, although such excretion diminishes during adaptation to cold and may last four months, even if the animals are placed in surroundings with normal room temperature (23°C). On the other hand, urinary glucocor-

ticoid and aldosterone elimination is subject to definite seasonal changes that are independent of ambient temperature.

Arcari, G., Gaetani, M., Glässer, A. H., Turolla, E.: "Restraint-induced gastric ulcers in the golden hamster." *J. Pharm. Pharmacol.* **20**: 73 (1968). J22,648/68

Noble, G. A.: "Leishmania braziliensis: physical and chemical stress in hamsters." *Exp. Parasitol.* **29**: 30-32 (1971).

G81,736/71

In hamsters, various stressors, and particularly restraint, significantly diminished resistance to inoculation with *Leishmania braziliensis*.

Sokolov, V. I.: "The reaction of the adrenal cortex of intact and castrated rodents to formalin stress." *Zh. Evol. Biokhim. Fiziol.* **10** No. 2: 171-175 (1974) (Russian). Engl. transl.: *J. Evol. Biochem. Physiol.* **10**: 149-153 (1974). J18,986/74

Adrenocortical mitotic activity in hamsters and rabbits stressed by formalin is altered after orchidectomy.

Al-Lami, F., Farman, N.: "Ultrastructural and histochemical study of the adrenal medulla in normal and cold-stressed Syrian hamsters." *Anat. Rec.* **181**: 113-129 (1975).

J19,965/75

Hedgehog. Suomalainen, P.: "Further investigations on the physiology of hibernation." *Proc. Finn. Acad. Sci. & Letters*, pp. 131-144. Helsinki, 1953. C852/53

The changes characteristic of hibernation in the hedgehog are compared to those of the G.A.S. Relationships between these two phenomena are discussed.

Lindner, E.: "Die Sacculi Mitochondriales der Diskochondrien und Sphaerochondrien in der Nebennierenrinde vom Igel (*Erinaceus europaeus L.*)" (The mitochondrial sacculi in discochondria and sphaerochondria of the adrenal cortex among hedgehogs [*Erinaceus europaeus L.*]). *Z. Zellforsch. Mikrosk. Anat.* **72**: 212-235 (1966). G39,703/66

In the hedgehog during hibernation, despite diminished function, the adrenal mitochondria retain their EM characteristics—discochondria and sphaerochondria are clearly demonstrable—although the amount of dense matrix is increased.

Horse. Alexander, F., Ash, R. W.: "The effect of emotion and hormones on the con-

centration of glucose and eosinophils in horse blood." *J. Physiol.* **130**: 703-710 (1955). C51,993/55

Handling and repeated venipuncture as well as EP in doses adequate to produce hyperglycemia failed to elicit eosinopenia in ponies, whereas ACTH in adequate dosages did induce this effect. Insulin hypoglycemia and histamine likewise caused eosinopenia in this species.

Forenbacher, S., Rode, B.: "Investigations on the role played by the insular apparatus in the pathogenesis of paralytic myoglobinuria in the horse." *Zentralbl. Veterinaermed.* **8**: 1-11 (1961). D12,281/61

Morphologic changes in the pancreas of the horse after exposure to a variety of agents may represent stress effects, although this has not been proven.

Irvine, C. H. G.: "Thyroxine secretion rate in the horse in various physiological states." *J. Endocrinol.* **39**: 313-320 (1967). F91,501/67

By use of labeled thyroxine, it has been found that adaptation to cold and muscular training increases the thyroxine secretion rate of the horse.

James, V. H. T., Horner, M. W., Moss, M. S., Rippon, A. E.: "Adrenocortical function in the horse." *J. Endocrinol.* **48**: 319-335 (1970). H32,502/70

In the horse, surgical trauma or hypoglycemia increases plasma cortisol, whereas exercise is much less effective in this respect. The cortisol variations are not necessarily associated with changes in the eosinophil count. "It is concluded that the mechanisms of control of adrenocortical function in the horse are not dissimilar to those described for other mammalian species."

Dieterich, R. A., Helleman, D. F.: "Hematology, biochemistry, and physiology of environmentally stressed horses." *Can. J. Zool.* **51**: 867-873 (1973). J24,387/73

Marsupial. Hopwood, P. R., King, S.: "Marsupial stress syndrome." *Aust. Vet. J.* **48**: 71-72 (1972). J20,508/72

Needham, A. D., Dawson, T. J., Hales, J. R. S.: "Forelimb blood flow and saliva spreading in the thermoregulation of the red kangaroo, *Megaleia rufa*." *Comp. Biochem. Physiol. [A]* **49**: 555-565 (1974).

H93,882/74

Mink. Gilbert, F. F., Bailey, E. D.: "The

effect of visual isolation on reproduction in the female ranch mink." *J. Mammal.* **48**: 113-118 (1967). J11,146/67

Isolation of female ranch minks from other members of the species inhibits sexual development and fertility.

Gilbert, F. F., Bailey, E. D.: "Visual isolation and stress in female ranch mink particularly during the reproductive season." *Can. J. Zool.* **47**: 209-212 (1969). J20,525/69

"Visual isolation is apparently more stressful to female mink during the anoestrous period but reduces stress during oestrus and pregnancy. The increased adrenal steroid output of control mink as part of the stress syndrome during the critical reproductive period might be responsible for increased *in utero* losses. But increased adrenocortical output associated with the stress of *long term* visual isolation might result in insufficient gonadal stimulation resulting in fewer pregnancies."

Mongoose. Stemmermann, G. N., Hayashi, T.: "A survey of the normal and morbid anatomy of the Hawaiian feral mongoose." *Am. J. Pathol.* **55**: 67a-68a (1969). H13,927/69

Among Hawaiian feral mongooses, acute stress ulcers are common and probably related to the method of capture. Yet, the finding of healing ulcers shows that these lesions also occur in the wild.

Monkey. Bahn, R. C., Glick, D.: "Studies in histochemistry: effects of stress conditions, ACTH, cortisone and desoxycorticosterone on the quantitative histological distribution of ascorbic acid in adrenal glands of the rat and monkey." *Endocrinology* **54**: 672-684 (1954). B94,671/54

In monkeys (*M. rhesus*, *M. cynomolgus*), as well as in rats, various stressors (cold, struggling, ether anesthesia, hypoxia and hyperthermia) cause a decrease in the ascorbic acid content of the outer fasciculata and reticularis zones of the adrenal cortex. Intraperitoneal ACTH produces the same result.

Mason, J. W., Harwood, C. T., Rosenthal, N. R.: "Influence of some environmental factors on plasma and urinary 17-hydroxycorticosteroid levels in the rhesus monkey." *Am. J. Physiol.* **190**: 429-433 (1957). C42,224/57

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "Volume of the infarct in the

anterior lobe of the monkey's pituitary gland shortly after stalk section." *Nature* **198**: 1205-1206 (1963). D69,623/63

Marsh, J. T., Lavender, J. F., Chang, S. S., Rasmussen, A. F.: "Poliomyelitis in monkeys: decreased susceptibility after avoidance stress." *Science* **140**: 1414-1415 (1963).

D69,198/63

In monkeys (*M. cynomolgus*), "avoidance stress" prior to inoculation with type I poliovirus protected against the fatal effect of the infection. The circulating lymphocytes decreased significantly during stress. These findings contrast sharply with earlier observations in which stressors diminished the resistance of mice to virus infection. However, the schedule of exposure to stress may be important (10 refs.).

Meier, R. M., Greenhoot, J. H., Shonley, I., Goodman, J. R., Porter, R. W.: "Sex differences in the serum cholesterol response to stress in monkeys." *Nature* **199**: 812-813 (1963).

E24,291/63

Stress caused by restraint decreased serum cholesterol in rhesus monkeys of both sexes, but particularly in males. A review of earlier data shows that some researchers found an increase, others a decrease, in plasma cholesterol levels in both animals and man, but the reasons for these discrepancies are not known (11 refs.).

Elmadjian, F., Forchielli, E.: "Characterization of hormonal steroids of the chimpanzee: changes observed in adrenal cortical function during simulated and actual space flight." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 535-544. New York and London: Academic Press, 1965.

E5,498/65

Detailed report on changes in the urinary excretion and blood level of various steroids (corticoids, estrogens, androgens and so on) in chimpanzees during actual or simulated space flights. "Interpretation of the above data is difficult due to the varying degrees of time-lapse from the point of termination of the stress to the time of sampling."

St. Clair, R. W., MacNinch, J. E., Middleton, C. C., Clarkson, T. B., Lofland, H. B.: "Changes in serum cholesterol levels of squirrel monkeys during importation and acclimation." *Lab. Invest.* **16**: 828-832 (1967).

H1,895/67

In squirrel monkeys (*Saimiri sciureus*) captured in Colombia, serum cholesterol rose

significantly after transportation to North Carolina. This response was much less obvious in animals kept in a semisecluded environment than in those caged in laboratories with relatively high noise levels, and in frequent contact with men. The cholesterol changes could be completely accounted for by a similar alteration in β -lipoprotein cholesterol without any alteration in α -lipoprotein cholesterol. "It is suggested that the observed changes in serum cholesterol may reflect the squirrel monkeys' reaction to 'stress' resulting from changes in environment." However, the relative importance of relocation, captivity, noise and contact with men is difficult to appraise.

Hill, C. W., Greer, W. E., Felsenfeld, O.: "Psychological stress, early response to foreign protein, and blood cortisol in vervets." *Psychosom. Med.* **29**: 279-283 (1967).

G48,085/67

In vervet monkeys (*Cercopithecus aethiops*) exposed to psychogenic stress (noise, light, handling) serum cortisol levels rose considerably, and antibody formation to bovine serum albumin was delayed and diminished.

McHugh, P. R., Smith, G. P.: "Negative feedback in adrenocortical response to limbic stimulation in *Macaca mulatta*." *Am. J. Physiol.* **213**: 1445-1450 (1967).

F92,213/67

In conscious chair-confined *Macaca mulatta* the rise in plasma 17-OHCS following intravenous administration of cortisol was modified by stimulation of certain brain lesions with bipolar electrodes. The results obtained furnished "evidence for a negative feedback effect of injected hydrocortisone on the 17-OHCS response to amygdaloid stimulation but not to hypothalamic stimulation, and suggest the presence of a neural mechanism for negative feedback located functionally between amygdala and hypothalamus."

Lang, C. M.: "Effects of psychic stress on atherosclerosis in the squirrel monkey (*Saimiri sciureus*)."
Proc. Soc. Exp. Biol. Med. **126**: 30-34 (1967). F90,255/67

About two years of exposure to restraint, alone or combined with conditioned avoidance, accelerated the development of atherosclerosis, increased urinary 17-KS excretion and raised serum cholesterol.

Wheeler, T. E., New, A. E.: "A study of blood serum potassium concentration and stress in the squirrel monkey (*Saimiri*

sciureus)."
NAM1-1041. U.S. Naval Aerosp. Med. Inst. 1-8 (1968). J23,751/68

Brown, G. M., Grotta, L. J., Penney, D. P., Reichlin, S.: "Adrenal regulation in the wild captive squirrel monkey: a model of chronic stress." *Can. Psychiatr. Assoc. J.* **15**: 425-431 (1970). G78,935/70

Brown, G. M., Grotta, L. J., Penney, D. P., Reichlin, S.: "Pituitary-adrenal function in the squirrel monkey." *Endocrinology* **86**: 519-529 (1970). H22,206/70

Radiosteroid assays indicate that "the major steroid in squirrel monkey plasma is cortisol, that the values in resting, undisturbed caged animals are indeed uniquely high (405 $\mu\text{g}/100 \text{ ml} \pm \text{SE } 43$), and are capable of increasing in response to capture (672 $\mu\text{g}/100 \text{ ml} \pm \text{SE } 72$) and chair restraint (1024 $\mu\text{g}/100 \text{ ml} \pm \text{SE } 52$), that the bound fraction of plasma cortisol is not greater than in other primates, that the turnover rate of cortisol is extremely high (30 mg/day in chair restrained animals), that adrenal function in these animals is inhibited only by relatively large doses of dexamethasone, and that they are relatively unresponsive to exogenous ACTH."

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971). H37,353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound and aversive conditioning) increase plasma STH and cortisol levels but the two responses are not parallel and presumably are regulated by diverse mechanisms. In the case of chair restraint, STH values fall to resting levels whereas cortisol continues to rise.

Brown, G. M., Schalch, D. S., Reichlin, S.: "Hypothalamic mediation of growth hormone and adrenal stress response in the squirrel monkey." *Endocrinology* **89**: 694-703 (1971). H45,128/71

In squirrel monkeys, the stress of emotional excitement (chair restraint, capture) increased plasma STH and corticoid levels, but the two changes were not parallel. The STH response to capture and ether was blocked by small lesions in either the anterior or posterior ME, while adrenal reaction to capture and chair restraint were blocked by lesions in the posterior ME. STH responses to ether were enhanced by midline optic chiasm lesions. However, great individual

variations interfered with the precise evaluation of these data.

Penney, D. P., Brown, G. M.: "The fine structural morphology of adrenal cortices of normal and stressed squirrel monkeys." *J. Morphol.* **143**: 447-466 (1971).

G85,767/71

In squirrel monkeys, EM observations show a close correlation between hyperdevelopment of the agranular reticulum and increased plasma cortisol levels during the stress of chair restraint. There is also "depletion and disorientation of membranes both of the agranular endoplasmic reticulum and mitochondria and a loss of ribosomes, lysosomes and, to some degree, intracellular lipid."

Baumann, H., Urmantscheeva, T. G., Wolter, F., Martin, G., Gurk, C.: "Multivariate evoked potential-Studien zur Quantifizierung zentralnervöser Adaptationsprozesse unter Stresseinfluss bei Rhesusmacacen" (Multivariate evoked potential studies for the qualification of central nervous adaptation processes under the influence of stress in Rhesus macaca). *Acta Biol. Med. Ger.* **31**: 415-422 (1973).

J8,564/73

Baumann, H., Urmantscheeva, T. G., Gurk, C., Martin, G., Wolter, F.: "Quantitative evoked potential analyses in behavioural neurophysiology. A model of a stress-induced borderline hypertension in rhesus monkeys." *Acta Biol. Med. Ger.* **33**: 419-427 (1974).

J21,955/74

Beach, J. E., Blair, A. M. J. N., Pirani, C. L., Cox, G. E., Dixon, F. J.: "An unusual form of proliferative arteriopathy in macaque monkeys (Macacca sps)." *Exp. Molec. Pathol.* **21**: 322-338 (1974).

J19,230/74

Natelson, B. H., Smith, G. P., Stokes, P. E., Root, A. W.: "Plasma 17-hydroxycorticosteroids and growth hormone during defense reactions." *Am. J. Physiol.* **226**: 560-568 (1974).

H83,654/74

Electric stimulation of the hypothalamus in rhesus monkeys caused a rise in plasma 17-OHCS, especially during the initial excitement. Although increases were obtained after stimulation of various sites scattered throughout the anterior, tuberal and posterior parts of the lateral hypothalamus, plasma STH was elevated only when posterior sites were stimulated. This pattern of a smaller hypothalamic area for STH than for ACTH release has also been observed in the rat,

cat and squirrel monkey, and is probably a general principle of organization.

"Monkeys agree—noise is upsetting!" *Med. Times* **102**: 71-76 (1974).

J17,048/74

Review on the effect of noise (industrial, rock music, intermittent gunfire) upon rhesus monkeys. Blood cortisol levels showed an initial rise followed by a drop during the third hour of exposure "despite behavioral indications that the animals continued to be stressed." [Based on an earlier article by Watson (H.S.).]

Michailov, M. L., Gnüchtel, U., Nitschkoff, S., Baumann, R., Gnauck, G.: "Verhalten von Fettsäuren im Blutplasma von Affen nach Einwirkung kurzfristiger Stressoren" (Plasma fatty acid changes in baboons after acute stress). *Acta Biol. Med. Ger.* **32**: 675-680 (1974).

J16,605/74

In baboons (*Papio hamadryas*), various stressors (restraint, jealousy) cause a rise in unsaturated plasma FFA, especially oleic acid, and a relative decrease in saturated FFA, particularly palmitinic acid.

Mouse. Anthony, A.: "Effects of noise on eosinophil levels of audiogenic-seizure-susceptible and seizure-resistant mice." *J. Acoust. Soc. Am.* **27**: 1150-1153 (1955).

E80,679/55

"A prolonged eosinopenia occurs with several successive noise bursts at a moderately low level (ca 250 eosinophils/cu mm blood) in seizure-resistant mice and at lower levels (ca 100 eosinophils/cu mm blood) in mice which experience convulsions during treatment. It was concluded that noise stimulation acts as a mild stress stimulus and is harmful only when it results in the production of fatal convulsions."

Bevan, W.: "Sound-precipitated convulsions: 1947 to 1954." *Psychol. Bull.* **52**: 473-504 (1955).

D78,855/55

Review of genetic and stress factors causing audiogenic convulsions. It is deplored that "despite general preference for a physiological model, nothing has been done to assay systematically physiological differences among susceptible and nonsusceptible animals. Although electroshock convulsions have been discussed within the framework of Selye's adaptation syndrome hypothesis, and although audiogenic seizures have been regarded as a stress phenomenon by both physiologically and psychologically biased in-

vestigators, no vigorous attempt to exploit Selye's logic has been made for the latter phenomenon" (145 refs.).

Anthony, A.: "Changes in adrenals and other organs following exposure of hairless mice to intense sound." *J. Acoust. Soc. Am.* **28**: 270-274 (1956). E82,034/56

On the basis of observations in hairless mice, it was concluded that both immobilization and intense sound vibrations on the skin surface can act as stressors. When the sound is very intense, the systemic response is similar to that seen after skin burns. Here, heat and not sound is considered to be the responsible stressor.

Anthony, A., Marks, B.: "Noise-induced convulsions in mice." *Experientia* **15**: 320-321 (1959). E80,668/59

Certain strains of mice are considered to be "seizure resistant," but noise sometimes caused convulsions among mongrel mice of the Swiss Albino type. The incidence of convulsions was highest among mice exposed to intense high frequency noise.

Smith, L. W., Molomut, N., Gottfried, B.: "Effect of subconvulsive audiogenic stress in mice on turpentine induced inflammation." *Proc. Soc. Exp. Biol. Med.* **103**: 370-372 (1960). C81,345/60

Thiessen, D. D., Nealey, V. G.: "Adrenocortical activity, stress response and behavioral reactivity of five inbred mouse strains." *Endocrinology* **71**: 267-270 (1962). D29,041/62

Bronson, F. H., Eleftheriou, B. E.: "Adrenal responses to crowding in *Peromyscus* and C57BL/10J mice." *Physiol. Zool.* **36**: 161-166 (1963). D63,122/63

Southwick, C. H.: "*Peromyscus leucopus*: an interesting subject for studies of socially induced stress responses." *Science* **143**: 55-56 (1964). F35/64

The white-footed mouse is particularly suitable for the study of social interactions in stress physiology. It possesses "tolerance of very high cage densities among social congeners; marked behavioral intolerance among social strangers; exceptionally large adrenal glands; and adrenal and eosinophil responses sensitive to social disturbance."

Levine, S., Treiman, D. M.: "Differential plasma corticosterone response to stress in four inbred strains of mice." *Endocrinology* **75**: 142-144 (1964). F15,512/64

Friedman, S. B., Ader, R.: "Parameters relevant to the experimental production of "stress" in the mouse." *Psychosom. Med.* **27**: 27-30 (1965). G26,082/65

"Merely moving mice from standard laboratory cages to experimental cages resulted in a significant decrease in weight gain. Mice subjected to periodic shock preceded by a stimulus light lost a greater amount of weight during the observation period than mice subjected to any of the other experimental conditions."

Castellion, A. W., Swinyard, E. A., Goodman, L. S.: "Effect of maturation on the development and reproducibility of audiogenic and electroshock seizures in mice." *Exp. Neurol.* **13**: 206-217 (1965). J22,995/65

Foss, C. R., Horvath, S. M.: "Reactions of wild and albino mice in response to forced swimming." *Proc. Soc. Exp. Biol. Med.* **120**: 588-592 (1965). F59,402/65

The ability of wild and domestic albino mice to swim until exhaustion was more limited in water of 20°C than 37°C. The drop in colonic temperature was an excellent indication of exhaustion in water of 28°C or less; but colonic temperature remained normal or even rose at higher temperatures. There was no significant difference in either colonic temperature or endurance between the two strains.

Lehmann, A.: "Action de crises répétées d'épilepsie acoustique sur le taux de noradrénaline des zones corticales et sous-corticales du cerveau de souris" (Effects of repeated acoustic epileptic seizures on noradrenaline levels of the cortical and subcortical zones of the brain in mice). *C.R. Soc. Biol. (Paris)* **159**: 62-64 (1965).

F44,990/65
In seizure-susceptible mice, repeated exposure to sound produces eventually fatal convulsive attacks. Mortality is also increased by reserpine, but is decreased by MAO inhibitors. Audiogenic seizures, especially if they are lethal, greatly diminish the NEP content of the brain, particularly in its subcortical layer. In conjunction with the observation that MAO inhibitors protect, it may be assumed that NEP depletion is the cause of lethality in audiogenic seizures. However, oft repeated exposure to sound elicits convulsions of diminishing intensity and eventually complete insensitivity ensues. Yet even in these resistant animals, the brain NEP concentra-

tion is low. Perhaps lethality depends upon a particularly rapid catecholamine loss.

Schlesinger, K., Boggan, W., Freedman, D. X.: "Genetics of audiogenic seizures: I. Relation to brain serotonin and norepinephrine in mice." *Life Sci.* **4**: 2345-2351 (1965).

G36.091/65

The brain levels of NEP and 5-HT were highest in strains of mice with the greatest susceptibility to audiogenic seizures.

Treiman, D. M., Levine, S.: "Plasma corticosteroid response to stress in four species of wild mice." *Endocrinology* **84**: 676-680 (1969).

H10,031/69

Burlet, C.: "Variations des activités phosphatasiques acides du système hypothalamo-neurohypophysaire du lérot dans différentes conditions expérimentales" (Acid phosphatase activity in the hypothalamic-neurohypophyseal system of the lerot [garden door-mouse] under various conditions). *C.R. Soc. Biol. (Paris)* **163**: 486-488 (1969).

H15,751/69

In the lerot or garden doormouse (*Eliomys quercinus L.*), stress (sound, ether) enhances the acid phosphatase activity in the ME and neurohypophysis with a simultaneous increase in vasopressin discharge.

Levine, S., Treiman, D. M.: "Determinants of individual differences in the steroid response to stress." In: Bajusz, E., *Physiology and Pathology of Adaptation Mechanisms: Neural—Neuroendocrine—Humoral*, pp. 171-184. Oxford, London and Edinburgh: Pergamon Press, 1969.

E8,168/69

Comparative studies on the corticosteroid secretion of four strains of inbred mice exposed to electroshock show considerable genetic differences.

Müller, E. E., Miedico, D., Giustina, G., Cocchi, D.: "Ineffectiveness of hypoglycemia, cold exposure and fasting in stimulating GH secretion in the mouse." *Endocrinology* **88**: 345-350 (1971).

H35,410/71

In mice, radioimmunoassayable STH did not decrease under the influence of insulin hypoglycemia or cold exposure, whereas fasting caused a slight depletion of pituitary and an increase of plasma STH levels. "A possible explanation of our results is that the mouse is a species in which, due to the very elevated metabolic rate, the growth hormone secretion, already maximal in basal conditions, cannot be further increased by any of

the stimuli which are highly active in other animal species."

Dung, H. C., Swigart, R. H.: "Experimental studies of 'lethargic' mutant mice." *Tex. Rep. Biol. Med.* **30**: 273-288 (1971).

J10,269/71

A "lethargic" mutant recessive gene occurred spontaneously in BALB/cGn mice. Among the characteristics of these mice was a particular sensitivity to "swimming stress."

Poirel, C., Bouten, F., Hengartner, O.: "Analyse chronobiologique des rythmes circadiens de la crise audiogène chez la souris Swiss/Albinos (Rb)" (Chronobiologic analysis of the circadian rhythms of audiogenic seizure in the Swiss/Albinos [Rb] mouse). *Ann. ACFAS* **40**: 128 (1973).

H87,899/73

In mice genetically predisposed to audiogenic seizures, the mathematical relationship of these to the circadian rhythm has been analyzed.

Halevy, S., Altura, B. M.: "Sex and genetics as factors influencing resistance to traumatic shock." *Fed. Proc.* **33**: 298 (1974).

H84,061/74

Certain "strains of mice could be used as models to explore further the roles of sex and genetics in resistance to traumatic shock."

Weltman, A. S., Johnson, L., Sackler, A. M.: "Behavioral and adrenal relationships to audiogenic-seizure susceptibility in BALB/cJ mice." *Life Sci.* **14**: 725-736 (1974).

J15,334/74

"Various findings (total leukocyte and adrenal corticosterone) indicated hypoadrenal function in the audiogenic-seizure susceptible mice" (39 refs.).

Svendsen, U. G.: "Thymus dependency of periorteritis nodosa in DOCA and salt treated mice." *Acta Pathol. Microbiol. Scand. [A]* **82**: 30-34 (1974).

J16,185/74

Severe periorteritis nodosa develops in the kidneys, with fewer lesions of the heart and pancreas, in unilaterally nephrectomized paired NMRI mice treated with DOCA plus sodium chloride, but not in littermates with congenital thymus aplasia.

Ciaranello, R. D., Lipsky, A., Axelrod, J.: "Association between fighting behavior and catecholamine biosynthetic enzyme activity in two inbred mouse sublines." *Proc. Natl. Acad. Sci. U.S.A.* **71**: 3006-3008 (1974).

J16,804/74

Fighting behavior after isolation is geneti-

cally determined and associated with characteristic changes in the catecholamine biosynthetic enzyme activity of the adrenals.

Opossum. Than, K. A., McDonald, I. R.: "Effect of cortisol on insulin sensitivity of the marsupial brush-tailed opossum, *Trichosurus vulpecula* (Kerr)." *J. Endocrinol.* **63**: 473-481 (1974). H98,344/74

Pig. Baur, L. S., Filer, L. J. Jr.: "Influence of body composition of weanling pigs on survival under stress." *J. Nutr.* **69**: 128-134 (1959). D77,050/59

Juszkiewicz, T., Jones, L. M.: "The effects of chlorpromazine on heat stress in pigs." *Am. J. Vet. Res.* **22**: 553-557 (1961).

J10,364/61

As judged by adrenal ascorbic acid determinations, "chlorpromazine diminishes stressful response of the pituitary-adrenal axis in pigs due to hyperthermia, increases the survival rate at 40C., and decreases the body weight loss."

Yoon, Y. H.: "Pathological studies on the baby pig with hypoglycemia." *J. Kor. Vet. Med. Assoc.* **6**: 1222-1232 (1962) (Korean, with English summary). G16,777/62

In baby pigs, stress induced by exposure to cold or starvation caused changes typical of the G.A.S. such as loss of adrenal lipids, hypoglycemia and eosinopenia (24 refs.).

Tournut, J., Le Bars, H., Labie, C., Khamouma, M.: "Prévention des effets de l'immobilisation forcée chez le Porc par certains neuroleptiques" (Prevention of the effects of forced immobilization in the pig by certain neuroleptics). *C.R. Acad. Sci. (Paris)* **260**: 5415-5418 (1965). G66,777/65

In pigs, immobilization causes loss of weight and gastric ulcers which can be considerably diminished by chlorpromazine and other neuroleptic agents.

Addis, P. B., Johnson, H. R., Thomas, N. W., Judge, M. D.: "Effect of temperature acclimation on porcine physiological responses to heat stress and associated properties of muscle." *J. Anim. Sci.* **26**: 466-469 (1967). J23,509/67

Ballarini, G.: "Contributo alla conoscenza del comportamento in *Sus scrofa*. 'Stress,' incremento di aggressività e 'tail biting' nel suino: azione di trattamenti cortisonici" (Contribution to the knowledge of behavior in *Sus scrofa*. "Stress," increase of aggres-

sivity and tail-biting in swine: action of corticoid treatments). *Bull. Soc. Ital. Biol. Sper.* **43**: 1036-1039 (1967). G52,769/67

Judge, M. D., Briskey, E. J., Cassens, R. G., Forrest, J. C., Meyer, R. K.: "Adrenal and thyroid function in stress-susceptible pigs (*Sus domesticus*)."*Am. J. Physiol.* **214**: 146-151 (1968). F92,962/68

Marple, D. N., Topel, D. G., Matsushima, C. Y.: "Influence of induced adrenal insufficiency and stress on porcine plasma and muscle characteristics." *J. Anim. Sci.* **29**: 882-886 (1969). J22,014/69

Howe, J. M., Addis, P. B., Howard, R. D., Judge, M. D.: "Environment-induced adrenocortical lipid in 'stress-susceptible' pigs." *J. Anim. Sci.* **28**: 70-72 (1969). J23,077/69

Large lipid masses were "observed in the zona reticularis of the adrenal glands of pigs (known to be 'stress susceptible') reared in psychrometric chambers." They were induced by fluctuating environmental temperatures and were possibly related to the stress susceptibility of these animals.

Kowalczyk, T.: "Etiologic factors of gastric ulcers in swine." *Am. J. Vet. Res.* **30**: 393-400 (1969). J23,078/69

In pigs, gastric ulcers are common and probably often caused by stress (63 refs.).

Symoens, J.: "Vorbeugen und Heilung von Aggressivität und Stress bei Schweinen durch das Neuroleptikum Azaperone" (Prevention and treatment of aggression and stress in pigs with the neuroleptic Azaperone). *Dtsch. Tierärztl. Wochenschr.* **77**: 144-148 (1970). J23,887/70

Sair, R. A., Lister, D., Moody, W. G., Cassens, R. G., Hoekstra, W. G., Briskey, E. J.: "Action of curare and magnesium on striated muscle of stress-susceptible pigs." *Am. J. Physiol.* **218**: 108-114 (1970). H20,306/70

Schmidt, G. R., Kastenschmidt, L. L., Cassens, R. G., Briskey, E. J.: "Serum enzyme and electrolyte levels of 'stress-resistant' Chester White pigs and 'stress-susceptible' Poland China pigs." *J. Anim. Sci.* **31**: 1168-1171 (1970). J20,886/70

Lister, D., Sair, R. A., Will, J. A., Schmidt, G. R., Cassens, R. G., Hoekstra, W. G., Briskey, E. J.: "Metabolism of striated muscle of stress-susceptible pigs breathing oxygen or nitrogen." *Am. J. Physiol.* **218**: 102-107 (1970). H20,305/70

- Stefanovic, M. P., Bayley, H. S., Slinger, S. J.: "Effect of stress on swine: heat and cold exposure and starvation on vanilmandelic acid output in the urine." *J. Anim. Sci.* **30**: 378-381 (1970). J22,015/70
- Allen, W. M., Berrett, S., Harding, J. D. J., Patterson, D. S. P.: "Plasma levels of muscle enzymes in the Pietrain pig in relation to the acute stress syndrome." *Vet. Rec.* **87**: 410-411 (1970). J20,889/70
- Osborne, J. C., Meredith, J. H.: "Cardiac output in weanling piglets with bacterial endotoxin shock superimposed on surgical shock." *Cornell Vet.* **61**: 470-476 (1971). J21,155/71
- Reddy, M. V. V., Kastenschmidt, L. L., Cassens, R. G., Briskey, E. J.: "Studies on stress-susceptibility: the relationship between serum enzyme changes and the degree of stress-susceptibility." *Life Sci. [II]* **10**: 1381-1391 (1971). G88,453/71
- Stress-susceptible pigs exhibit a particularly pronounced increase in certain plasma enzymes when exposed to various stressors.
- Muggenburg, B. A., Kowalczyk, T., Olson, W.: "Effect of ambient temperature on gastric lesions and gastric secretion in swine." *Am. J. Vet. Res.* **32**: 603-608 (1971). J17,593/71
- In pigs exposed to the recording of a pig in distress, ambient temperature influences gastric secretion and the development of stress ulcers.
- Marple, D. N., Judge, M. D., Aberle, E. D.: "Pituitary and adrenocortical function of stress susceptible swine." *J. Anim. Sci.* **35**: 995-1000 (1972). J19,905/72
- Goodman, A. A., Osborne, M. P.: "An experimental model and clinical definition of stress ulceration." *Surg. Gynecol. Obstet.* **134**: 563-571 (1972). H52,672/72
- Hemorrhagic shock produced in piglets is a useful model for the study of stress ulcers.
- Norton, L., Nolan, P., Sales, J. E. L., Eiseman, B.: "A swine stress ulcer model." *Ann. Surg.* **176**: 133-138 (1972). G93,135/72
- Adult pigs are unusually resistant to the production of gastric ulcers by the stress of hemorrhage, whereas young piglets are particularly sensitive (19 refs.).
- Marple, D. N., Aberle, E. D., Forrest, J. C., Blake, W. H., Judge, M. D.: "Endocrine responses of stress susceptible and stress resistant swine to environmental stressors." *J. Anim. Sci.* **35**: 576-579 (1972). J20,502/72
- Rantsios, A.: "Some observations on the histology of the adrenal zona glomerulosa in Pietrain pigs." *Vet. Rec.* **90**: 369-370 (1972). J20,516/72
- Sales, J. E. L.: "Ischaemia as a factor in the aetiology of stress ulceration." *Br. J. Surg.* **59**: 309-310 (1972). J19,878/72
- In piglets, stress ulcers of the stomach were produced by severe hemorrhage.
- Marple, D. N., Cassens, R. G.: "Increased metabolic clearance of cortisol by stress-susceptible swine." *J. Anim. Sci.* **36**: 1139-1142 (1973). J19,910/73
- Goodman, A. A., Osborne, M. P.: "Stress ulcer. A definition, a discussion of other stress-associated upper gastrointestinal lesions, and an experimental model." *Am. J. Surg.* **125**: 461-463 (1973). J2,449/73
- Stress ulcers produced in piglets by hemorrhage could not consistently be prevented by vagotomy and pyloroplasty, despite reduction of gastric acid.
- Ball, R. A., Annis, C. L., Topel, D. G., Christian, L. L.: "Clinical and laboratory diagnosis of porcine stress syndrome." *Vet. Med. Small Anim. Clin.* **68**: 1156-1159 (1973). J22,001/73
- Swatland, H. J., Cassens, R. G.: "Observations on the postmortem histochemistry of myofibers from stress susceptible pigs." *J. Anim. Sci.* **37**: 885-891 (1973). J22,018/73
- Richardson, R. S., Norton, L. W., Sales, J. E. L., Eiseman, B.: "Gastric blood flow in endotoxin-induced stress ulcer." *Arch. Surg.* **108**: 191-195 (1973). G99,516/73
- In pigs, endotoxin shock invariably caused stress ulcers of the stomach, with changes in the gastric circulation.
- Brooks, G. A., Cassens, R. G.: "Respiratory functions of mitochondria isolated from stress-susceptible and stress-resistant pigs." *J. Anim. Sci.* **37**: 688-691 (1973). J22,016/73
- Marple, D. N., Cassens, R. G.: "A mechanism for stress-susceptibility in swine." *J. Anim. Sci.* **37**: 546-550 (1973). J22,021/73
- Eikelenboom, G., Bergh, S. G. van den:

"Mitochondrial metabolism in stress-susceptible pigs." *J. Anim. Sci.* **37**: 692-696 (1973).

J22,011/73

Voloshchik, P. D., Morozov, V. N.: "Effect of stress factors on the state of piglets." *Veterinariia* No. 3: 32-34 (1973) (Russian).

J24,474/73

Ball, R. A., Topel, D. G., Marple, D. N., Annis, C. L.: "Glucocorticoid induced stress susceptibility in swine: adrenocortical pathology." *Can. J. Comp. Med.* **38**: 153-159 (1974).

J20,921/74

EM studies and gross observations led the authors to the conclusion that adrenocortical atrophy is not a feature of the porcine stress syndrome, and that localized deposits of stainable lipid are not evident within the zona reticularis of glucocorticoid-treated pigs. "Consequently, the findings reported here bear a somewhat limited resemblance to those observed in pigs affected by porcine stress syndrome and cast some doubt on whether adrenal hypofunction plays a role in the pathogenesis of the latter condition."

Aberle, E. D., Merkel, R. A., Forrest, J. C., Alliston, C. W.: "Physiological responses of stress susceptible and stress resistant pigs to heat stress." *J. Anim. Sci.* **38**: 954-959 (1974).

J21,590/74

Marple, D. N., Jones, D. J., Alliston, C. W., Forrest, J. C.: "Physiological and endocrinological changes in response to terminal heat stress in swine." *J. Anim. Sci.* **39**: 79-82 (1974).

J21,596/74

Weiss, G. M., Topel, D. G., Siers, D. G., Ewan, R. C.: "Influence of adrenergic blockade upon some endocrine and metabolic parameters in a stress susceptible and a fat strain of swine." *J. Anim. Sci.* **38**: 591-597 (1974).

J21,591/74

Allen, W. M. "The acute stress syndrome in the Pietrain pig and the probably possible relationship to transport deaths and inferior quality meat." *Br. Vet. J.* **130**: 93 (1974).

J20,876/74

Marple, D. N., Cassens, R. G., Topel, D. G., Christian, L. L.: "Porcine corticosteroid-binding globulin: binding properties and levels in stress-susceptible swine." *J. Anim. Sci.* **38**: 1224-1228 (1974).

J21,599/74

"Swine from a herd bred to be stress-susceptible had significantly higher mean plasma cortisol and corticosteroid-binding globulin (CBG) levels with a significantly

lower mean cortisol-CBG association constant than normal swine."

Campion, D. R., Eikelenboom, G., Cassens, R. G.: "Isometric contractile properties of skeletal muscle from stress susceptible and stress resistant pigs." *J. Anim. Sci.* **39**: 68-72 (1974).

J21,585/74

Addis, P. B., Nelson, D. A., Ma, R. T. I., Burroughs, J. R.: "Blood enzymes in relation to porcine muscle properties." *J. Anim. Sci.* **38**: 279-286 (1974).

J22,026/74

Comparative studies on the blood enzymes of stress-susceptible and stress-resistant pigs.

Curtis, S. E.: "Responses of the piglet to perinatal stressors." *J. Anim. Sci.* **38**: 1031-1036 (1974).

J21,586/74

"Evidence reviewed suggests that stress from the prenatal respiratory-gas environment is directly related to intrapartal stillbirth and reduced neonatal survivability and that stress from the postnatal thermal environment is very likely related directly and indirectly to neonatal mortality in the piglet."

Johansson, G., Jonsson, L., Lannek, N., Blomgren, L., Lindberg, P., Poupa, O.: "Severe stress-cardiopathy in pigs." *Am. Heart J.* **87**: 451-457 (1974).

H85,436/74

"In 23 healthy young pigs stress was produced by preventing escape behavior by pharmacologic restraint (Celourin chloride)." All of them developed infarctoid myocardial necroses which were sometimes fatal.

Norton, L., Mathews, D., Avrum, L., Eisenman, B.: "Pharmacological protection against swine stress ulcer." *Gastroenterology* **66**: 503-508 (1974).

J12,432/74

In pigs, hemorrhagic shock induces stress ulcers of the stomach which can be prevented by cholestyramine (that binds bile acids), methysergide (a 5-HT antagonist) and methylprednisolone, but only under certain conditions of dosage and timing, so that the clinical usefulness of this approach is still problematic.

Rokkanen, P., Jussila, J., Paatsama, S., Lahdensuu, M., Mäkelä, V., Ehnholm, C., Myllylä, G.: "Traumatic shock after severe limb tissue damage in pigs. An experimental study." *Acta Chir. Scand.* **140**: 85-90 (1974).

J12,278/74

Rabbit. Kracht, J., Kracht, U.: "Zur Histopathologie und Therapie der Schreckthyrotoxikose des Wildkaninchens" (The histopa-

thology and therapy of fright thyrotoxicosis in wild rabbits). *Virchows Arch. [Pathol. Anat.]* **321**: 238-274 (1952). B68,863/52

In some strains of wild rabbits, fear induced by a pursuing dog or man causes "stress thyrotoxicosis" with histologic signs of thyroid hyperactivity and exophthalmos.

Kracht, J., Spaethe, M.: "Über Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. II. Mitteilg. Untersuchungen über den 'Hypophysenhemmstoff' p-Oxypropiophenon" (Interrelation between the thyroid and the adrenal cortex. II. Report: Studies on the "hypophyseal inhibitor" p-oxypropiophenone). *Virchows Arch. [Pathol. Anat.]* **323**: 629-644 (1953). B85,143/53

Wild rabbits respond to frightening stimuli not only with adrenocortical enlargement, but also with a marked discharge of TTH which causes thyroid hypertrophy. This peculiar response can be prevented by hypophysectomy or methylthiouracil. p-Oxypropiophenone is inactive.

Kracht, J., Spaethe, M.: "Über Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. III. Mitt. Die thyreotrope Belastungsreaktion" (Interrelation between the thyroid and the adrenal cortex. III. Report: The thyrotropic stress reaction). *Virchows Arch. [Pathol. Anat.]* **324**: 83-109 (1953). B87,399/53

In wild rabbits, fear produces an acute discharge of TTH, often with an actual inhibition of ACTH secretion. "The symptomatology and the cause of fear thyrotoxicosis can be classified in terms of the phases of the alarm reaction, resistance and exhaustion (Selye). Increased thyrotropic function causes inhibition of ACTH secretion."

Griffiths, M. E., Calaby, J. H., McIntosh, D. L.: "The stress syndrome in the rabbit." *C.S.I.R.O. Wildl. Res.* **5**: 134-148 (1960).

D12,295/60

Detailed description of the stress syndrome in the wild rabbit, in which adrenal ascorbic acid content is extremely variable and cortical lipid granules increase after the animal has been kept in the laboratory for a "settling-in period." Cold has little effect on cortical ascorbic acid or lipid droplets, but subcutaneous formalin causes a threefold increase in adrenal size. Noise gives "cross resistance" to cold, but formalin does not.

Schäfer, H., Voss, C., Henschel, H. J., Hartmann, N.: "Jodtyrosin-Dejodesen im Stoffwechsel der Schilddrüsen-Hormone (Io-

dtyrosine deiodases in the metabolism of thyroid hormones). *Hoppe Seylers Z. Physiol. Chem.* **341**: 268-283 (1965).

J24,473/65

In wild rabbits, experimentally induced fright causes characteristic changes in the iodotyrosine deiodase content of various tissues which may be involved in the mechanism of stress-induced hyperthyroidism in animals and man (37 refs.).

Milin, R.: "The effects of fright on morphodynamics of testes." *Med. Pregl.* **19**: 453-458 (1966) (Serbo-Croatian).

G60,378/66

In hares kept in captivity in the presence of a hunting dog, testicular atrophy results as a consequence of fear.

Sildjajeva, R., Rozhold, O., Havlíček, V.: "Changes in the adrenal cortex of rabbits in emotional stress." *Activ. Nerv. Sup. (Praha)* **11**: 58-60 (1969).

J23,083/69

Lybeck, H., Leppäläluoto, J., Virkkunen, P.: "The effect of pertinent and non-pertinent stimuli on the secretions of thyrotropin and corticotropin." *Int. J. Neurosci.* **5**: 47 (1973).

J19,727/73

ACTH secretion rises under the influence of cold in both the rat and the rabbit, but TTH release remains unchanged in the latter. [If this difference does depend upon strain in rabbits, then the stressor effect of cold varies from that of fear, since some wild rabbits develop acute hyperthyroidism when chased by a dog (H.S.).]

Roussel, A., Daniel, J. Y., Assenmacher, I.: "Les glucocorticostéroïdes circulants du Lapin, et leurs fluctuations nyctémérales" (Circulating glucocorticoids and circadian variations in rabbits). *C.R. Acad. Sci. (Paris)* **277**: 341-344 (1973). J6,395/73

In rabbits, both plasma corticosterone and cortisol undergo circadian variations, with a peak during the day and a drop at the end of the night. However, the two corticoids do not show complete parallelism.

Khitrov, N. K., Demurov, E. A.: "Concerning the method of acute experiments on rabbits." *Patol. Fiziol. Éksp. Ter.* **10** No. 2: 76-78 (1974) (Russian).

J22,901/74

Biochemical effects of stress caused by restraint in the rabbit.

Sokolov, V. I.: "The reaction of the adrenal cortex of intact and castrated rodents to formalin stress." *Zh. Evol. Biokhim. Fiziol.* **10** No. 2: 171-175 (1974) (Russian). Engl.

transl.: *J. Evol. Biochem. Physiol.* **10**: 149–153 (1974). J18,986/74

Adrenocortical mitotic activity in hamsters and rabbits stressed by formalin is altered after orchidectomy.

Rat. Hammett, F. S.: "Studies of the thyroid apparatus. V. The significance of the comparative mortality rates of parathyroidectomized wild Norway rats and excitable and non-excitable albino rats." *Endocrinology* **6**: 221–229 (1922). 13,183/22

Rogers, P. V., Richter, C. P.: "Anatomical comparison between the adrenal glands of wild Norway, wild Alexandrine and domestic Norway rats." *Endocrinology* **42**: 46–55 (1948). B4,924/48

In general, wild rats have proportionally much heavier adrenal glands than domesticated strains, presumably because the latter are more protected against the stressors of competitive life. The reduced size of the adrenals in the laboratory rats can be ascribed to comparative cortical atrophy, the medulla not being affected.

Covian, M. R.: "Role of emotional stress in the survival of adrenalectomized rats given replacement therapy." *J. Clin. Endocrinol. Metab.* **9**: 678 (1949). B48,388/49

In contrast to domesticated strains, wild Norway rats cannot be indefinitely maintained on sodium chloride after adrenalectomy and are particularly sensitive to the fatal effects of electroshock, "indicating that the emotional state of captive wild rats is such that therapy sufficient to offset the loss of adrenals in laboratory rats is insufficient to keep the wild rats alive."

Richter, C. P.: "Domestication of the Norway rat and its implications for the problem of stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 19–47. Baltimore: Williams & Wilkins, 1950. B51,893/50

The organ weights of wild Norway rats (large adrenals, small thymus and so on) as well as many functional characteristics resemble those typical of the G.A.S. and in this respect differ from those of domesticated rats. Presumably, this can be ascribed to the more sheltered existence of the laboratory animals.

Richter, C. P., Rogers, P. V., Hall, C. E.: "Failure of salt replacement therapy in adrenalectomized recently captured wild Nor-

way rats." *Endocrinology* **46**: 233–242 (1950). D92,528/50

Unlike domesticated rats, wild Norways could not be maintained with sodium chloride after adrenalectomy, presumably because of their violent reactions to the usual stressor stimuli of daily life.

Woods, J. W.: "Differences in adrenal response to adverse conditions in wild and domesticated Norway rats." *Fed. Proc.* **12**: 159 (1953). B78,653/53

Wild and domesticated Norway rats were exposed to various stressors (cold, noise, fighting). "The results show that the wild rat endures the conditions of these experiments without a decrease in the amount of assayable ascorbic acid or stainable lipid in his adrenal cortex while results with the white rat are in agreement with the numerous reports of ascorbic acid and lipid depletion following similar stimulation." As indicated by ascorbic acid depletion, the adrenals of the wild rat are less sensitive than those of domesticated rats to traumatization of the intestines, hemorrhage, ether anesthesia, unilateral adrenalectomy or even ACTH administration.

Greenberg, L. A., Lester, D.: "The effect of alcohol on audiogenic seizures of rats." *Q. J. Stud. Alcohol* **14**: 385–389 (1953). J23,511/53

In rats, audiogenic seizures were largely inhibited by moderate ethanol intake.

Sines, J. O.: "Experimental production and control of stomach lesions in the rat." *J. Psychosom. Res.* **4**: 297–300 (1960). J23,258/60

Certain strains of rats are especially susceptible to restraint gastric ulcers. Such lesions can be controlled by anticholinergics but are increased by large doses of chlorpromazine. This "suggests that stomach lesion development in the rat is at least in part dependent upon parasympathetic hyperactivity."

Cole, J.: "A stress reaction in rats (*Rattus norvegicus*)."*Arzneim. Forsch.* **14**: 1048–1050 (1964). F22,700/64

Valtin, H., Schroeder, H. A.: "Familial hypothalamic diabetes insipidus in rats (Brattleboro strain)." *Am. J. Physiol.* **206**: 425–430 (1964). F1,711/64

In the strain of rats with familial hypothalamic diabetes insipidus, which can be corrected by vasopressin, the ability to concen-

urate urine in response to stress, dehydration, hypertonic saline or nicotine is greatly impeded.

Mikhail, A. A., Broadhurst, P. L.: "Stomach ulceration and emotionality in selected strains of rats." *J. Psychosom. Res.* **8**: 477-479 (1965). G27,799/65

Sackler, A. M., Weltman, A. S., Kreger, A. S.: "Metabolic and endocrine aspects of audiogenic-seizure susceptibility in female rats." *Exp. Med. Surg.* **24**: 258-269 (1966). F87,334/66

McCann, S. M., Antunes-Rodrigues, J., Nallar, R., Valtin, H.: "Pituitary-adrenal function in the absence of vasopressin." *Endocrinology* **79**: 1058-1064 (1966).

F74,055/66

In rats having hereditary hypothalamic diabetes insipidus and lacking vasopressin, stressors (ether, bleeding) raised plasma corticosterone, but to a significantly lesser extent than in normal controls. CRF activity in the stalk-ME and the pituitary ACTH concentration were essentially the same in the two strains. Presumably, "although vasopressin is not the corticotrophin-releasing factor, it may play a small role in adrenal cortical response to stress."

Weltman, A. S., Sackler, A. M.: "Timidity and metabolic elimination patterns in audiogenic-seizure susceptible and resistant female rats." *Experientia* **22**: 627-629 (1966).

G16,051/66

There is a positive relationship between timidity and seizure susceptibility in rats exposed to "auditory stress." At the same time, there is an increase in diuresis and the quantity of feces.

Arimura, A., Saito, T., Bowers, C. Y., Schally, A. V.: "Pituitary-adrenal activation in rats with hereditary hypothalamic diabetes insipidus." *Acta Endocrinol. (Kbh.)* **54**: 155-165 (1967). F76,127/67

In rats with hereditary hypothalamic diabetes insipidus, the basic plasma corticosterone concentrations are normal, and their reactions to stressors (ether, histamine, vasopressin, acetylcholine) are also within normal limits. Since these polyuric rats lack vasopressin, the latter is unlikely to be the physiologic CRF. On the other hand, the CRF content of the hypothalamus of these hereditarily stigmatized rats is normal, although their posterior lobe contains no CRF but a normal amount of ACTH.

Ader, R., Friedman, S. B., Grota, L. J.: "'Emotionality' and adrenal cortical function: effects of strain, test, and the 24-hour corticosterone rhythm." *Anim. Behav.* **15**: 37-44 (1967). G46,135/67

Weltman, A. S., Sackler, A. M., Owens, H.: "Effects of levels of audiogenic-seizure susceptibility on endocrine function of rats." *Physiol. Behav.* **3**: 281-284 (1968).

H5,154/68

Rats susceptible to audiogenic seizures developed adrenal hypertrophy and thymus involution upon exposure to the stressor effect of an alarm bell.

Sines, J. O., McDonald, D. G.: "Heritability of stress-ulcer susceptibility in rats." *Psychosom. Med.* **30**: 390-394 (1968).

G60,432/68

Martin, M. S., Martin, F., André, C., Lambert, R.: "Sélection du Rat Wistar en fonction de sa sensibilité à l'ulcère de contrainte" (Selection of Wistar rats as a function of sensitivity to restraint ulcers). *C.R. Soc. Biol. (Paris)* **162**: 2126-2128 (1968). H14,408/68

Selective breeding of rats to obtain strains that are resistant or sensitive to restraint ulcers.

Monastyrskaya, B. I., Prakh'e, I. B., Khaunina, R. A.: "The influence of sound on the hypophysis-adrenal system of healthy rats and those genetically highly sensitive to sound." *Bull. Éksp. Biol. Med.* **68** No. 12: 36-39 (1969) (Russian). J22,841/69

In rats genetically predisposed to audiogenic convulsions, hypertrophy of the pituitary and adrenals is manifest upon exposure to the stress of sound.

Ader, R.: "Adrenocortical function and the measurement of 'emotionality.'" *Ann. N.Y. Acad. Sci.* **159**: 791-805 (1969).

H18,024/69

Plasma and adrenal corticosterone measurements in rats failed to reveal any relationship to "emotionality" as appraised by the response to handling and open field activity.

Treiman, D. M., Fulker, D. W., Levine, S.: "Interaction of genotype and environment as determinants of corticosteroid response to stress." *Dev. Psychobiol.* **3**: 131-140 (1970). G82,877/70

In very young rats, "highly significant and opposing genetic and maternal effects interacted to limit extreme plasma corticosterone

concentrations following stress" (electroshock).

Allen, H. M.: "Gastrointestinal erosions in wild rats subjected to 'social stress.'" *Life Sci. [I]* 11: 351-356 (1972). G90,995/72

Lybeck, H., Leppäläluoto, J., Virkkunen, P.: "The effect of pertinent and non-pertinent stimuli on the secretions of thyrotropin and corticotropin." *Int. J. Neurosci.* 5: 47 (1973).

J19,727/73

ACTH secretion rises under the influence of cold in both the rat and the rabbit, but TTH release remains unchanged in the latter. [If this difference does depend upon the strain of rabbits, then the stressor effect of cold varies from that of fear, since some wild rabbits develop acute hyperthyroidism when chased by a dog (H.S.).]

Alexander, N. "Psychosocial hypertension in members of a Wistar rat colony." *Proc. Soc. Exp. Biol. Med.* 146: 163-169 (1974).

H87,183/74

Various social conditions (particularly aggregation and isolation) can cause hypertension in the rat.

Friedman, R.: "The effect of punishment on the blood pressure of rats with a genetic susceptibility to experimental hypertension," p. 78. Thesis, State University of New York at Stony Brook, 1974. J22,102/74

Hallbäck, M., Folkow, B.: "Cardiovascular responses to acute mental 'stress' in spontaneously hypertensive rats." *Acta Physiol. Scand.* 90: 684-698 (1974). J13,405/74

Genetically hypertensive rats showed more pronounced cardiovascular responses to the stressor effect of sound than did either normotensive controls or renal hypertensive rats of a normal strain. Hence, in his case, hyperreactivity is genetically conditioned.

Barnett, J. L., Cheeseman, P., Cheeseman, J., Douglas, J. M., Phillips, J. G.: "Adrenal responsiveness in ageing Brattleboro rats with hereditary diabetes insipidus." *Age and Ageing* 3: 189-195 (1974). J17,972/74

"Although the resting plasma corticosterone levels were drastically depressed in homozygous DI [diabetes insipidus] rats, there was no impairment of the response to stress; the adrenal glands of homozygous rats were significantly more responsive to stress than the corresponding heterozygous rats."

Wiley, M. K., Pearlmuter, A. F., Miller, R. E.: "Decreased adrenal sensitivity to

ACTH in the vasopressin-deficient (Brattleboro) rat." *Neuroendocrinology* 14: 257-270 (1974).

H88,352/74

In vasopressin-deficient Brattleboro rats, homozygous for diabetes insipidus, plasma corticosterone concentrations during stress (ether, laparotomy) rose much less than in genetically normal controls. That they did respond to some extent confirms that vasopressin is not identical with CRF. In vitro observations suggest that in the vasopressin-deficient strain, the adrenal glands themselves are relatively insensitive to ACTH. The presence of vasopressin in the internal milieu during early life may permanently influence adrenal sensitivity (18 refs.).

Murgas, K., Czako, M., Dobráková, M.: "Participation of 'emotionality' in activation of the adrenal cortex of rats in some stress situations." *Acta Neurobiol. Exp. (Warsz.)* 34: 467-475 (1974).

J15,408/74

Through the use of plasma corticosterone levels as indicators of stress, a relationship was found between the excitability of individual animals and the activity of their adrenal cortex upon exposure to various stressors.

Friedman, R., Dahl, L. K.: "The effect of chronic conflict on the blood pressure of rats with a genetic susceptibility to experimental hypertension." *Psychosom. Med.* (In press).

J24,878/

Rats genetically susceptible to experimental hypertension were exposed to several aversive stimuli. "Despite weekly fluctuations, a pattern emerged wherein subjects exposed to an approach (food)-avoidance (shock) conflict usually exhibited the highest blood pressures followed closely by rats given the same amount of food and shock but independent of their behavior." Usually the blood pressures returned to normal after the stressful experience, but there was "some indication in a few rats that the 'stress-induced' elevations could be maintained for extended periods following removal of the stress."

Sheep. Clegg, M. T., Ganong, W. F.: "The effect of hypothalamic lesions on ovarian function in the ewe." *Endocrinology* 67: 179-186 (1960).

J12,312/60

In ewes, stereotaxic lesions in various parts of the hypothalamus interfered selectively with diverse manifestations of adenohypophyseal activity. In two animals with stalk lesions, peripheral 17-OHCS failed to show a rise after stress (laparotomy), but in none

of the animals was there any significant adenohypophyseal atrophy.

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "The effect of stalk section on the volume of the pituitary gland of the sheep." *Acta Endocrinol. (Kbh.)* **43** Supp. 81: 1-27 (1963). E25,464/63

In sheep, the pituitary stalk was transected, a plate being inserted between the cut ends to prevent vascular regeneration. Comparatively small areas of the adenohypophysis escaped infarction, and the infundibular process decreased in volume. The location of the infarcted areas was attributed to differential distribution of the stalk vessel.

Bost, J., Dorleac, E.: "Influence de trois types de stimulation sonore sur le taux plasmatique des acides gras non estérifiés (FFA) chez le Mouton" (Effects of three types of auditory stimulation on plasma levels of non-esterified fatty acids in lambs). *C.R. Soc. Biol. (Paris)* **160**: 2340-2343 (1966).

F80,786/66

In lambs, various types of auditory stimulation greatly increased plasma FFA, although adaptation eventually occurred.

Panaretto, B. A., Ferguson, K. A.: "Comparison of the effects of several stressing agents on the adrenal glands of normal and hypophysectomized sheep." *Aust. J. Agric. Res.* **20**: 115-124 (1969). J24,295/69

Adrenocortical hemorrhages are seen in intact, but not in hypophysectomized and ACTH-maintained sheep, following treatment with EP, endotoxin or metyrapone.

Panaretto, B. A., Vickery, M. R.: "The rates of plasma cortisol entry and clearance in sheep before and during their exposure to a cold, wet environment." *J. Endocrinol.* **47**: 273-285 (1970). H28,932/70

In sheep exposed to cold, "decreased cortisol clearance rates did not appear to contribute to the great increases in plasma concentration until rectal temperature was about 34°." Curiously, the adrenal cortex and liver of the sheep were heavily infiltrated with fat after severe hypothermia.

Thwaites, C. J.: "Embryo mortality in the heat stressed ewe. III. The role of the corpus luteum, thyroid and adrenal glands." *J. Reprod. Fertil.* **21**: 95-107 (1970).

H21,604/70

Increased embryo mortality in ewes stressed during pregnancy is ascribed to the G.A.S.

Slee, J.: "Resistance to body cooling in male and female sheep, and the effects of previous exposure to chronic cold, acute cold and repeated short cold shocks." *Anim. Prod.* **12**: 13-21 (1970). J10,493/70

Resistance of shorn female sheep to cold can be greatly increased by a single previous exposure of a few hours. Females are more resistant to cooling than are males. Daily short cold shocks reduced cold resistance and inhibited acclimatization in females, but not in males.

Tollersrud, S., Baustad, B., Flatlandsmo, K.: "Effects of physical stress on serum enzymes and other blood constituents in sheep." *Acta Vet. Scand.* **12**: 220-229 (1971) (Norwegian). J20,894/71

Panaretto, B. A., Vickery, M. R.: "The distribution of cortisol and its rate of turnover in normal and cold-stressed shorn sheep." *J. Endocrinol.* **55**: 519-531 (1972). H64,137/72

Alexander, G., Bell, A. W., Hales, J. R. S.: "The effect of cold exposure on the plasma levels of glucose lactate, free fatty acids and glycerol and on the blood gas and acid-base status in young lambs." *Biol. Neonate* **20**: 9-21 (1972). J7,653/72

"When young lambs were exposed to very cold conditions, but maintained normal body temperature, there were substantial increases in the plasma concentration of glucose, lactic acid, free fatty acids and glycerol; muscle glycogen was depleted by about one third after three quarter h of exposure." Venous blood revealed an acidosis that was aggravated by infusions of EP or NEP.

Purchas, R. W.: "The response of circulating cortisol levels in sheep to various stresses and to reserpine administration." *Aust. J. Biol. Sci.* **26**: 477-489 (1973). J3,638/73

Alexander, D. P., Britton, H. G., Nixon, D. A., Ratcliffe, J. G., Redstone, D.: "Corticotrophin and cortisol concentrations in the plasma of the chronically catheterised sheep fetus." *Biol. Neonate* **23**: 184-192 (1973). J10,051/73

In chronically catheterized sheep fetuses, plasma ACTH levels were unusually elevated. Plasma cortisol was not strictly related to ACTH in individual samples but showed a high correlation in pooled data. The process of catheterization itself may have acted as a stressor.

Panaretto, B. A.: "Relationship of visceral blood flow to cortisol metabolism in cold-stressed sheep." *J. Endocrinol.* **60**: 235-245 (1974). H83,404/74

As long as sheep exposed to cold are capable of maintaining their body temperature, plasma cortisol levels are raised conjointly with cortisol metabolic clearance rates (radio-cortisol). Following continued exposure, when the animals lose their ability to maintain normal rectal temperatures, the plasma cortisol levels rise still further, but the metabolic clearance rates fall significantly below normal. The latter change is ascribed largely to reductions in hepatic and renal blood flow.

Hales, J. R. S., Brown, G. D.: "Net energetic and thermoregulatory efficiency during panting in the sheep." *Comp. Biochem. Physiol. [A]* **49**: 413-422 (1974).

H93,878/74

Clapp, J. F., Patel, N., Abrams, R. M.: "Fetal metabolic response to surgical stress" (abstracted). *Physiologist* **17**: 196 (1974).

H89,878/74

In lamb fetuses, surgical stress causes changes in oxygen and glucose utilization, lactate production and amino acid uptake.

Squirrel. Noble, G. A.: "Stress and parasitism. I. A preliminary investigation of the effects of stress on ground squirrels and their parasites." *Exp. Parasitol.* **11**: 63-67 (1961).

G38,126/61

In ground squirrels (*Citellus armatus*), exposure to various stressors increased susceptibility to infection with protozoa, mostly *Trichomonas*.

Tupaia. Sorenson, M. W., Conaway, C. H.: "Observations of tree shrews in captivity." *Sabah Soc. J.* **2**: 77-91 (1964).

J12,748/64

Sorenson, M. W., Conaway, C. H.: "Observations on the social behavior of tree shrews in captivity." *Folia Primatol.* (Basel) **4**: 124-145 (1966). J11,006/66

General review and personal observations on the effect of captivity upon behavior, particularly stress manifestations, in various tree shrews.

Autrum, H., Holst, D. von: "Sozialer 'Stress' bei Tupajas (*Tupaia glis*) und seine Wirkung auf Wachstum, Körbergewicht und Fortpflanzung" (Social stress in *tupaias* [*Tupaia glis*] and its effect on growth, body

weight and fertility). *Z. Vergl. Physiol.* **58**: 347-355 (1968). G58,325/68

Description of the autonomic nervous responses characteristic of social stress in the tree shrew.

Holst, D. von: "Sozialer Stress bei Tupajas (*Tupaia belangeri*). Die Aktivierung des sympathischen Nervensystems und ihre Beziehung zu hormonal ausgelösten ethologischen und physiologischen Veränderungen" (Social stress in *Tupaia* [*Tupaia belangeri*]. Activation of the sympathetic nervous system and its relation to hormonal stimulated ethologic and physiologic changes). *Z. Vergl. Physiol.* **63**: 1-58 (1969). G90,282/69

The hairs on the tail of the tree shrew normally lie flat, but they become erect and bushy at the slightest stimulation and thus act as a readily appraisable indicator of sympathetic activity. This response is elicited especially by other members of the species through sexual excitation or aggression. On the basis of studies on the mechanism of this reaction, "an attempt to interpret the results according to Selye's 'general adaptation syndrome' is made" (several hundred refs.).

Holst, D. von: "Renal failure as the cause of death in *Tupaia belangeri* exposed to persistent social stress." *J. Comp. Physiol.* **78**: 236-273 (1972). G93,301/72

When two adult male *Tupaia* are introduced, they immediately begin to fight. Subsequently, merely seeing the victor induces stress manifestations in the defeated *Tupaia*. This is associated with a constant decline in body weight, liver glycogen, blood hemoglobin and kidney weight, eventually resulting in fatal uremia. "The evidence from natural populations, when examined along with the findings from tree-shrews, show the great significance which social stress may have in the origin of renal disease—possibly in man as well as in animals."

Holst, D. von: "Die Funktion der Nebennieren männlicher *Tupaia belangeri*. Nebennierengewicht, Ascorbinsäure und Glucocorticoide im Blut bei kurzem und andauerndem soziopsychischem Stress" (The function of the adrenals in male *Tupaia belangeri*. Adrenal weight, ascorbic acid and glucocorticoids in the blood after acute and prolonged psychosocial stress). *J. Comp. Physiol.* **78**: 289-306 (1972). G93,303/72

Male *Tupaia*, after being defeated by a trained fighter, were separated from him by a wire mesh so that they could continually

see the victor without being attacked. The fight was repeated every one or two days. Under these conditions, the defeated *Tupaia* died in less than twenty days owing to the "psychosocial stress" associated with adrenal enlargement and increased ascorbic acid concentration. Plasma glucocorticoid levels initially dropped and then rose above normal. An elevation of adrenal ascorbic acid also occurred in *Tupaia* exposed to various other stressors, in contrast to the characteristic depletion in most other species.

D'Souza, F., Martin, R. D.: "Maternal behaviour and the effects of stress in tree shrews." *Nature* **251**: 309-311 (1974).

J23,295/74

In tree shrews, the noise of a fire bell accelerates the suckling rhythm but decreases the quantity of milk given over a forty-eight hour period. More severe stress causes cannibalism.

Vole. Clarke, J. R.: "The effect of fighting on the adrenals, thymus and spleen of the vole (*Microtus agrestis*)."
J. Endocrinol. **9**: 114-126 (1953). B77,639/53

Voles kept in a cage viciously attack any strangers of the same species introduced among them. The fighting results in adrenal enlargement and thymic atrophy characteristic of the alarm reaction, but instead of the usual splenic atrophy there is enlargement of the spleen, perhaps because of secondary infection.

Roth, R. R.: "The effect of temperature and light combinations upon the gonads of male red-back voles."
Biol. Reprod. **10**: 309-314 (1974).

J12,665/74

Various Mammals. Scharrer, E., Scharrer, B.: "Secretory cells within the hypothalamus."
Res. Public Assoc. Nerv. Ment. Dis. **20**: 170-194 (1940). 78,342/40

Excellent and well illustrated review on secretory neurons in the hypothalamus of various vertebrates.

Elton, R. L., Zarrow, I. G., Zarrow, M. X.: "Depletion of adrenal ascorbic acid and cholesterol: a comparative study."
Endocrinology **65**: 152-157 (1959). C71,402/59

"Exposure to severe cold produced significant depression of adrenal ascorbic acid in opossums and dogs, but failed to do so in frogs, toads, chickens, mice, hamsters, rabbits, and cats. ACTH failed to produce such a depletion in frogs, toads, chickens, rab-

bits, cats, or dogs; significant depressions were observed in opossums, mice and hamsters. Adrenal cholesterol concentrations remained unchanged in most species tested; however, increases were observed in rabbits following cold exposure, and in frogs, following ACTH treatment" (24 refs.).

Brodie, D. A., Hanson, H. M.: "A study of the factors involved in the production of gastric ulcers by the restraint technique."
Gastroenterology **38**: 353-360 (1960).

C87,271/60

Mice, rats, guinea pigs and hamsters exhibited a high incidence of gastric ulcers following restraint, whereas rabbits and monkeys were much more resistant. Fasting predisposed rats to this type of stress ulcer. Young rats proved to be more susceptible than old. Hypophysectomy and bilateral sub-diaphragmatic vagotomy did not significantly reduce the incidence of restraint ulcers, whereas bilateral adrenalectomy significantly increased it.

Christian, J. J.: "Phenomena associated with population density."
Proc. Natl. Acad. Sci. U.S.A. **47**: 428-449 (1961).

D79,921/61

Crowding produces typical manifestations of the G.A.S. in a variety of species, including *Mus*, *Rattus*, *Microtus*, *Clethrionomys*, *Marmota*, *Oryctolagus*, *Lepus*, *Sylvilagus*, *Cervus*, *Myocastor*, dog, guinea pig, monkey and man. The diminution in gonadotropic hormone production associated with the increased ACTH secretion characteristic of stress is an important factor in regulating population density (73 refs.).

Christian, J. J.: "The pathology of overpopulation."
Milit. Med. **128**: 571-603 (1963).

E22,467/63

A review of the literature on the effects of overpopulation in various species. In the mouse, woodchuck (*Marmota monax*) and Japanese deer (*Cervus nippon*), increased population density elicits structural and functional adrenal hyperactivity which—depending upon the species—is associated with decreased fertility, aggressiveness or renal glomerular disease.

Simoes, J.: *Stress nos Animais de Laboratorio* (Stress in laboratory animals), p. 43. Bahia, Brazil: Rockefeller Found. e Fund. Desenv. Cienc., 1963 (Portuguese).

G21,915/63

Monograph on the effect of stress upon

various experimental animals, especially under laboratory conditions (73 refs.).

Duvernoy, H., Koritke, J. G.: "Les vaisseaux sous-épendymaires du recessus hypophysaire" (Subependymal vessels of the hypophyseal recess). *J. Hirnforsch.* **10**: 227-245 (1968). J12,676/68

Extensive histologic studies on the subependymal origins of the hypothalamo-adenohypophyseal portal vessels in *various mammals* and *birds*. There exist numerous connections between the subependymal vessels and the cavity of the third ventricle, from which they are separated only by a thin and often discontinuous ependymal membrane. "Such a structure will possibly allow exchanges between the blood of the hypophysis and the ventricular liquid which is continuously in motion in the third ventricle."

Johke, T.: "Factors affecting the plasma prolactin level in the cow and the goat as determined by radioimmunoassay." *Endocrinol. Jap.* **17**: 393-401 (1970).

H39,458/70

Radioimmunologic determinations in *cows* and *goats* led to the conclusion that various stressors (venipuncture, pain, restraint, emotional disturbances) elevate the plasma LTH level, but milking is most effective in eliciting this response.

Augee, M. L., McDonald, I. R.: "Role of the adrenal cortex in the adaptation of the monotreme *Tachyglossus aculeatus* to low environmental temperature." *J. Endocrinol.* **58**: 513-523 (1973). H77,116/73

Various investigations suggest that although adrenocortical function has not developed very well in *monotremes* (the lowest order of mammals), their adrenocortical secretions are indispensable for resistance to cold. "The metabolic defect in adrenalectomized echidnas appears to be a failure of adequate mobilization of energy reserves to sustain increased metabolic heat production through muscular activity. In both intact and adrenalectomized echidnas the major factor leading to torpor was a fall in plasma glucose concentration." Adrenal hypertrophy in intact echidnas stressed by fasting or cold also shows the importance of these glands for resistance.

Birds. Siegel, H. S.: "The relation between crowding and weight of adrenal glands in

chickens." *Ecology* **40**: 495-498 (1959). J10,863/59

In laying *chickens*, crowding increases adrenal weight, although pituitary and thyroid weights remain unaffected.

Siegel, H. S.: "Egg production characteristics and adrenal function in White Leghorns confined at different floor space levels." *Poultry Sci.* **38**: 893-898 (1959).

J10,896/59

Crowding definitely diminished egg production in *chickens*. Although this was usually accompanied by adrenal hypertrophy, the two changes did not run strictly parallel. Presumably both were due to stress.

Brown, K. I.: "'Stress' and its implications in *poultry* production." *World Poultry Sci. J.* **15**: 255-263 (1959). D96,230/59

Sturkie, P. D., Textor, K.: "Relationship of blood pressure levels in *chickens* to resistance to physical stresses." *Am. J. Physiol.* **200**: 1155-1156 (1961). D10,931/61

Miller, R. A.: "Hypertrophic adrenals and their response to stress after lesions in the median eminence of totally hypophysectomized pigeons." *Acta Endocrinol. (Kbh.)* **37**: 565-576 (1961). D80,692/61

In *pigeons*, hypophysectomy causes adrenal atrophy but the interrenal tissue becomes hypertrophic during stress elicited by formaldehyde or insulin, even in the absence of the pituitary. Very large lesions in the ME and ventral hypothalamus produce adrenal hypertrophy rather than atrophy, even after total hypophysectomy. The suprarenals also react to formaldehyde. "It appears that the interrenal tissue of the pigeon responds to a humoral stimulus not of hypophyseal origin in the absence of the hypophyseal-hypothalamic system."

Brown, K. I.: "The validity of using plasma corticosterone as a measure of stress in the turkey." *Proc. Soc. Exp. Biol. Med.* **107**: 538-542 (1961). D20,460/61

In *turkeys*, the main free corticosteroid found in the plasma is corticosterone. Its concentration increases under the influence of ACTH and various stressors (water deprivation, cold). Hypophysectomy does not significantly alter the resting plasma corticosterone level, but prevents its rise under stress. Presumably, plasma corticosterone is a valid indicator of stress in these birds, although the adrenals are relatively autonomous in that their basic corticoid production

continues in the absence of the anterior pituitary.

Thompson, W. R., O'Kieffe, M. W.: "Imprinting: its effect on the response to stress in chicks." *Science* **135**: 918-919 (1962).

D21,133/62

Young *chicks* imprinted to surrogate mothers showed increased resistance to the stress of exposure to a doorbell (as judged by their activity level), both in the presence and in the absence of their surrogate mothers. No such difference was seen upon exposure to the more severe stress of total food and water deprivation.

Donoso, A. O.: "Concentration de l'adrénaline et de la noradrénaline dans le plasma de quelques espèces d'oiseaux. Action de divers facteurs" (Adrenaline and noradrenaline concentrations in the plasma of *various species of bird*. The effect of diverse factors). *C. R. Soc. Biol. (Paris)* **156**: 790-795 (1962).

D34,423/62

Huchzermeyer, F.: "Die Stress-Situation beim Geflügel aus der Sicht des Tierarztes" (The stress situation in *fowl* as viewed by the veterinarian). *Dtsch. Tierärztl. Wochenschr.* **70**: 109-111 (1963).

J23,945/63

Alterauge, W.: "Die Stress-Situation beim Geflügel aus der Sicht des Tierarztes" (The stress situation in *poultry* from the viewpoint of the veterinarian). *Dtsch. Tierärztl. Wochenschr.* **72**: 86-87 (1965).

J24,914/65

Whittow, G. C., Sturkie, P. D., Stein, G. Jr.: "Cardiovascular changes in restrained chickens." *Poultry Sci.* **44**: 1452-1459 (1965).

J23,501/65

Siegel, H. S., Gross, W. B.: "Social grouping, stress and resistance to coliform infection in cockerels." *Poultry Sci.* **44**: 1530-1536 (1965).

G37,829/65

In *cockerels* subjected to various types of social grouping, "evidences of mild stress such as lower total leucocytes, increased adrenal weight, reduced bursa weight and/or reduced adrenal cholesterol concentrations were discernible." *E. coli* infection caused more severe leukopenia and plasma-corticosterone rises, but under certain conditions it also resulted in "cross" or "nonspecific" resistance as suggested by Selye."

Gross, W. B., Siegel, H. S.: "The effect of social stress on resistance to infection with

Escherichia coli or *Mycoplasma gallisepticum*." *Poultry Sci.* **44**: 998-1001 (1965).

J11,921/65

"Social stress" was produced in *chickens* by moving males into cages with other birds according to a schedule that kept contact with previously encountered birds to a minimum. After two weeks, their resistance to *E. coli* inoculation was increased but their sensitivity to *Mycoplasma gallisepticum* remained unchanged.

Kemény, A., Kemény, V., Kozma, M., Vecsei, P.: "Effect of thermal stress on steroidogenesis by chicken adrenal tissue in vitro with ³H-pregnenolon as precursor." *Endokrinologie* **50**: 182-187 (1966).

F72,465/66

"After a severe stress on the thermal regulation mechanism of the young *chicken*, the ability to incorporate the precursor into the corticoids begins to get exhausted."

Burton, R. R., Sluka, S. J., Besch, E. L., Smith, A. H.: "Hematological criteria of chronic acceleration stress and adaptation." *Aerosp. Med.* **38**: 1240-1243 (1967).

G63,027/67

Study on stress and adaptation in *chickens*.

Kendler, J., Harry, E. G.: "Systemic *Escherichia coli* infection as a physiological stress in chickens." *Res. Vet. Sci.* **8**: 212-218 (1967).

J23,505/67

In *chickens*, *coli*-septicemia caused a characteristic stress syndrome with involution of the spleen and bursa, associated with increased bursal β -glucuronidase.

Freeman, B. M.: "Effect of stress on the ascorbic acid content of the adrenal gland of *Gallus domesticus*." *Comp. Biochem. Physiol.* **23**: 303-305 (1967).

F90,188/67

In young *chickens*, adrenal ascorbic acid is depleted within ten minutes of handling. However, this decrease is only of a very short duration and has therefore been missed by many previous investigators (14 refs.).

Miller, R. A.: "Regional responses of interrenal tissue and of chromaffin tissue to hypophysectomy and stress in pigeons." *Acta Endocrinol. (Kbh.)* **55**: 108-118 (1967).

F79,962/67

In *pigeons*, the cortical and medullary cells of the adrenals are intermixed and hence three distinct cortical zones such as are seen in mammals cannot be distinguished. Yet there is some evidence that certain regions

of the avian interrenal tissue may be homologous with the mammalian cortical zones. Hypophysectomy causes only a slight decrease in the weight of the pigeon adrenal, due mainly to atrophy of interrenal (cortical) cells near the center of the gland. Stress (repeated injections of formalin when they are on a low sodium diet) elicits hypertrophy and hyperplasia of both interrenal and chromaffin tissue, even in hypophysectomized pigeons.

Thaxton, P., Sadler, C. R., Glick, B.: "Immune response of chickens following heat exposure or injections with ACTH." *Poultry Sci.* **47**: 264-266 (1968). G58,548/68

In *chickens* exposed to heat, treatment with ACTH or cortisone before antigen injection depresses the antibody response to sheep red blood cells. Such treatment also inhibits the development of the bursa of Fabricius and the spleen. This "might be explained by an interference with phagocytosis or immunoglobulin producing cells brought about by direct effect of the treatment or by some humoral substance like corticosterone."

Burton, R. R., Smith, A. H.: "Criteria for physiological stress produced by increased chronic acceleration." *Proc. Soc. Exp. Biol. Med.* **128**: 608-611 (1968). H2,172/68

"Physiological fitness relative to exercise capacity, sexual development, and survival of an individual with respect to a stressful environment, increased chronic acceleration, may be quantitatively determined in the *chicken* by hematological methods."

Frankel, H. M., Frascella, D.: "Blood respiratory gases, lactate, and pyruvate during thermal stress in the *chicken*." *Proc. Soc. Exp. Biol. Med.* **127**: 997-999 (1968). F99,196/68

Atherton, R. W., Ramm, G. M.: "General observations, erythrocyte counts and hemoglobin concentration in *chick* embryos subjected to centrifugal stress." *Aerosp. Med.* **40**: 389-391 (1969). J22,401/69

Sturkie, P. D., Poorvin, D., Ossorio, N.: Levels of epinephrine and norepinephrine in blood and tissues of duck, pigeon, turkey, and chicken." *Proc. Soc. Exp. Biol. Med.* **135**: 267-270 (1970). H32,255/70

In *ducks*, *pigeons*, *turkeys* and *chickens*, the plasma concentration of EP is considerably higher than that of NEP. The effect of excitement (handling) or lack of it (pentobarbital sedation) on plasma and tissue catecholamines is also reported. [The few super-

ficially described experiments do not lend themselves to interpretation (H.S.).]

Lawzewitsch, I. von, Sarrat, R.: "Das neurosekretorische Zwischenhirn-Hypophysensystem von Vögeln nach langer osmotischer Belastung" (The neurosecretory hypothalamo-hypophyseal system of birds after long-term osmotic stress). *Acta Anat. (Basel)* **77**: 521-539 (1970). G84,461/70

It is concluded that "the hypothalamo-hypophyseal neurosecretory system of *cocks* under a chronic stress of a 0.3 m NaCl solution ad libitum, resulting in an exhaustion of the system, enters into a period of adaptation during which new neurosecretory material is stored by the cells of the nucleus. This adaptation could either result from the synthesizing ability of the neurosecretory cells being increased by a prolonged stress or from the decrease in hormonal demand due to functional changes in the periphery."

Bhattacharyya, T. K., Ghosh, A.: "Influence of surgical and steroid bursectomy on the behavior of adrenal ascorbic acid during stress in juvenile pigeons." *Gen. Comp. Endocrinol.* **15**: 420-424 (1970).

H35,126/70

In juvenile *pigeons*, bursectomy facilitated the depletion of adrenal ascorbic acid during stress (formalin). Cortisol caused involution of the bursa but left adrenal ascorbic acid levels unaltered after exposure to stress.

Cowan, D. F., Johnson, W. C.: "Amyloidosis in the white Pekin *duck*. I. Relation to social environmental stress." *Lab. Invest.* **23**: 551-555 (1970). G80,215/70

Hamilton, P. B., Harris, J. R.: "Interaction of aflatoxicosis with *Candida albicans* infections and other stresses in *chickens*." *Poultry Sci.* **50**: 906-912 (1971).

J21,253/71

Parker, J. T., Boone, M. A.: "Thermal stress effects on certain blood characteristics of adult male *turkeys*." *Poultry Sci.* **50**: 1287-1295 (1971). J20,533/71

Freeman, B. M.: "Stress and the domestic fowl: a physiological appraisal." *World Poultry Sci. J.* **27**: 263-275 (1971) (about 110 refs.). J21,811/71

Gross, W. B., Colmano, G.: "Effect of infectious agents on *chickens* selected for plasma corticosterone response to social stress." *Poultry Sci.* **49**: 1213-1217 (1971).

J23,532/71

Palokangas, R., Hissa, R.: "Thermoregulation in young black-headed gull (*Larus ridibundus L.*)" *Comp. Biochem. Physiol. [A]* **38**: 743-750 (1971). H36,410/71

Exposure of the *black-headed gull* to cold slightly elevates plasma corticosterone and NEP concentrations, whereas it significantly decreases EP content.

Siegel, H. S.: "Adrenals, stress and the environment." *World Poultry Sci. J.* **27**: 327-349 (1971). G87,043/71

A review of the literature suggests that in birds the hypothalamus is the source of an extrahypophyseal, ACTH-like polypeptide. "In any case, the adrenal glands of birds do respond directly to ACTH by hypertrophy and increased secretion of corticosteroids. Although various environmental stimuli produce evidence of a 'stress response' in birds, it is often necessary that several criteria of response be evaluated because specific responses to a particular stimulus may contradict or mask a single response." A period of apparent refractoriness to ACTH occurs in young birds, perhaps as a consequence of low reserve in steroid precursors (about 70 refs.).

Bhattacharyya, T. K., Ghosh, A.: "Cellular modification of interrenal tissue induced by corticoid therapy and stress in three avian species." *Am. J. Anat.* **133**: 483-493 (1972). G89,788/72

In three avian species (*quail, parakeet* and *myna*), dexamethasone caused atrophy of the cortical elements in the interrenal tissue, in which cortical and medullary cells are intermixed. However, zonal differences in the compensatory atrophy of the cortical cells were not detectable. "Following exposure to acute formalin stress at the termination of chronic corticoid therapy, the interrenal tissue regularly responded by hypertrophy in all three types of birds." The prompt response of the atrophic interrenal gland to stress also suggests that the hypothalamo-hypophyseal regulation of the adrenal is different from that in mammals (23 refs.).

Péczely, P.: "Effect of ether stress on CRF-ACTH system of the domestic *pigeon*." *Acta Biol. Acad. Sci. Hung.* **23**: 23-29 (1972). G99,695/72

"In 15 min after the stress, the CRF activity and the ACTH content of the pituitary gland decreased by 17 and 55 per cent, respectively, and the corticosterone produc-

tion of the adrenals increased by 218 per cent."

Levine, A. M., Higgins, J. A., Barrnett, R. J.: "Biogenesis of plasma membranes in salt glands of salt-stressed domestic *ducklings*: localization of acyltransferase activity." *J. Cell Sci.* **11**: 855-873 (1972).

J19,377/72

Smith, R. M.: "Circulation, respiratory volumes and temperature regulation of the pigeon in dry and humid heat." *Comp. Biochem. Physiol. [A]* **43**: 477-490 (1972).

H60,824/72

Description of respiratory and cardiovascular changes allegedly characteristic of stress in *pigeons* exposed to humid heat.

Rhees, R. W., Abel, J. H. Jr., Frame, J. R.: "Effect of osmotic stress and hormone therapy on the hypothalamus of the *duck* (*Anas platyrhynchos*)." *Neuroendocrinology* **10**: 1-22 (1972).

H58,144/72

Bouillé, C., Herbuté, S., Baylé, J. D.: "Modulatory influences of central nervous structures on pituitary-adrenocortical activity: effect of chronic deafferentation of the hypothalamus in the pigeon." *J. Physiol. (Paris)* **66**: 437-446 (1973). J9,213/73

In Carneau *pigeons*, deafferentation of the hypothalamus with a modified Halász knife suppressed the usual circadian variations in plasma corticosterone levels. Responses to ether stress were reduced but not abolished.

Abati, A. L., McGrath, J. J.: "Physiological responses to acute hypoxia in altitude-acclimatized *chickens*." *J. Appl. Physiol.* **34**: 804-808 (1973) (32 refs.). H81,614/73

Wise, P. M., Frye, B. E.: "Functional development of the hypothalamo-hypophyseoadrenal cortex axis in the chick embryo, *Gallus domesticus*." *J. Exp. Zool.* **185**: 277-291 (1973). J7,865/73

Studies on *chick* embryos, based mainly on plasma corticosterone determinations after stress produced by opening the shell and breaking one shank. "The adrenal exhibits significant autonomous functional capability prior to day 14, and the pituitary becomes important in maintaining both the resting level of hormone and the stress response between days 14 and 16 of incubation. The hypothalamus does not appear to control normal resting levels of corticosterone, but is essential for the stress response." The initial autonomy of the adrenal is demon-

strated by the persistence of significant plasma corticosterone levels after decapitation of the embryo.

Halawani, M. E. el, Waibel, P. E., Appel, J. R., Good, A. L.: "Effects of temperature stress on catecholamines and corticosterone of male turkeys." *Am. J. Physiol.* **224**: 384-388 (1973). H65,841/73

In male *turkeys*, neither heat nor stress had any pronounced effect upon adrenal, brain or heart catecholamine concentrations; however, plasma corticosterone levels rose. When α -MT (an inhibitor of catecholamine biosynthesis) was given prior to stress exposure, catecholamine concentrations fell markedly, unless the birds had previously been adapted to hot or cold environments. "These findings indicate that an increased rate of catecholamine and corticosterone release seems to be required during the initial response to temperature stress, and may be associated with the adaptive changes leading to temperature acclimation" (20 refs.).

Bouillé, C., Baylé, J. D.: "Experimental studies on the adrenocorticotrophic area in the pigeon hypothalamus." *Neuroendocrinology* **11**: 73-91 (1973). H66,001/73

In *pigeons*, hypothalamic control of stress-induced adrenocortical activity was examined by means of hypothalamic lesions combined with hypophysectomy or pituitary autografts. "A well-defined adrenocorticotrophic area is present in the posterior medial and lateral hypothalamic region. Destruction of the area leads to the same decrease of the plasma corticosterone level as is seen after adeno-hypophysectomy and also prevents the progressive recovery of adrenocortical function after autografting. The adrenal cortical response to various stressful stimuli is suppressed after lesioning of this same area." It remains to be seen whether the residual adrenocortical responsiveness of hypophysectomized pigeons is due to partial autonomy of the gland or to some extrahypophyseal control system. In any case, corticotrophic activity is abolished by destruction of the regulating hypothalamic area and hence the hypothesis of the functional autonomy of the pigeon adrenal "is invalidated."

Buckland, R. B., Blagrave, K.: "Effect of feeding chlorpromazine, metyrapone and pargyline to *chicks* on plasma corticoid levels and the effect of stress on their relationship to body weight." *Poultry Sci.* **52**: 1215-1217 (1973). J22,017/73

Reid, B. L., Weber, C. W.: "Dietary protein and sulfur amino acid levels for laying hens during heat stress." *Poultry Sci.* **52**: 1335-1343 (1973). J22,020/73

Brown, K. I., Nestor, K. E.: "Some physiological responses of *turkeys* selected for high and low adrenal response to cold stress." *Poultry Sci.* **52**: 1948-1954 (1973).

J22,002/73

Holmes, P. W., Smith, B. L.: "Ethanol consumption by pigeons under stress." *Q. J. Stud. Alcohol* **34**: 764-768 (1973).

J21,557/73

Pigeons chronically exposed to repeated electroshocks voluntarily drank solutions of 1 to 4 percent ethanol in preference to water.

Mitchell, B. W., Siegel, H. S.: "Physiological response of *chickens* to heat stress measured by radio telemetry." *Poultry Sci.* **52**: 1111-1119 (1973). J22,022/73

Nvota, J., Lamošová, D., Fáberová, A.: "Critical periods in the development of chicks." *Physiol. Bohemoslov.* **22**: 337-343 (1973).

J21,555/73

The stress of restraint during a critical period of about three to four weeks after hatching produced a maximal decrease in thyroid activity in adulthood and a significant drop in the BMR of the *chick*. "The critical phase for regulation of the function of the pituitary-adrenal and pituitary-gonad axis was found to be the period between the 15th and 21st day after hatching. Exposure to stress in this phase caused a significantly greater reaction of the adrenals to stress situations in the adult hens and significantly stimulated sexual maturation (egg-laying)."

Duncan, I. J. H.: "The behaviour of the domestic fowl in stressful situations." *Br. Vet. J.* **130**: 89-90 (1974). J20,870/74

Howard, B. R.: "The assessment of stress in *poultry*." *Br. Vet. J.* **130**: 88-89 (1974). J20,868/74

Baylé, J. D., Bouillé, C.: "Activité corticosurrénalienne après lésion de l'hippocampe chez le pigeon" (The adrenal cortex function after lesion of the hippocampus in the pigeon). *Gen. Comp. Endocrinol.* **22**: 360-361 (1974). H83,189/74

Bilateral electrolytic lesions in the hippocampus in *pigeons* raise the basic plasma corticosterone level. The response to immobilization stress is only slightly reduced. Conversely, stimulation of the hippocampus diminishes plasma corticosterone.

Péczely, P., Szokoly, P. M.: "The effect of acute and chronic stimulation on ACTH cell of the pigeon's adenohypophysis." *Gen. Comp. Endocrinol.* **22**: 367 (1974).

H83,210/74

In pigeons, acute insulin hypoglycemia and fourteen-day treatment with metyrapone were studied in connection with their effect upon the epsilon cells (which were stained light red by Herland's stain). "Insulin stress causes a strong hypertrophy of the ACTH cells. The endoplasmic reticulum shows an extreme hyperplasia, and the quantity of the secretion granules and the ACTH content of the pars distalis decrease. Metyrapone treatment causes hypertrophy and hyperplasia of the ACTH cells. The quantity of the endoplasmic reticulum increases; the cisternae are dilated, and they form vesicles. A great number of secretory granules appear, mainly on the periphery of the cells. The ACTH content of the pars distalis increases." These findings are in accordance with the assumption that the epsilon cells of birds are the source of ACTH, and that acute and chronic stimulation leads to different EM changes.

Brown, K. I., Nestor, K. E.: "Implications of selection for high and low adrenal response to stress." *Poultry Sci.* **53**: 1297-1306 (1974).

J21,587/74

Turkey lines were selected for high and low adrenal reactions to stress (heat). "Elevated plasma corticosterone in response to stress will probably induce elevated plasma catecholamines. This combination may result in hyperactivity, higher blood pressure, poorer feed efficiency, and poorer reproductive performance. The converse would be true of low adrenal response."

Gross, W. B.: "Stressor effects of initial bacterial exposure of chickens as determined by subsequent challenge exposures." *Am. J. Vet. Res.* **35**: 1225-1228 (1974).

J23,893/74

Chickens bred for a low concentration of plasma corticosterone "inoculated initially with live or killed *Escherichia coli* had increased resistance to *E. coli*, lessened resistance to *Mycoplasma gallisepticum*, and reduced capability to produce antibody." Chickens selected for a high corticosterone concentration were less responsive to the initial inoculation. Metyrapone blocked the resistance induced by the exposure to *E. coli*.

Nestor, K. E., Brown, K. I., Renner,

P. A.: "Effect of genetic changes in egg production, growth rate, semen yield and response to cold stress on early mortality of turkey poulets." *Poultry Sci.* **53**: 204-210 (1974).

J21,594/74

Groscolas, R.: "Effet d'une exposition à la chaleur sur la température corporelle et quelques paramètres hématologiques du manchot empereur, *Aptenodytes forsteri*" (Effect of heat exposure on body temperature and hematology in the emperor penguin, *Aptenodytes forsteri*). *Comp. Biochem. Physiol. [A]* **50**: 533-543 (1975).

H98,407/75

Reptiles. Miller, M. R.: "The normal histology and experimental alteration of the adrenal of the viviparous lizard, *Xantusia vigilis*." *Anat. Rec.* **113**: 309-323 (1952).

B36,730/52

In the viviparous Yucca night lizard, as in other lacertilians, the adrenals consist of dorsal medullary and ventral interrenal portions. Hypophysectomy, cortisone and DOC cause lipid depletion and involution of the interrenal cells. ACTH likewise depletes them of lipids but induces hypertrophy and, in large doses, even degenerative changes. Similar alterations indicative of hyperactivity are obtained by the stress of starvation.

Daly, O. W., Davis, G., Siegel, S. M.: "General and comparative biology of experimental atmospheres and other stress conditions: experiments with the turtle, *Pseudemys scripta elegans*." *Aerosp. Med.* **36**: 363-368 (1965).

G28,211/65

Turtles "showed an ability to adapt to a range of atmospheres varying from anaerobic to those containing 100 per cent oxygen, to high and low atmospheric pressures, ultraviolet radiation and reduced temperatures. Such adaptability makes the turtle an excellent specimen for stress experimentation."

Algauhari, A. E. I.: "Experimental studies on the blood sugar in reptiles. Effect of fasting, temperature and insulin administration in *Psammophis sibilans*." *Z. Vergl. Physiol.* **54**: 395-399 (1967).

G45,974/67

In the snake *Psammophis sibilans* the blood sugar is remarkably constant, and fasting up to five months as well as extreme temperature variations fail to alter it. However, this snake is also very (though not completely) resistant to insulin hypoglycemia, and it is questionable whether the constant level of its blood sugar upon exposure to

otherwise active stressors really does indicate resistance to stress as such.

Spigel, I. M., Ramsay, A.: "Excretory electrolytes and response to stress in a reptile." *J. Comp. Physiol. Psychol.* **68**: 18-21 (1969). G67,129/69

"Elevated urinary alkali metal (combined Na^+ and K^+) was observed in electrically shocked turtles."

Banerjee, S. K.: "Histochemical studies on the neurosecretory system of the common garden lizard *Calotes versicolor* (Daudin) under experimental condition." *Histochemie* **23**: 59-62 (1970). J21,402/70

Gist, D. H.: "Effects of mammalian ACTH on liver and muscle glycogen levels in the South American caiman (Caiman sclerops)." *Gen. Comp. Endocrinol.* **19**: 1-6 (1972).

H58,201/72

In the South American *caiman*, liver and muscle glycogen concentrations were not affected even after twenty days of starvation, but relative hepatic weight decreased. ACTH augmented the liver glycogen in July and October, but not in February or May. Apparently, the pituitary-adrenal axis is operative in reptiles.

Webb, G. J. W., Johnson, C. R.: "Head-body temperature differences in turtles." *Comp. Biochem. Physiol. [A]* **43**: 593-611 (1972). H60,828/72

Extensive review and personal observations on temperature regulation in *turtles* exposed to "heat stress." [No special studies have been made of the characteristic stress effects (H.S.).]

Meurling, P., Klefbohm, B., Larsson, L.: "Transplantation of the pars intermedia in an elasmobranch and a lizard." *Gen. Comp. Endocrinol.* **22**: 347 (1974). H83,146/74

In the *lizard* (*Anolis carolinensis*), the neuro-intermediate lobe grafted beneath the dorsal skin results in a local distinct small dark patch owing to MTH discharge. Exposure to stressors (kind not described) causes a rapid release of MTH.

Sturbaum, B. A., Riedesel, M. L.: "Temperature regulation responses of ornate box turtles, *Terrapene ornata*, to heat." *Comp. Biochem. Physiol. [A]* **48**: 527-538 (1974). H87,003/74

Turtles are particularly resistant to high temperatures. "Exposure to 38 and 41°C was not a heat stress for these turtles as evi-

denced by absence of restless activity, very little evaporative weight loss, no frothing and no change in heart rate.... Weight loss appears to be a much better index of thermal stress than is heart rate."

Haider, S., Sathyanesan, A. G.: "Hypothalamo-hypophysial neurosecretory and portal system of the Indian wall lizard, *Hemidactylus flaviviridis*." *Acta Anat. (Basel)* **88**: 502-519 (1974). J15,789/74

Ellis, R. A., Goertemiller, C. C. Jr.: "Cytological effects of salt-stress and localization of transport adenosine triphosphatase in the lateral nasal glands of the desert *Iguana*, *Dipsosaurus dorsalis*." *Anat. Rec.* **180**: 285-298 (1974). J17,759/74

Crews, D.: "Effects of group stability, male-male aggression and male courtship behaviour on environmentally-induced ovarian recrudescence in the lizard *Anolis carolinensis*." *J. Zool.* **172**: 419-441 (1974) (about 40 refs.). J15,306/74

Abdel-Raheem, K. A.: "Effect of hypothermia on the electrolyte composition of tissues of reptiles." *Comp. Biochem. Physiol. [A]* **50**: 195-199 (1975). H96,699/75

Amphibians. Houssay, B. A., Biasotti, A., Sammartino, R.: "Modifications fonctionnelles de l'hypophyse après les lésions infundibulo-tubériennes chez le crapaud" (Functional changes of the hypophysis after lesions of the lobus infundibularis in toads). *C.R. Soc. Biol. (Paris)* **120**: 725-727 (1935). 56,016/35

In the *toad*, the hypothalamus consists of a pars basalis, lamina terminalis and lobus infundibularis. The latter is attached to the hypophysis. Lesions of the lobus infundibularis cause circulatory arrest in the principal lobe of the hypophysis with increased absorption of MTH, darkening of the animal and other hormonal derangements.

Green, J. D.: "Vessels and nerves of amphibian hypophyses. A study of the living circulation and of the histology of the hypophysial vessels and nerves." *Anat. Rec.* **99**: 21-53 (1947). B4,690/47

Detailed description of the hypophyseal portal system in the *bullfrog* and *Ambystoma*.

Chiakulas, J. J., Scheving, L. E., Winston, S.: "The effects of exogenous epinephrine and environmental stress stimuli on the

mitotic rates of larval *urodele* tissues." *Exp. Cell. Res.* **41**: 197-205 (1966).

G37,592/66

Mukherji, M.: "Adrenal cortex in stress and hibernation; a histochemical study in toad (*Bufo melanostictus*)."*Acta Histochem.* (Jena) **29**: 297-303 (1968). F98,729/68

Under ordinary conditions, various stressors (cold, acute dehydration) and ACTH caused depletion of adrenocortical lipids in the *toad*, but the hibernating adrenal responded only to dehydration shock.

Berchtold, J. P.: "Contribution à l'étude ultrastructurale des cellules interrénales de *Salamandra salamandra* L. (Amphibien Urodèle). II. Action de l'ACTH endogène" (A contribution to the ultrastructural study of the interrenal cells of *Salamandra salamandra* L. [Urodele Amphibian]. II. The effects of endogenous ACTH). *Z. Zellforsch.* **110**: 517-539 (1970) (about 50 refs.).

G79,811/70

Deparis, P.: "Modifications hématologiques provoquées par la manipulation et la saignée chez *Pleurodeles waltl* Michah (Amphibien, Urodèle)" (Hematologic modifications induced by manipulation and bleeding in *Pleurodeles waltl* Michah [Amphibian, Urodele]). *J. Physiol.* (Paris) **64**: 19-30 (1972). G91,179/72

In the *newt Pleurodeles*, hemorrhage causes pronounced neutrophilia followed within a few hours by lymphopenia and eosinopenia. The same results are obtained by other stressors, even by mere manipulation of the animals. These hematologic variations are ascribed to stress under the influence of corticoids.

Funkhouser, D., Goldstein, L.: "Urea response to pure osmotic stress in the aquatic toad *Xenopus laevis*."*Am. J. Physiol.* **224**: 524-529 (1973). H67,004/73

Juráni, M., Murgaš, K., Mikulaj, L., Babušková, F.: "Effect of stress and environmental temperature on adrenal function in *Rana esculenta*."*J. Endocrinol.* **57**: 385-391 (1973). H71,773/73

Gona, A. G., Gona, O.: "Prolactin-releasing effects of centrally-acting drugs in the red-spotted *newt*."*Neuroendocrinology* **14**: 365-368 (1974). H89,271/74

Turney, L. D., Hutchison, V. H.: "Metabolic scope, oxygen debt and the diurnal oxygen consumption cycle of the *leopard frog*,

Rana pipiens."*Comp. Biochem. Physiol. [A]* **49**: 583-601 (1974). H93,883/74

Juráni, M., Mikulaj, L.: "The effect of repeated stress upon the reaction of interrenal tissue in frogs and hens."*Gen. Comp. Endocrinol.* **22**: 401 (1974). H83,309/74

In frogs (*Rana ridibunda*) and hens (*Gallos domesticus*), brief immobilization causes hyperactivity of the interrenal tissue, as indicated by increased plasma corticosterone levels and excess synthesis of corticoids by adrenal homogenates. This response is more pronounced after the first than after subsequent immobilizations.

Fish. Merrick, A. W.: "Cardiac glycogen following fulminating anoxia."*Am. J. Physiol.* **176**: 83-85 (1954). G62,149/54

In the *goldfish*, the cardiac glycogen stores are extremely high and difficult to exhaust, even by fulminating anoxia. "Cardiac glycogen is an emergency stand-by used by the heart during periods of anoxic stress." However, complete removal of cardiac glycogen is not necessary for the induction of cardiovascular and respiratory failure, and the observations do not prove any particular resistance of this fish to other stressors.

Mahon, E. F., Hoar, W. S., Tabata, S.: "Histophysiological studies of the adrenal tissues of the goldfish."*Can. J. Zool.* **40**: 449-464 (1962). D58,580/62

The distribution of chromaffin (medullary) and interrenal (cortical) tissues is variable in fish. In some, they are completely separated; in others, they approach the condition in higher vertebrates. In the *goldfish* (*Carassius auratus*), they are closely intermixed. ACTH did not modify the granulation of the interrenal cells, but caused condensation of their cytoplasm with predominance of the "type I" nuclei, as well as alterations in the chromaffin cells. "High temperature produced an exhaustion of large areas of the interrenal cells and alterations in the chrome cells. It is suggested that sudden heat exposure leads to release of secretions and that death occurs before the cells can make an adaptive response. On the other hand, the picture associated with chilling was less extreme and more variable and, in this case, it is probable that the more slowly acting low temperature permits time for considerable cell activation" (36 refs.).

Ball, J. N., Slicher, A. M.: "Influence of hypophysectomy and of an adrenocortical in-

hibitor (SU-4885) on the stress-response of the white blood cells in the teleost fish, *Mollieenesia latipinna Le Sueur*." *Nature* **196**: 1331-1332 (1962). D50,507/62

(*Salmo gairdnerii*) at successive stages in the sexual cycle." *Endocrinology* **78**: 791-800 (1966). F63,818/66

Fontaine, M., Mazeaud, M., Mazeaud, F.: "L'adrénalinémie du *Salmo* *salar* L. à quelques étapes de son cycle vital et de ses migrations" (Adrenalinemia in the *Salmo* *salar* L. during some stages of its vital cycle and its migrations). *C.R. Acad. Sci. (Paris)* **256**: 4562-4565 (1963). J10,785/63

In the *Pacific salmon*, plasma 17-OHCS concentrations rose at various phases of migration upstream during the spawning season, as well as after bleeding, confinement in a tank or injection of ACTH. Spawning steelhead trout showed an even higher rise in plasma corticoids after ACTH injection than did spawning salmon.

In the *salmon* the blood EP content rises during migration to its spawning grounds. This coincides with the previously demonstrated increase in the activity of the interrenal body and in blood corticoid concentrations.

Slicher, A. M., Pickford, G. E., Pang, P. K. T.: "Effects of 'training' and of volume and composition of the injection fluid on stress-induced leukopenia in the *mummichog*." *Progr. Fish-Culturist* **28**: 216-219 (1966). G47,904/66

Mazeaud, M.: "Influence de divers facteurs sur l'adrénalinémie et la noradrénalinémie de la carpe" (Influence of different factors on blood adrenaline and noradrenaline in the carp). *C.R. Soc. Biol. (Paris)* **158**: 2018-2021 (1964). F36,962/64

Comparative studies on the stressor effects particularly the leukopenia produced by several agents in the *mummichog* (*Fundulus heteroclitus*). Earlier literature on the actions of hypophysectomy, ACTH and various stressors upon other fish is briefly reviewed.

In the *carp*, muscular activity and hypoxia cause a slight increase in the EP and a marked rise in the NEP content of the blood. The latter values also rise considerably after hemorrhage and trauma.

Rasmussen, R. A., Rasmussen, L. E.: "Some observations on the protein and enzyme levels and fractions in normal and stressed elasmobranchs." *Trans. N.Y. Acad. Sci.* **29**: 397-413 (1967). J10,798/67

Thomson, D. A.: "Ostracitoxin: an ichthyotoxic stress secretion of the boxfish, *Ostracion lentiginosus*." *Science* **146**: 244-245 (1964). F21,880/64

In various *elasmobranchs*, stressors (muscular fatigue, hypoxia, confinement, osmotic and temperature shock) produced serum and brain enzyme changes interpreted as characteristic of stress.

Under conditions of stress, the *boxfish* exudes a nonprotein hemolytic poison designated "ostracitoxin." Introduction of a newly captured, highly excited specimen into an aquarium can cause the death of all other fish within a few minutes. Partial purification of the toxin suggests that it may be a steroid saponin. It is poisonous also for vertebrates. [Its possible relationship to pheromones is not mentioned (H.S.).]

Stabrowskii, E. M.: "The distribution of adrenaline and noradrenaline in the organs of the baltic lamprey *Lampetra fluviatilis* at rest and under various functional stress." *Zh. Evol. Biokhim. Fiziol.* **3** No. 3: 216-221 (1967). J11,822/67

Fleming, W. R., Pasley, J. N.: "Effect of cold shock, disease, and mammalian corticoids on the spleen of *Lepomis macchirus*." *Proc. Soc. Exp. Biol. Med.* **120**: 196-199 (1965). F53,560/65

In the *lamprey*, chromaffin cells containing EP and NEP are found in various organs, but particularly in the heart. The stress of hypoxia diminishes the EP level in the heart, skeletal muscles and liver, whereas the NEP content increases in liver tissue. "It is suggested that the chromaffin tissue of the lamprey heart acts as the medulla of mammalian suprarenals."

In the *blue-gill fish*, cortisol causes splenic hypertrophy. DOC and various stressors induce atrophy with pigment deposition in the spleen.

Todd, W. R., Laastuen, L. E., Thomas, A. E.: "Effect of amino acid imbalance on liver glycogen levels in young salmon." *Comp. Biochem. Physiol.* **23**: 431-435 (1967). F92,686/67

Hane, S., Robertson, O. H., Wexler, B. C., Krupp, M. A.: "Adrenocortical response to stress and ACTH in Pacific salmon (*Oncorhynchus tshawytscha*) and steelhead trout

In the *chinook salmon* (*Oncorhynchus tshawytscha*), stress was induced by a special device that forced them to swim strongly

against a current until they became exhausted and were swept through an electrical field into an outlet. This stress was associated with a drop in liver glycogen that could be counteracted by a glycine-containing diet whose effect was in turn blocked by concurrent feeding with tyrosine.

Fagerlund, U. H. M.: "Plasma cortisol concentration in relation to stress in adult sockeye salmon during the freshwater stage of their life cycle." *Gen. Comp. Endocrinol.* **8**: 197-207 (1967). F83,321/67

In *salmon*, various forms of stress (handling, physical exercise, disease) greatly increase plasma cortisol concentrations.

Hill, C. W., Fromm, P. O.: "Response of the interrenal gland of rainbow trout (*Salmo gairdneri*) to stress." *Gen. Comp. Endocrinol.* **11**: 69-77 (1968). H2,458/68

Although very intense acute stressors raise plasma cortisol in the rainbow trout, the effect of chronic low-level stress is transitory in this respect. Plasma cortisol concentrations "do not appear to be a useful indicator of the existence of chronic stressful conditions."

Yamashita, H.: "Haematological study of a species of *rockfish*, *Sebasticus marmoratus*. IV. Change of the amount of blood elements and the electrophoretic pattern of serum protein under the influence of stress." *Bull. Jap. Soc. Sci. Fish.* **34**: 1066-1071 (1968).

J12,696/68

Leibson, L. G., Plisetskaya, E. M.: "Hormonal control of blood sugar level in cyclostomes." *Gen. Comp. Endocrinol. Supp.* **2**: 528-534 (1969). H27,325/69

Review of the literature showing that the chromaffin cells of *cyclostomes* produce catecholamines, and the interrenal cells, corticoids. Changes in the environment as well as surgical and physical stressors of various kinds induce hyperglycemia in cyclostomes, presumably as a result of catecholamine liberation.

Mazeaud, M.: "Adrénalinémie et noradrénalinémie chez la Lamproie marine (*Petromyzon marinus L.*)" (Adrenalinemia and noradrenalinemia in the sea lamprey [*Petromyzon marinus L.*]}. *C.R. Soc. Biol. (Paris)* **163**: 349-352 (1969). H15,743/69

In the *lamprey*, various stressors (surgical trauma, forced exercise, bleeding) greatly increase plasma NEP and to a lesser extent EP concentrations. Presumably these increases

are a nonspecific defense mechanism. Comparable data on other fish are discussed (7 refs.).

Mazeaud, M.: "Influence de stress sur les teneurs en catécholamines du plasma et des corps axillaires chez un Sélaïen, la Roussette (*Scyliorhinus canicula L.*)" (Effects of stress on catecholamine content in the plasma and axillary bodies in a Selachian, the Roussette [*Scyliorhinus canicula L.*]}. *C.R. Soc. Biol. (Paris)* **163**: 2262-2266 (1969).

H26,453/69

In the *Roussette* (spotted dogfish), which possesses no adrenal medulla comparable to that of mammals but has suprarenal and axillary chromaffin bodies, various types of stressors can raise the blood catecholamine concentration, although the changes are generally less pronounced than in mammals and become evident only during intense and prolonged stress. Short exposure may even produce an inverse response. The literature on catecholamine release during stress in other fish and lower vertebrates is briefly reviewed (10 refs.).

Fontaine, M.: "Les poissons migrateurs" (Migrating fish). *Atomes* **24**: 715-720 (1969).

G81,184/69

Brief, semipopular review on the stressor effect of seasonal migration in fish.

Wedemeyer, G.: "Stress-induced ascorbic acid depletion and cortisol production in two salmonid fishes." *Comp. Biochem. Physiol.* **29**: 1247-1251 (1969). H13,688/69

In the coho *salmon* and rainbow trout, interrenal ascorbic acid decreased and serum cortisol increased upon exposure to stressors (cold, forced exercise).

Szakolczai, J.: "Reaction of the intestine of the *carp* (*Cyprinus carpio L.*) to environmental stress." *Acta Vet. Acad. Sci. Hung.* **19**: 153-159 (1969).

J23,971/69

Kimbrell, G. M., Weinrott, M. R., Morris, E. K. Jr., Scheid, J., Sangston, D.: "Alarm pheromone and avoidance conditioning in *goldfish*, *Carassius auratus*." *Nature* **225**: 754 (1970).

H21,093/70

"The alarm reaction in fish is believed to be produced by a chemical substance (pheromone) secreted by specialized cells in the epidermis." A crude preparation of "alarm pheromone," dropped into an aquarium, causes "not only 'fright' and 'alarm' behaviour but also flight or withdrawal." Presumably, the pheromone can enhance avoid-

ance conditioning. [It is not clear whether the "alarm reaction" described here is equivalent to the first phase of the G.A.S. (H.S.).]

Wedemeyer, G.: "The role of stress in the disease resistance of fishes." In: Snieszko, S. F., *A Symposium on Diseases of Fishes and Shell Fishes*, pp. 30-35. Washington, D.C.: Amer. Fish. Soc., Spec. Publ. No. 5, 1970.

J12,695/70

Henderson, I. W., Chan, D. K. O., Sandor, T., Jones, I. C.: "The adrenal cortex and osmoregulation in teleosts." In: Benson, G. K. and Phillips, J. G., *Hormones and the Environment*, pp. 31-55. Cambridge: Cambridge University Press, Mem. Soc. Endocrinol., No. 18, 1970.

E9,136/70

Review on the role of corticoids in osmoregulation among *teleosts*, with a brief section on adrenal responses to various other forms of stress, such as the prolonged swimming without feeding from Europe to spawning grounds 3,000 mi. away.

Pickford, G. E., Srivastava, A. K., Slicher, A. M., Pang, P. K. T.: "The stress response in the abundance of circulating leucocytes in the killifish, *Fundulus heteroclitus*. I. The cold-shock sequence and the effects of hypophysectomy." *J. Exp. Zool.* **177**: 89-96 (1971).

G83,471/71

In the *killifish*, brief immersion in very cold water causes peculiar waves of leucopenia followed by leucocytosis, a phenomenon ascribed to stress. Hypophysectomy inhibits the leukocytic phase.

Pickford, G. E., Srivastava, A. K., Slicher, A. M., Pang, P. K. T.: "The stress response in the abundance of circulating leucocytes in the *killifish*, *Fundulus heteroclitus*. II. The role of catecholamines." *J. Exp. Zool.* **177**: 97-108 (1971).

G83,472/71

Pickford, G. E., Srivastava, A. K., Slicher, A. M., Pang, P. K. T.: "III. The role of the adrenal cortex and a concluding discussion of the leucocyte-stress syndrome." *J. Exp. Zool.* **177**: 109-117 (1971).

G83,473/71

The singular leukocytic response of *killifish* is ascribed to stress. On the basis of some experiments, "a tentative interpretation of the cold-shock sequence is proposed on the assumption that catecholamines (presumably epinephrine) are leucopenic and that cortisol is leucocytic."

Saddler, J. B., Cardwell, R.: "The effect of tagging upon the fatty acid metabolism of

juvenile pink salmon." *Comp. Biochem. Physiol. [A]* **39**: 709-721 (1971).

J19,852/71

In tagged *salmon*, excessive fatty acid transfer from muscle to liver was ascribed to the stressor effect of the operation itself. The literature on other stress manifestations, particularly increased cortisol production in salmons following exposure to various stressors, is reviewed.

Cardwell, R. D., Saddler, J. B., Smith, L. S.: "Hematological effects of Dennison tagging upon juvenile pink salmon (*Oncorhynchus gorbuscha*)."*Comp. Biochem. Physiol. [A]* **38**: 497-508 (1971).

H39,511/71

In juvenile pink *salmon*, implantation of Dennison tags, handling, netting and the length of exposure to anesthetics required for this procedure are considered to be stressors responsible for certain hematologic and plasma protein alterations. [It remains to be proved whether these changes are really characteristic of stress and could be produced by other stressors (H.S.).]

Singley, J. A., Chavin, W.: "Cortisol levels of normal goldfish, *Carassius auratus* L., and response to osmotic change." *Am. Zool.* **11**: 653 (1971).

J12,378/71

In *goldfish*, blood cortisol levels show a clearcut circadian rhythm and a particularly rapid increase following exposure to a variety of stressors.

Baskin, F., Masiarz, F. R., Agranoff, B. W.: "Effect of various stresses on the incorporation of [³H] orotic acid into *goldfish* brain RNA." *Brain Res. (Amst.)* **39**: 151-162 (1972).

J20,141/72

Umminger, B. L., Gist, D. H.: "Effects of thermal acclimation on physiological responses to handling stress, cortisol and aldosterone injections in the *goldfish*, *Carassius auratus*."*Comp. Biochem. Physiol. [A]* **44**: 967-977 (1973).

H64,677/73

Goldfish subjected to stressful handling and sham injection procedures responded with a hyperglycemia and a decline in serum chloride and sodium concentrations. Carcass water content was not affected."

Haider, S., Sathyanesan, A. G.: "Osmotic stress induced histochemical changes in the ependyma and the preoptic neurons of the teleost fish *Rita rita* (Ham.) with a note on the periventricular vascularization." *Z. Mikrosk. Anat. Forsch.* **87**: 549-560 (1973).

J9,414/73

Jackim, E., LaRoche, G.: "Protein synthesis in *Fundulus heteroclitus* muscle." *Comp. Biochem. Physiol. [A]* **44**: 851-866 (1973).

H64,672/73

In *Fundulus heteroclitus*, incorporation of ^{14}C -leucine into muscle protein was reduced by fasting, lack of oxygen and maintenance in tanks with insufficient volumes of water. This effect was ascribed to stress.

Marvin, D. E. Jr., Burton, D. T.: "Cardiac and respiratory responses of rainbow trout, bluegills and brown bullhead catfish during rapid hypoxia and recovery under normoxic conditions." *Comp. Biochem. Physiol. [A]* **46**: 755-765 (1973).

H77,185/73

Hypoxia produced immediate increases in heart and ventilation rates in three species of fish. "When the mean heart rate for each species at 1 hr post-stress was compared with its pre-stress rate, differences in recovery patterns were found in all species."

Banerji, T. K., Ghosh, A.: "Effect of heat exposure on the catechol hormone content of the teleostean adrenal tissue." *Folia Histochim. Cytochem. (Krakow)* **11**: 191-194 (1973).

J12,429/73

Redgate, E. S.: "Neural control of pituitary adrenal activity in *Cyprinus carpio*." *Gen. Comp. Endocrinol.* **22**: 35-41 (1974).

H81,914/74

"The prompt responses of plasma cortisol concentration to stimuli, such as sound, hypothalamic stimulation, the photoperiod, and restraint, indicate that the pituitary adrenal system of the carp is controlled by neural pathways in the brain of this teleost."

Griffith, R. W., Umminger, B. L., Grant, B. F., Pang, P. K. T., Pickford, G. E.: "Serum composition of the coelacanth, *Latimeria chalumnae* Smith." *J. Exp. Zool.* **187**: 87-102 (1974).

J11,587/74

In the coelacanth after capture, handling or exposure to cold, "high serum lactate (16.5 mM/l) and glucose (6.57 mM/l) levels were probably indicative of stress."

Jones, R. T., Price, K. S. Jr.: "Osmotic responses of spiny dogfish (*Squalus acanthias* L.) embryos to temperature and salinity stress." *Comp. Biochem. Physiol. [A]* **47**: 971-979 (1974).

H82,644/74

In the spiny dogfish the effect of temperature upon acclimation to osmotic responses was determined, with the result that: "some combinations of temperature and salinity

during the 62-hr experiment apparently stressed the animals since animals exposed to 16 and 36 parts per 1000 salinity at 20°C died after 26 hr." [It is not clear why the results are ascribed to stress rather than to the specific effects of the agents used (H.S.).]

Polenov, A. L., Garlov, P. E.: "The hypothalamo-hypophyseal system in acipenseridae. IV. The functional morphology of the neurohypophysis of *Acipenser güldenstädti* Brandt and *Acipenser stellatus* Pallas after exposure to different salinities." *Cell Tissue Res.* **148**: 259-275 (1974).

J13,587/4

Németh, S., Juráni, M.: "Hepatic tyrosine aminotransferase (TAT) in stressed trouts and rats." *Gen. Comp. Endocrinol.* **22**: 388 (1974).

H83,271/4

In trout living under crowded conditions and in rats traumatized by the Noble-Collip drum, plasma cortisol increased, but hepatic tyrosine aminotransferase activity was elevated only in the rats. This finding agrees with previous studies suggesting that the enzyme response is not observable in vertebrates below the evolutionary level of amphibians.

Casellas, E., Smith, L., D'Aoust, B. G.: "Effects of stress on salmonid blood clotting mechanisms" (abstracted). *Physiologist* **17**: 371 (1974).

H89,978/4

Rotermund, A. J. Jr., Johnson, H. A.: "Temperature-induced alteration of hepatic ultrastructure and function within the goldfish, *Carassius auratus*" (abstracted). *Physiologist* **17**: 389 (1974).

H89,987/4

Hattingh, J., Pletzen, A. J. J. van: "The influence of capture and transportation on some blood parameters of fresh water fish." *Comp. Biochem. Physiol. [A]* **49**: 607-609 (1974).

H93,884/74

Demael-Suard, A., Garin, D., Brichon, G., Mure, M., Peres, G.: "Neoglycogenèse à partir de la glycine ^{14}C chez la tanche (*Tinca vulgaris* L.) au cours de l'asphyxie" (Neoglycogenesis from glycine ^{14}C in the tench [*Tinca vulgaris* L.] during asphyxia). *Comp. Biochem. Physiol. [A]* **47**: 1023-1033 (1974).

H82,645/74

In the tench, increased cortisol, catecholamine and insulin secretion produces changes in carbohydrate metabolism that are ascribed to the stress of handling and asphyxia.

Silbergeld, E. K.: "Blood glucose: a sensitive indicator of environmental stress in

fish." *Bull. Environ. Contam. Toxicol.* **11**: 20-25 (1974). J9,883/74

In the freshwater fish *johnny darter* (*Etheostoma nigrum Rafinesque*) a rise in blood glucose is a sensitive indicator of stress after exposure to a variety of stressors (handling, capture, insecticide).

Maetz, J., Lahlou, B.: "Actions of neurohypophysial hormones in fishes." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7, Endocrinology*, Vol. IV, Part 1, pp. 521-544. Washington, D.C.: American Physiological Society, 1974.

E10,739/74

Review on stress-induced changes in vasoressin secretion and the consequent alterations in water and electrolyte metabolism (140 refs.).

Simon, N., Reinboth, R.: "Adenohypophyse und Hypothalamus. Histophysiologische Untersuchungen bei *Lepomis* (Centrarchidae)" (Adenohypophysis and hypothalamus. Histophysiologic studies on the *Lepomis* [Centrarchidae]). *Adv. Anat. Embryol. Cell Biol.* **48**: 1-82 (1974). J15,761/74

Monograph on the hypothalamo-hypophyseal system of a teleost (*Centrarchidae*) with respect to its anatomy and function under normal conditions and after various hormone treatments or surgical interventions. Special attention is given to the identification of

nerve centers and anterior pituitary cells responsible for the selective secretion of diverse adenohypophyseal hormones, as well as to changes in the pituitary during the annual reproductive cycle and its responsiveness to prolongation of the daily light period (about 160 refs.).

Gronow, G.: "Über die Anwendung des an Säugetieren erarbeiteten Begriffes 'Stress' auf Knochenfische" (The applicability of the "stress" concept, originally developed in mammals, to bony fishes). *Zool. Anz. (Jena)* **192**: 316-331 (1974). J19,021/74

"In mammals and teleosts alike, besides a decreased discharge of thyrotropine, gonadotropines and (partly) somatotropine, an increased liberation of corticotropine, catecholamines and corticosteroids occurs in stress."

Narasimham, C., Parvatheswarao, V.: "Adaptations to osmotic stress in a freshwater euryhaline teleost, *Tilapia mossambica*. X. Role of mucopolysaccharides." *Acta Histochem. (Jena)* **51**: 37-49 (1974).

J21,845/74

Singley, J. A., Chavin, W.: "Serum cortisol in normal goldfish (*Carassius auratus L.*)."
Comp. Biochem. Physiol. [A] **50**: 77-82 (1975). H96,696/75

Data on the circadian rhythm of serum cortisol in normal and cold-stressed goldfish.

Invertebrates

In the cockroach, the corpora cardiaca contain a substance with adrenergic properties alleged to be closer to EP than to NEP. This substance is released during stress and causes temporary paralysis, which presumably has an adaptive value by making the insect inconspicuous and less subject to attack. Similar effects are elicited by extracts of corpora cardiaca. The latter also appear to regulate circadian cycles of activity in this species.

In the desert locust, the intercerebralis-corpora cardiaca system plays a major role in oocyte development. Blood from ovipositing or stressed females accelerates the beat of the locust heart in vitro, and the same effect is obtained by extracts of corpora cardiaca. Another arthropod, the millipede, widely distributed in Louisiana and Mississippi, emits a highly pungent aromatic secretion (consisting of benzaldehyde and hydrogen cyanide) when disturbed in various ways. This substance is discharged by special paired glands and evidently has a defensive function, as it repulses attacking fire ants.

Among other invertebrates, data on nonspecific, usually defensive responses—which

may or may not be closely related to stress as we know it in vertebrates—have been described in the silk worm, grasshopper, house fly, drosophila and a variety of crustaceans and molluscs.

Invertebrates

(See also our earlier stress monographs, p. xiii)

Barton-Browne, L., Dodson, L. F., Hodgson, E. S., Kiraly, J. K.: "Adrenergic properties of the cockroach corpus cardiacum." *Gen. Comp. Endocrinol.* 1: 232-236 (1961).

D13,086/61

Corpora cardiaca extract from the *cockroach* inhibits the contractions of the uterus and colon of the rat but loses much of this property if the roaches are previously exposed to electric shocks. The active principle of the extract is closer to EP than to NEP. When it is injected into roaches, it temporarily paralyzes them. It remains to be shown whether "the release of an adrenergic factor from the corpus cardiacum is necessarily an adaptive reaction to stress, similar to the well-known vertebrate adrenal response."

Hodgson, E. S.: "Hormonal control of reproductive and adaptive behavior. Neurosecretion and behavior in arthropods." *Gen. Comp. Endocrinol.* Supp. 1: 180-187 (1962).

D23,449/62

In *cockroaches*, injection of EP causes a sluggishness similar to that elicited by corpora cardiaca extract or exposure to different stressors. "It remains to be shown, also, to what extent the release of neurosecretory hormones from the corpora cardiaca is normally produced by stresslike stimuli during the life of the animal, and what selective advantage the behavioral results would confer."

Highnam, K. C.: "Variations in neurosecretory activity during oocyte development in *Schistocerca gregaria*." *J. Endocrinol.* 24: iv-v (1962).

D23,864/62

Blood from the pars intercerebralis-corpora cardiaca system of the desert *locust* plays a major role in the control of oocyte development. "Blood from ovipositing and from stressed females will accelerate the rate of beating of the locust heart in vitro. Homogenates of corpora cardiaca also accelerate the rate of heart-beat."

Fukuda, S.: "Endocrine regulation during development. II. Hormonal control of dia-

pause in the silkworm." *Gen. Comp. Endocrinol.* Supp. 1: 337-340 (1962).

D23,465/62

Observations on *silkworms* "led the author to the assumption that the production of diapause or nondiapause eggs is affected by nonspecific stressful stimuli." After localized thermocauterization, trauma, injury to the nervous system, injection of EP, of thyroid preparations, or of air, insertion of a piece of glass or silkworm cocoon into the body cavity, "some of the moths from diapause pupae laid varying number of nondiapause eggs together with diapause eggs and some of those from nondiapause pupae deposited some diapause eggs besides nondiapause eggs."

Blum, M. S., Woodring, J. P.: "Secretion of benzaldehyde and hydrogen cyanide by the millipede *Pachydesmus crassicutis* (Wood)." *Science* 138: 512 (1962).

D36,850/62

When disturbed in various ways, the *millipede Pachydesmus crassicutis* (an arthropod widely distributed in Louisiana and Mississippi) emits a highly pungent aromatic secretion consisting of a mixture of benzaldehyde and hydrogen cyanide. The substance which is discharged by paired glands exerts a defensive function, for example, repulsing attacking fire ants. [Although this reaction is nonspecific, it remains to be proven that it represents a true manifestation of stress elicited by any type of demand (H.S.).]

Siegel, S. M., Daly, O., Halpern, L., Giamarro, C., Davis, G.: "The general and comparative biology of experimental atmospheres and other stress conditions: some notes on the behavior of *insects* and other invertebrates." *Aerosp. Med.* 34: 817-820 (1963) (14 refs.).

G30,721/63

Voge, M.: "Sensitivity of cysticercoids of *Hymenolepis microstoma* (Cestoda: Cyclophyllidea) to high temperature stress." *J. Parasitol.* 49: 152-153 (1963).

J23,195/63

Sonleiter, F. J.: "The stress factor in *insect* colonies." *Bull. W.H.O.* 31: 545-549 (1964).

J24,625/64

Ewing, L. S.: "Fighting and death from

stress in a cockroach." *Science* **155**: 1035-1036 (1967). J22,668/67

In the cockroach *Nauphoeta cinerea*, fighting may result in death in subordinates without evidence of external damage. "The situation is likened to death from stress as found in mammals."

Brady, J.: "Control of the circadian rhythm of activity in the cockroach. I. The role of the corpora cardiaca, brain and stress." *J. Exp. Biol.* **47**: 153-163 (1967). G49,950/67

Studies on the roles of the corpora cardiaca, brain and stress (minor trauma) in the circadian activity rhythm of the cockroach.

Adiyodi, K. G., Nayar, K. K.: "The conjugated plasma proteins in adult females of *Periplaneta americana* (L.) under starvation and other stress." *Comp. Biochem. Physiol.* **27**: 95-104 (1968). H3,342/68

Biochemical studies, especially on conjugated plasma proteins in cockroaches exposed to various stressors such as hypothermia, starvation, restraint and electroshock. [Although most of the changes are described in relation to the various phases of the G.A.S., only some of them appear to be truly nonspecific (H.S.).]

Dogra, G. S., Ewen, A. B.: "The effects of salt stress on the cerebral neurosecretory system of the grasshopper, *Melanoplus sanguinipes* (F.) (Orthoptera)." *Experientia* **25**: 940-941 (1969). H17,458/69

Studies on the effects of "salt stress" on the cerebral neurosecretory system of the grasshopper. [It remains to be proved that various concentrations of sodium chloride act as nonspecific stressors, and not through specific mechanisms (H.S.).]

Barkman, R. C.: "Response of the tissue of *Orconectes rusticus* to salinity stress." *Comp. Biochem. Physiol.* **36**: 285-290 (1970). H30,409/70

Studies on the adaptation of crayfish (*Orconectes rusticus*) to "salinity stress." [Although the observations undoubtedly prove that the crayfish can adapt to osmotic stimuli, it remains to be shown whether this is a nonspecific manifestation of stress (H.S.).]

Yu, S. J., Terriere, L. C.: "Induction of microsomal oxidase in the housefly and the action of inhibitors and stress factors." *Pestic. Biochem. Physiol.* **1**: 173-179 (1971). G87,248/71

Rather indirect evidence suggests that stress affects microsomal oxidase production in the housefly.

Rounds, H. D.: "A comparison of extracts of cockroach nerve-cord and gut after forced activity." *Comp. Gen. Pharmacol.* **2**: 1-4 (1971) J19,472/71

"Foregut extracts from stressed animals contained significantly more cardioacceleratory activity than those of the unstressed animals while hindgut extracts showed no significant change."

Bayne, B. L.: "Some effects of stress in the adult on the larval development of *Mytilus edulis*." *Nature* **237**: 459 (1972).

H55,882/72

Observations on *Mytilus edulis* (mussels) suggest that "sub-lethal temperature and nutritive stressors on the adult have a measurable effect on the larval development during periods of maximum morphogenetic activity, and a minimal effect during the main phase of larval growth. This interpretation predicts a further period of 'failure' in the development of larvae from stressed adults at the time of metamorphosis."

Hannan, J. V., Evans, D. H.: "Water permeability in some euryhaline decapods and *Limulus polyphemus*." *Comp. Biochem. Physiol.* [A] **44**: 1199-1213 (1973).

H65,728/73

Rather indirect evidence suggesting that handling and changing from one tank to another can cause stress in crustaceans as well as in fish.

Cripps, R. A., Reish, D. J.: "The effect of environmental stress on the activity of malate dehydrogenase and lactate dehydrogenase in *Neanthes arenaceodentata* (Annelida: Polychaeta)." *Comp. Biochem. Physiol.* [B] **46**: 123-133 (1973). H72,318/73

Matheson, A. C., Arnold, J. T. A.: "Resistance to carbon dioxide, an anoxic stress in *Drosophila melanogaster*." *Experientia* **29**: 364-365 (1973). H71,372/73

Exposure to carbon dioxide is considered to be an "anoxic stress" for *Drosophila melanogaster*. [No evidence is given that its effect is actually due to stress (H.S.).]

Florey, E., Kriebel, M. E.: "The effects of temperature, anoxia and sensory stimulation on the heart rate of unrestrained crabs." *Comp. Biochem. Physiol.* [A] **48**: 285-300 (1974). H82,294/74

Nagabhushanam, R., Lomte, V. S.: "Endocrinology of the freshwater lamellibranch, *Parreysia corrugata*." *5th Asia and Oceania Congr. Endocr.*, pp. 118-119. Chandigarh, India, 1974. H82,153/74

In the freshwater *lamellibranch*, two types of neurosecretory cells (Types A and B) are uniformly distributed on the dorsal surface of the cerebral, visceral and pedal ganglia. A rise in temperature (35°C) caused emptying of the neurosecretory cells in the cerebral ganglia.

Telford, M.: "Blood glucose in crayfish. II. Variations induced by artificial stress." *Comp. Biochem. Physiol. [A]* **48**: 555-560 (1974). H87,005/74

"Blood glucose levels in *Orconectes propinquus* and *Cambarus robustus* increase four- or fivefold when the *crayfish* are handled out of water for 2-min periods. Hyperglycemia can be caused by substances added to the water; crayfish do not have to be exposed to air to cause this effect." Literature on stress in other *crayfish* is reviewed.

Falkowski, P. G.: "Facultative anaerobiosis in *Limulus polyphemus*: phosphoenol-pyruvate carboxykinase and heart activities." *Comp. Biochem. Physiol. [B]* **49**: 749-759 (1974). H94,885/74

The horseshoe crab (*Limulus polyphemus*) is particularly resistant to "anoxic stress."

Feng, S. Y., Winkle, W. van: "The effect of temperature and salinity on the heart beat of *Crassostrea virginica*." *Comp. Biochem. Physiol. [A]* **50**: 473-476 (1975).

H98,404/75

Study on the heartbeat of *oysters*.

Mullins, D. E., Cochran, D. G.: "Nitrogen metabolism in the American *cockroach*. I. An examination of positive nitrogen balance with respect to mobilization of uric acid stores." *Comp. Biochem. Physiol. [A]* **50**: 489-500 (1975). H98,405/75

Mullins, D. E., Cochran, D. G.: "II. An examination of negative nitrogen balance with respect to mobilization of uric acid stores." *Comp. Biochem. Physiol. [A]* **50**: 501-510 (1975). H98,406/75

Plants and Microorganisms

Several investigations suggest that nonspecific stress reactions occur also in plants. The so-called "stress-satellite DNA" is induced in growing seedlings of certain plants when exposed to various stressors. This DNA is presumed to be of bacterial origin and therefore cannot be "taken as evidence for the amplification of ribosomal-RNA genes under this condition of physiological stress."

In tobacco plants grown in culture solution, various stressors impair shoot turgor.

A more detailed discussion of the many data concerning nonspecific stress reactions in plants would be beyond the scope of this treatise.

Plants

(See also our earlier stress monographs, p. xiii)

Zatyko, J.: "A növények életképessé gének növelése 'veszélyt jelző' informaciokkal" (Enhancement of viability of plants by "danger-indicating" information). *Fertődi Növényterm. Kutató, Int. Közl.* **2**: 83-90 (1965) (Hungarian). G78,905/65

Report on experiments "extending to plants the validity of the theory of 'stress' elaborated by Selye in animal tests. The present experiments deal with the case of 'cross resistance' or 'nonspecific resistance' of fun-

damental importance in the theory of 'stress'" (7 refs.).

Cannon, R. E., Shane, M. S.: "The effect of antibiotic stress on protein synthesis in the establishment of lysogeny of *Plectonema boryanum*." *Virology* **49**: 130-133 (1972). G92,363/72

Evidence is presented for the establishment of lysogeny in *Plectonema boryanum* by LPP-1D and LPP-2 phycoviruses after treatment of the alga with chloramphenicol.

Mizrahi, Y., Richmond, A. E.: "Hormonal modification of plant response to water

stress." *Aust. J. Biol. Sci.* **25**: 437-442 (1972). G92,927/72

In tobacco plants grown in culture solution, various stressors impaired the water balance as evidenced by a decline of shoot turgor.

Pearson, G. G., Ingle, J.: "The origin of stress-induced satellite DNA in plant tissues." *Cell Different.* **1**: 43-51 (1972).

G90,501/72

A so-called "stress-satellite DNA" is induced in growing seedlings of various *Cucurbitaceae* exposed to darkness, trauma and other stressors. The present observations suggest that, in response to cold storage, the appearance of the stress-satellite is of bacterial origin and therefore cannot be "taken as evidence for the amplification of the ribosomal-RNA genes under this condition of physiological stress."

Zatyko, J.: "Érvényes-e a növényekre Selye stress-elmélete?" (Is Selye's stress theory applicable to plants?) *Az élet és Tudomány Kalendáriuma* **73**: 37-41 (1973) (Hungarian). G96,678/73

Brief summary in lay language of scientific evidence indicating that stress can occur in plants.

Newman, E. I.: "Competition and diversity in herbaceous vegetation." *Nature* **244**: 310 (1973). H78,385/73

Few species develop at "low-stress" sites where conditions for growth of herbaceous vegetation are highly favorable, in comparison with intermediate-stress sites.

Zatyko, J. M.: "Effect of low concentration colchicine on the cytokinin content of pinto bean leaves." *Naturwissenschaften* **60**: 105-106 (1973). J5,100/73

In pinto beans (*Phaseolus vulgaris L.*), treatment with synthetic cytokinins enhances resistance to various noxious agents (for example, high or low temperatures, fungi, viruses, chemical mutagens, colchicine and so

on). "The data support the idea that there may be a non-specific protective mechanism, in which significance is attributed to cytokinin hormones. We venture to compare it with Selye's stress theory, which describes the endocrinologic basis of the non-specific protective mechanism of the body. Corticoids, the adrenal hormones, play an important role in this mechanism and we suggest that cytokinins in plants may play an analogous role to corticoids in man."

Lacroix, L. J., Nalborczyk, E.: "The effect of low temperature acclimation on temperature sensitive carbon dioxide exchange of rape seedlings" (abstracted). *Proc. Can. Fed. Biol. Soc.* **17**: 101 (1974). H92,134/74

"Most plants respond to low temperature stress (acclimation) by metabolic changes which result in increased frost tolerance."

Coxon, D. T., Price, K. R., Howard, B., Osman, S. F., Kalan, E. B., Zacharius, R. M.: "Two new vетисpirane derivatives: stress metabolites from potato (*Solanum tuberosum*) tubers." *Tetrahedron Lett.* No. 34: 2921-2924 (1974). J20,766/74

Chemical description of vетисpirane and other sesquiterpenes, which are considered to be "stress metabolites" obtainable from infected potato tubers.

Microorganisms

(See also our earlier stress monographs, p. xiii)

Bissonnette, G. K., Jezeski, J. J., McFeters, G. A., Stuart, D. G.: "Influence of environmental stress on enumeration of indicator bacteria from natural waters." *Appl. Microbiol.* **29**: 186-194 (1975).

J22,070/75

"Bacterial cells may become physiologically injured due to the environmental stress imposed by the aquatic environment" (25 refs.).

TUMORS

It is hardly surprising that both experimental and spontaneous tumors can evoke typical manifestations of the G.A.S. since they are evidently severe stressors. Very large, necrotizing transplantable tumors also produce certain hitherto unexplained,

apparently more specific changes, namely extramedullary hemopoiesis, especially in the spleen, liver and adrenals.

Tumors

(See also our earlier stress monographs, p. xiii)

McEuen, C. S., Selye, H.: "Histologic changes in the adrenals of tumor-bearing rats." *Am. J. Med. Sci.* **189**: 423-424 (1935). 36,705/35

In rats bearing large necrotizing Walker tumors, the adrenals were enlarged and contained many lymphocytic and leukocytic infiltrations. Since similar islands are occasionally seen after various infections, they cannot be regarded as specific to tumors.

Hilf, R., Burnett, F. F., Borman, A.: "The effect of Sarcoma 180 and other stressing agents upon adrenal and plasma corticosterone in mice." *Cancer Res.* **20**: 1389-1393 (1960). C94,528/60

In mice, growing Sarcoma 180 tumors cause adrenal and plasma corticoid changes similar to those obtained with other stressors.

Hilf, R., Breuer, C., Borman, A.: "The effect of Sarcoma 180 and other stressing

agents upon adrenal adenine nucleotide-metabolizing enzymes." *Cancer Res.* **21**: 1439-1444 (1961). D15,008/61

In mice, Sarcoma 180 transplants caused typical stress reactions, with a rise in blood corticoids and an increase in adrenal ATPase activity. "Liver 5'-nucleotidase activity was elevated by tumor growth but not altered by the other stresses studied."

Moore, D. C., Holton, C. P., Marten, G. W.: "Psychologic problems in the management of adolescents with malignancy. Experiences with 182 patients." *Clin. Pediatr.* **8**: 464-473 (1969). J22,517/69

Ertl, N.: "'Systemic effects' during the growth of malignant experimental tumors." *Oncology (Basel)* **27**: 415-429 (1973).

J6,691/73

In rats bearing Walker carcinosarcomas, there is thymus atrophy and adrenal hypertrophy in association with hepatomegaly. [These are deemed to be the "systemic effects" of growing tumors without considering the possible role of stress (H.S.).]

COMBINED EFFECT OF VARIOUS AGENTS

(See also Resistance under Characteristic Manifestations of Stress [Functional Changes] and Treatment)

Multiple Stressors (Cross-resistance and Cross-sensitization)

Even the earliest studies on the G.A.S. showed that several stressors applied simultaneously can have a cumulative effect. For example, cold and hunger decrease resistance to almost any stressor, and concurrent application of various drugs and/or physical agents may result in the summation of their stressor potency. In this case, it became customary to speak of "cross-sensitization." On the other hand, during or immediately following an alarm reaction produced by one stressor, there may develop a "cross-resistance" against the damaging effect of another. In all these instances, it is very important to distinguish between specific and truly nonspecific or stressor effects. Certain agents may augment or diminish each other's toxicity merely because one increases or decreases the specific effect of the other. For example, all specific antidotes, blocking agents and remedies work through this type of mechanism, just

as do factors that cause specific hypersensitivity. These pharmacologic interactions do not fall within the scope of this monograph; here, we shall consider only evidence of nonspecific, that is, stress-induced, changes in resistance.

As we saw in the section on age as a conditioning factor, the literature is somewhat contradictory with regard to the effect of handling and gentling neonatal rats upon their resistance to various stressors later in life. This may depend upon differences in the experimental conditions used by various investigators, but the subject as such is certainly pertinent to the problem of cross-resistance as originally defined.

Most of the so-called exogenous conditioning agents may be regarded as acting through cross-resistance or cross-sensitization, as long as their effect is nonspecific.

According to one theory, schizophrenics are less responsive to stressors because they are already under stress, and virtually all forms of so-called nonspecific prophylaxis and therapy (for example, muscular exercise, hot or cold baths, shock treatments, and so on) are actually instances of cross-resistance. The phenomenon has also been found in a local variant in that topical tissue resistance can be produced by repeated application of different stressors to the same body region or even by a systemically applied agent having a topical stressor effect. The most striking demonstrations of local cross-resistance and cross-sensitization have been observed using the granuloma pouch technique, which permits the concurrent or consecutive application of several stressors to the same tissue region.

A perusal of the literature on systemic and local cross-resistance reveals that many of the statements are apparently contradictory, one study showing an increase, another a decrease, in resistance following exposure to stress under seemingly identical conditions. It must be kept in mind, however, that cross-resistance or cross-sensitization depends on a large number of factors, such as duration and intensity of the stressor action, associated specific effects of the stressors, age, genetic background, species susceptibility, and so on. That is why the interested reader must primarily consult the original publications cited in this section and should interpret each case with the preceding considerations in mind. The only valid generalization that we can make is that under appropriate conditions both cross-sensitization and cross-resistance can be produced at will by the consecutive application of various stressors.

Undoubtedly, a preparatory overproduction and secretion of certain stress hormones by the hypophysis and the adrenals may play an important role; for example, an increased glucocorticoid discharge elicited by a stressor can surely augment resistance to agents which are damaging mainly because they provoke responses (inflammation, immune reactions) whose suppression is advantageous under given conditions. On the other hand, a preparatory slow discharge of potentially noxious reserves of hormones and other endogenous toxic metabolites may likewise be beneficial in offering protection against severe stressors whose toxicity is due mainly to a sudden flooding of the organism by substances of this type. In any event, it is unlikely that all forms of cross-resistance and cross-sensitization could be dependent upon a single mechanism; that is, a pituitary or adrenal hormone discharge could hardly be implicated in those types of cross-resistance that have been demonstrated after hypophysectomy or adrenalectomy.

One review (Selye, C95,972/61, p. 446) deals with most of the fundamental aspects involved in nonspecific or cross-resistance and sensitization; it provides a more detailed analysis of the pertinent literature than can be given here.

Multiple Stressors (Cross-resistance, Cross-sensitization)

(See also our earlier stress monographs, p. xiii, and cf. Resistance under Morphology)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937).

38,798/37

In rats, "hunger and cold are very active factors in aggravating the effects of alarming stimuli. In fact, cold or any other stimulus which is able to cause an alarm reaction by itself acts in a similar way. Thus it is possible, for instance, to obtain a typical alarm reaction by giving one quarter of the alarming dose of 4 different drugs within 48 hours, although one quarter of the alarming dose of any one of these drugs has no effect by itself."

Selye, H.: "The prevention of adrenalin lung edema by the alarm reaction." *Am. J. Physiol.* **122**: 347-351 (1938). A7,154/38

In rats, an alarm reaction produced by EP, formaldehyde, cold, forced exercise or surgical trauma increases resistance to the lung edema elicited by subsequent intravenous injection of EP. "This observation invalidates the possibility that the alarm reaction increases resistance only because it delays the absorption of toxic agents into the blood stream." The pulmonary edema normally produced in rats given large amounts of intravenous sodium chloride after bilateral nephrectomy can be prevented by an alarm reaction (forced exercise). This is a good example of cross-resistance.

Fischer, R., Agnew, N.: "A hierarchy of stressors." *J. Ment. Sci.* **101**: 383-386 (1955). C7,812/55

Schizophrenic patients may be less responsive to stressors because they are already under stress. "The concept of a hierarchy of stressors is introduced. Such a concept explains the different adaptive answers elicited if an organism is threatened (1) by a life stressor of primary importance or (2) by 'alarming' stimuli directed toward less basic urges and needs. Stressors of primary importance may establish new adaptive responses, while stressors perceived as less important are practically disregarded if the organism is already under stress of similar importance and magnitude."

Adolph, E. F.: "General and specific

characteristics of physiological adaptations."

Am. J. Physiol. **184**: 18-28 (1956).

C12,038/56

In rats, adaptation was induced to single stressors such as cold air, simulated altitude, hypoxia, water, sodium chloride or sucrose. In most cases, after discontinuation of stressor treatment the disappearance of adaptation was slower than its induction. There was cross-resistance between some stressors, but more often adaptation was specific (28 refs.).

Griffiths, M. E., Calaby, J. H., McIntosh, D. L.: "The stress syndrome in the rabbit." *C.S.I.R.O. Wildl. Res.* **5**: 134-148 (1960).

D12,295/60

Detailed description of the stress syndrome in the wild rabbit, in which adrenal ascorbic acid content is very variable and cortical lipid granules increase after the animal has been kept in the laboratory for a "settling-in period." Cold has little effect on cortical ascorbic acid or lipid droplets, but subcutaneous formalin causes a threefold increase in adrenal size. Noise gives "cross-resistance" to cold, but formalin does not.

Winokur, G., Stern, J. A., Graham, D. T.: "Stress as an inhibitor of pathological processes." *Psychiatr. Res. Rep. APA* **12**: 73-80 (1960).

J11,150/60

In cancer-susceptible mice, various stressors inhibit the loss of hair caused by painting with methylcholanthrene.

Bajusz, E., Selye, H.: "Adaptation to the cardiac necrosis-eliciting effect of stress." *Am. J. Physiol.* **199**: 453-456 (1960).

C83,948/60

"True cross-resistance to the cardiotoxic action of various stressors can be demonstrated under these circumstances, in rats sensitized by F-COL [9α -fluoro-hydrocortisone] and Na-acetate: the cardiac necrosis-producing effect of muscular exercise could be prevented by pretreatment with cold, that of cold by muscular exercise, that of noradrenaline by restraint, that of restraint by noradrenaline, and that of bone fractures by muscular exercise."

McMichael, R. E.: "The effects of preweaning shock and gentling on later resistance to stress." *J. Comp. Physiol. Psychol.* **54**: 416-421 (1961).

G46,161/61

Review of the literature and personal observations on the effect of various stressors (administered immediately after birth) upon resistance to other stressors in later life.

Selye, H., Bajusz, E., Strelbel, R.: "Cross-resistance to cardiotoxic agents." *Can. J. Biochem.* **39**: 519-525 (1961). C90,422/61

The ESCN produced in rats by various stressors in combination with fluorocortisol and sodium salts could be prevented by gradual adaptation to the stressors.

Selye, H.: "Nonspecific resistance." *Ergeb. Allg. Pathol. Pathol. Anat.* **41**: 208-241 (1961). C95,972/61

Extensive review on nonspecific or cross-resistance and sensitization, with numerous instances of both the systemic and the local variants. Very often stressors are used to induce this type of resistance as, for example, in the so-called "nonspecific therapy." Protection by stressors against the most diverse inflammatory lesions is particularly striking, and certain types of cross-resistance are demonstrable even in adrenalectomized animals. In some cases, increased thyroid hormone secretion also appears to induce tolerance. A special section is devoted to interrelations between systemic and local nonspecific resistance, that is, the influence of the L.A.S. upon the G.A.S. and vice versa (85 refs.).

Selye, H.: "Nonspecific resistance." *Patol. Fiziol. Éksp. Ter.* **5** No. 3: 3-14; No. 4: 3-15 (1961) (Russian). C99,248/61

Review on stress, especially in relation to nonspecific resistance.

Selye, H.: "Stress and cardiovascular disease." *World Wide Abstr. Gen. Med.* **4**: 8-13 (1961). C93,900/61

Review on the effect of stress upon the development of cardiovascular disease, particularly CHD. Special emphasis is placed upon the production of cardiac necrosis following humoral conditioning by sudden exposure to unaccustomed stress, and upon the fact that previous exposure to a stressor (for example, exercise) can protect the heart against this type of damage.

Schutz, K.: "Practical application of Selye's stress concept." *Ulster County Med. Bull.* **11**: 16-17 (1962). D43,449/62

Brief résumé of the literature concerning the therapeutic actions of stressors.

Strelbel, R., Bajusz, E., Selye, H.: "Fasting as a protective stressor against the potential cardiotoxic action of various agents." *Cardiologia* (Basel) **41**: 179-190 (1962).

C95,845/62

"In the rat fasting can protect the heart

against the production of necrosis, inflammation and/or calcification by various agents such as: plasmocid, papain, dihydrotachysterol plus NaH_2PO_4 , dihydrotachysterol plus Ca-acetate, nephrectomy plus $\text{Na}_3\text{citrate}$ and restraint after sensitization with fluorocortisol plus Na-acetate. These observations furnish additional examples of stress-induced cross-resistance of cardiac muscle, assuming that here—as in earlier experiments with other stressors—fasting acts through its nonspecific effect."

Leonov, B. V., Lomova, M. A., Rudakov, I. A.: "Connection of radiosensitivity of rats with antioxidative activity of bone marrow and content of unesterified fatty acids in their blood under conditions of 'stress.'" *Radiobiologia* **3**: 518-522 (1963) (Russian). Engl. trans.: *Radiobiology* **3**: 43-49 (1963). J24,546/63

Experiments on rats "suggested that the increased expenditure of antioxidants under conditions of 'stress' may be connected with mobilization of fats from fat depots and that one of the mechanisms of the increase of radiosensitivity of animals in 'stress' can be the oxidation of mobilized lipids." It is assumed that cross-sensitization by stressors to x-rays may result from the loss of antioxidants during stress.

Broadbent, D. E.: "Differences and interactions between stresses." *Q. J. Exp. Psychol.* **15**: 205-211 (1963). J11,836/63

In man simultaneous application of different stressors showed that "the effects of heat appear to be independent of those of noise and sleeplessness, while the latter two conditions partially cancel each other. It is therefore argued that noise and sleeplessness affect the same mechanism in opposite directions, while heat affects some other mechanism. Tentatively, noise is regarded as over-arousing and lack of sleep as under-arousing."

Swinyard, E. A., Miyahara, J. T., Clark, L. D., Goodman, L. S.: "The effect of experimentally-induced stress on pentylenetetrazol seizure threshold in mice." *Psychopharmacologia* (Berlin) **4**: 343-353 (1963).

E21,626/63

Various stressors decreased the pentylenetetrazol seizure threshold in mice.

Wallgren, H., Tirri, R.: "Studies on the mechanism of stress-induced reduction of alcohol intoxication in rats." *Acta Pharmacol. (Kbh.)* **20**: 37-38 (1963). E25,256/63

Review of the literature showing that various stressors (fear, trauma) have a sobering effect on ethanol intoxication. A similar action of exercise has been demonstrated in rats. This type of cross-resistance is not prevented by hypophysectomy.

Pirozyński, T., Parus, N.: "Les modifications neuro-endocrines déterminées par le stress thérapeutique appliquée aux malades psychiques" (Neuroendocrine changes caused by therapeutic stress applied to mental patients). *Ann. Méd. Psychol.* **1**: 567-593 (1964). G13,498/64

Selye, H., Gabbiani, G., Tuchweber, B.: "Protection by restraint against parathyroid-extract intoxication in absence of the adrenals." *Am. J. Physiol.* **207**: 573-576 (1964). E24,132/64

Restraint protects the rat against the soft tissue calcification normally produced by large doses of parathyroid extract. This protection is evident even in adrenalectomized animals maintained on corticoids.

Gauron, E.: "Infantile shock traumatization and subsequent adaptability to stress." *J. Genet. Psychol.* **104**: 167-178 (1964).

J22,968/64

In rats, "previous experience with shock produced decremental performance on a stressful test involving the repetition of shock, but not on a stressful test not involving shock nor on a nonstressful test."

Fridrich, R.: "Die Auswirkungen von Kombinationsschäden auf den bestrahlten Organismus" (The effects of combined stress on the irradiated organism). *Strahlentherapie* **124**: 302-307 (1964). G19,723/64

In mice, production of stress by traumatic injuries (removal of part of the omentum) forty-eight hours before or after x-irradiation offers considerable protection. This type of increased resistance is ascribed to the stressor effect of pituitary-adrenocortical mobilization, ("cross-resistance") since it can be blocked by morphine or barbiturates that inhibit hypothalamic reactivity (40 refs.).

Jahnke, V.: "Stress and pathologic calcification." *J. Am. Osteopath. Assoc.* **65**: 258-267 (1965). J23,646/65

Most experimental calciphylactic syndromes can be prevented by pretreatment with stressors.

Stahnke, H. L.: "Stress and the toxicity of venoms." *Science* **150**: 1456-1457 (1965). F57,253/65

The resistance to scorpion or rattlesnake venom is diminished by previous exposure to various stressors.

Fridrich, R.: "Beitrag zur zentral-nervösen Beeinflussung des Strahlensyndroms" (Contribution on central nervous system mediation in the radiation syndrome). *Radiol. Clin. Biol.* **34**: 78-82 (1965). J23,648/65

Goldberg, D. H.: "The physiological effects of multiple stressors." *Behav. Sci.* **11**: 438-443 (1966). J23,001/66

Jacobs, I. A., Kowalski, C.: "A method for inducing stress in a laboratory setting." *Int. J. Soc. Psychiatry* **12**: 273-278 (1966). J22,677/66

Technique for studying the interaction between a physical (cold) and an interpersonal (severe criticism) stressor in man.

Sanchez, C., Miya, T. S., Bousquet, W. F.: "Effects of conditioning upon stress responses in the rat." *Proc. Soc. Exp. Biol. Med.* **123**: 615-618 (1966). F73,973/66

Pretreatment of rats with small amounts of intravenous sodium chloride for five days inhibited the marked elevation of plasma corticosterone induced by saline in unpretreated controls. Similar pretreatment offered no protection however, against the more pronounced stressor effect of intravenous histamine. The resting plasma corticosterone and ascorbic acid levels did not show any consistent seasonal variations, and there was no manifest relationship between the two values. This "suggests that caution be employed in relying upon adrenal ascorbic acid determinations as an index of adrenocortical activity or response to stressors."

Ducommun, P., Vale, W., Sakiz, E., Guillemin, R.: "Reversal of the inhibition of TSH secretion due to acute stress." *Endocrinology* **80**: 953-956 (1967). F83,273/67

In rats, chronic mild stress (transfer from the animal room to the laboratory, handling and brief ether anesthesia at different times of the day) prevents the usual inhibition of TTH secretion by acute stress (sojourn in a noisy centrifuge). This inhibition is also reversed by reserpine. Furthermore, chronic stress leads to continuously increased resting levels of plasma TTH.

Short, L. L., Newsom, B. D., Brady, J. F.: "X-radiation effects on vibration tolerance of rats." *Aerosp. Med.* **38**: 140-143 (1967). J22,609/67

Djahanguiri, B., Sadeghi, D., Hemmati, S.: "Système orthosympathique et ulcères gastriques expérimentaux" (The orthosympathetic system and experimental gastric ulcers). *Arch. Int. Pharmacodyn. Ther.* **173**: 154-161 (1968). F99,278/68

In rats, cold increases the ulcerogenic effect of restraint, whereas α -adrenergic blocking agents prevent it.

Schattenfroh, C., Stracke, U., Eger, W.: "Änderung der Leberfunktion durch Tourniquet Mesenterialgefäßligatur und Immobilisation im Tierexperiment" (Change in liver function due to tourniquet, mesenteric vessel ligation and immobilization in animal experiments). *Brunns Beitr. Klin. Chir.* **216**: 560-568 (1968). J22,743/68

In rats, stress induced by traumatic injuries offers immediate protection against the hepatic necrosis normally produced by allyl alcohol.

Vácha, J., Pospíšil, M.: "Individual differences in the stress response of mice and their relationship to the differences in radiation tolerance." *Med. Exp.* (Basel) **19**: 58-63 (1969). H17,170/69

In mice, pretreatment with various stressors (starvation, isolation) increases x-ray tolerance, but only if the stress produced is of moderate intensity.

Horwitz, K. B., Ball, R. J., Schmidt, J. P.: "Resistance to infection of mice and hamsters following short term acceleration stress." *Aerosp. Med.* **40**: 1248-1251 (1969). H44,833/69

Brief exposure to acceleration significantly protected mice, but not hamsters, against subsequent infection with *Clostridium tetani* or *S. typhimurium*. Cortisol secretion was not demonstrable in the stressed mice. It is suggested that the previously documented effect of stress and cortisol in lowering resistance to infection does not occur following very short exposure.

Anderlik, P., Báños, Z., Szeri, I., Koltay, M., Virág, I.: "Response to stressors of mice undergoing graft-versus-host reaction." *Experientia* (Basel) **26**: 94-95 (1970). H21,168/70

In mice, intravenous injection of homologous splenic cells causes lymphopenia with body weight loss. Following such treatment, these animals no longer respond to a second stressor with further lymphopenia.

Martin, M. S., Martin, F., Lambert, R.:

"Effets des stimulations audio-visuelles sur la fréquence de l'ulcère de contrainte chez le Rat Wistar" (Effects of audio-visual stimulations on the incidence of restraint ulcer in Wistar rats). *C.R. Soc. Biol. (Paris)* **164**: 1748-1750 (1970). H39,492/70

In rats, audiovisual stimulation increases the frequency of gastric ulcers produced by restraint.

Frenkl, R.: "Pituitary-adrenal response to various stressors in trained and untrained organisms." *Acta Physiol. Acad. Sci. Hung.* **39**: 41-46 (1971). G86,808/71

"The pituitary-adrenal reaction of albino rats trained by regular swimming was found to be similarly reduced to histamine and surgical intervention as to the accustomed physical effort. The effect of the other investigated stressors (endotoxin, ether, epinephrine) was independent from previous training. It is suggested that the response is reduced whenever the stressor would elicit the endocrine through a pathway similar to that activated by swimming."

Afrapetian, G. M., Aizina, N. L., Ovaki-mov, V. G., Ivanov, V. N.: "Effect of some modifying agents on the radioresistance formation in an organism under gamma-irradiation." *Radiobiologia (Mosk.)* **11**: 880-883 (1971) (Russian). J20,643/71

In mice, exposure to various stressors can augment resistance to total body gamma-irradiation.

Parrot, J.: "The measurement of stress and strain." In: Singleton, W. T., Fox, J. G., et al., *Measurement of Man at Work. An Appraisal of Physiological and Psychological Criteria in Man-Machine Systems*, pp. 27-33. London: Taylor and Francis, 1971.

J18,094/71

Observations on the interaction between different stressors applied simultaneously.

Forsyth, R. P., Hoffbrand, B. I., Melmon, K. L.: "Hemodynamic effects of angiotensin in normal and environmentally stressed monkeys." *Circulation* **44**: 119-129 (1971). G84,832/71

Avoidance schedules and other environmental stressors greatly sensitized rhesus monkeys to the pressor effect of infused angiotensin II.

Fregly, M. J.: "Cross-adaptations and their significance." *Rev. Can. Biol.* **30**: 223-237 (1971). H46,693/71

Ritchie, W. P. Jr., Roth, R. R., Fischer, R. P.: "Studies on the pathogenesis of 'stress ulcer': effect of hemorrhage, transfusion, and vagotomy in the restrained rat." *Surgery* **71**: 445-451 (1972). G89,104/72

"Restraint-induced ulcers in the rat resemble posttraumatic 'stress ulcers' in man in that they are acute and multiple, occur mainly in the stomach, are confined to the oxytic cell area, and are not associated with gastric acid hypersecretion." The production of these ulcers is enhanced by hemorrhage and greatly diminished by vagotomy.

Wilkinson, R.: "One stress on top of another." *New Society* July 13, 1972, pp. 74-75. J13,724/72

Review on cross-resistance and cross-sensitization in daily life.

Hecht, K., Poppei, M., Peschel, M., Trepotow, K., Moritz, V.: "Optimierungsaspekte in der zerebro-viszeralen Blutdruckregulation unter chronischem Einfluss kombinierter Stressoren" (Optimizing effects in cerebrovisceral blood pressure regulation following chronic exposure to combined stressors). *Acta Biol. Med. Ger.* **31**: 813-825 (1973).

J11,605/73

Observations on rats showed that "whereas chronic single presentation of stressors (learning, intermittent limitation of mobility) led to pronounced neurotically induced dysregulations of the blood pressure paralleling disturbances of the central nervous system and the carbohydrate metabolism, combination of the two stressors, or combination of one stressor with other environmental factors, produced an established compensatory effect." Presumably, treatment with a combination of stressors need not entail summation of their effects in all respects (19 refs.).

Paisey, R. B., Angers, M., Frenk, S.: "Plasma cortisol levels in malnourished children with and without superimposed acute stress." *Arch. Dis. Child.* **48**: 714-716 (1973). J6,618/73

Plasma cortisol levels were essentially normal in malnourished children with marasmus or kwashiorkor, unless superimposed stress (infection, hypoglycemia, acidosis) caused a rise.

Daniels-Severs, A., Goodwin, A., Keil, L. C., Vernikos-Danellis, J.: "Effect of chronic crowding and cold on the pituitary-adrenal system: responsiveness to an acute

stimulus during chronic stress." *Pharmacology* (Basel) **9**: 348-356 (1973).

H77,763/73

Friedman, S. B., Ader, R., Grota, L. J.: "Protective effect of noxious stimulation in mice infected with rodent malaria." *Psychosom. Med.* **35**: 535-537 (1973).

J21,558/73

Carmichael, S. W.: "Fluorescence microscopy of the adrenal medulla of the newborn puppy after asphyxia and hypothermia." *Acta Anat.* (Basel) **87**: 131-140 (1974).

J12,617/74

"Hypothermia reduces the release of catecholamines from the adrenal medulla to such a degree that there is little or no depletion of catecholamines during 32 min of total anoxia."

Frankenhaeuser, M., Dunne, E., Bjurström, H., Lundberg, U.: "Counteracting depressant effects of alcohol by psychological stress." *Psychopharmacologia* (Berlin) **38**: 271-278 (1974).

J19,037/74

In men and women, electric shocks decreased and ethanol increased reaction time. When both agents were applied simultaneously, the impairment produced by alcohol was significantly reduced by shock.

Messerschmidt, O., Sedlmeier, H., Maurer, G.: "Untersuchungen über Kombinations-schäden. 19. Mitteilung. Der Gehalt an Corticoiden in den Nebennieren von Mäusen, die durch Ganzkörperbestrahlungen in Kombination mit offenen Hautwunden belastet wurden" (Examinations of combined injuries. 19th report. Whole body irradiation combined with open cutaneous lesions affecting the adrenal corticosteroids in mice). *Strahlentherapie* **148**: 87-94 (1974).

J17,719/74

In mice, tolerance to x-irradiation may be increased during the first few days following trauma. This is ascribed to "nonspecific resistance caused by activation of the pituitary-adrenocortical system in Selye's sense."

Tharp, G. D., Jackson, J. L.: "The effect of exercise training on restraint ulcers in rats." *Eur. J. Appl. Physiol.* **33**: 285-292 (1974).

J21,750/74

In rats, "treadmill running provides no protection against gastric ulceration induced by restraint-cold stress."

Attinger, E. O., Attinger, F. M., Ahuja, D., Adams, M., Maffeo, C.: "Cardiovascular and

respiratory adjustments to multiple stress." *Fed. Proc.* **33**: 333 (1974). H84,090/74

Solez, K., Miller, M., Quarles, P. A., Finer, P. M., Heptinstall, R. H.: "Experimental papillary necrosis of the kidney. IV. Medullary plasma flow." *Am. J. Pathol.* **76**: 521-528 (1974). H91,765/74

In rats the renal papillary necrosis caused by bromoethylamine hydrobromide can be prevented by reserpine, perhaps owing to the stressor effect of the latter. However, brief exposure to cold or restraint did not replicate this protective action.

Balazs, T.: "Development of tissue resistance to toxic effects of chemicals." *Toxicology* **2**: 247-255 (1974). J13,976/74

Review and personal observations on the development of topical tissue resistance following repeated systemic treatment with drugs having a topical damaging effect. This phenomenon represents an instance of cross-resistance, presumably related to the L.A.S. (32 refs.).

Hadjiolova, I.: "Veränderungen des Plasma- und Nebennierenrindencorticosterons bei Ratten während Hypokinesie und zusätzlicher Stress-Einwirkungen" (Influence of hypokinesia and subsequent stress upon the rat plasma and adrenal corticosterone level). *Int. Arch. Arbeitsmed.* **33**: 59-70 (1974).

J17,473/74

Studies on plasma and adrenal corticosterone in rats exposed to different stressors (heat, restraint, noise) alone or in combination. "A moderate increase in the levels of both plasma and adrenal corticosterone was observed after 24 hrs of hypokinesia. In a subsequent period of 60 days the corticosterone levels did not differ significantly from the levels found in the control animals. However, a marked decrease in adrenal weight and a slighter response to additional thermal stress were demonstrated after 60 days of hypokinesia. Differences between the restrained and the control animals were also found in the adaptation to chronic auditory stress."

III. CHARACTERISTIC MANIFESTATIONS OF STRESS

In this chapter, we shall discuss all the functional, chemical and morphologic changes that are truly nonspecific and which hence characterize the stress response. Some of these are of diagnostic value in that they permit us to recognize stress. A special section is devoted to the so-called "stress tests" that are commonly used to determine whether a procedure or activity is particularly stressful, or to predict how a person is likely to respond to stressors as, for example, in responsible administrative posts, or in emergencies during catastrophes, fires, combat or aviation.

Another reason why we had to devote such a large section to the characteristics of stress is that, in medical research, we are continuously faced with the necessity of distinguishing specific symptoms and signs of disease, or actions of remedies, from their nonspecific side effects. It is somewhat arbitrary to separate the "physiologic" manifestation of stress from the progression of the same effect to a point where we would call it pathologic, that is, a stress-induced malady. Hence, the reader should also consult Chapter IV, Diseases of Adaptation. For example, minor stress-induced changes in behavior, cognition, and emotion will be discussed in this chapter under Nervous System, whereas major, definitely morbid derangements of a similar kind will be found in the section, Neuropsychiatric Diseases of Adaptation.

CHEMICAL CHANGES

Most of the studies concerned with the biochemistry of stress have dealt with hormones and hormone-like substances. One reason for this is that the G.A.S. was first characterized on the basis of observations on the mediating role of the hypophysis-adrenocortical axis. Furthermore, even today, we know much more about this field; the neuroendocrine mechanisms that transmit the initial stimulus of the "First Mediator" humoral substances (for example, CRF, EP, NEP, 5-HT) are recognized as playing a decisive role.

However, many other biochemical changes, not involved in the actual mediation of the stress response, proved to be characteristic of it. Hence, we shall also have to deal here with alterations in body weight and in the BMR as well as in the metabolism of lipids, proteins, carbohydrates, electrolytes and enzymes.

Body Weight

In the earliest studies a loss of body weight was recognized as a particularly characteristic response to stress, no matter how produced. Usually, the general catabolism

of energy-yielding materials responsible for this change is most intense during the first days, after which the rate of weight loss tends to diminish. The reason for this reaction is that most stressors cause a decrease in appetite and hence in caloric intake, so that the requirements must be supplied by endogenous sources, namely, the breakdown of fat, protein and carbohydrate stores.

Paradoxically, sometimes—especially under the influence of chronic psychogenic stress of moderate intensity—people have a tendency to eat more, because a full stomach has a tranquilizing effect and also takes their mind off the psychogenic irritant to which they are exposed. Such people tend to become overweight as they are driven to food in a manner very similar to that of subjects who turn to alcohol or drugs for much the same reason.

Body Weight

(See also our earlier stress monographs, p. xiii)

Hart, J. S., Heroux, O.: "Utilization of body reserves during exposure of mice to low temperatures." *Can. J. Biochem.* **34**: 414-421 (1956). E93,320/56

"Mice acclimated for four weeks to 6°C had a body water content on an absolute and on a fat-free basis that was greater than that of mice acclimated to 23°C. When exposed to freezing temperatures, the weight loss and loss of water were greater in the cold acclimated group. Fat was the major tissue energy reserve utilized under these conditions. In both acclimation groups it accounted for 85 to 89% of the total calories, the remainder being supplied mostly by protein." The results are discussed in relation to the catabolic changes characteristic of stress.

Roubicek, C. B.: "Stress adaptation in the rat as measured by postweaning growth." *Growth* **30**: 79-85 (1966). G39,305/66
"The detrimental effects of high tempera-

ture on animal weight are due to the difference in the slope of the growth curve, rather than to a longer adjustment period."

Imms, F. J.: "The effects of stress on the growth rate and food and water intake of rats." *J. Endocrinol.* **37**: 1-8 (1967).

F76,001/67

Wilson, S. P., Doolittle, D. P., Dunn, T. G., Malven, P. V.: "Effect of temperature stress on growth, reproduction, and adrenocortical function of mice." *J. Hered.* **63**: 324-330 (1972). G99,980/72

Stewart, A. H.: "The effect of emotion on growth." *Child Welfare* **51**: 171-177 (1972). J20,144/72

In very young children, growth may be stunted as a consequence of psychogenic stress.

Hunter, C., Clegg, E. J.: "Changes in body weight of the growing and adult mouse in response to hypoxic stress." *J. Anat. (Lond.)* **114**: 185-199 (1973). J2,541/73

Basal Metabolic Rate (BMR)

Surprisingly few investigators have dealt with changes in the BMR during stress. Of course, it is generally known that in very severe stress, as exemplified by the final stages of traumatic, hemorrhagic or toxic shock, the BMR decreases, whereas the reverse is true in the acute alarm reaction, for example, that produced by pain, emotional arousal, or extreme muscular effort. However, the BMR is particularly subject to conditioning factors which influence it through specific effects; hence it is not a very reliable characteristic of stress.

Basal Metabolic Rate (BMR)

(See also our earlier stress monographs, p. xiii)

Cannon, W. B.: "Traumatic shock." In: Lewis, D., Pool, E. H. et al., *Surgical Monographs*, p. 201. New York and London: D. Appleton, 1923. E142/23

Early observations on soldiers wounded during World War I and severely injured experimental animals concerning the decrease in BMR produced by trauma and hemorrhage. It can largely be overcome by appropriate blood transfusions and may be due to reduced oxygen supply.

Jugenburg, A.: "Über die Einwirkung der Röntgenbestrahlung auf den Gasstoffwechsel Experimentelle Untersuchungen an Meerschweinchen" (The effect of x-irradiation on oxygen consumption in guinea pigs). *Acta Radiol.* (Stockh.) Supp. 3: 168-169 (1928). A32,641/28

In severely x-irradiated guinea pigs, the BMR decreases.

Post, R. S., Visscher, P. H., Wiggers, C. J.: "Sequential changes in oxygen consumption during oligemic and normovolemic shock, and their meaning." *Am. J. Physiol.* 153: 71-80 (1948). B25,993/48

Studies on dogs in normovolemic and oligemic shock produced by hemorrhage with or without restoration of the withdrawn heparinized blood show that reduction of oxygen consumption is not a necessary concomitant of irreversible shock. "Even when body temperature is kept constant oxygen consumption is not a measure of basal metabolic rate during shock. This is due to the fact that oxygen uptake is predominately affected by reduction in oxygen transport capacity, excessive respiratory effort and varying degrees of acidosis with accumulation of oxygen debt."

Kirschner, L. B., Prosser, C. L., Quastler, H.: "Increased metabolic rate in rats after x-irradiation." *Proc. Soc. Exp. Biol. Med.* 71: 463-467 (1949). B37,743/49

Novák, L.: "Adaptation metabolism as an indicator of the degree of radiation injury to the organism." *Physiol. Bohemoslov.* 7: 150-159 (1958). C53,088/58

Heinecker, R.: "Individuelle Unterschiede in der Reaktion von Kreislauf und Gasstoffwechsel auf dosierte Belastungen: Cold

Pressor Test, Flickerlicht, Lärm, körperliche Arbeit" (Individual differences in the reaction of circulation and oxygen consumption to standardized stress. Cold Pressor Test, flicker-light, sound, muscular work). *Arch. Kreislaufforsch.* 30: 1-2 (1959).

C72,354/59

Extensive review on changes in the BMR and circulatory apparatus induced in man by the Cold Pressor Test, light, sound, muscular work and other stressors.

Paré, W. P.: "Premature aging as a function of long-term environmental stress." *J. Genet. Psychol.* 104: 185-191 (1964).

G41,960/64

A review on the relationship between stress and aging revealed that with old age the BMR decreases and the prostate undergoes hypertrophy. In experiments on rats chronically exposed to stressors (sound, electric shocks), aging defined in terms of BMR and prostatic hypertrophy, was in fact accelerated. The animals also showed eosinopenia and lymphopenia. It was concluded that "an animal's environment may 'require' or 'cause' adaptive responses that produce irreversible damage and hence shorten lifespan. A concept such as 'normal' aging may be misleading since aging cannot be represented as a unitary concept. Aging is the cumulative effect of responses made by biological systems as these systems adapt themselves to environmental stressors" (21 refs.).

Mitkova, N.: "Changes in the metabolism and in the functional activity of the thyroid in workers exposed to noise and vibrations." *Abstr. Bulg. Sci. Lit. Biol. Med.* 8: 51 (1965).

F47,432/65

In boilermiths, exposure to vibration and noise during their work increases the BMR.

Strydom, N. B., Wyndham, C. H., Williams, C. G., Morrison, J. F., Bredell, G. A. G., Joffe, A.: "Oral/rectal temperature differences during work and heat stress." *J. Appl. Physiol.* 20: 283-287 (1965).

G27,148/65

Studies on the relationship of the BMR to oral and rectal temperatures under different conditions. Despite the title, the authors made no effort to show a relationship to stress, and presumably studied the specific effects of work at different temperatures.

Harrison, T. S., Seaton, J. F., Feller, I.: "Relationship of increased oxygen consump-

tion to catecholamine excretion in thermal burns." *Ann. Surg.* **165**: 169-172 (1967).

G44,078/67

In seriously burned patients an increase in BMR occurs simultaneously with a rise in the excretion of EP and NEP. Catecholamines may help to provide the burned patient with an increased energy supply from oxidatively available stores of fat and muscle (13 refs.).

Macho, L., Palkovič, M., Mikulaj, L., Kvetňanský, R.: "Tissue metabolism in rats adapted to immobilization stress." *Physiol. Bohemoslov.* **17**: 173-178 (1968).

G60,598/68

Bünte, H.: "Der Energiehaushalt des chirurgischen Patienten" (The energy metabolism of postoperative patients). *Bruns Beitr. Klin. Chir.* **216**: 577-586 (1968).

G83,616/68

In postoperative patients the BMR rises concurrently with body temperature and tissue catabolism. The contrary is true later, during the anabolic recovery phase (50 refs.).

Corson, S. A., Corson, E. O., Kirilcuk, V., Hajek, J., Hajkova, M.: "Individual differences in oxygen consumption under emotional stress." *Fed. Proc.* **28**: 648 (1969).

H10,465/69

Depending upon racial or constitutional factors, certain dogs respond to the emotional stress of an anticipated "fight-or-flight" situation with a rise in BMR even if they do not actually perform excessive muscular work.

Oyama, J., Chan, L.: "Oxygen consumption and carbon dioxide production in rats during acute centrifugation stress and after adaptation to chronic centrifugation." *Fed. Proc.* **32**: 392 (1973).

H67,544/73

In rats, stress produced by continuous centrifugation causes a pronounced hypothermia and a decrease in BMR. However, with continued exposure to the stressor, adaptation occurs and the BMR rises above normal. The authors conclude that "the principal factor responsible for the centrifugation stress-induced hypothermia in rats is a decrease in their rate of heat production."

HORMONES AND HORMONE-LIKE SUBSTANCES

Corticoids

The abstracts presented in this section deal primarily with the effect of various stressors upon plasma and urinary corticoids as well as their metabolites. Some data are also presented on the changes in the corticoid content of tissues (for example, the brain, muscles, CSF) but in this regard, the pertinent literature is too scanty for detailed evaluation.

The most striking data in the literature abstracted in this section reveal the fairly regular and intense increase in glucocorticoid secretion—observed primarily in man but also in many other species such as the monkey, rabbit, rat, fish—under the influence of various stressors.

Evidence of increased glucocorticoid production in man has been noted especially during the anxiety preceding surgery, in stress induced by surgical operations, burns, malignancies and other diseases, aircraft piloting, vibration, the work of underwater demolition teams, circadian variations, electroshock, shift work, and various types of emotional arousal, including sitting for academic examinations.

In several studies, a rise in mineralocorticoids, particularly aldosterone and 18-OH-DOC, has also been observed in people discussing "stressful subjects," sitting for examinations, experiencing preoperative anxiety, undergoing electroshock and being admitted to intensive care units.

In general, these increases in corticoid production were associated with other manifestations of stress, such as enhanced catecholamine and STH secretion, eosinopenia, fibrinolysis.

It is well known that after going through the stages of alarm and resistance, an organism kept in a state of continuous stress eventually reaches the stage of exhaustion. This is characterized by the loss of all adaptability and by changes in the adrenals which suggest hyperactivity similar to that of the alarm reaction. These alterations are sometimes accompanied by hemorrhages and small necrotic lesions, at least in certain animals exposed to stressors that may have a specific adrenotoxic effect.

Such findings have led many investigators to speak of "adrenal exhaustion." While this may occur under very special conditions (for example, in the Waterhouse-Friderichsen syndrome or after severe damage with diphtheria toxin), it is certainly not often observed in patients exposed chronically to common stressor agents. In fact, studies on agonal patients revealed an impaired metabolism of corticoids, despite continued secretion by the adrenals. Under these conditions, terminal patients excreted most of their 17-OHCS in conjugated form.

Radiocortisol, injected intracardially, is rapidly excreted in rats under normal conditions, but during stress its clearance from the muscles (the main area of storage) is greatly delayed.

Some investigators emphasized that adrenal ascorbic acid depletion does not closely parallel the rise in plasma corticoids during stress; hence, the former cannot be regarded as a reliable indicator of corticoid synthesis and/or release.

During the NASA Gemini VII mission, one group of investigators reported a striking decrease of 17-OHCS during flight. Another study called attention to an inflight rise in aldosterone excretion, and concluded that the secretion of this hormone may be one characteristic of man's adaptation to a weightless environment.

Contrary to expectations, the presumably severe emotional stress preceding suicide as well as depressive illness itself is not associated with high levels of cortisol in the cerebral cortex, whereas patients who died from stressful somatic diseases exhibited elevated brain cortisol, proportionate to the duration and severity of their physical illness.

In some instances, it has been possible to show that treatment with exogenous corticoids partially inhibits the stress-induced excess endogenous corticoid production through the well-known feedback mechanism.

Only a few studies have attempted to identify individual corticoids and their metabolites in the adrenal venous blood.

After perusing the data in this section, the reader is advised also to consult the section on hormone secretion in the discussions devoted to each Stressor and Conditioning Agent.

Corticoids

(See also our earlier stress monographs, p. xiii)

Ingle, D. J.: "The biologic properties of cortisone: a review." *J. Clin. Endocrinol.* **10:** 1312-1354 (1950). B51,704/50
Review on the biologic properties of corti-

sone and other glucocorticoids, with special reference to the G.A.S. and the diseases of adaptation (189 refs.).

Moncrief, J. A., Weichselbaum, T. E., Elman, R.: "Changes in adrenocortical steroid concentration of peripheral plasma

following surgery." *Surg. Forum* **4**: 469-473 (1954). J11,248/54

17-OHCS levels were measured in the fasting plasma of chronically ill patients and those with malignancies. The levels were higher in the latter group and rose in both groups after major operations.

Bayliss, R. I. S.: "Factors influencing adrenocortical activity in health and disease." *Br. Med. J.* February 26, 1955, pp. 495-501.

C6,392/55

Review on the various factors influencing blood corticoid levels in health and disease. Elevated values are found in pregnancy, emotional disturbances and after surgery, but "no consistent increase in adrenal activity has been observed after administration of adrenaline salicylates, or deep x-irradiation in ordinary therapeutic dosage."

Hetzl, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man." *J. Clin. Endocrinol. Metab.* **15**: 1057-1068 (1955).

C8,424/55

In patients a one-hour discussion of "stressful subjects" caused diuresis with increased 17-OHCS, nitrogen, sodium and potassium elimination.

Venning, E. H., Dyrenfurth, I.: "Effect of stress upon excretion of aldosterone." *J. Clin. Endocrinol. Metab.* **16**: 961 (1956).

C14,919/56

In healthy individuals, urinary aldosterone excretion was frequently raised during "stressful experiences such as examinations or the presentation of papers at meetings."

Sandberg, A. A., Eik-Nes, K., Migeon, C. J., Samuels, L. T.: "Metabolism of adrenal steroids in dying patients." *J. Clin. Endocrinol. Metab.* **16**: 1001-1016 (1956).

C20,121/56

In agonal patients the plasma clearance of intravenous radiocortisol was delayed, and terminal patients excreted most of the 17-OHCS in conjugated form. These and other findings are interpreted as indicating that elevated plasma corticoid levels in dying patients "are due to impaired metabolism of these steroids in the presence of continued production and secretion of steroids by the adrenal cortex at normal or reduced rates."

Hume, D. M., Nelson, D. H., Miller, D. W.: "Blood and urinary 17-hydroxycor-

ticosteroids in patients with severe burns." *Ann. Surg.* **143**: 316-329 (1956).

C15,326/56

17-OHCS in the plasma and urine of severely burned patients was greatly increased, and subsequent examinations revealed no evidence of adrenal exhaustion. Indeed, the adrenal was capable of responding to exogenous ACTH during the postburn period (10 refs.).

Nelson, D. H.: "Adrenocortical secretion and factors affecting that secretion." In: Selye, H. and Heuser, G., *Fifth Annual Report on Stress*, pp. 169-184. New York: MD Publications, 1956.

C15,956/56

Review of the literature and personal observations on the identification of individual corticoids secreted under the influence of various stressors into the adrenal venous blood in different species (145 refs.).

Nelson, D. H., Egdahl, R. H., Hume, D. M.: "Corticosteroid secretion in the adrenal vein of the non-stressed dog exposed to cold." *Endocrinology* **58**: 309-314 (1956).

D85,585/56

In dogs, the 17-OHCS concentration of adrenal venous blood was elevated subsequent to surgical trauma and following warming after a period of exposure to cold.

Lamson, E. T., Elmadjian, F., Hope, J. M., Pincus, G., Jorjorian, D.: "Aldosterone excretion of normal, schizophrenic and psycho-neurotic subjects." *J. Clin. Endocrinol. Metab.* **16**: 954 (1956).

C14,904/56

In schizophrenics, aldosterone excretion is somewhat diminished on the average, but individual variations are very great. Insulin shock treatment causes a rise in aldosterone elimination.

Schwartz, T. B., Shields, D. R.: "Urinary excretion of formaldehydogenic steroids and creatinine. A reflection of emotion tension." *Psychosom. Med.* **18**: 159-172 (1956).

C25,345/56

In students undergoing stressful final examinations, increased urinary corticoid excretion occurs fairly regularly, but urinary volume and creatinine elimination are not clearly related to this stressor.

Firschein, H. E., Venuto, F. de, Fitch, W. M., Pearce, E. M., Westphal, U.: "Distribution of injected cortisol-4-C¹⁴ in normal and shocked rats." *Endocrinology* **60**: 347-358 (1957).

J10,793/57

In rats, radiocortisol injected intracardially is rapidly excreted under normal conditions. However, after stress or injection of corticosterone, clearance from muscles (the main area of storage) is greatly delayed. The same is true after tourniquet shock.

Venning, E. H., Dyrenfurth, I., Beck, J. C.: "Effect of anxiety upon aldosterone excretion in man." *J. Clin. Endocrinol. Metab.* **17**: 1005-1008 (1957).

C38,804/57

In students sitting for oral examinations, the degree of anxiety was graded in terms of an arbitrary scale. The rise in aldosterone excretion roughly paralleled the degree of anxiety and was associated with increased 17-OHCS elimination.

Genest, J.: "III. Clinical states associated with abnormal aldosterone excretion." *Can. Med. Assoc. J.* **77**: 780-785 (1957).

J7,341/57

Mental and emotional stress (especially anxiety states) as well as surgical operations can raise aldosterone production.

Birke, G., Dunér, H., Liljedahl, S. O., Pernow, B., Plantin, L. O., Troell, L.: "Histamine, catechol amines and adrenocortical steroids in burns." *Acta Chir. Scand.* **114**: 87-98 (1958). J10,862/58

In severely burned patients, blood and urinary histamine, EP and NEP content, as well as the excretion of corticoids (17-KGS) were considerably increased during the first twenty-four hours, but the duration of the rise varied according to the substances examined. Their role in the genesis of burn shock is discussed.

Marchbanks, V. H.: "Effect of flying stress on urinary 17-hydroxycorticosteroid levels. Observations during a 22½-hour mission." *J. Aviat. Med.* **29**: 676-682 (1958).

C58,431/58

Urinary "steroids were increased almost two-fold in the pilot" of a B-52 aircraft on a 22.5 hour nonstop flight from Florida to Argentina to New York. "The 17-OH-CS urinary output is a favorable index for measuring stress in flying personnel."

Euler, U. S. von, Gemzell, C. A., Levi, L., Ström, G.: "Cortical and medullary adrenal activity in emotional stress." *Acta Endocrinol. (Kbh.)* **30**: 567-573 (1959).

C66,890/59

Brief technical note on cortical and medul-

lary adrenal activity during emotional stress, based on new techniques of corticoid and catecholamine determinations.

Mason, J. W., Brady, J. V., Polish, E., Bauer, J. A., Robinson, J. A., Rose, R. M., Taylor, E. D.: "Patterns of corticosteroid and pepsinogen change related to emotional stress in the monkey." *Science* **133**: 1596-1598 (1961). D4,949/61

In rhesus monkeys, conditioned avoidance sessions of seventy-two hours caused an increase in 17-OHCS levels and an initial drop, followed by a prolonged, marked elevation in the pepsinogen concentration of the plasma.

Bugard, P.: "Etude hormonale et métabolique de la fatigue. II. Personnel volant à bord d'avions intercontinentaux" (Hormonal and metabolic study of fatigue. II. Crew members on intercontinental flights). *Ann. Endocrinol. (Paris)* **22**: 1008-1016 (1961).

D22,366/61

Hyperaldosteronism was more pronounced on jets than on conventional aircraft, and was definitely related to emotional tension. A decrease in 17-KS was evident in men but not in women. Excretion of 17-OHCS and creatinine was raised under the same conditions. Allegedly, endocrine-metabolic examinations can provide valuable early indices of fatigue among aviators.

Hyde, P. M., Skelton, F. R.: "Influence of stress on plasma and adrenal corticosterone levels in rats with intact and regenerating adrenals." *Endocrinology* **69**: 250-256 (1961). D9,289/61

"Rats with two regenerating adrenals responded to stress with higher peripheral plasma levels of corticosterone than did animals with one regenerating gland, but these values were always less than those of the controls."

Fukui, S.: "The influence of stress upon the excretion of adreno-cortical hormone in pulmonary tuberculosis. II." *Kekkaku* **37**: 125-129 (1962) (Japanese). J23,475/62

Elmadjian, F.: "Epinephrine, norepinephrine, and aldosterone: release and excretion." In: Schaefer, K. E., *Man's Dependence on the Earthly Atmosphere*, pp. 100-116. New York and London: Macmillan, 1962.

D30,946/62

Studies on EP and NEP secretion during stressful life situations in normal people and psychiatric patients "support the hypothesis

that active, aggressive, emotional displays are related to increased excretion of norepinephrine, whereas tense, anxious, but passive emotional displays are related to increased excretion of epinephrine." Aldosterone elimination was elevated in certain anxiety states without demonstrable increases in catecholamine excretion. The stressors examined were manipulation of the Hoagland-Werthessen pursuit meter, hockey, boxing, basketball, baseball and anxiety-inducing interviews.

Yates, F. E., Urquhart, J.: "Control of plasma concentrations of adrenocortical hormones." *Physiol. Rev.* **42**: 359-443 (1962).

D30,548/62

Very meticulous and detailed review of the literature on the stressors and feedback system responsible for corticoid concentrations in the plasma and tissues (727 refs.).

Hedner, P., Rerup, C.: "Plasma corticosteroid levels and adrenal ascorbic acid after intravenous corticotrophin injections and 'stressful' stimuli in the rat." *Acta Endocrinol. (Kbh.)* **39**: 527-538 (1962).

D21,246/62

In rats the increase in plasma corticoid levels unlike the depletion of adrenal ascorbic acid produced by ether anesthesia is blocked by dexamethasone. The corresponding effects of unilateral adrenalectomy are less readily influenced. Apparently, corticoids can only partially inhibit the stress-induced endogenous corticoid discharge. [Of course, if these feedback mechanisms were perfect during stress, the latter could never significantly increase corticoid production (H.S.).]

Arguelles, A. E., Ibeas, D., Ottone, J. P., Chekherdemian, M.: "Pituitary-adrenal stimulation by sound of different frequencies." *J. Clin. Endocrinol. Metab.* **22**: 846-852 (1962).

D28,851/62

In healthy young men, and even more markedly in anxious psychoneurotic patients, exposure to various pure sound frequencies for one-hour periods caused substantial elevations in 17-OHCS and 17-KGS excretion. "Adrenal cortical function in man may be remarkably sensitive to auditory stimulation, probably through the effect of ACTH released by intense sound."

Hedner, P.: "Adrenocortical activity studied by determining plasma corticosteroids. With special regard to the effect of exogenous corticotrophin." *Acta Endocrinol. (Kbh.)* **44** Supp. 86: 1-30 (1963).

E36,550/63

Monograph on the value of plasma corticoid determinations in assessing adrenocortical activity during stress.

Knigge, K. M., Hoar, R. M.: "A procedure for measuring plasma binding of adrenal corticoids; effect of acute and chronic stress." *Proc. Soc. Exp. Biol. Med.* **113**: 623-627 (1963).
E21,455/63

In guinea pigs and rats, the acute stressor effect of ether or pentobarbital anesthesia and the chronic stress of cold exposure markedly increase peripheral plasma corticoid levels; "the increment in corticoids during acute stress is predominately unbound, while the increment during chronic cold is associated with protein."

Pankov, Y. A.: "Some data on the changes of the adrenal cortex function in the animals during development of stress." *Probl. Endokrinol. Gormonoter.* **9** No. 6: 3-6 (1963) (Russian).
E33,281/63

Fazekas, I. G.: "Über die Mobilisierbarkeit des Corticosterongehaltes der 'Peripherischen Hormondepoten'" (On the mobilization of the corticosterone content of the 'peripheral hormone depot'). *Endokrinologie* **46**: 133-138 (1964) (44 refs.).

F16,013/64

Vecsei-Weisz, P., Kemény, V., Harangozó, M.: "Further investigations concerning functional changes in the adrenal cortex at the resistance stage of the general adaptation syndrome." *Acta Physiol. Acad. Sci. Hung.* **27**: 265-273 (1965).
G34,303/65

"The resistance stage of the general adaptation syndrome has been evoked in rats by the repeated administration of formalin, and the resulting functional changes were studied by the in vitro incubation of surviving adrenal slices. The aldosterone production was found to be augmented, the corticosterone production unaltered. After adding a progesterone precursor to the incubation medium the rate of production of corticosterone and aldosterone increased. The increase in aldosterone production after formalin treatment was equal to that in the controls. The increase in corticosterone synthesis was more pronounced in formalin-treated animals."

Blivaiss, B. B., Litta-Modignani, R., Galansino, G., Foa, P. P.: "Endocrine and metabolic response of dogs to whole body vibration." *Aerosp. Med.* **36**: 1138-1144 (1965).
F75,989/65

In dogs, horizontal whole body vibration produced an increase of plasma 17-OHCS and EP but not of 5-HT or NEP. This response persisted but was less severe under pentobarbital anesthesia.

Dörner, G., Stahl, F., Wendt, F., Schädlich, M.: "Beurteilung der Nebennierenrindefunktion beim Operationsstress durch fluormetrische Bestimmung von unkonjugiertem Kortisol und Kortikosteron im Plasma und Harn" (Evaluation of adrenal cortex function in surgical stress by fluorometric determination of unconjugated cortisol and corticosterone in plasma and urine). *Brun's Beitr. Klin. Chir.* **212**: 467-480 (1966).

G45,937/66

With an improved method for the fluorometric determination of unconjugated cortisol and corticosterone (11-OHCS), a distinct rise in blood and urine was noted. "The method easily allows to estimate quantitatively stress reactions of the hypothalamic-anterior lobe pituitary-suprarenal cortical system."

D'Amelio, G., Marchiori, C., Busonera, G., Celon, E.: "Modificazioni della eliminazione urinaria delle catecolamine dei 17-idrossicorticoidi e dei 17-ketosteroidi, nello stress da stimolazione vestibolare" (Changes in urinary elimination of catecholamines, 17-hydroxycorticosteroids and 17-ketosteroids in stress caused by vestibular stimulation). *Endocrinol. Sci. Cost.* **29**: 57-63 (1966).

J24,555/66

Sanchez, C., Miya, T. S., Bousquet, W. F.: "Effects of conditioning upon stress responses in the rat." *Proc. Soc. Exp. Biol. Med.* **123**: 615-618 (1966).

F73,973/66

Pretreatment of rats with small amounts of intravenous sodium chloride for five days inhibited the marked elevation of plasma corticosterone induced by saline in unpretreated controls. Similar pretreatment offered no protection, however, against the more pronounced stressor effect of intravenous histamine. The resting plasma corticosterone and ascorbic acid levels did not show any consistent seasonal variation, and there was no manifest relationship between the two values. This finding "suggests that caution be employed in relying upon adrenal ascorbic acid determinations as an index of adrenocortical activity or response to stressors."

Bridges, P. K., Jones, M. T.: "Personality, physique and the adrenocortical response to

a psychological stress." *Br. J. Psychiatry* **113**: 601-605 (1967). G47,391/67

In male medical students, plasma cortisol levels rose considerably during oral examinations.

Wegmann, H. M., Klein, K. E., Brüner, H.: "Die Auswirkung fliegerischer Belastung auf einige Blutkomponenten" (Effects of flying stress on certain components of the blood). *Int. Z. Angew. Physiol.* **23**: 293-304 (1967).

G45,957/67

Among the indicators examined in jet pilots training for Starfighter F-104 G flights, corticoids and certain enzyme activities in the blood proved most sensitive to stress, whereas other enzymes and blood sugar variations were unreliable (24 refs.).

Oyama, T., Takiguchi, M., Kudo, T., et al.: "Effects of halothane anesthesia and surgical operation on adrenocortical function." *Jap. J. Anesthesiol.* **16**: 361-368 (1967) (Japanese).

J24,054/67

In man, halothane anesthesia produces a rise in plasma corticoids that becomes more pronounced following surgical intervention.

Fazekas, I. G., Fazekas, A. T.: "Die Corticosteroid-Fraktionen des menschlichen Gehirns" (Corticosteroids and their derivatives in the human brain). *Endokrinologie* **51**: 183-210 (1967).

F86,025/67

Extensive studies on concentrations of various corticoids and their derivatives in different parts of the brain in normal people (accidental death) and in patients who suffered from alcoholism or chronically distressful diseases (37 refs.).

Hill, C. W., Fromm, P. O.: "Response of the interrenal gland of rainbow trout (*Salmo gairdneri*) to stress." *Gen. Comp. Endocrinol.* **11**: 69-77 (1968).

H2,458/68

Although very intense acute stressors raise plasma cortisol in rainbow trout, the effect of chronic low-level stress is transitory. Plasma cortisol levels "do not appear to be a useful indicator of the existence of chronic stressful conditions."

Oyama, T., Saito, T., Isomatsu, T., Samejima, N., Uemura, T., Arimura, A.: "Plasma levels of ACTH and cortisol in man during diethyl ether anesthesia and surgery." *Anesthesiology* **29**: 559-564 (1968).

G57,525/68

Mason, J. W., Jones, J. A., Ricketts, P. T., Brady, J. V., Tolliver, G. A.: "Urinary aldosterone and urine volume responses to 72 hr.

avoidance sessions in the monkey." *Psychosom. Med.* **30**: 733-745 (1968).

H6,461/68

"Urinary aldosterone levels showed marked fluctuations in relation to 72-hr. conditioned avoidance sessions in the monkey. Two different response patterns were observed. The first was a biphasic response characterized by an initial depression during avoidance, followed by a rebound elevation during the recovery period. The second was characterized by an elevation, in some cases quite marked, during avoidance with a return to basal level during the recovery period" (53 refs.).

Golikov, P. P., Popova, A. M.: "Corticosterone secretion and some indices of stress reaction." *Patol. Fiziol. Éksp. Ter.* **13** No. 1: 71-72 (1969) (Russian). J22,379/69

In rats, neither the corticosterone and ascorbic acid content of the adrenals nor the blood eosinopenia is an accurate indicator of the intensity of stress caused by restraint, but both do give approximations of it.

Winkler, G., Graef, V.: "Nachwirkungen einmaliger Nebennierenrindenstimulierung auf den Verlauf der Aldosteronausscheidung im Harn" (The effect of a single stimulation of the adrenal cortex on the course of urinary aldosterone excretion). *Z. Klin. Chem. Klin. Biochem.* **7**: 179-180 (1969). J22,932/69

In man, the stress of exhaustive muscular exercise increases aldosterone and potassium excretion as well as sodium retention, followed by a decrease in aldosterone and potassium elimination, which in turn initiates a rebound phenomenon. This cyclicity must be taken into account in evaluating pertinent information.

Plumpton, F. S., Besser, G. M.: "The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects." *Br. J. Surg.* **56**: 216-219 (1969). H9,868/69

In patients undergoing major surgery or experiencing insulin hypoglycemia, the concurrent administration of prednisolone usually, though not always, failed to cause the increase in plasma corticoids normally elicited by these stressors, but only for a limited length of time.

Lutwak, L., Whedon, G. D., Lachance, P. A., Reid, J. M., Lipscomb, H. S.: "Mineral, electrolyte and nitrogen balance studies of the Gemini-VII fourteen-day orbital space

flight." *J. Clin. Endocrinol. Metab.* **29**: 1140-1156 (1969). H16,831/69

Studies on two astronauts during two weeks of orbital space flight (NASA Gemini-VII) showed considerable individual variability of metabolic responses. "In one man, significant increases in urinary calcium occurred during the second week of flight, and persisted during the recovery phase; calcium balance became less positive in flight in both subjects. Urinary phosphate excretion increased substantially in flight in both subjects despite reduction in phosphate intake. Urinary nitrogen and sulfate excretion decreased in flight but less than would be expected from the reduction in intake. Patterns of excretion of magnesium, sodium, potassium and chloride were different for each subject and could in part be correlated with changes in adrenocortical steroid production. The principal hormonal change was a striking decrease during flight in the urinary excretion of 17-hydroxycorticosteroids."

Conroy, R. T. W. L., Elliott, A. L., Mills, J. N.: "Circadian rhythms in plasma concentration of 11-hydroxycorticosteroids in men working on night shift and in permanent night workers." *Br. J. Ind. Med.* **27**: 170-174 (1970). H24,017/70

Comparative studies were made of plasma corticoids in newspaper printing shop employees who regularly worked at night, and in engineering factory workers on monthly rotation shifts. Among the newspaper workers maximal concentrations were noted around 14:00 when they awoke, whereas the pattern was much more irregular in the engineering shift employees. "It appears that the adrenal cortical rhythm can be adapted to night work in a community in which this is universal, accepted and lifelong, but that such adjustment is unusual in men on night shift work for limited periods, and whose associates are mainly following a usual nyctohemeral existence."

Rubin, R. T., Rahe, R. H., Clark, B. R., Arthur, R. J.: "Serum uric acid, cholesterol and cortisol levels. Interrelationships in normal men under stress." *Arch. Intern. Med.* **125**: 815-819 (1970). G74,760/70

In healthy young U.S. Navy men undergoing underwater demolition training, physical and psychologic stress is associated with increases in serum uric acid, cholesterol and cortisol concentrations (34 refs.).

Katz, J. L., Weiner, H., Gallagher, T. F.,

Hellman, L.: "Stress, distress, and ego defenses. Psychoendocrine response to impending breast tumor biopsy." *Arch. Gen. Psychiatry* **23**: 131-142 (1970). G77,008/70

Women waiting for breast tumor biopsy showed widely different psychologic defense patterns and anxiety. The associated corticoid excretion also varied considerably, and was only roughly proportionate to the psychiatric score regarded as indicative of stress.

Golstein-Golaire, J., Vanhaelst, L., Bruno, O. D., Leclercq, R., Copinschi, G.: "Acute effects of cold on blood levels of growth hormone, cortisol, and thyrotropin in man." *J. Appl. Physiol.* **29**: 622-626 (1970).

G79,353/70

In man, a two-hour exposure to 4°C caused no change in plasma STH concentrations and only moderate variations in plasma cortisol, but TTH values rose as expected.

Takahashi, K., Daughaday, W. H., Kipnis, D. M.: "Regulation of immunoreactive growth hormone secretion in male rats." *Endocrinology* **88**: 909-917 (1971).

H37,347/71

Plasma immunoreactive STH rose more in gentled rats than in nongentled controls, whereas plasma corticosterone levels showed the opposite relationship. Pentobarbital anesthesia caused a significant rise in plasma STH in both gentled and nongentled rats and a corresponding decrease in plasma corticosterone. Ether, hypertonic glucose, 2-deoxyglucose, insulin and EP caused a marked suppression of plasma STH and an increase in plasma corticosterone; these changes were partly or totally blocked by pentobarbital anesthesia.

Brown, G. M., Schalch, D. S., Reichlin, S.: "Hypothalamic mediation of growth hormone and adrenal stress response in the squirrel monkey." *Endocrinology* **89**: 694-703 (1971). H45,128/71

In squirrel monkeys the stress of emotional excitement (chair restraint, capture) increased plasma STH and corticoid levels but the two changes did not run parallel. The STH response to capture and ether was blocked by small lesions in either the anterior or posterior ME, while adrenal responses to capture and chair restraint were blocked by lesions in the posterior ME. STH responses to ether were enhanced by midline optic chiasm lesions. However, great individual variations interfered with the precise evaluation of these data.

Coppen, A., Brooksbank, B. W. L., Noguera, R., Wilson, D. A.: "Cortisol in the cerebrospinal fluid of patients suffering from affective disorders." *J. Neurol. Neurosurg. Psychiatry* **34**: 432-435 (1971).

G90,735/71

The cortisol concentrations in the CSF of patients with depression or mania showed no significant differences.

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971).

H37,353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound, aversive conditioning) increase plasma STH and cortisol levels, but the two responses are not parallel and presumably are regulated by diverse mechanisms. In the case of chair restraint, STH values fall to resting levels while cortisol continues to rise.

Lantos, C. P., Dahl, V., Basso, N., Cordero-Funes, J. R., Wassermann, G. F.: "A correlative study between adrenal function and the duration and intensity of an experimentally produced disease of adaptation." *J. Steroid Biochem.* **2**: 335-347 (1971).

G88,441/71

In rats, stress produced by repeated intramuscular injections of formaldehyde caused a particularly pronounced increase in the secretion of aldosterone, and to a lesser extent of corticosterone, into the adrenal vein blood. 18-OH-DOC discharge was less markedly raised, and was not as clearly correlated with the intensity and duration of stress as were the other two corticoids. Plasma renin concentrations diminished during stress. The authors believe that "the present results exclude the possibility that the increased aldosterone secretion was secondary to an augmented plasma angiotensin concentration."

Courtney, G. A., Marotta, S. F.: "Adrenocortical steroids during acute exposure to environmental stresses: I. Disappearance of infused cortisol." *Aerosp. Med.* **43**: 46-51 (1972).

J20,019/72

Courtney, G. A., Marotta, S. F.: "II. Uptake and release of infused cortisol by the hind limb of dogs." *Aerosp. Med.* **43**: 52-55 (1972).

J20,018/72

In dogs, the disappearance rate of infused cortisol was not very consistently affected by a variety of stressors.

Juráni, M., Mikulaj, L., Murgaš, K.: "Phylogenetic aspects of adrenocortical activity during the process of adaptation." *Adv. Exp. Med. Biol.* **33**: 619-629 (1972). J23,809/72

Bailey, R. E., Bartos, D., Bartos, F., Castro, A., Dobson, R. L., Grettie, D. P., Kramer, R., Macfarlane, D., Sato, K.: "Activation of aldosterone and renin secretion by thermal stress." *Experientia* **28**: 159-160 (1972). H54,154/72

Devlin, J. G., Varma, M. P. S., Kuti, J., O'Boyle, A.: "Studies on growth hormone release and cortisol with intravenous glucose loading." *Ir. J. Med. Sci.* **141**: 69-78 (1972). J19,599/72

Data on patients under extreme stress following myocardial infarction or major surgical interventions. "1. Growth hormone release is not readily suppressible by glucose in the stress situation studied. 2. Circulating catecholamines are probably not primarily involved in releasing excess growth hormone, as insulin release is more frequently elevated at the same time. 3. The paradoxical rise in glucose which can occur in extreme stress, appears to be a reversion to a primitive pattern of growth hormone secretion which is observed in the newborn infant. 4. The effect of glucose in adequately suppressing A.C.T.H. while producing statistically insignificant suppression of growth hormone releases, suggests either that the A.C.T.H. secreting cell is more sensitive to the direct effect of glucose, or that extra-pituitary factors, either neuronal or hormonal, may be of more significance in controlling growth hormone release."

Christison, G. I., Johnson, H. D.: "Cortisol turnover in heat-stressed cows." *J. Anim. Sci.* **35**: 1005-1010 (1972). J19,902/72

Stoeckel, H., Korpassy, A.: "Das Verhalten der Aldosteronexkretion und Hydrokortisonsekretion bei prolongiertem Stress und Langzeitbeatmung" (Investigations of hydrocortisone secretion and aldosterone excretion in patients with prolonged stress and long-term artificial respiration). *Z. Prakt. Anaesth.* **7**: 28-37 (1972). H65,375/72

In all of 11 intensive care patients with various diseases, aldosterone and cortisol secretion was increased for prolonged periods.

Leach, C. S., Alexander, W. C., Johnson, P. C.: "Adrenal and pituitary response of the

Apollo 15 crew members." *J. Clin. Endocrinol. Metab.* **35**: 642-645 (1972).

H61,627/72

"Inflight studies during the 14-day Gemini 7 mission showed increased urinary aldosterone excretion." Inflight specimens were not collected during the Apollo 15 mission, but when pre- and postflight levels were compared, postflight elevated excretion of urinary aldosterone was again manifest. "Increased secretion of this hormone could be one of man's adaptations to the weightless environment."

Rahe, R. H., Rubin, R. T., Gunderson, E. K. E.: "Measures of subjects' motivation and affect correlated with their serum uric acid, cholesterol, and cortisol." *Arch. Gen. Psychiatry* **26**: 357-359 (1972).

G90,674/72

Among trainees of a U.S. Navy Underwater Demolition Team, "predominantly positive correlations were seen between the subjects' serum uric acid levels and their estimates of their own motivation. Their serum cholesterol concentrations demonstrated consistently negative correlations with their motivational and pleasant affect scores. Highest correlations were positive ones found between the subjects' serum cholesterol levels and their unpleasant affect scores. Serum cortisol correlations with the three psychological criteria demonstrated wide variability around a zero correlation baseline."

Korpassy, A., Stoeckel, H., Vecsei, P.: "Investigations of hydrocortisone secretion and aldosterone excretion in patients with severe prolonged stress." *Acta Anaesthesiol. Scand.* **16**: 161-168 (1972). G97,967/72

Among patients in an intensive care unit for various reasons, as well as in normal post-operative patients, "excessive hyperaldosteronism and hypercortisolism were found in all of the cases, although the relationships between these hormones were variable."

Engquist, A., Winther, O.: "Variations of plasma cortisol and blood fibrinolytic activity during anaesthetic and surgical stress." *Br. J. Anaesth.* **44**: 1291-1297 (1972). J672/72

In man, during thirty to ninety-three minutes of surgical stress, "enhancement of fibrinolysis was significantly correlated with increase of plasma cortisol levels."

Hartley, L. H., Mason, J. W., Hogan, R. P., Jones, L. G., Kotchen, T. A., Mougey,

E. H., Wherry, F. E., Pennington, L. L., Ricketts, P. T.: "Multiple hormonal responses to graded exercise in relation to physical training." *J. Appl. Physiol.* **33**: 602-606 (1972). H79,757/72

In man the stress of heavy bicycle exercise increased plasma STH, cortisol and EP values but decreased insulin concentration.

Wise, L., Margraf, H. W., Ballinger, W. F.: "Adrenal cortical function in severe burns." *Arch. Surg.* **105**: 213-220 (1972).

G92,241/72

"Severely burned patients have prolonged high levels of free plasma cortisol and a decrease in plasma corticosteroid binding globulin... The sustained increase of 17-ketogenic steroids, as opposed to the rapid decrease of Porter-Silber chromogens, suggests that corticosteroids other than cortisol are secreted in larger than normal quantities, in response to the prolonged stress of severe burns" (22 refs.).

Brooksbank, B. W. L., Brammall, M. A., Cunningham, A. E., Shaw, D. M., Camps, F. E.: "Estimation of corticosteroids in human cerebral cortex after death by suicide, accident, or disease." *Psychol. Med.* **2**: 56-65 (1972). G97,911/72

The cortisol content of the frontal cerebral cortex of healthy individuals who had committed suicide was as low or lower than that of control patients who died suddenly without antecedent illness. "It is concluded therefore that neither the presumed severe emotional stress preceding suicide nor depressive illness itself is associated with high levels of cortisol in the cerebral cortex." On the other hand, in patients who died from stressful somatic diseases, brain cortisol was raised proportionately to the duration and severity of their physical illness.

Roussel, A., Daniel, J. Y., Assenmacher, I.: "Les glucocorticostéroïdes circulants du Lapin, et leurs fluctuations nyctémérales" (Circulating glucocorticoids and circadian variations in rabbits). *C.R. Acad. Sci. (Paris)* **277**: 341-344 (1973). J6,395/73

In rabbits, both plasma corticosterone and cortisol undergo circadian variations, with a peak during the day and a drop at the end of the night. However, the two corticoids do not show complete parallelism.

Kraus, M., Erdösová, R.: "Effects of chronic environmental stimulation on the activity of the rat adrenal cortex." In: Németh,

Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 129-141. Bratislava: Slovak Academy of Sciences, 1973. E10,463/73

In rats repeatedly submitted to the stress of nervous stimuli (for example, electroshock), corticosterone formation gradually decreases, whereas aldosterone and 18-OH-DOC become more conspicuous (30 refs.).

Hogan, R. P., Kotchen, T. A., Boyd, A. E., Hartley, L. H.: "Effect of altitude on renin-aldosterone system and metabolism of water and electrolytes." *J. Appl. Physiol.* **35**: 385-390 (1973). J5,657/73

In healthy young males, exposure to a simulated altitude of 12,000 ft. decreased plasma renin activity and urinary aldosterone excretion in proportion to the symptoms of acute mountain sickness that were manifested. It remains to be proven whether these changes are due to stress or to the specific effects of anoxia (45 refs.).

Turton, M. B., Deegan, T.: "Central and peripheral levels of plasma catecholamines, cortisol, insulin and non-esterified fatty acids." *Clin. Chim. Acta* **48**: 347-352 (1973). J8,031/73

In patients undergoing cardiac catheterization, elevations of EP, NEP, FFA and cortisol, and decreased levels of insulin are ascribed to stress. However, certain differences are noted in the concentration of these substances in various vascular territories.

Smith, G. P.: "Adrenal hormones and emotional behavior." *Prog. Physiol. Psychol.* **5**: 299-351 (1973). J11,271/73

Review mainly concerned with the role of catecholamines and corticoids in affecting or being produced by psychogenic stress (about 120 refs.).

Spat, A., Józán, S.: "Displacement analysis of aldosterone and corticosterone in the rat adrenal venous blood." *J. Steroid Biochem.* **4**: 509-518 (1973). J9,302/73

Simultaneous determination of aldosterone and corticosterone in the adrenal venous blood of rats is possible by means of a new technique. Even the mild stress of changing the environment caused consistent increases in corticosterone, but rises in aldosterone were only irregularly observed even after severe surgical stress.

Kraus, M., Erdösová, R.: "Effect of chronic stress on the production ofaldo-

sterone, 18-hydroxydeoxycorticosterone and corticosterone in rat adrenal glands." *Česk. Fysiol.* **22**: 469 (1973) (Czech).

J22,896/73

Kudoh, S., Funyu, T., Shiraiwa, Y., Tamura, M., Terayama, Y., Nigawara, K.: "Metabolism of adrenocortical hormone in surgical stress." *Tohoku J. Exp. Med.* **110**: 139-148 (1973). H75,877/73

Marple, D. N., Cassens, R. G.: "Increased metabolic clearance of cortisol by stress-susceptible swine." *J. Anim. Sci.* **36**: 1139-1142 (1973). J19,910/73

Rahe, R. H., Rubin, R. T., Arthur, R. J.: "The three investigators study. Serum uric acid, cholesterol, and cortisol variability during stresses of everyday life." *Psychosom. Med.* **36**: 258-268 (1974). J21,223/74

The authors studied their own responses to various life events. "Marked elevations in serum cholesterol were seen in one investigator throughout an unpleasant residential move; repeated peaks in serum cortisol were seen in one investigator during times of anguish and anger over personal disappointments and work changes. Two of the three men showed uric acid elevations into the 'gout range' prior to eagerly taking on a physical change. Occasionally, serum uric acid and cortisol values reached magnitudes previously reported as characteristic of men entering underwater demolition training and jumping into the ocean from hovering helicopters."

Ortiz, G. A., Argüelles, A. E., Crespin, H. A., Sposari, G., Villafaña, C. T.: "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium." *Horm. Res.* **5**: 57-64 (1974).

H81,167/74

In aircraft factory workers exposed to turbine noise for three hours, there was generally a marked elevation of catecholamine excretion, blood cholesterol levels, FFA values, blood pressure and pulse frequency. Unexpectedly, the plasma corticoid concentrations were slightly subnormal, but this may have been due to circadian variations.

Follenius, M., Brandenberger, G.: "Influence de l'exercice musculaire sur l'évolution de la cortisolémie et de la glycémie chez l'homme" (Effect of muscular exercise on diurnal variations of plasma cortisol and

glucose in normal men). *Eur. J. Appl. Physiol.* **33**: 23-33 (1974). J16,058/74

In man, exercise on a bicycle ergometer raises plasma cortisol within ten minutes. Blood glucose decreases at first but is elevated to the initial level twenty minutes after cessation of work.

Fazekas, A. T. A.: "Konzentration und Verteilung von Cortisol in peripheren Geweben und Nebennieren unter physiologischen und pathophysiologischen Bedingungen" (Concentration and distribution of cortisol in peripheral tissues and adrenals under physiologic and pathophysiologic conditions), p. 346. Thesis, University of Ulm, 1974.

E10,669/74

Monograph on the cortisol content of the adrenals and various other tissues of guinea pigs as influenced by x-irradiation, pregnancy, age, corticoids, ACTH and so on. The distribution of radioactive cortisol in tissues plays a significant part in determining the blood level and excretion rate of the hormone during stress and after ACTH administration (394 refs.)

Fazekas, I. G., Fazekas, A. T. A.: *Corticosteroide in Organen und Geweben* (Corticosteroids in organs and tissues), p. 413. Erlangen: VLE Verlags, 1974.

E10,668/74

Monograph on the distribution of twelve corticoids as determined by paper chromatography in the organs of rats, guinea pigs, dogs, cats and rabbits, showing great differences in their concentrations in the brain, heart, lungs, spleen, liver, kidney, muscles and adrenals. Special attention is given to the effect of various stressors and hormones on the metabolism and distribution of corticoids (numerous refs.).

Carroll, B. J., Heath, B., Jarrett, D. B.: "Corticosteroids in brain tissue." *Endocrinology* (In press). J20,878/

"A clear circadian variation of brain corticosteroid values was found in mice, together with a rapid elevation of the tissue levels in response to stress. Reduction of both plasma and tissue concentrations was observed after adrenalectomy and in response to dexamethasone treatment of mice. Between 24 and 48 hours *post mortem* mouse brain corticosteroid values decreased greatly." Brain areas not concerned with adrenocortical regulation contain particularly large amounts of corticoids.

Various Steroids

Urinary 17-KS may represent the metabolites of testoids or corticoids. Since it is often difficult to ascertain from the descriptions of the techniques used how the results should be interpreted, observations on the excretion of all these steroid metabolites will be presented here together. In general, it may be said that various stressors raise the excretion of corticoid, and decrease the elimination of testoid metabolites in consonance with the findings that adrenal function is increased while testicular activity is diminished during stress.

In man, 17-KS excretion exhibits circadian variations similar to those of corticoid elimination. In normal individuals, 17-KS excretion usually rises during the first three days after traumatic injury, but subsequently falls until convalescence. The rise is not observed in debilitated patients, probably because "due to a previous alarm, they are already in the stage of resistance or even approaching the stage of exhaustion." It was concluded that these findings support the concept that "alterations in adrenal cortical function are an integral part of the adaptation syndrome of Selye and a link in our understanding of the part this syndrome plays in clinical medicine." In these, as in many other studies, 17-KS excretion has obviously been considered to be characteristic of corticoid production, but this is not always justified. To properly evaluate alterations in testosterone secretion, it is best to measure blood or urinary testosterone itself, or its glucuronide. For example, under the influence of psychogenic stress, plasma testosterone is usually decreased.

Colonized squirrel monkeys showed elevated 17-OHCS but unchanged 17-KS and catecholamine excretion. The dominant animals had the highest 17-OHCS and the lowest catecholamine levels, whereas subordinate monkeys showed lower 17-OHCS and elevated catecholamine concentrations. The 17-KS level did not always parallel that of 17-OHCS. It is concluded that perhaps high corticoid production is necessary for the maintenance of dominance, but these results on primates differ from most studies on rodents in which other methods of dominance determination were used.

Various Steroids

(See also our earlier stress monographs, p. xiii)

Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., Reifenstein, E. C.: "Colorimetric assay of 17-ketosteroids in urine. A survey of the use of this test in endocrine investigation, diagnosis, and therapy." *J. Clin. Endocrinol.* 1: 234-256 (1941).

A36,086/41

Depending upon the technique used, urinary 17-KS may represent androgen or corticoid metabolites. Various stressors lower the production of the former while raising that of the latter.

Forbes, A.: *The 17-Ketosteroid Excretion in Stress. Preliminary Report.* The Josiah Macy, Jr. Foundation Report. New York, 1942.

B27,227/42

Among four thousand patients with the most diverse types of stress-producing diseases, urinary 17-KS output was first enhanced and subsequently diminished.

Pincus, G.: "Studies of the role of the adrenal cortex in the stress of human subjects." *Rec. Prog. Horm. Res.* 1: 123-145 (1947). 98,426/47

Excellent review on the biochemical changes characteristic of the G.A.S. in man, with special reference to 17-KS excretion and blood count under the influence of circadian variations, the stresses of daily life, operating a Hoagland-Werthessen pursuit meter, flying and exposure to heat. The response of schizophrenics is abnormal in many respects, and the question is raised whether adrenal malfunction may play a pathogenic role in mental disease (20 refs.).

Forbes, A. P., Donaldson, E. C., Reifenstein, E. C. Jr., Albright, F.: "The effect of trauma and disease on the urinary 17-ketosteroid excretion in man." *J. Clin. Endocrinol.* **7**: 264-288 (1947). 98,825/47

In normal individuals, 17-KS excretion usually rises for about one to three days following injury and almost always falls later until convalescence is achieved. "In those debilitated patients where an alarm is not followed by a rise in 17-ketosteroids it is probable that, due to a previous alarm, they are already in the stage of resistance or even approaching the stage of exhaustion.... In chronically ill or debilitated individuals on the other hand, the initial level is subnormal and the response to injury usually small or absent. It is believed that these findings are further evidence that alterations in adrenal cortical function are an integral part of the adaptation syndrome of Selye and a link in our understanding of the part this syndrome plays in clinical medicine."

Pincus, G.: "Adrenal cortex function in stress." *Ann. N.Y. Acad. Sci.* **50**: 635-645 (1949). B37,780/49

General review of changes in adrenocortical function during stress and psychiatric illness. Special emphasis is placed upon blood sugar, blood lymphocytes, corticoids and 17-KS.

Zimmermann, W.: "Die Ausscheidung der 17-Ketosteroide im Harn als Methode zur Beurteilung der Nebennierenrindenaktivität" (Urinary 17-ketosteroid excretion as a method for the appraisal of adrenal cortex activity). *Klin. Wochenschr.* **29**: 371 (1951).

J6,106/51

Review on the value of urinary 17-KS determinations in the appraisal of clinical stress situations.

Thorn, G. W., Jenkins, D., Laidlaw, J. C.: "The adrenal response to stress in man." *Rec. Prog. Horm. Res.* **8**: 171-215 (1953).

B73,567/53

Extensive review on clinical indices of adrenal responses to stress in man and the role of the G.A.S. in the pathogenesis of diseases of adaptation. Special emphasis is placed upon reactivity to infusions of ACTH, corticoids and EP, as well as upon the diagnostic value of blood eosinophils and 17-KS excretion, as indicators of adrenocortical participation in stress responses (47 refs.).

Kitay, J. I.: "Pituitary-adrenal function

in the rat after gonadectomy and gonadal hormone replacement." *Endocrinology* **73**: 253-260 (1963). E23,024/63

The pituitary-adrenal function during stress is partly dependent upon gonadal hormones, as shown by experiments on gonadectomized rats or those treated with male and/or female hormones. "Testosterone depressed ACTH secretion and steroid clearance but increased adrenal responsiveness to ACTH, whereas estradiol exerted a consistently stimulatory effect."

Mason, J. W., Taylor, E. D., Brady, J. V., Tolliver, G. A.: "Urinary estrone, estradiol, and estriol responses to 72-hr. avoidance sessions in the monkey." *Psychosom. Med.* **30**: 696-709 (1968). H6,458/68

"Urinary estrone, estradiol and estriol all show a similar biphasic response to 72-hr. conditioned avoidance sessions in the monkey, characterized by a decline in levels during avoidance, usually followed by a rebound elevation in the recovery period" (40 refs.).

Mason, J. W., Tolson, W. W., Robinson, J. A., Brady, J. V., Tolliver, G. A., Johnson, T. A.: "Urinary androsterone, etiocholanolone, and dehydroepiandrosterone responses to 72-hr. avoidance sessions in the monkey." *Psychosom. Med.* **30**: 710-720 (1968).

H6,459/68

"Urinary androsterone, etiocholanolone, and dehydroepiandrosterone levels show substantial responses in association with 72-hr. avoidance sessions." In most cases, there is a biphasic response characterized by a decline during avoidance, followed by a rebound elevation during recovery.

Mason, J. W., Kenion, C. C., Collins, D. R., Mougey, E. H., Jones, J. A., Driver, G. C., Brady, J. V., Beer, B.: "Urinary testosterone response to 72-hr. avoidance sessions in the monkey." *Psychosom. Med.* **30**: 721-732 (1968). H6,460/68

In association with seventy-two hour avoidance sessions there is an initial decrease of urinary testosterone during avoidance followed by a rebound elevation during the recovery period (25 refs.).

Rose, R. M.: "Androgen responses to stress. I. Psychoendocrine relationships and assessment of androgen activity." *Psychosom. Med.* **31**: 405-417 (1969). G70,682/69

17-KS have often been used as an indication of androgen secretion during stress. However, this test is unreliable because

glucocorticoids may also be metabolized to 17-KS. "To properly evaluate alterations in testosterone secretion, which is the most potent of androgens, it is best to measure blood or urinary production rates. It is also possible to measure the excretion of testosterone glucuronide to evaluate the possible inhibition of testosterone secretion during exposure to potential stress."

Matsumoto, K., Takeyasu, K., Mizutani, S., Hamanaka, Y., Uozumi, T.: "Plasma testosterone levels following surgical stress in male patients." *Acta Endocrinol.* (Kbh.) **65**: 11-17 (1970). H30,322/70

In man, plasma testosterone decreased after surgical interventions but returned to normal by the sixth postoperative day.

Wise, L., Margraf, H., Ballinger, W. F.: "The effect of surgical trauma on the excretion and conjugation pattern of 17-ketosteroids." *Surgery* **71**: 625-630 (1972). G89,558/72

Aono, T., Kurachi, K., Mizutani, S., Hamanaka, Y., Uozumi, T.: "Influence of major surgical stress on plasma levels of testosterone, luteinizing hormone and follicle-stimulating hormone in male patients." *J. Clin. Endocrinol. Metab.* **35**: 535-542 (1972). H59,966/72

Leshner, A. I., Candland, D. K.: "Endocrine effects of grouping and dominance rank in squirrel monkeys." *Physiol. Behav.* **8**: 441-445 (1972). G90,599/72

17-OHCS, 17-KS and total catecholamine excretions were used as indices of social stress in colonized and isolated squirrel monkeys. "Compared to the isolated animals, the colonized monkeys showed elevated 17-OHCS but unchanged catecholamine and 17-KS levels. In the colonized group the dominant animals had the highest 17-OHCS levels and the lowest catecholamine levels, while the subordinate animals showed lower 17-OHCS levels and elevated catecholamine levels. 17-KS levels were related to dominance rank by a J-shaped function." Presumably, high adrenocortical output is necessary for the maintenance of dominance. These results on primates differ from most studies on rodents which use other methods to determine dominance.

Kreuz, L. E., Rose, R. M., Jennings, J. R.: "Suppression of plasma testosterone levels

and psychological stress." *Arch. Gen. Psychiatry* **26**: 479-482 (1972).

G89,651/72

Among young officer candidates, plasma testosterone was decreased during the "stressful part of the course."

Carstensen, H., Amér, I., Wide, L., Amér, B.: "Plasma testosterone, LH and FSH during the first 24 hours after surgical operations." *J. Steroid Biochem.* **4**: 605-611 (1973). J10,319/73

In patients, plasma LH and testosterone decreased four to five hours after surgery. LH subsequently returned to normal, whereas testosterone remained low over the twenty-four-hour observation period. No change in plasma FSH was noted.

Daly, J. R., Evans, J. I.: "Daily rhythms of steroid and associated pituitary hormones in man and their relationship to sleep." *Adv. Steroid Biochem. Pharmacol.* **4**: 61-110 (1974). J15,152/74

Detailed review on the function of the hypothalamo-pituitary-adrenal axis in man during sleep, with a description of the methodology for EEG measurement of sleep and a periodic obtention of blood specimens by means of an intravenous catheter throughout the night. The plasma corticoids drop gradually from a zenith at 08:00 to a nadir at midnight. The circadian rhythm of plasma testosterone has been less carefully studied but appears to run parallel to that of cortisol; however, unlike the latter, it cannot be inhibited by dexamethasone. The circadian variations of FSH and LH likewise receive comparatively little attention, but sleep-related rises in LH secretion are regularly observed during adolescence. There are two phases of cortisol elimination, "basal" and "impulsive"; only the latter shows an early morning peak sensitive to corticoid inhibition (about 220 refs.).

Howland, B. E., Beaton, D. B., Jack, M. I.: "Changes in serum levels of gonadotropins and testosterone in the male rat in response to fasting, surgery and ether." *Experientia* **30**: 1223-1225 (1974). H98,258/74

Rose, R. M., Bernstein, I. S., Gordon, T. P.: "Consequences of social conflict on plasma testosterone levels in rhesus monkeys." *Psychosom. Med.* **37**: 50-61 (1975). J23,314/75

ACTH

In comparison with the vast literature on the corticoid content of blood and urine during stress, there is relatively little on plasma ACTH. Few investigators have made accurate ACTH determinations in the plasma because the necessary technology is somewhat complicated. However, available data merely confirm what could be expected, namely, that whenever there is evidence of increased corticoid secretion, the ACTH content of the plasma is also high.

Even the first observations in rats have shown that the response of the pituitary is extremely rapid. As soon as two minutes after application of stressors, there is a definite rise in plasma ACTH. This is particularly pronounced after adrenalectomy, which in itself suffices to cause an ACTH discharge by eliminating the corticoid feedback mechanism.

Various stressors (sound, histamine, cold, pain) differ in the intensity and speed of the ACTH discharge that they provoke in rats, but essentially their effects are quite comparable. Ether first augments, then inhibits ACTH release, whereas pentobarbital exerts only an inhibitory effect. The suppression by anesthetics and sedatives has been ascribed to a depression of the brain stem reticular system activity.

In patients exposed to various stressors, especially surgical trauma, radioimmuno-logic assays revealed an almost tenfold increase in plasma ACTH with relatively brief peaks, which can easily be missed in the event of single determinations.

In man, the ACTH (radioimmunoassay) concentration of the plasma is highest in the evening and lowest in the morning. The reverse is true in the rat, presumably because it is a nocturnal animal, and thus its activity cycle is opposite to that of man.

Normally, the ACTH content of the CSF parallels that of the plasma, but following the stress of pneumoencephalography, the plasma ACTH content rises, whereas that of the CSF remains normal, suggesting that the transfer from plasma to CSF is slow.

ACTH

(See also our earlier stress monographs, p. xiii)

Sydnor, K. L., Sayers, G.: "Blood and pituitary ACTH in intact and adrenalectomized rats after stress." *Endocrinology* **55**: 621-636 (1954). B99,016/54

Two minutes after application of stressors in rats, there is a rapid increase in the ACTH content of the blood but not in that of the pituitary. Adrenalectomy enhances the increase in ACTH caused by stressors.

Royce, P. C., Sayers, G.: "Blood ACTH: effects of ether, pentobarbital, epinephrine and pain." *Endocrinology* **63**: 794-800 (1958). C61,941/58

In rats, painful stimuli markedly elevate blood ACTH within a few minutes. "Ether first excites, then inhibits ACTH release. Pentobarbital exhibits only a depressant action. The excitatory action of ether is blocked by decerebration and by destruction

of the median eminence area of the hypothalamus. The excitatory action of epinephrine is manifest in the decerebrate but not in the median eminence lesioned rat. Since ether and pentobarbital depress the brain stem reticular system, it is reasonable to speculate that the action of these two agents in inhibiting ACTH release involves this multi-synaptic conduction system."

Rochefort, G. J., Rosenberger, J., Saffran, M.: "Depletion of pituitary corticotrophin by various stresses and by neurohypophysial preparations." *J. Physiol.* **146**: 105-116 (1959). C67,709/59

In rats, various stressors (sound, histamine, cold) differ in the intensity and speed with which they deplete the anterior or posterior pituitary of its ACTH content; hence the differentiation between "neurogenic" and "systemic" stressors appears to be justified. CRF causes a prompt and sustained fall in the ACTH content of the anterior pituitary

with only a momentary dip at sixty minutes in the posterior lobe. Commercial and synthetic vasopressin preparations are less effective than CRF; hence, the latter is assumed to be the physiologic releasing substance. Pretreatment with cortisol decreases but does not abolish the sensitivity of the anterior lobe to CRF.

Holub, D. A., Kitay, J. I., Jailer, J. W.: "Alteration of pituitary ACTH secretion in rats after injection and handling." *Endocrinology* **65**: 968-971 (1959).

C78,363/59

Timmer, R. F.: "Bioassay of anterior pituitary hormones of the rat after severe stress." *Tex. Rep. Biol. Med.* **18**: 309-317 (1960).

D41,923/60

Oyama, T., Saito, T., Isomatsu, T., Samejima, N., Uemura, T., Arimura, A.: "Plasma levels of ACTH and cortisol in man during diethyl ether anesthesia and surgery." *Anesthesiology* **29**: 559-564 (1968).

G57,525/68

Yalow, R. S., Varsano-Aharon, N., Echendemia, E., Berson, S. A.: "HGH and ACTH secretory responses to stress." *Horm. Metab. Dis.* **1**: 3-8 (1969).

H12,001/69

In man, electroshock therapy was always followed by an abrupt rise in plasma ACTH, but without significant alterations in STH release. Histalog, an analogue of histamine, caused an elevation of plasma STH twenty to thirty minutes after the increase in plasma ACTH. "Dissociation of ACTH and growth responses to these stimuli as well as to surgery and vasopressin suggests that the two hormones are not discharged through a common pathway responding in a nondiscriminatory fashion to all noxious stimuli. The secretory response of growth hormone to a variety of stimuli characterized by carbohydrate deficit, established in previous studies, seems to be independent of pathways responding generally to 'stress.'"

Matsuyama, H., Ruhmann-Wennhold, A., Nelson, D. H.: "Radioimmunoassay of plasma ACTH in intact rats." *Endocrinology* **88**: 692-695 (1971).

H36,540/71

In rats, which are most active at night, the ACTH (radioimmunoassay) content of the plasma was higher between 18:00 and 03:00 than between 08:00 and 12:00. This is the opposite of the circadian pattern in man. Metyrapone increased plasma ACTH after two to eight hours. Five minutes after ex-

posure to stress even more pronounced rises were observed.

Newsome, H. H., Rose, J. C.: "The response of human adrenocorticotrophic hormone and growth hormone to surgical stress." *J. Clin. Endocrinol. Metab.* **33**: 481-487 (1971). H45,875/71

Observations on patients who have undergone various forms of surgery suggest that STH and ACTH plasma levels rise in a parallel fashion and are presumably mediated through a common afferent pathway in the spinal cord.

Matsuyama, H., Ruhmann-Wennhold, A., Johnson, L. R., Nelson, D. H.: "Disappearance rates of exogenous and endogenous ACTH from rat plasma measured by bioassay and radioimmunoassay." *Metabolism* **21**: 30-35 (1972). H50,163/72

Kokka, N., Garcia, J. F., George, R., Elliott, H. W.: "Growth hormone and ACTH secretion: evidence for an inverse relationship in rats." *Endocrinology* **90**: 735-743 (1972).

H52,549/72

In rats, noise, vibration, ether, cold, insulin, pentylenetetrazol, amphetamine and 2-D-deoxyglucose caused a rise in plasma corticosterone with a corresponding fall in STH. Gentling or administration of pentobarbital lowers corticosterone and increases STH in plasma. The results are interpreted as indicating an inverse relationship between ACTH and STH secretion that is in accordance with the "pituitary-shift" theory.

Nelson, D. H., Ruhmann-Wennhold, A.: "The assay of ACTH in plasma." *Mt. Sinai J. Med.* **40**: 315-322 (1973). J3,809/73

Description of a sensitive and accurate radioimmunoassay of ACTH in plasma which revealed an almost tenfold increase in patients exposed to various stressors, particularly surgical trauma. However, the peaks are relatively short and may readily be missed in single determinations. The circadian variations generally show a peak around 06:00.

Kendall, J. W., McGilvra, R., Lamorena, T. L.: "ACTH in cerebrospinal fluid and brain" (abstracted). *Program 55th Ann. Meeting Endocr. Soc.*, p. A-78. Chicago, 1973. H72,960/73

Previous reports have indicated that ACTH is present in the CSF of unstressed men in approximately the same concentration as in plasma. The stress of pneumoencephalog-

rathy causes a pronounced rise of ACTH in plasma but not in CSF, suggesting that transport from plasma into the CSF is slow.

Cook, D. M., Kendall, J. W., Greer, M. A., M. A., Kramer, R. M.: "The effect of acute or chronic ether stress on plasma ACTH concentration in the rat." *Endocrinology* **93**: 1019-1024 (1973). H77,245/73

Yates, F. E., Maran, J. W.: "Stimulation and inhibition of adrenocorticotropin release." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp. 367-404. Washington,

D. C.: American Physiological Society, 1974.
E10,758/74

Urquhart, J.: "Physiological actions of adrenocorticotropic hormone." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp. 133-157. Washington, D.C.: American Physiological Society, 1974.
E10,749/74

Allen, C. F., Allen, J. P., Greer, M.A.: "Absence of nyctohemeral variation in stress-induced ACTH secretion in the rat." *Aviat. Space Environ. Med.* **46**: 296-299 (1975).
J22,153/75

STH (Somatotrophic or Growth Hormone)

Hypoglycemia is a potent stimulus for STH secretion, and hence, stressors (for example, insulin) that cause a fall in blood sugar increase the plasma STH level in various species, including man. This response is inhibited by glucocorticoids.

On the other hand, the plasma STH levels are suppressed by glucose administration and subsequently rise as the blood glucose diminishes even without there being actual hypoglycemia. Stressors (for example, fasting, exercise) likewise inhibit the glucose-induced STH secretion, perhaps because of accelerated sugar utilization.

The response to stress is dependent on numerous conditioning factors. However, under ordinary conditions, a variety of stressors (insulin, fasting, muscular exercise, anesthesia during surgery, electroconvulsive therapy, emotional stress, pyrogens) increase plasma STH in man. At the same time, plasma FFA levels rise, even without any change in plasma insulin. Presumably, STH discharge is at least partly responsible for the mobilization of readily oxidizable FFA to satisfy the increased energy requirements during stress.

In one carefully conducted study, the stress of arterial catheterization caused a rise in the serum immunoreactive STH in man, but infusion of NEP and a cold pressor test failed to duplicate this response. Plasma STH often rises during periods of muscular work, while insulin values remain unchanged or even decrease. The failure of plasma insulin to rise in response to stress-induced hyperglycemia is consistent with the finding that EP infusion impairs insulin discharge. Possibly, certain stressors are diabetogenic, not only because of EP and corticoid release, but also because of an STH discharge combined with EP-induced suppression of insulin secretion.

According to some investigators, in man, the acute stress of electroshock is less active in causing STH secretion than are stressors with long-lasting effects (for example, physical or mental trauma, endotoxins). The selective suppression of STH secretion by dexamethasone does not interfere with STH production during insulin hypoglycemia. This finding further supports the view that the secretion of the two hormones is relatively independent.

Endotoxin usually elevates ACTH and STH levels almost simultaneously in the plasma of man. However, in rats, there is no strict parallelism between ACTH and STH release during stress, perhaps because of different thresholds of stimulation or

different pathways through which the secretion of these hormones can be differentially regulated. In any event, the dissociation between STH and ACTH (or glucocorticoid) secretion has been demonstrated following exposure to a variety of stressors. Thus, heat raises serum STH in man much more readily than it does the glucocorticoid level. Similar observations were made on U.S. marines injured in battle. Here again, a rise in plasma STH proved to be a more constant manifestation of stress than the elevation of plasma cortisol.

Despite certain above-mentioned exceptions, in general the stress-induced STH discharge parallels ACTH and glucocorticoid secretion, and since animal experiments have shown that the latter can be blocked by hypothalamic or infundibular lesions, it is presumably mediated through the CNS. Yet the fact that STH and ACTH secretion can be elicited independently of each other confirms that release of the two hormones is not mediated through the same mechanism. The same is true of LTH whose secretion is likewise often, but not always, parallel to that of STH during stress. For example, in nursing women, plasma LTH may rise considerably without any associated increase in STH production.

In patients undergoing surgery and receiving morphine (in connection with anesthesia), plasma cortisol and STH rises were largely blocked, but adrenocortical responsiveness to exogenous ACTH was maintained.

The STH content of human fetal plasma rises during the stress of delivery and this response may prevent neonatal hypoglycemia.

Serum STH is greatly increased in man following ingestion of L-dopa (a precursor of dopamine) whereas chlorpromazine (an antiadrenergic drug) depresses the STH level.

There is some evidence that STH secretion is stimulated both by dopaminergic and by serotonergic pathways. In any event, in the rat and in man, 5-HT antagonists, such as cyproheptadine, or the pineal hormone melatonin, can inhibit STH release.

Most of the studies on STH secretion during stress have been performed in man and the rat. However, it has also been demonstrated that in pigeons there is a definite circadian cycle of plasma STH which reaches a peak at 06:00 and a low point at 18:00.

The rhesus monkey has been most extensively used for studies on stress-induced STH secretion. In this species, intravenous lysine-vasopressin increased plasma STH, but so did a variety of other stressors, such as pain, hemorrhage, surgical trauma, conditioned avoidance sessions and allegedly, even chlorpromazine. In squirrel monkeys, rises in plasma STH and cortisol were observed after capture, chair restraint, intense sound, and aversive conditioning, but the two responses were not parallel.

Much less attention has been given to the effect of stress upon the STH content of the pituitary. Usually, formaldehyde injections and ringing of a doorbell raised pituitary STH, while cold depleted it. Fasting caused a biphasic reaction according to one group of investigators, whereas others found that starvation for four days progressively depleted the STH content of the rat adenohypophysis. Such a depletion has also been noted after treatment with EP, vasopressin, cold or insulin. Although individual reports differ, depending upon the intensity and the duration of the stress applied, it may be said that in general the pituitary STH content decreases as the plasma level rises, as might be expected in the event of its discharge from the gland at a rate which cannot be easily compensated for by resynthesis.

To summarize the many contradictory reports just surveyed, the bulk of evidence

supports the view that a rise in blood glucose (produced by administration of glucose or catecholamines) is associated with a decrease in STH secretion, whereas hypoglycemia (induced by fasting or insulin) exerts an opposite effect.

Although, in general, stress produces an increased discharge of both STH and ACTH, their rates of release are not necessarily parallel. This fact as well as the identification by electrolytic lesions of separate centers regulating the discharge of ACTH and STH show that their production during stress is not strictly interdependent.

It also appears well established that, as a rule, an increase in plasma STH is associated with a decreased concentration of this hormone within the adenohypophysis. This finding may be expected if we agree that, normally, a discharge of STH from the gland into the blood is not easily compensated for by rapid resynthesis.

Evidently, depending upon experimental conditions (nutritional status, species differences, severity of stress, associated specific effects and intensity of the eliciting agent), stress may activate or inhibit some of the many regulating mechanisms more or less selectively. This explains why the results are not always identical, but in general it may be concluded that a discharge of STH is characteristic of the stress response.

STH

(See also our earlier stress monographs, p. xiii)

Roth, J., Glick, S. M., Yalow, R. S., Berzon, S. A.: "Hypoglycemia: a potent stimulus to secretion of growth hormone." *Science* **140**: 987-988 (1963).

D66,637/63

Frantz, A. G., Rabkin, M. T.: "Human growth hormone. Clinical measurement, response to hypoglycemia and suppression by corticosteroids." *N. Engl. J. Med.* **271**: 1375-1381 (1964). F27,768/64

In man insulin hypoglycemia increases plasma STH (radioimmunoassay). This response is inhibited by glucocorticoids.

Roth, J., Glick, S. M., Yalow, R. S., Berzon, S. A.: "The influence of blood glucose on the plasma concentration of growth hormone." *Diabetes* **13**: 355-361. (1964).

F20,340/64

In man, insulin hypoglycemia increases by glucose and stimulated by hypoglycemia (or even by a rapid fall in blood glucose without hypoglycemia) and by interference with intracellular glucose utilization, for example, by 2-deoxy-D-glucose. Various stressors (fasting, exercise) likewise inhibit STH secretion after oral glucose administration.

Halász, B.: "Neural control of growth hormone secretion." In: Taylor, S., *Proceedings of the Second International Congress of*

Endocrinology, London, 1964, Part 1, pp. 517-521. Amsterdam, New York and London: Excerpta Medica Foundation, Int. Cong. Series No. 83, 1965. F48,877/65

Glick, S. M., Roth, J., Yalow, R. S., Berzon, S. A.: "The regulation of growth hormone secretion." *Rec. Prog. Horm. Res.* **21**: 241-283 (1965). E5,095/65

Immunobioassays show increased plasma STH values in man following treatment with insulin, fasting, muscular exercise, anesthesia in surgery and other stressor agents. On the other hand, glucose depresses STH secretion.

Friedman, R. C., Reichlin, S.: "Growth hormone content of the pituitary gland of starved rats." *Endocrinology* **76**: 787-788 (1965). F35,443/65

The STH content of the adenohypophysis of rats decreases progressively during starvation for twenty-four to ninety-six hours.

Schalch, D. S.: "The effect of physical stress and exercise in the human on growth hormone and insulin secretion." *Clin. Res.* **13**: 334 (1965). F61,179/65

In man, various stressors (muscular exercise, electroconvulsive therapy, major surgery) increased plasma STH (radioimmunoassay) and FFA levels without affecting plasma insulin. It is possible that STH discharge "may be at least in part responsible for the mobilization of the readily oxidizable FFA which takes place during periods of increased energy requirements."

Ketterer, H., Powell, D., Unger, R. H.: "Growth hormone response to surgical stress." *Clin. Res.* **14**: 65 (1966).

F82,744/66

Radioimmunoassays show that the plasma STH level rises in man within one hour of surgery, reaches a peak within two to four hours, and may continue high for days postoperatively.

Greenwood, F. C., Landon, J.: "Growth hormone secretion in response to stress in man." *Nature* **210**: 540-541 (1966).

F65,986/66

In man, anxiety-causing emotional stress or injection of pyrogen (kind not specified) increased plasma STH levels.

Krulich, L., McCann, S. M.: "Influence of stress on the growth hormone (GH) content of the pituitary of the rat." *Proc. Soc. Exp. Biol. Med.* **122**: 612-616 (1966).

F67,299/66

In rats, pituitary STH activity (epiphyseal cartilage test) was initially decreased and then increased after splenectomy. Formalin injections and ringing of a doorbell raised pituitary STH, cold (3°C) depleted it, and fasting caused a biphasic reaction with an initial depletion followed by a return to normal and secondary depletion after about three days. These and other data suggest that STH secretion in the rat "is very labile and influenced by a variety of stresses as well as by alterations in the supply of available carbohydrate."

Meyer, V., Knobil, E., "Stimulation of growth hormone secretion by vasopressin in the rhesus monkey." *Endocrinology* **79**: 1016-1018 (1966).

F73,022/66

In unanesthetized rhesus monkeys restrained in primate chairs, Pitressin and lysine-vasopressin administered intravenously increased plasma STH levels, but "this action may not be a specific one."

Müller, E. E., Arimura, A., Sawano, S., Saito, T., Schally, A. V.: "Growth hormone-releasing activity in the hypothalamus and plasma of rats subjected to stress." *Proc. Soc. Exp. Biol. Med.* **125**: 874-878 (1967).

F87,123/67

In rats, stress produced by formalin did not induce STH depletion of the pituitary or alter hypothalamic STH-RF activity. On the other hand, exposure to cold did cause these effects.

Copinschi, G., Hartog, M., Earll, J. M., Havel, R. J.: "Effect of various blood

sampling procedures on serum levels of immunoreactive human growth hormone." *Metabolism* **16**: 402-409 (1967).

F83,864/67

Arterial catheterization causes a rise of serum immunoreactive STH in man. For unknown reasons, infusion of NEP and a cold-pressor test elicited no similar change, although the literature shows many examples of an increase in man and animals after exposure to various stressors (28 refs.).

Schalch, D. S.: "The influence of physical stress and exercise on growth hormone and insulin secretion in man." *J. Lab. Clin. Med.* **69**: 256-269 (1967).

G44,274/67

In man, plasma STH often rose during periods of physical stress or exercise, while insulin values remained unchanged or were decreased. EP did not reproduce the release of STH. The failure of plasma insulin levels to rise in response to stress-induced hyperglycemia is consistent with the finding that EP infusion impairs insulin discharge. Plasma glucose and FFA levels rose as expected during physical exercise. Presumably, certain stressors are diabetogenic not only because of EP and corticoid release but also because of a discharge of STH on the one hand, and an EP-induced suppression of insulin secretion on the other.

Frohman, L. A., Horton, E. S., Lebovitz, H. E.: "Growth hormone releasing action of a pseudomonas endotoxin (Piromen)." *Metabolism* **16**: 57-67 (1967).

F75,314/67

In man, intravenous *pseudomonas* endotoxin elevates plasma ACTH and STH levels.

Meyer, V., Knobil, E.: "Growth hormone secretion in the unanesthetized rhesus monkey in response to noxious stimuli." *Endocrinology* **80**: 163-171 (1967).

F75,369/67

In rhesus monkeys with indwelling venous catheters, plasma STH values increased suddenly after various stressors such as pain, hemorrhage, histamine, EP, chlorpromazine, and on occasion, pentobarbital (35 refs.).

Müller, E. E., Saito, T., Arimura, A., Schally, A. V.: "Hypoglycemia, stress and growth hormone release: blockade of growth hormone release by drugs acting on the central nervous system." *Endocrinology* **80**: 109-117 (1967).

F75,362/67

The pituitary STH content (tibia test) was diminished by various stressors (EP, vasopressin, cold, insulin). This effect of insulin hypoglycemia was prevented by dexametha-

sone, and it was assumed that the discharge of pituitary STH "observed after insulin administration may reflect a nonspecific stress effect of the hypoglycemic stimulus."

Müller, E. E.: "Ricerche sul controllo nervoso della secrezione di ormone somatotropo" (On the nervous control of somatotropic hormone secretion). *Rass. Fisiopat. Clin. Ter.* **40**: 175-226 (1968).

H6,967/68

Extensive review of the literature on the mechanism of STH secretion. Numerous observations suggest that during stress the hypothalamus discharges the corresponding releasing factor, and that various stressors increase STH through this pathway which is activated by brain catecholamines.

Schalch, D. S., Reichlin, S.: "Stress and growth hormone release." In: Pecile, A. and Müller, E. E., *Growth Hormone*, pp. 211-225. Amsterdam, New York and London: Excerpta Medica Foundation, Int. Congr. Ser. No. 158, 1968. E8,296/68

Proceedings of a symposium on STH in which this contribution is especially devoted to a survey of that hormone's participation in stress. In both man and squirrel monkeys a variety of stressors cause release of STH. A hypothalamic link is involved, as indicated by the fact that hypoglycemic stress and psychogenic stress responses are blocked by lesions in the ventral hypothalamus. Intrahypothalamic infusions of glucose also blocked the STH response to systemic hypoglycemia. Surprisingly, stress appears to inhibit STH secretion in the rat. In apparent conflict with the literature, the authors were unable to confirm by immunoassay the existence of an STH-RF (42 refs.).

Müller, E. E., Pecile, A.: "Studies on the neural control of growth hormone secretion." In: Pecile, A. and Müller, E. E., *Growth Hormone*, pp. 253-266. Amsterdam, New York and London: Excerpta Medica Foundation, Int. Congr. Ser. No. 158, 1968.

E8,299/68

Observations on rats show that many but not all stressors increase the plasma STH (tibia test) content. Although many similarities in the mechanism of control of ACTH and STH are apparent, a different threshold of stimulation and/or different nervous pathways relaying impulses to the CNS might be the cause of this dissociation. A stimulus releasing STH acts via the hypothalamus,

and catecholamines may be considered as mediators of the STH-RF.

Müller, E. E., dal Pra, P., Pecile, A.: "Influence of brain neurohumors injected into the lateral ventricle of the rat on growth hormone release." *Endocrinology* **83**: 893-896 (1968). H3,581/68

In rats, EP, NEP and dopamine injected into the lateral ventricle induced depletion of pituitary STH, whereas 5-HT, acetylcholine, vasopressin and oxytocin did not share this STH-releasing effect. Presumably, adrenergic mediators participate in the neurohumoral control of STH secretion.

Mason, J. W., Wool, M. S., Wherry, F. E., Pennington, L. L., Brady, J. V., Beer, B.: "Plasma growth hormone response to avoidance sessions in the monkey." *Psychosom. Med.* **30**: 760-773 (1968). H6,463/68

In rhesus monkeys, plasma immunoreactive STH levels usually rise during conditioned avoidance sessions. Venipuncture in itself tends to elevate the "baseline" (45 refs.).

Helge, H., Weber, B., Quabbe, H. J.: "Growth-hormone release and venepuncture." *Lancet* January 25, 1969 p. 204.

H7,240/69

After a brief review of the literature on stress-induced increases in plasma STH, the authors report personal observations showing that venipuncture reduces this effect more commonly in children than in adults or newborns. "These observations suggest that, for children more often than for newborns or adults, a rather harmless medical procedure can represent an iatrogenic stress."

Geisen, K., Meder, R.: "Effekt von Wärme auf das Wachstumshormon beim Menschen" (Effect of heat on growth hormone in man). *Z. Kinderheilkd.* **106**: 308-313 (1969). H17,060/69

In four men taking hot baths the plasma STH and to a lesser extent FFA values rose, whereas plasma cortisol levels remained constant. Literature is cited to show that other stressors (pyrogens, physical exercise, heat) likewise raise the plasma STH level.

Yalow, R. S., Varsano-Aharon, N., Echemendia, E., Berson, S. A.: "HGH and ACTH secretory responses to stress." *Horm. Metab. Dis.* **1**: 3-8 (1969). H12,001/69

In man, electroshock therapy was always

followed by an abrupt rise in plasma ACTH, but without significant alterations in STH release. Histalog, an analogue of histamine, caused an elevation of plasma STH twenty to thirty minutes after the increase in plasma ACTH. "Dissociation of ACTH and growth responses to these stimuli as well as to surgery and vasopressin suggests that the two hormones are not discharged through a common pathway responding in a nondiscriminatory fashion to all noxious stimuli. The secretory response of growth hormone to a variety of stimuli characterized by carbohydrate deficit, established in previous studies, seems to be independent of pathways responding generally to 'stress.'"

Takasawa, T.: "Influence of ether anesthesia and surgical stimulation on the levels of blood human growth hormone and insulin concentrations." *Jap. J. Anesthesiol.* **19**: 271-284 (1970) (Japanese). J24,058/70

In patients under ether anesthesia and during the subsequent surgical interventions, the blood STH concentration rose, whereas the blood insulin content showed no significant change.

Meder, R., Geisen, K.: "Untersuchungen zur wärmeinduzierten STH-Sekretion beim Menschen" (Heat-induced STH secretion in man). *Z. Kinderheilkd.* **108**: 297-304 (1970). H30,451/70

In man the heat-induced elevation of serum STH can be partially suppressed by glucose. Serum glucocorticoids increase only after exposure to more severe stress. Hence, a rise of STH is regarded as the most sensitive stress indicator.

Greene, W. A., Conron, G., Schalch, D. S., Schreiner, B. F.: "Psychologic correlates of growth hormone and adrenal secretory responses of patients undergoing cardiac catheterization." *Psychosom. Med.* **32**: 599-614 (1970). G80,365/70

In patients undergoing cardiac catheterization, "behavioral differences in categories of affect, arousal and degree of interpersonal engagement were used to reliably delineate four major types of psychologic reaction designated anxious-engaged, anxious-not engaged, depressed and calm. There were no elevations of cortisol or growth hormone during the procedure in either the calm or the depressed patients. Anxious-not engaged patients showed major elevations of both cortisol and growth hormone. All the anxious-engaged

patients showed initial high and even increasing levels of cortisol but no increases in growth hormone."

Nagy, I., Kurcz, M., Halmy, L., Mosonyi, L., Baranyai, P., Kiss, C.: "Effect of stress, drugs and hypothalamic extract on anterior pituitary somatotropin content in the rat." *Acta Physiol. Acad. Sci. Hung.* **38**: 357-370 (1970). G87,641/70

Contrary to some earlier claims, insulin, cold, hemorrhage, laparotomy, swimming, suckling, vasopressin, oxytocin and hypothalamic extract all failed to affect the STH content of the adenohypophysis in rats.

Carey, L. C., Cloutier, C. T., Lowery, B. D.: "Growth hormone and adrenal cortical response to shock and trauma in the human." *Ann. Surg.* **174**: 451-460 (1971).

G86,425/71

In U.S. Marines injured during battle, plasma STH levels rose markedly and constantly, whereas cortisol concentrations remained normal or were only slightly elevated. Possibly, STH provides an additional energy source in the form of FFA. The literature on STH secretion during various other types of stress is briefly reviewed. In the discussion following this paper, it is mentioned that, apparently, cortisol excretion is minimal in stress associated with severe shock. However, some investigators found very high cortisol levels following fatal traumatic injury (26 refs.).

Werder, K. von, Schwarz, K.: "Regulation der Sekretion von Wachstumshormon beim Menschen" (The regulation of growth hormone secretion in man). *Dtsch. Med. Wochenschr.* **96**: 2012-2018 (1971).

H44,002/71

Review of the literature on factors regulating STH secretion in man. Among the stressors shown to be effective are surgical interventions, physical and mental trauma, endotoxins and many other long-lasting agents. Acute stress caused by electroshock has proven comparatively inactive. Contrary to the results of some investigations, ACTH does not appear to be a stimulator of STH production, since the suppression of ACTH secretion by dexamethasone does not interfere with the release of STH during insulin hypoglycemia. Even the STH secretion elicited by metyrapone is attributed to a direct effect of the drug upon the hypothalamus rather than to increased ACTH secretion. The rise in blood STH produced by ACTH

or vasopressin is considered to be nonspecific (71 refs.).

Favino, A., Scoz, R., Trecate, G.: "Effetti della stimolazione acustica sulla secrezione di ormone somatotropo umano" (Effect of acoustic stimulation on growth hormone secretion in man). *Boll. Soc. Ital. Biol. Sper.* **47**: 704-708 (1971). H89,995/71

In man the intense noise of an industrial plant raised plasma STH levels. [No technical details are given (H.S.).]

Stubbe, P., Wolf, H.: "The effect of stress on growth hormone, glucose and glycerol levels in newborn infants." *Horm. Metab. Res.* **3**: 175-179 (1971). H42,368/71

In full-term newborn infants the stress of heel pricks caused a decrease in blood STH, whereas glucose and glycerol concentrations were increased, presumably as a consequence of catecholamine release. "The failure of the newborn infant to increase growth hormone concentration, as do individuals during later life, is evidence that adaptation of metabolic and hormonal reactions occurs during the postnatal period."

Brown, G. M., Schalch, D. S., Reichlin, S.: "Patterns of growth hormone and cortisol responses to psychological stress in the squirrel monkey." *Endocrinology* **88**: 956-963 (1971). H37,353/71

In squirrel monkeys, various stressors (capture, chair restraint, intense sound, aversive conditioning) increase plasma STH and cortisol levels, but the two responses are not parallel and presumably are regulated by diverse mechanisms. In the case of chair restraint, STH values fall to resting levels while cortisol continues to rise.

Müller, E. E., Miedico, D., Giustina, G., Cocchi, D.: "Ineffectiveness of hypoglycemia, cold exposure and fasting in stimulating GH secretion in the mouse." *Endocrinology* **88**: 345-350 (1971). H35,410/71

In mice, radioimmunoassayable STH did not decrease under the influence of insulin hypoglycemia or cold exposure, whereas fasting caused a slight depletion of pituitary and an increase of plasma STH levels. "A possible explanation of our results is that the mouse is a species in which, due to the very elevated metabolic rate, the growth hormone secretion, already maximal in basal conditions, cannot be further increased by any of the stimuli which are highly active in other animal species."

Werder, K. von, Hane, S., Forsham, P.: "Hemmung der Stress-bedingten Cortisol- und STH-Sekretion durch endogenen und exogenen Hyperkortizismus" (Inhibition of stress-induced cortisol and STH secretion through endogenous and exogenous hypercorticoidism). *Verh. Dtsch. Inn. Med.* **77**: 1040-1043 (1971). H92,639/71

In man, the rise in plasma STH following the stress of surgical operations or insulin hypoglycemia is inhibited by dexamethasone. Apparently, glucocorticoids exert a negative feedback effect upon STH secretion, although this is not as marked as their influence upon ACTH release.

Newsome, H. H., Rose, J. C.: "The response of human adrenocorticotrophic hormone and growth hormone to surgical stress." *J. Clin. Endocrinol. Metab.* **33**: 481-487 (1971). H45,875/71

Observations on patients who have undergone various forms of surgery suggest that STH and ACTH plasma levels rise in a parallel fashion and are presumably mediated through a common afferent pathway in the spinal cord.

Devlin, J. G., Varma, M. P. S., Kuti, J., O'Boyle, A.: "Studies on growth hormone release and cortisol with intravenous glucose loading." *Ir. J. Med. Sci.* **141**: 69-78 (1972). J19,599/72

Data on patients under extreme stress following myocardial infarction or major surgical interventions. 1. Growth hormone release is not readily suppressible by glucose in the stress situation studied. 2. Circulating catecholamines are probably not primarily involved in releasing excess growth hormone, as insulin release is more frequently elevated at the same time. 3. The paradoxical rise in glucose which can occur in extreme stress, appears to be a reversion to a primitive pattern of growth hormone secretion which is observed in the newborn infant. 4. The effect of glucose in adequately suppressing A.C.T.H. while producing statistically insignificant suppression of growth hormone releases, suggests either that the A.C.T.H. secreting cell is more sensitive to the direct effect of glucose, or that extra-pituitary factors, either neuronal or hormonal, may be of more significance in controlling growth hormone release."

Hanssen, K. F., Asfeldt, V. H.: "Human growth hormone secretion during major surgical stress and the influence of pre-treatment

with dexamethasone." *Horm. Metab. Res.* **4**: 57 (1972). H51,815/72

The plasma STH rise which occurs during the first hour after surgical operations in man is not inhibited by dexamethasone, although ACTH secretion is suppressed.

Mitra, R., Johnson, H. D.: "Growth hormone response to acute thermal exposure in cattle." *Proc. Soc. Exp. Biol. Med.* **139**: 1086-1089 (1972). H54,712/72

In cattle, exposure to heat causes a rise in blood STH.

Okada, Y., Matsuoka, T., Kumahara, Y.: "Human growth hormone secretion during exposure to hot air in normal adult male subjects." *J. Clin. Endocrinol. Metab.* **34**: 759-763 (1972). H54,871/72

In four normal obese adult males exposed to hot air (48°C) for one hour after an overnight fast, elevation of body temperature was associated with increased plasma STH and FFA levels. No significant changes in cortisol, total thyroxine-iodine, blood glucose or hematocrit were noted during heat exposure. In two subjects, administration of glucose before heat exposure prevented the rise in plasma STH.

Hartley, L. H., Mason, J. W., Hogan, R. P., Jones, L. G., Kotchen, T. A., Mougey, E. H., Wherry, F. E., Pennington, L. L., Ricketts, P. T.: "Multiple hormonal responses to graded exercise in relation to physical training." *J. Appl. Physiol.* **33**: 602-606 (1972). H79,757/72

In man the stress of heavy bicycle exercise increased plasma STH, cortisol and EP values, but decreased insulin concentration.

Fekete, M., Milner, R. D. G., Soltész, G., Assan, R., Mestyán, J.: "Plasma glucagon, thyrotropin, growth hormone and insulin response to cold exposure in the human newborn." *Acta Paediatr. Scand.* **61**: 435-441 (1972). G92,222/72

In full-term and premature babies, exposure to cold caused no significant change in plasma insulin, glucagon, STH or TTH concentrations.

Kokka, N., Garcia, J. F., George, R., Elliott, H. W.: "Growth hormone and ACTH secretion: evidence for an inverse relationship in rats." *Endocrinology* **90**: 735-743 (1972). H52,549/72

In rats, noise, vibration, ether, cold, insulin, pentylenetetrazol, amphetamine and 2-D-deoxyglucose caused a rise in plasma corti-

costerone with a corresponding fall in STH. Gentling or administration of pentobarbital lowered corticosterone and increased STH in plasma. The results are interpreted as indicating an inverse relationship between ACTH and STH secretion that is in accordance with the "pituitary-shift" theory.

Lundbaek, K., Johansen, K., Ørskov, H., Speich, E.: "Anxiety, growth hormone and glucose tolerance in normal children." *Acta Med. Scand.* **192**: 539-542 (1972). G98,671/72

Emotional stress decreases glucose tolerance in children, perhaps partly because it stimulates STH secretion.

Brown, G. M., Reichlin, S.: "Psychologic and neural regulation of growth hormone secretion." *Psychosom. Med.* **34**: 45-61 (1972). G88,877/72

A number of stressors (trauma, electroshock therapy, pyrogens, hypoglycemia, posterior pituitary extract, and even emotional arousal) have been shown to increase plasma STH levels in man and monkeys. Yet there is also a considerable rise in plasma STH levels during sleep in man. The literature on the pituitary and plasma STH concentrations of rats exposed to various stressors is somewhat contradictory and difficult to interpret. However, in most species, stress causes an STH discharge which parallels glucocorticoid secretion, and which may be interpreted as a manifestation of stress comparable to the discharge of ACTH. Since the response can be blocked by hypothalamic or infundibular lesions, it is presumably mediated through the CNS. However, the mechanisms for STH and corticoid discharge are independent, since a dissociation between the two is frequently found in man and monkeys after exposure to various stimuli (196 refs.).

Frantz, A. G., Kleinberg, D. L., Noel, G. L.: "Studies on prolactin in man." *Rec. Prog. Horm. Res.* **28**: 527-590 (1972). E10,243/72

In man the plasma content of STH and LTH rises after various forms of stress, particularly muscular exercise and major surgical interventions. However, there is no strict parallelism between the blood concentrations of the two hormones following psychogenic stress. For example, in nursing women, plasma LTH rises, usually without any associated increase in STH concentration.

Reier, C. E., George, J. M., Kilman, J. W.: "Cortisol and growth hormone re-

sponse to surgical stress during morphine anesthesia." *Anesth. Analg. (Cleve.)* **52**: 1003-1010 (1973). J8,185/73

After surgery, the usual increase in plasma cortisol and STH was blocked by large doses of morphine used in connection with anesthesia. Adrenocortical responsiveness was not affected, as indicated by the continued efficacy of exogenous ACTH in raising plasma cortisol. The blockade of these hormone secretions during stress did not seem to influence the clinical condition. "Nonetheless, since it is thought that the adrenocortical response is essential for stress survival, the recommendation that morphine in doses larger than 2 mg./kg. be avoided, appears prudent."

McKeown, B. A., John, T. M., George, J. C.: "Circadian rhythm of plasma growth hormone levels in the pigeon." *J. Interdiscipl. Cycle Res.* **4**: 221-227 (1973).

J9,766/73

Radioimmunoassays revealed that in pigeons there is a definite circadian cycle of plasma STH, reaching a peak at 06:00 and a low point at 18:00. This rhythm is correlated with corresponding changes in FFA levels.

Turner, R. C., Oakley, N. W., Beard, R. W.: "Human fetal plasma growth hormone prior to the onset of labour." *Biol. Neonate* **22**: 169-176 (1973). J6,903/73

The STH content of human fetal plasma rises during induction of labor, presumably owing to the stressor effect of delivery. This response may prevent neonatal hypoglycemia.

Collu, R., Jéquier, J. C., Letarte, J., Leboeuf, F., Ducharme, J. R.: "Effect of stress and hypothalamic deafferentation on the secretion of growth hormone in the rat." *Neuroendocrinology* **11**: 183-190 (1973).

H68,127/73

In rats, ether and auditory stressors were equally effective in diminishing plasma STH (radioimmunoassay) in controls and frontally deafferented animals. Ether stress also inhibited STH secretion in completely deafferented animals, whereas auditory stress was ineffective. α -MT pretreatment blocked the effect of ether stress after deafferentation. These and other data "seem to indicate that ether stress is transmitted through a humoral, dopaminergic pathway, while auditory stress follows a nervous pathway." [The many observations indicating increased STH

secretion during stress are not discussed (H.S.).]

Parkhie, M. R., Johnson, H. D.: "Hypothalamic growth hormone releasing factor: release and synthesis after exposure to a high ambient temperature." *Proc. Soc. Exp. Biol. Med.* **142**: 311-315 (1973). H64,888/73

Studies on the release and synthesis of hypothalamic STH-RF in rats exposed to heat. In general, resynthesis keeps pace with the RF discharge (27 refs.).

Massara, F., Camanni, F., Molinatti, G. M.: "Liberazione di ormone somatotropo in seguito a stimolazione alfa-adrenergica nell'uomo" (Somatotropic hormone secretion following α -adrenergic stimulation in man). *Folia Endocrinol. (Roma)* **26**: 476-482 (1973). H83,466/73

Observations in man suggest that stimulation of α -adrenergic receptors excites CNS centers to cause STH secretion.

Shire, J. G. M.: "Growth hormone and premature ageing." *Nature* **245**: 215-216 (1973). H78,587/73

In certain strains of dwarf mice, premature aging is associated with decreased STH production and depressed ^3H -thymidine uptake by several tissues including the thymus. These dwarf mice are also deficient in other hormones, and not all strains show premature aging. Hence, "the altered uptake of thymidine in dwarf mice close to death could be caused by stress rather than by premature ageing."

McCann, S. M., Ajika, K., Fawcett, C. P., Hefco, E., Illner, P., Negro-Vilar, A., Orias, R., Watson, J. T., Krulich, L.: "Hypothalamic control of the adenohypophyseal response to stress by releasing and inhibiting neurohormones." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 67-77. Bratislava: Slovak Academy of Sciences, 1973. E10,458/73

Report based mainly on plasma hormone determinations and observations on rats whose hypothalamus-pituitary system was isolated with the Halász knife. The authors were led to the conclusion that "following the application of a stressful stimulus, afferent impulses are probably generated which pass to the brainstem and thence to the hypothalamus where they influence release of the various releasing and inhibiting hormones which control the AP. We would postulate that the afferent pathways are similar for all

AP hormones and that the differential patterns of release are brought about by specific intrahypothalamic mechanisms. Consistent with this hypothesis is the differential localization of the various releasing and inhibiting factors in the hypothalamus." Mere transfer from the stockroom to the laboratory sufficed to cause a dramatic increase in the serum STH and LH values within less than one hour.

Müller, E. E.: "Nervous control of growth hormone secretion." *Neuroendocrinology* 11: 338-369 (1973). H71,999/73

Review on the neural control of STH secretion in mammals. Electrolytic lesions in discrete hypothalamic areas reduced pituitary and plasma radioimmunoassayable STH and impaired somatic growth. Such lesions caused diminished STH discharge in response to insulin but not after electric stimulation of brain areas. Hypothalamic STH secretion seems to be governed by an STH-releasing neurohormone which has been purified, isolated and synthesized, and represents a straight-chain acidic decapeptide. There is also proof of an inhibitory hypothalamic factor whose function in STH secretion is not yet clear. The STH-RF decreases in the hypothalamus and increases in the plasma when STH release is enhanced. Catecholamines play a significant role in the neurohormonal control of STH secretion. Serum STH is greatly increased in man following ingestion of L-dopa (a precursor of dopamine), whereas chlorpromazine, an antiadrenergic drug, depresses the STH level. During deep sleep, human STH secretion apparently is independent of alterations in brain catecholamine turnover, but like other anterior pituitary hormones, STH is subject to a feedback on itself which decreases its own secretion (about 150 refs.).

Kato, Y., Dupré, J., Beck, J. C.: "Plasma growth hormone in the anesthetized rat: effects of dibutyryl cyclic AMP, prostaglandin E₁, adrenergic agents, vasopressin, chlorpromazine, amphetamine and L-dopa." *Endocrinology* 93: 135-146 (1973). H72,167/73

Dibutyryl cAMP and a very large number of drugs influencing CNS activity increased plasma STH in the rat. In several instances, this was inhibited by adrenergic blocking agents. Yet the authors maintain that "stressful agents" such as histamine, formalin, laparotomy and insulin failed to

cause a significant increase in plasma STH. [This is difficult to reconcile with the authors' assumption that STH discharge in the rat depends upon adrenergic stimuli, unless the stressors used were not sufficiently severe to induce a catecholamine discharge (H.S.).]

Cleghorn, J. M.: "Endocrine spotlights on brain and behaviour." *Can. Psychiatr. Assoc. J.* 18: 449-451 (1973). J21,579/73

Review of the literature on STH release during stress.

Takahashi, Y.: "Growth hormone secretion during sleep." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 316-325. Tokyo: Igaku Shoin, 1974.

E10,878/74

Kumahara, Y., Okada, Y., Miyai, K., Matsuo, T., Iwatsubo, H.: "Human growth hormone secretion in response to cold and hot air." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 309-315. Tokyo: Igaku Shoin, 1974.

E10,877/74

Reichlin, S.: "Regulation of somatotrophic hormone secretion." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp. 405-447. Washington, D.C.: American Physiological Society, 1974. E10,759/74

Goodman, H. M., Schwartz, J.: "Growth hormone and lipid metabolism." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp. 211-231. Washington, D.C.: American Physiological Society, 1974.

E10,752/74

Brown, G. M., Martin, J. B.: "Corticosterone, prolactin, and growth hormone responses to handling and new environment in the rat." *Psychosom. Med.* 36: 241-247 (1974). J18,329/74

Dunn, J. D., Schindler, W. J., Hutchins, M. D., Scheving, L. E., Turpen, C.: "Daily variation in rat growth hormone concentration and the effect of stress on periodicity." *Neuroendocrinology* 13: 69-78 (1974).

H81,378/74

In rats, stress produced by ether or immobilization caused a marked reduction of STH and abolished its circadian rhythm in plasma.

Singh, A. K., Chansouria, J. P. N., Singh, R. K., Wahi, R. S., Udupa, K. N.: "Hormonal and metabolic alterations following surgical trauma." *5th Asia and Oceania Congr. Endocr.*, pp. 50-51. Chandigarh, India, 1974. H82,068/74

In patients the stress of major surgery caused an increase in plasma STH, cortisol and FFA, with a decrease in plasma insulin.

Natelson, B. H., Smith, G. P., Stokes, P. E., Root, A. W.: "Plasma 17-hydroxycorticosteroids and growth hormone during defense reactions." *Am. J. Physiol.* **226**: 560-568 (1974). H83,654/74

In rhesus monkeys, electric stimulation of the hypothalamus caused a rise in plasma 17-OHCS, especially during the initial excitement. Although increases were obtained after stimulation of various sites scattered throughout the anterior, tuberal and posterior parts of the lateral hypothalamus, plasma STH rose only when posterior sites were stimulated. This pattern of a smaller hypothalamic area for STH than for ACTH release has also been observed in the rat, cat and squirrel monkey and it is probably a general principle of organization.

Lin, T., Tucci, J. R.: "Provocative tests of growth-hormone release. A comparison of results with seven stimuli." *Ann. Intern. Med.* **80**: 464-469 (1974). J12,327/74

In man, insulin, glucagon, L-dopa, and less regularly, ACTH or physical exercise increase plasma STH levels. Metyrapone has no such effect.

Brown, W. A., Krieger, D. T., Woert, M. H. van, Ambani, L. M.: "Dissociation of growth hormone and cortisol release following apomorphine." *J. Clin. Endocrinol. Metab.* **38**: 1127-1130 (1974). H87,291/74

In man, apomorphine-induced STH release is probably not mediated through systemic stress but through a specific effect on dopamine receptor sites in the ME, since it is not associated with cortisol release.

Smythe, G. A., Lazarus, L.: "Suppression of human growth hormone secretion by melatonin and cyproheptadine." *J. Clin. Invest.* **54**: 116-121 (1974). H87,405/74

In the rat as in man, STH secretion, stimulated by serotonergic pathways, can be inhibited by treatment with 5-HT antagonists such as cyproheptadine and the pineal gland hormone, melatonin. [In this respect, these

compounds resemble the actions of somatostatin (H.S.).]

Ogawa, N.: "Growth hormone releasing factor activity in the stalk-median eminence and plasma growth hormone response to the ether-laparotomy stress in the rat." *Endocrinol. Jap.* **21**: 33-38 (1974). H86,183/74

In rats exposed to the stressor effect of laparotomy under ether anesthesia, a diminution of STH secretion was attributed to suppression of STH-RF discharge or to increased excretion of an inhibitory factor.

George, J. M., Reier, C. E., Lanese, R. R., Rower, J. M.: "Morphine anesthesia blocks cortisol and growth hormone response to surgical stress in humans." *J. Clin. Endocrinol. Metab.* **38**: 736-741 (1974). H86,212/74

Strosser, M. T., Bucher, B., Briaud, B., Lutz, B., Koch, B., Mialhe, C.: "Effet de la chaleur sur la sécrétion de l'hormone de croissance et sur l'activité du cortex surrénalien du Rat" (Effect of heat upon growth hormone secretion and adrenal cortical activity in the rat). *J. Physiol. (Paris)* **68**: 181-191 (1974). J14,464/74

In rats a sudden change of the ambient temperature from 20° to 34°C produces a rapid increase in ACTH and a decrease in STH content of the plasma. The literature on STH secretion during stress is partially reviewed.

Adamson, L., Hunter, W. M., Ogunremi, O. O., Oswald, I., Percy-Robb, I. W.: "Growth hormone increase during sleep after daytime exercise." *J. Endocrinol.* **62**: 473-478 (1974). H96,047/74

Lovinger, R. D., Connors, M. H., Kaplan, S. L., Ganong, W. F., Grumbach, M. M.: "Effect of L-dihydroxyphenylalanine (L-dopa), anesthesia and surgical stress on the secretion of growth hormone in the dog." *Endocrinology* **95**: 1317-1321 (1974). H94,147/74

In dogs, pentobarbital anesthesia and surgical stress failed to cause significant alterations in plasma STH, whereas L-dopa elicited a pronounced rise, as it did in man.

Seggie, J. A., Uhlir, I. V., Brown, G. M.: "Stress response patterns of plasma corticosterone, prolactin and growth hormone in the rat" (abstracted). *Proc. Can. Fed. Biol. Soc.* **17**: 82 (1974). H92,123/74

Mason, J. W., Wherry, F. E., Pennington,

L. L.: "Plasma growth hormone response to capture and venipuncture in caged monkeys." *Proc. Soc. Exp. Biol. Med.* **147**: 85-87 (1974). H95,517/74

Very high plasma STH values were often observed in cage-housed rhesus monkeys after capture, restraint and venipuncture.

Suematsu, H., Kurokawa, N., Tamai, H., Ikemi, Y.: "Changes of serum growth hormone in psychosomatic disorders." *Psychother. Psychosom.* **24**: 161-164 (1974). J16,922/74

Wise, P. H., Burnet, R. B., Geary, T. D., Berriman, H.: "Selective impairment of growth hormone response to physiological stimuli." *Arch. Dis. Child.* **50**: 210-214 (1975). J23,868/75

In children with defective growth due to STH deficiency, "EEG-monitored slow-wave sleep provided discriminatory serum growth hormone responses equivalent to those obtained by arginine and insulin-hypoglycaemia provocation. Exercise was less effective but was able to provide a useful screening test."

Frankel, R. J., Jenkins, J. S.: "Hypothalamic-pituitary function in anorexia nervosa." *Acta Endocrinol. (Kbh.)* **78**: 209-221 (1975). H96,571/75

Description of hormonal derangements in anorexia nervosa. The sulfation factor is deficient, and through a negative feedback, it could be responsible for the enhanced STH secretion.

Newsome, H. H. Jr.: "Growth hormone in surgical stress." *Surgery* **77**: 475-477 (1975). J23,317/75

During surgical trauma, STH secretion is increased in man.

Wright, P. D., Johnston, I. D. A.: "The effect of surgical operation on growth hormone levels in plasma." *Surgery* **77**: 479-486 (1975). J23,318/75

The authors assume that increased STH secretion is a response to glucose intolerance caused by operative interventions in man.

Rose, R. M., Hurst, M. W.: "Plasma cortisol and growth hormone responses to intravenous catheterization." *J. Hum. Stress* **1**: 22-36 (1975). H97,894/75

In patients, the first catheterization tended to produce parallel rises in plasma STH and cortisol, but the STH responses were much more variable. In general, the findings "suggest a definite endocrine adaptation to catheterization by the second or third hour of the experience."

Collu, R., Jéquier, J. C., Chabot, C., Letarte, J., Leboeuf, G., Ducharme, J. R.: "Pituitary response to auditory stress: effect of treatment with α -methyl-p-tyrosine (α -MT)." *Endocrinology* (In press). J18,335/

In rats, auditory stress increases plasma corticosterone through catecholaminergic, and decreases plasma STH through noncatecholaminergic, pathways, as judged by the effect of pretreatment with α -MT.

FSH (Follicle-stimulating Hormone) and LH (Luteinizing Hormone)

Indirect evidence suggests that in various animal species acute stress can cause ovulation, whereas chronic stress tends to inhibit the estrous or menstrual cycle, presumably through some effect on FSH and LH production or activity. However, there are comparatively few data in the literature concerning direct determinations of these gonadotropins in the blood during stress.

In ovariectomized rats, acute stress (ether, hemorrhage) produced an elevation of plasma FSH, LH and LTH within two minutes.

On the basis of cytochemical changes in the pituitary, it was assumed that stressors increase gonadotropin (LH, FSH) production simultaneously with an enhanced ACTH discharge. This would be contrary to the concept of a "shift in anterior pituitary hormone secretion" during stress.

In rats, the stress of laparotomy under ether allegedly elevates LTH but not LH titers; these discrepancies may depend upon the period in the estrous cycle when the stressor is applied. Apparently, even mere transfer of a rat from the stockroom to the laboratory suffices to cause a pronounced increase in serum LH and STH.

FSH and LH

(See also our earlier stress monographs, p. xiii)

Arvay, A., Balázs, L.: "Changes in the gonadotropic function of the adenohypophysis in response to nervous stress." *Acta Physiol. Acad. Sci. Hung.* **14**: 317-325 (1958). C69,256/58

On the basis of cytochemical changes in the rat pituitary, it is assumed that stressors increase gonadotropin production simultaneously with enhanced ACTH secretion. This would be incompatible with the theory of a "shift in anterior pituitary hormone secretion" during stress.

McCann, S. M., Ramirez, V. D.: "The neuroendocrine regulation of hypophyseal luteinizing hormone secretion." *Rec. Prog. Horm. Res.* **20**: 131-170 (1964).

E4,214/64

Review on the neural control of pituitary LH secretion, with a brief section on the effect of stressors (66 refs.).

Everett, J. W.: "Central neural control of reproductive functions of the adenohypophysis." *Physiol. Rev.* **44**: 373-431 (1964).

F14,325/64

Review on the neural control of gonadotropic hormone production by the adenohypophysis, with a short section on stressors (471 refs.).

Eleftheriou, B. E., Church, R. L.: "Effects of repeated exposure to aggression and defeat on plasma and pituitary levels of luteinizing hormone in C57BL/6J mice." *Gen. Comp. Endocrinol.* **9**: 263-266 (1967).

F89,914/67

Observations on fighter mice suggest that "repeated exposure to defeat produces a neural stimulation, similar to other forms of stress, that possibly may act through the hypothalamus to release neurohumoral substance(s) that release hypophysial LH in defeated mice."

Neill, J. D.: "Effect of 'stress' on serum prolactin and luteinizing hormone levels during the estrous cycle of the rat." *Endocrinology* **87**: 1192-1197 (1970).

H34,070/70

In rats the stress of laparotomy under ether elevated serum LTH but not LH titers. The LTH release varied according to stages of the estrous cycle.

Ajika, K., Kalra, S. P., Fawcett, C. P., Krulich, L., McCann, S. M.: "The effect of

stress and Nembutal on plasma levels of gonadotropins and prolactin in ovariectomized rats." *Endocrinology* **90**: 707-715 (1972).

H52,545/72

"The stress of etherization and bleeding produced an elevation within 2 min. in the plasma levels of prolactin, LH, and FSH in ovariectomized rats....Nembutal blocked the stress-induced elevations of plasma prolactin and LH but did not affect the levels of FSH. The effect of Nembutal is thought to be on the CNS since the Nembutalized rats responded to hypothalamic extract or ovine LRF with dramatic elevations in plasma LH."

Maeda, A.: "Effects of thiopental anesthesia and surgical stress on the plasma LH levels in man." *Jap. J. Anesthesiol.* **21**: 624-634 (1972) (66 refs., Japanese).

H76,330/72

Aono, T., Kurachi, K., Mizutani, S., Hamanaka, Y., Uozumi, T.: "Influence of major surgical stress on plasma levels of testosterone, luteinizing hormone and follicle-stimulating hormone in male patients." *J. Clin. Endocrinol. Metab.* **35**: 535-542 (1972).

H59,966/72

McCann, S. M., Ajika, K., Fawcett, C. P., Hefco, E., Illner, P., Negro-Vilar, A., Orias, R., Watson, J. T., Krulich, L.: "Hypothalamic control of the adenohypophyseal response to stress by releasing and inhibiting neurohormones." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 67-77. Bratislava: Slovak Academy of Sciences, 1973. E10,458/73

Report based mainly on plasma hormone determinations and observations on rats whose hypothalamus-pituitary system was isolated with the Halász knife. The authors were led to the conclusion that "following the application of a stressful stimulus, afferent impulses are probably generated which pass to the brainstem and thence to the hypothalamus where they influence release of the various releasing and inhibiting hormones which control the AP. We would postulate that the afferent pathways are similar for all AP hormones and that the differential patterns of release are brought about by specific intrahypothalamic mechanisms. Consistent with this hypothesis is the differential localization of the various releasing and inhibiting factors in the hypothalamus." Mere transfer from the stockroom to the laboratory sufficed to cause a dramatic in-

crease in the serum STH and LH values within less than one hour.

Carstensen, H., Amér, I., Wide, L., Amér, B.: "Plasma testosterone, LH and FSH during the first 24 hours after surgical operations." *J. Steroid Biochem.* **4**: 605-611 (1973). J10,319/73

In patients, plasma LH and testosterone concentrations decreased four to five hours after surgery. LH subsequently returned to normal, whereas testosterone remained low over the twenty-four hour observation period. No change in plasma FSH was noted.

Daly, J. R., Evans, J. I.: "Daily rhythms of steroid and associated pituitary hormones in man and their relationship to sleep." *Adv. Steroid Biochem. Pharmacol.* **4**: 61-110 (1974). J15,152/74

Detailed review on the function of the hypothalamo-pituitary-adrenal axis in man during sleep, with a description of the methodology for EEG measurement of sleep and a periodic obtention of blood specimens by means of an intravenous catheter throughout the night. The plasma corticoids drop gradually from a zenith at 08:00 to a nadir at midnight. The circadian rhythm of plasma testosterone has been less carefully studied but appears to run parallel to that of cortisol; however, unlike the latter, it cannot be inhibited by dexamethasone. The circadian variations of FSH and LH likewise receive comparatively little attention, but sleep-related rises in LH secretion are regularly observed during adolescence. There are two phases of cortisol elimination, "basal" and "impulsive;" only the latter shows an early morning peak sensitive to corticoid inhibition (about 220 refs.).

Valenti, G., Tarditi, E., Ceda, G. P., Banchini, A.: "Sui meccanismi di regolazione omeostatica del sistema gonadotropo-secerente. Considerazioni sul ritmo circadiano della gonadotropina LH" (On the mechanism of homeostatic regulation of the gonadotrophin-secreting system. Considerations on the circadian rhythm of LH). *Minerva Med.* **65**: 2526-2540 (1974). J17,020/74

Kawakami, M., Terasawa, E., Arita, J.: "Effects of hippocampal ablation on stress-induced gonadotropin secretion: an observation of the sexual difference." *Endocrinol. Jap.* **21**: 289-296 (1974). H96,221/74

Various stressors increased FSH in females and in orchidectomized, folliculoid-pretreated males, but this effect was suppressed by hippocampal ablation. Serum LH was not altered by stressors in either sex. "Hippocampal ablation, however, brought about LH release in stressed females and abolished stress-induced increase in LH in orchidectomized estrogen primed males."

Howland, B. E., Beaton, D. B., Jack, M. I.: "Changes in serum levels of gonadotropins and testosterone in the male rat in response to fasting, surgery and ether." *Experientia* **30**: 1223-1225 (1974). H98,258/74

Euker, J. S., Meites, J., Riegle, G. D.: "Effects of acute stress on serum LH and prolactin in intact, castrate and dexamethasone-treated male rats." *Endocrinology* **96**: 85-92 (1975). H98,033/75

In rats, ACTH, LTH and LH concentrations in the blood may be increased by some stressors. Hence a shift in anterior pituitary production is by no means the rule.

LTH (The Luteotropic or Lactotropic Hormone, Prolactin)

In rats with well-developed mammary glands, after estradiol pretreatment, various stressors (cold, restraint, formaldehyde) initiated lactation. This was ascribed to the enhancement of LTH secretion, although the plasma levels of the hormone were not actually determined. It has been postulated that stressors (laparotomy, hemorrhage), like suckling, can induce LTH release from the pituitary by suppressing the production of LTH-inhibiting hypothalamic material. Stressors also reduce the LTH content of the pituitary in the rat, whereas bovine ME extracts inhibit the stress-induced fall in pituitary LTH, even after the combined stimuli of nursing plus stress. This has been interpreted as additional evidence of an LTH-inhibitory hypothalamic factor.

Stressors (laparotomy, ether) elevated serum LTH but not LH titers in the rat, a

peak being reached within a few minutes in both sexes. On the other hand, handling for four days lowered serum LTH in females but raised it in males.

Most authors agree that, in man, various stressors (for example, surgery under ether anesthesia, exercise, insulin, sexual intercourse) increase both the LTH and the STH content of the plasma. However, there is no strict parallelism between the blood concentration of the two hormones, either following psychogenic stress or in lactating women whereas LTH secretion is raised in the absence of any associated increase in STH production.

Both nicotine and ether increase plasma LTH and TTH in the rat, but suckling raises LTH without any change in TTH levels.

A series of stressors (mostly traumatic) suppressed the diurnal, but not the nocturnal, peaks of LTH secretion in the rat. Retrochiasmatic sections abolished both surges. Septal lesions failed to affect either the baseline or the stress level of LTH in the rat although the plasma corticosterone concentrations were elevated following exposure to stressors. Presumably, the production of corticosterone and LTH is under different neural control mechanisms.

Comparative studies on other species, such as hamsters, newts and cattle, also revealed LTH discharges during stress, but on the whole the literature on all species is rather contradictory. Apparently, the release of LTH following exposure to stressors depends on the intensity and duration of the stimulus, the stage of the cycle, the availability of LTH in the pituitary, and numerous other factors.

LTH

(See also our earlier stress monographs, p. xiii)

Swingle, W. W., Seay, P., Perlmutt, J., Collins, E. J., Barlow, G. Jr., Fedor, E. J.: "An experimental study of pseudopregnancy in rat." *Am. J. Physiol.* **167**: 586-592 (1951). B65,305/51

In rats a variety of stressors can produce pseudopregnancy owing to LTH release.

Nicoll, C. S., Talwalker, P. K., Meites, J.: "Initiation of lactation in rats by nonspecific stresses." *Am. J. Physiol.* **198**: 1103-1106 (1960). C87,153/60

In estradiol-pretreated rats, various stressors (cold, restraint, formaldehyde) initiated lactation. "It is concluded that nonspecific stresses can promote the secretion of prolactin and ACTH from the anterior pituitary in amounts adequate to induce lactation in estrogen-primed rats."

Gavazzi, G., Giuliani, G., Martini, L., Pecile, A.: "Action de plusieurs stress sur la libération de prolactine (hormone lutéotrophique-L.T.H.)" (Action of repeated stress on the liberation of prolactin [luteotropic hormone-L.T.H.]). *Ann. Endocrinol. (Paris)* **22**: 788-791 (1961). D17,166/61

Grosvenor, C. E.: "Effect of nursing and stress upon prolactin-inhibiting activity of the rat hypothalamus." *Endocrinology* **77**: 1037-1042 (1965). F58,062/65

Stressors (laparotomy, bleeding), like suckling, cause LTH release from the pituitary. On the basis of experiments with hypothalamic extracts, it is suggested that "the acute stimuli of nursing and stress effect the release of prolactin in the rat by suppressing the release of a prolactin-inhibiting substance from the hypothalamus."

Grosvenor, C. E., McCann, S. M., Nallar, R.: "Inhibition of nursing-induced and stress-induced fall in pituitary prolactin concentration in lactating rats by injection of acid extracts of bovine hypothalamus." *Endocrinology* **76**: 883-889 (1965). F39,155/65

In rats, exposure to various stressors, as well as nursing, reduces the LTH content of the pituitary. Nembutal prevents the fall of LTH after laparotomy and bleeding. Acid extracts of bovine stalk-ME inhibit the stress-induced fall in pituitary LTH concentration following the combined stimuli of nursing and stress. There may exist "a hypothalamic inhibitory factor in the normal regulation of prolactin release in response to nursing or stress."

Neill, J. D.: "Effect of 'stress' on serum prolactin and luteinizing hormone levels during the estrous cycle of the rat." *Endocrinology* **87**: 1192-1197 (1970).

H34,070/70

In rats the stress of laparotomy under ether elevated serum LTH but not LH titers. The LTH release varied according to stages of the estrous cycle.

Bryant, G. D., Linzell, J. L., Greenwood, F. C.: "Plasma prolactin in goats measured by radioimmunoassay: the effects of teat stimulation, mating behavior, stress, fasting and of oxytocin, insulin and glucose injections." *Hormones* **1**: 26-35 (1970).

G76,754/70

In goats, plasma LTH measured by radioimmunoassay showed considerable rises following copulation (in both males and females), oxytocin injections and the mild stress of restraint, as well as during lactation. Conversely, fasting and insulin caused a fall in serum LTH (19 refs.).

Nagy, I., Kurcz, M., Kiss, C., Baranyai, P., Mosonyi, I., Halmy, L.: "The effect of suckling, stress and drugs on pituitary prolactin content in the rat." *Acta Physiol. Acad. Sci. Hung.* **38**: 371-380 (1970).

G87,642/70

Johke, T.: "Factors affecting the plasma prolactin level in the cow and the goat as determined by radioimmunoassay." *Endocrinol. Jap.* **17**: 393-401 (1970).

H39,458/70

Radioimmunologic determinations in cows and goats led to the conclusion that various stressors (venipuncture, pain, restraint, emotional disturbances) elevate the plasma LTH level, but milking is most effective in this respect.

Raud, H. R., Kiddy, C. A., Odell, W. D.: "The effect of stress upon the determination of serum prolactin by radioimmunoassay." *Proc. Soc. Exp. Biol. Med.* **136**: 689-693 (1971).

H37,004/71

In cattle, various stressors, including removal of blood samples for determinations, raise the radioimmunologically demonstrable LTH level of the serum.

Wakabayashi, I., Arimura, A., Schally, A. V.: "Effect of pentobarbital and ether stress on serum prolactin levels in rats." *Proc. Soc. Exp. Biol. Med.* **137**: 1189-1193 (1971).

H46,646/71

In rats the stress of ether anesthesia in-

creased serum LTH levels to a peak within 2.5 minutes of interrupting administration of the anesthetic. This response was the same in both sexes, but handling for four days lowered serum LTH in female rats, whereas the same procedure raised it in males. Pentobarbital markedly increased serum LTH in females, but only slightly in males. Apparently, various stressors affect serum LTH, but the extent and even the direction of the changes are largely sex-dependent.

Terkel, J., Blake, C. A., Sawyer, C. H.: "Serum prolactin levels in lactating rats after suckling or exposure to ether." *Endocrinology* **91**: 49-53 (1972). H56,107/72

Observations on rats "suggest that suckling and ether 'stress' trigger the release of LTH by different mechanisms."

Dunn, J. D., Arimura, A., Scheving, L. E.: "Effect of stress on circadian periodicity in serum LH and prolactin concentration." *Endocrinology* **90**: 29-33 (1972).

H50,464/72

Noel, G. L., Suh, H. K., Stone, J. G., Frantz, A. G.: "Human prolactin and growth hormone release during surgery and other conditions of stress." *J. Clin. Endocrinol. Metab.* **35**: 840-851 (1972).

H62,342/72

On the basis of observations during major surgery under anesthesia, exercise, insulin injections and sexual intercourse, it was concluded that "prolactin in human beings is at least as responsive as growth hormone to release by stress in most situations."

Frantz, A. G., Kleinberg, D. L., Noel, G. L.: "Studies on prolactin in man." *Rec. Prog. Horm. Res.* **28**: 527-590 (1972).

E10,243/72

In man the plasma content of STH and LTH rises after various forms of stress, particularly muscular exercise and major surgical interventions. However, there is no strict parallelism between the blood concentrations of the two hormones following psychogenic stress. For example, in nursing women the plasma LTH level rises usually without any associated increase in STH concentration.

Gala, R. R., Loginsky, S. J.: "Correlation between serum prolactin levels and incidence of mammary tumors induced by 7,12-dimethylbenz[α]anthracene in the rat." *J. Natl. Cancer Inst.* **51**: 593-597 (1973).

J5,797/73

Rats that secrete large amounts of LTH after ether stress fail to develop mammary tumors under the influence of 7,12-dimethylbenz[α]anthracene.

L'Hermite, M.: "The present status of prolactin assays in clinical practice." *Clin. Endocrinol. Metab.* **2**: 423-449 (1973).

J8,615/73

Review on the conditions associated with increased LTH secretion, some of which are manifestly active stressors, while others are more specifically related to milk production. They are summarized in the table below.

Blake, C. A.: "Stimulation of pituitary prolactin and TSH release in lactating and proestrous rats." *Endocrinology* **94**: 503-508 (1974).

H86,287/74

In rats, both nicotine and ether increased plasma LTH but not TTH. This was ascribed to stress. Suckling raised the LTH without influencing the TTH level of the plasma.

Freeman, M. E., Smith, M. S., Nazian, S. J., Neill, J. D.: "Ovarian and hypothalamic control of the daily surges of prolactin secretion during pseudopregnancy in the rat." *Endocrinology* **94**: 875-882 (1974).

H85,365/74

In rats, stimulation of the uterine cervix induces a pattern of two daily surges of LTH secretion, one diurnal, the other nocturnal. A series of stressors (aortic cannulation, blood sampling, surgical interventions) selectively and temporarily suppressed the diurnal but not the nocturnal surges. Hypothalamic retrochiasmatic cuts immediately abolished both surges.

Relkin, R.: "Effects of alterations in serum osmolality on pituitary and plasma prolactin levels in the rat." *Neuroendocrinology* **14**: 61-64 (1974). H83,086/74

In rats, infusion of large volumes of hypotonic saline decreased, whereas hypertonic saline increased, plasma levels of LTH. This

Conditions characterized by elevated blood prolactin levels

Physiological

- Nocturnal discharge (sleep)
- Luteal phase of menstrual cycle
- Pregnancy
- Postpartum period
- Suckling and breast manipulation
- Neonatal period
- Exercise
- Stressful situations
- Sexual intercourse

Pathological

- Syndromes characterised by amenorrhoea and galactorrhoea (Chiari-Frommel, Ahumada-Del Castillo, Argonz-Del Castillo, Forbes-Albright syndromes; oral contraceptive withdrawal)
- Pituitary tumours secreting prolactin
- Pituitary stalk section with disturbance of hypothalamo-pituitary relationships, e.g. by suprasellar and infrasellar tumours
- Juvenile hypothyroidism (athyreosis)
- Renal failure
- Ectopic production of the hormone by malignant tumors, e.g. undifferentiated bronchial carcinoma and hypernephroma
- Surgical stress

Pharmacological

- Insulin-induced hypoglycaemia
- Administration of synthetic TRH
- High dosages of oestrogens
- Psychotropic drugs, e.g. phenothiazines, butyrophenones, sulpiride, etc.
- Reserpine and α -methyldopa administration
- General anaesthesia

is probably not due to stress, since stimuli equal in stressor potency produced disparate results.

Euker, J. S., Riegle, G. D.: "Stress effects on serum prolactin in the female rat." *Fed. Proc.* **33**: 238 (1974). H83,894/74

In rats the effect of stressors on serum LTH "appears to be complex, relating not only to the stress intensity and to the stage of the cycle, but also to the initial hormonal levels at the time of stress." [The brief abstract does not lend itself to evaluation (H.S.).]

Donofrio, R. J., Reiter, R. J., Sorrentino, S. Jr., Blask, D. E., Talbot, J. A.: "A method for measurement of prolactin in the hamster by means of radioimmunoassay." *Neuroendocrinology* **13**: 79-92 (1974).

H81,379/74

In hamsters the combined stress of ether anesthesia and laparotomy significantly elevated plasma LTH levels but slightly depressed pituitary LTH, suggesting a release of the hormone. These results agreed with earlier observations in the rat.

Uhlir, I., Seggie, J., Brown, G. M.: "The effect of septal lesions on the threshold of adrenal stress response." *Neuroendocrinology* **14**: 351-355 (1974). H89,268/74

In rats with septal lesions, "baseline corticosterone values were unaltered, plasma corticosterone concentrations in lesioned animals were elevated in response to stimuli that did not produce a corresponding elevation in sham-lesioned and unlesioned animals. Neither baseline nor stress levels of prolactin were affected by septal lesions at the times studied. It is concluded that a septal lesion lowers the stimulation threshold for activation of the pituitary adrenal axis and is suggested that corticosterone and prolactin stress responses are under different neural control."

Gona, A. G., Gona, O.: "Prolactin-releasing effects of centrally-acting drugs in the red-spotted newt." *Neuroendocrinology* **14**: 365-368 (1974). H89,271/74

Karg, H., Schams, D.: "Prolactin release in cattle." *J. Reprod. Fertil.* **39**: 463-472 (1974). H89,417/74

Review on various factors, including stressors, which can produce LTH discharge.

Tindal, J. S.: "Hypothalamic control of secretion and release of prolactin." *J. Reprod. Fertil.* **39**: 437-461 (1974). H89,416/74

A detailed review of the literature reveals

that, in comparison to such specific stimuli as suckling or milking, various stressors produce only minor discharges of LTH.

Hart, I. C.: "The relationship between lactation and the release of prolactin and growth hormone in the goat." *J. Reprod. Fertil.* **39**: 485-499 (1974). H89,419/74

Review on stressors which produce LTH discharge.

Lawson, D. M., Gala, R. R.: "The influence of surgery, time of day, blood volume reduction and anaesthetics on plasma prolactin in ovariectomized rats." *J. Endocrinol.* **62**: 75-83 (1974). H90,049/74

In rats, various anesthetics (ether, pentobarbital and, to a lesser extent, urethane and chloral hydrate) increased plasma LTH.

Lamming, G. E., Moseley, S. R., McNeilly, J. R.: "Prolactin release in the sheep." *J. Reprod. Fertil.* **40**: 151-168 (1974).

H84,685/74

Comparative review of the literature and personal observations on the release of LTH during stress and suckling in sheep and other species.

Ferry, J. D., McLean, B. K., Nikitovitch-Winer, M. B.: "Tobacco-smoke inhalation delays suckling-induced prolactin release in the rat." *Proc. Soc. Exp. Biol. Med.* **147**: 110-113 (1974). H95,522/74

Experiments on rats suggest that "tobacco-smoke inhalation delays the suckling-induced release of prolactin, and provide the first evidence that smoke inhalation (nicotine?) can interfere with neuroendocrine reflexes associated with reproduction."

Seggie, J. A., Uhlir, I. V., Brown, G. M.: "Stress response patterns of plasma corticosterone, prolactin and growth hormone in the rat" (abstracted). *Proc. Can. Fed. Biol. Soc.* **17**: 82 (1974). H92,123/74

Horrobin, D. F., Manku, M. S., Karmali, R. A., Nassar, B. A., Greaves, M. W.: "Prolactin and prostaglandin synthesis." *Lancet* November 9, 1974, p. 1154. H95,470/74

Observations on rats suggest that increased LTH production during stress may stimulate prostaglandin synthesis.

Morishige, W. K., Rothchild, I.: "A paradoxical inhibiting effect of ether on prolactin release in the rat: comparison with effect of ether on LH and FSH." *Neuroendocrinology* **16**: 95-107 (1974). H97,694/74

Various experiments on rats suggest that

ether-induced stress may exert a depressing effect on the hypothalamic inhibitory and stimulatory factors regulating LTH secretion. The net effect appears to depend on preexisting levels of hypothalamic hormones.

Neill, J. D.: "Prolactin: its secretion and control." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp. 469-488. Washington, D.C.: American Physiological Society, 1974. E10,761/74

Brown, G. M., Martin, J. B.: "Corticosterone, prolactin, and growth hormone responses to handling and new environment in the rat." *Psychosom. Med.* **36**: 241-247 (1974). J18,329/74

Mueller, G. P., Chen, H. T., Dibbet, J. A., Chen, H. J., Meites, J.: "Effects of warm and cold temperatures on release of TSH, GH, and prolactin in rats." *Proc. Soc. Exp. Biol. Med.* **147**: 698-700 (1974).

H98,469/74

In rats exposed to heat or cold, the fact

that TTH and LTH secretion "responded oppositely to the same temperature changes suggests that different mechanisms regulate release of these two hormones under these conditions. The possible role of stress, and the interactions of the hypothalamic hypophysiotropic hormones and biogenic amines in the temperature-induced changes remain to be evaluated."

Euker, J. S., Meites, J., Riegle, G. D.: "Effects of acute stress on serum LH and prolactin in intact, castrate and dexamethasone-treated male rats." *Endocrinology* **96**: 85-92 (1975). H98,033/75

In rats, ACTH, LTH, and LH concentrations in the blood may be increased by some stressors. Hence, a shift in anterior pituitary production is by no means the rule.

Krulich, L., Hefco, E., Aschenbrenner, J. E.: "Mechanism of the effects of hypothalamic deafferentation on prolactin secretion in the rat." *Endocrinology* **96**: 107-118 (1975). H98,036/75

TTH (Thyrotropic Hormone, also known as Thyroid-Stimulating Hormone or TSH)

The release of TTH during stress is extremely variable and dependent upon a number of conditioning factors.

In wild rabbits, frightening stimuli may cause concomitant adrenocortical enlargement and a marked discharge of TTH with thyroid hypertrophy, and only the latter is inhibited by methylthiouracil.

In the rat, exposure to cold enhances TTH release, even when ACTH secretion is blocked by dexamethasone.

Mild stressors decreased plasma TTH and correspondingly raised plasma ACTH and corticoid concentrations in the rat. These observations would agree with the "pituitary-shift" theory. On the other hand, chronic stress leads to continuously-increased resting levels of plasma TTH.

A review of the literature shows that stress can either increase or decrease TTH secretion depending upon conditions (intensity and duration of stress, type of stressor used) and the animal species examined. This might explain the many apparent contradictions in the pertinent literature.

TTH

(See also our earlier stress monographs, p. xiii)

Kracht, J., Spaethe, M.: "Ueber Wechselbeziehungen zwischen Schilddrüse und Nebennierenrinde. II. Mitteilg. Untersuchungen

über den 'Hypophysenhemmstoff' p-Oxypropiophenon" (Interrelation between the thyroid and the adrenal cortex. II. Report. Studies on the "hypophyseal inhibitor" p-oxypropiophenone). *Virchows Arch. [Pathol. Anat.]* **323**: 629-644 (1953).

B85,143/53

Wild rabbits respond to frightening stimuli not only with adrenocortical enlargement but also with a marked discharge of TTH which causes thyroid hypertrophy. This peculiar response can be prevented by hypophysectomy or methylthiouracil.

Goldman, H.: "Effect of acute stress on the pituitary gland: endocrine gland blood flow." *Endocrinology* **72**: 588-591 (1963).

D60,687/63

In rats, the blood flow through the pituitary, adrenal, thyroid and ME was determined using ^{86}Rb . Under the influence of "ether stress," the blood flow increased within a few minutes in the adenohypophysis and even more in the thyroid. Stress after adrenalectomy caused a marked increase of the blood flow in both the anterior and the posterior pituitary but not in the thyroid. The blood flow in the ME remained unchanged under all these experimental conditions.

Ducommun, P., Sakiz, E., Guillemin, R.: "Dissociation of the acute secretions of thyrotropin and adrenocorticotropin." *Am. J. Physiol.* **210**: 1257-1259 (1966).

F68,175/66

In both normal and dexamethasone-treated rats, mild acute stress inhibits TTH secretion, but this is not necessarily associated with increased ACTH release. TTH secretion in response to cold is enhanced even when ACTH discharge is blocked. [This appears to agree with the concept of a "shift in anterior lobe hormone secretion," in that maximal secretion of one type interferes with the increased discharge of another (H.S.).]

Ducommun, P., Sakiz, E., Guillemin, R.: "Lability of plasma TSH levels in the rat in response to nonspecific exteroceptive stimuli." *Proc. Soc. Exp. Biol. Med.* **121**: 921-923 (1966).

F64,088/66

In rats, mild stressors (handling, transferring from one room to another, intraperitoneal injections) cause a rapid decrease in plasma TTH which is more or less inversely proportional to variations in plasma ACTH and corticoid concentrations.

Salaman, D. F.: "The action of stress on plasma TSH concentration in the rat." *J. Physiol. (Lond.)* **186**: 134P-135P (1966).

G41,626/66

In rats the stress of ether anesthesia produced a rapid drop in plasma TTH which paralleled an increased release of CRF and ACTH. [This short report of an oral com-

munication does not lend itself to definitive evaluation (H.S.).]

Ducommun, P., Vale, W., Sakiz, E., Guillemin, R.: "Reversal of the inhibition of TSH secretion due to acute stress." *Endocrinology* **80**: 953-956 (1967). F83,273/67

In rats, chronic mild stress (transfer from the animal room to the laboratory, handling, brief ether anesthesia at different times of the day) prevents the usual inhibition of TTH secretion by acute stress (sojourn in a noisy centrifuge). This inhibition is reversed by reserpine. Furthermore, chronic stress leads to continuously increased resting levels of plasma TTH.

Charters, A. C., Odell, W. D., Thompson, J. C.: "Effect of surgical stress on the anterior lobe of the pituitary gland: radioimmunoassay of blood thyroid stimulating, luteinizing, follicle stimulating, and growth hormones." *Surg. Forum* **19**: 376-378 (1968). J21,908/68

Fekete, M., Milner, R. D. G., Soltész, G., Assan, R., Mestyán, J.: "Plasma glucagon, thyrotropin, growth hormone and insulin response to cold exposure in the human newborn." *Acta Paediatr. Scand.* **61**: 435-441 (1972). G92,222/72

In full-term and premature babies, exposure to cold caused no significant change in plasma insulin, glucagon, STH or TTH concentration.

Leppäläluoto, J.: "Blood bioassayable thyrotrophin and corticosteroid levels during various physiological and stress conditions in the rabbit." *Acta Endocrinol. (Kbh.)* **70** Supp. 165: 1-38 (1972). H58,195/72

Doctoral dissertation on the effect of various stressors on the TTH and corticosterone content of the blood in rabbits.

Mason, J. W., Hartley, L. H., Kotchen, T. A., Wherry, F. E., Pennington, L. L., Jones, L. G.: "Plasma thyroid-stimulating hormone response in anticipation of muscular exercise in the human." *J. Clin. Endocrinol. Metab.* **37**: 403-406 (1973). H74,655/73

In man, small but consistent increases in immunoreactive plasma TTH were observed in anticipation of an exhaustive muscular exercise session.

Florsheim, W. H.: "Control of thyrotropin secretion." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp.

449-467. Washington, D.C.: American Physiological Society, 1974. E10,760/74

Mueller, G. P., Chen, H. T., Dibbet, J. A., Chen, H. J., Meites, J.: "Effects of warm and cold temperatures on release of TSH, GH, and prolactin in rats." *Proc. Soc. Exp. Biol. Med.* **147**: 698-700 (1974).

H98,469/74

In rats exposed to heat or cold, the fact that TTH and LTH secretion "responded oppositely to the same temperature changes suggests that different mechanisms regulate release of these two hormones under these conditions. The possible role of stress, and the interactions of the hypothalamic hypophysiotropic hormones and biogenic amines in the temperature-induced changes remain to be evaluated."

Blake, C. A.: "Stimulation of pituitary prolactin and TSH release in lactating and proestrous rats." *Endocrinology* **94**: 503-508 (1974). H86,287/74

In rats, both nicotine and ether increased plasma LTH but not TTH. This was ascribed

to stress. Suckling raised the LTH without influencing the TTH level of the plasma.

Mühlen, A. von zur, Lammers, M., Köberling, J., Hesch, R. D.: "TSH, T_3 and corticosterone in rats under various environmental conditions and after L- T_3 and D- T_3 administration" (abstracted). *Endocrinol. Exp.* **8**: 237 (1974). H89,185/74

In rats, various stressors (restraint, anesthesia, change of cage) raised plasma TTH and corticosterone values in approximately parallel fashion.

Rall, J. E.: "The role of the thyroid in endocrine control mechanisms." *Perspect. Biol. Med.* **17**: 218-226 (1974).

H81,929/74

A survey of the literature shows that stress can increase or decrease TTH secretion depending upon conditions and the species examined. The author concludes that, in general, stress mildly inhibits thyroid hormone secretion, but for example, in sheep the fear of a barking dog in an adjacent cage causes a rise in the thyroid hormone concentration of the thyroid vein.

Thyroid Hormones

The behavior of the pituitary-thyroid axis during stress becomes even more difficult to evaluate when we use the evidence of thyroid hormone secretion as an indicator.

In rats, the concentration of radioiodine in the thyroid and its distribution in the serum are influenced by a variety of stressors. EP and corticoids decrease serum protein-bound iodine, while fasting, cold or heat diminishes the radioiodine content of the thyroid. Decreased thyroid function has also been observed in rats stressed by formaldehyde, as indicated by a diminished uptake of radioiodine by the thyroid.

Allegedly, electroshock, swimming in cold water and EP at first inhibited radioiodine uptake by the rat thyroid even after hypophysectomy or adrenalectomy; the reverse was true twenty-four hours after application of the stressors. The acute response was ascribed to the release of a vasoconstrictor substance and the delayed reaction to increased TTH secretion.

Fractures of the femur cause a transient rise in the thyroxine secretion of the rat without any change in serum thyroxine or PBI. However, some authors maintain that free thyroxine and free T_3 rapidly rise in rat plasma after injuries, whereas the thyroxine-binding capacity of serum albumin falls. All these factors may influence thyroid function during stress.

Rats frightened by the presence of a dog showed a heightened radioiodine uptake and serum PBI with histologic changes in the thyroid indicative of increased function. "These observations suggest that experimental thyrotoxicosis can be produced in animals using this method."

In rabbits, various emotional (electroshock, restraint, light) and physical (trauma, hemorrhage) stressors induced a prompt inhibition of thyroid activity lasting one or two days, as evidenced by the release of radiolabeled hormones. Neither thyroid denervation nor adrenalectomy prevented this response. (*Cf.* TTH on p. 488.)

In the horse, adaptation to cold and muscular exercise raises the thyroxine secretion rate, as judged by labeled thyroxine determinations.

In man, during the acute phase of infection, the turnover of thyroxine was accelerated. In elderly persons, decreased thyroxine turnover under basal conditions appears to result from enhanced disposal rather than diminished secretion of the hormone.

Sleep deprivation augmented serum PBI in man concurrently with increased EP and NEP excretion.

In summary, we must conclude that an effect of stress upon thyroid function itself—like its influence on TTH secretion—is definitely demonstrable, but its intensity and direction depend on so many conditioning factors that generalizations would be difficult to make at this time.

Thyroid Hormones

(See also our earlier stress monographs, p. xiii)

Williams, R. H., Jaffe, H., Kemp, C.: "Effect of severe stress upon thyroid function." *Am. J. Physiol.* **159**: 291-297 (1949).

B43,573/49

In rats the concentration of radioiodine by the thyroid and its distribution in the serum are influenced by EP, trauma and typhoid vaccine. EP and adrenocortical extract decrease the quantity of PBI in the serum. Fasting, cold and heat diminish the concentration of radioiodine in the thyroid.

Paschkis, K. E., Cantarow, A., Eberhard, T., Boyle, D.: "Thyroid function in the alarm reaction." *Proc. Soc. Exp. Biol. Med.* **73**: 116-118 (1950). B46,261/50

"Rats under the influence of an alarming stimulus (formalin injection) showed decrease in thyroid function, the latter evidenced by diminished uptake of I-131 per milligram of thyroid tissue. Desoxycorticosterone acetate and adrenal cortical extract failed to influence thyroid uptake of I-131 significantly." These findings confirm "Selye's statement that the thyroid 'atrophy' is observed early during the alarm reaction."

Badrick, F. E., Brimblecombe, R. W., Reiss, J. M., Reiss, M.: "The influence of stress conditions on the uptake of ^{131}I by the rat thyroid." *J. Endocrinol.* **11**: 305-313 (1954). C279/54

Various stressors (electroshock, swimming in cold water, intraperitoneal EP) rapidly in-

hibit the uptake of ^{131}I by the thyroid in both intact and hypophysectomized or adrenalectomized rats. On the other hand, uptake of ^{131}I by the thyroid is increased twenty-four hours after application of the stressors. The acute response is ascribed to the release of a vasoconstrictor substance, whereas the delayed reaction is attributed to TTH secretion by the anterior pituitary.

Brown-Grant, K., Harris, G. W., Reichlin, S.: "The effect of emotional and physical stress on thyroid activity in the rabbit." *J. Physiol. (Lond.)* **126**: 29-40 (1954).

C6,508/54

In rabbits, various emotional (electroshock, restraint, light) and physical (trauma, hemorrhage, turpentine injection) stressors induced a prompt inhibition (lasting one to two days) in thyroid release of ^{131}I -labeled hormone. Neither thyroid denervation (steliate ganglionectomy) nor adrenalectomy prevented this inhibition.

Hetzel, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary nitrogen and electrolyte excretion during stressful life experiences, and their relation to thyroid function." *J. Psychosom. Res.* **1**: 177-185 (1956). E83,418/56

Studies on serum PBI, urine flow, total nitrogen, sodium and potassium "suggest that the thyroid may be participating in a rapid metabolic adjustment, but the mechanism involved is not clear from existing knowledge of the thyroid hormone."

Alexander, F., Flagg, G. W., Foster, S., Clemens, T., Blahd, W.: "Experimental

studies of emotional stress: I. Hyperthyroidism." *Psychosom. Med.* **23**: 104-114 (1961).
D2,647/67

Gejrot, T., Notter, G.: "Effects of surgical stress on thyroid function in man." *Acta Otolaryngol.* (Stockh.). **55**: 2-10 (1962).

D57,721/62

The uptake of radioiodide by the thyroid was decreased during the first forty-eight hours after surgery but increased thereafter.

Reichlin, S., O'Neal, L. W.: "Thyroid hormone levels of the blood after electroshock-induced convulsions in man." *J. Clin. Endocrinol. Metab.* **22**: 385-388 (1962).

D22,646/62

In man, electroshock causes a transient increase in plasma PBI.

Asch, L.: "Recherches sur l'élimination de l'iode radioactif par la thyroïde au cours du stress chez le rat" (Research on elimination of radioactive iodine by the thyroid during stress in the rat). *C.R. Soc. Biol. (Paris)* **157**: 363-365 (1963). D69,076/63

Ihio, T.: "Influence of surgical stress upon the tissue and organ distribution of radio-L-thyroxine (I-131)." *Bull. Kobe Med. Coll.* **26**: 84-106 (1964). J24,342/64

Falconer, I. R., Hetzel, B. S.: "Effect of emotional stress and TSH on thyroid vein hormone level in sheep with exteriorized thyroids." *Endocrinology* **75**: 42-48 (1964).

F15,497/64

In sheep the thyroid (and its blood supply) was exteriorized by transposition under the skin. Constant sampling showed a rise in the PBI content of the venous thyroid blood during stress (explosions, barking dog). This was manifest within fifteen to thirty minutes and lasted up to two hours. Restraint was followed by a similar increase in thyroid hormone excretion, but only in untrained animals.

Gregerman, R. I., Solomon, N.: "Acceleration of thyroxine and triiodothyronine turnover during bacterial pulmonary infections and fever: implications for the functional state of the thyroid during stress and in senescence." *J. Clin. Endocrinol. Metab.* **27**: 93-105 (1967). F76,145/67

Review of the literature and personal observations in man on the secretion and metabolism of thyroid hormones during stress and senescence. During the acute phase of infections, the turnover of thyroxine is accelerated. In the elderly, decreased thyroxine

turnover under basal conditions appears to be secondary to hormone disposal rather than to diminished secretion.

Irvine, C. H. G.: "Thyroxine secretion rate in the horse in various physiological states." *J. Endocrinol.* **39**: 313-320 (1967).

F91,501/67

By use of labeled thyroxine it has been found that adaptation to cold and muscular training increases the thyroxine secretion rate of the horse.

Hamburg, D. A., Lunde, D. T.: "Relation of behavioral, genetic, and neuroendocrine factors to thyroid function." In: Spuhler, J. N., *Genetic Diversity and Human Behavior*, pp. 135-170. Chicago: Aldine, 1967.

J16,064/67

Haibach, H., McKenzie, J. M.: "Increased free thyroxine postoperatively in the rat." *Endocrinology* **81**: 435-439 (1967).

F87,403/67

Mason, J. W.: "A review of psychoendocrine research on the pituitary-thyroid system." *Psychosom. Med.* **30**: 666-681 (1968) (86 refs.). H6,456/68

Mason, J. W., Mougey, E. H., Brady, J. V., Tolliver, G. A.: "Thyroid (plasma butanol-extractable iodine) responses to 72-hr. avoidance sessions in the monkey." *Psychosom. Med.* **30**: 682-695 (1968).

H6,457/68

During conditioned avoidance sessions, plasma thyroid hormone levels exhibit low but prolonged elevations without any evidence of eventual exhaustion (28 refs.).

Negoescu, I., Constantinesco, A., Don, M., Helteanu, C.: "Le stress et le transport des hormones thyroïdiennes" (Stress and transport of thyroid hormones). *Rev. Roum. Endocrinol.* **6**: 215-220 (1969). J15,906/69

In rats subjected to the stressor effect of repeated exposure to a magnetic field, the free thyroxine content of the blood was raised, whereas the albumin-bound fraction was diminished. PBI was not significantly altered (22 refs.).

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Conditions of work and their influence on psychological and endocrine stress reactions." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 8: 1-19 (1969).

G69,180/69

In Swedish officers deprived of sleep for seventy-five hours and performing on an

electronic shooting range or engaged in military staff work, EP and NEP excretion was increased, as were erythrocyte sedimentation and the amount of PBI, whereas serum iron was decreased. Some subjects developed ECG anomalies, particularly ST-T depression, and it took several days of rest for ECG patterns to return towards normal. Stressors imitating situations in civilian life produced essentially similar changes in proportion to their severity.

Richards, J. R., Harland, W. A., Orr, J. S.: "Factors affecting thyroid hormone metabolism in experimental trauma." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 151-161. Bratislava: Slovak Academy of Sciences, 1973. E10,465/73

In rats, fractures of the femur cause a transient increase in thyroxine secretion without any change in serum thyroxine or PBI. Others have shown that free thyroxine and T₃ levels in plasma rise rapidly after injuries, whereas the thyroxine-binding capacity of prealbumin decreases. "These alterations in the peripheral metabolism and transport of thyroxine may well play an important role in the metabolic consequences of injury."

Story, J. A., Griffith, D. R.: "Effect of ex-

ercise on thyroid hormone secretion rate in aging rats." *Horm. Metab. Res.* **6**: 403-406 (1974). H97,134/74

Gupta, R. C., Prasad, G. C., Udupa, K. N.: "Experimental production of thyrotoxicosis." *5th Asia and Oceania Congr. Endocr.*, p. 178. Chandigarh, India, 1974. H82,223/74

Rats exposed to fear by being kept in front of a dog's cage showed enhanced ¹³¹I uptake and increased PBI with histologic changes in the thyroid indicative of thyrotoxicosis. The serum cholesterol and body weight were lowered. "These observations suggest that experimental thyrotoxicosis can be produced in animals using this method."

Carter, J. N., Eastman, C. J., Corcoran, J. M., Lazarus, L.: "Effect of severe, chronic illness on thyroid function." *Lancet* October 26, 1974, pp. 971-974. H94,571/74

In patients with severe, chronic, nonthyroidal illnesses the mean total serum-T₃ levels are reduced to the hypothyroid range, apparently as a result of decreased conversion of T₄ to T₃. Depressed production of TTH-RF secondary to stress or undernutrition may also contribute by reducing thyroidal hormone output. [The apparently contrary observations on hyperthyroidism precipitated by stress are not discussed (H.S.).]

MTH (Melanotropic Hormone, also known as Melanophore-Stimulating Hormone or MSH)

Very little is known about the participation of the intermediate lobe hormone in the stress response. Besides, in several species, including man, the intermediate lobe is not clearly developed.

In lizards, a neuro-intermediate lobe grafted below the skin produces a small dark patch owing to MTH discharge; exposure to stressors enlarges the size of the pigmented area, presumably because of MTH release from the graft.

A review of the literature concerning plasma MTH in man revealed no clearcut correlation between the level of this hormone and that of cortisol during various diseases. A rise in plasma MTH was very pronounced after brain injury but this may have been a specific effect.

MTH

(See also our earlier stress monographs, p. xiii)

Vargas, L.: "Influencia de diferentes tipos de tensión o violencia sobre el nivel san-

guíneo de hormona melanofórica hipofisaria en el hombre" (Influence of different types of stress on pituitary melanophoric hormone blood levels in humans). *Arch. Biol. Med. Exp.* (Santiago) **1**: 210-215 (1964). G23,160/64

In man, various stressors (electroshock, emotional arousal, pregnancy, surgery) increase the MTH content of the blood. This response "could be a part of the adaptive neuro-endocrine mechanism of the stress."

Sandman, C. A., Kastin, A. J., Schally, A. V., Kendall, J. W., Miller, L. H.: "Neuroendocrine responses to physical and psychological stress." *J. Comp. Physiol. Psychol.* **84**: 386-390 (1973). J5,207/73

In rats, endogenous plasma levels of MTH and ACTH following various stressors were increased although neurogenic stressors were more effective in raising MTH. It is suggested that the latter "may facilitate adaptive behavior by leading to increased attention or awareness of the environment."

Novales, R. R.: "Actions of melanocyte-stimulating hormone" In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. 4, Part 2, pp. 347-366. Washington, D.C.: American Physiological Society, 1974. E10,757/74

Meurling, P., Klefbohm, B., Larsson, L.: "Transplantation of the pars intermedia in an elasmobranch and a lizard." *Gen. Comp. Endocrinol.* **22**: 347 (1974). H83,146/74

In the lizard (*Anolis carolinensis*) the neuro-intermediate lobe grafted below the dorsal skin produces a distinct small dark patch owing to MTH discharge. Exposure to stressors (kind not described) causes a rapid release of MTH.

Kastin, A. J., Hawley, W. D., Miller, M. C., Schally, A. V., Lancaster, C.: "Plasma MSH and cortisol levels in 567 patients with special reference to brain trauma." *Endocrinol. Exp.* (Bratisl.) **8**: 97-105 (1974).

H88,653/74

The literature on MTH release in response to stress is reviewed. Personal observations revealed that patients with various diseases showed no correlation between elevations in plasma cortisol and MTH. A rise in the latter was particularly pronounced with brain trauma.*

Vasopressin (Antidiuretic Hormone or ADH) and Oxytocin

In the section concerned with theories relating to the mechanism of the stress reaction, much will have to be said about vasopressin as a possible neurohumoral factor regulating ACTH secretion and its previously-suspected identity with CRF. It has long been known that vasopressin is released during emotional stress. This results in a delay of diuresis following a water load, which can in turn be prevented by EP or tyramine. Evidently, the end result of stress upon water diuresis will depend upon the relative production of vasopressin and EP.

Similar discrepancies between the relative amounts of various stimulators and inhibitors of some parameters influenced by stress probably explain why a parameter known to be stress dependent, can respond in diametrically opposed ways under different conditions.

In dogs, the surgical trauma of gastrectomy increases vasopressin secretion about thirtyfold. This effect is not modified by vagotomy but is abolished by cervical cordotomy. Presumably, ascending spinal pathways mediate this response to stress. Vasopressin discharge caused by stress (sound, ether) has also been noted in the garden dormouse. In man, a rise in plasma vasopressin levels was noted after various surgical interventions and anesthesia. Hence, it may be accepted as a well-established fact that a discharge of vasopressin is a characteristic manifestation of stress in various species.

Quite a few investigators have examined oxytocin secretion during stress, and there appears to be unanimity among these authors that the neurohypophyseal concentration of this hormone rises following exposure to various stressors.

Vasopressin

(See also our earlier stress monographs, p. xiii)

Verney, E. B.: "The antidiuretic hormone and the factors which determine its release." *Proc. R. Soc. [B]* **135**: 25-106 (1947).

B18,117/47

"Croonian Lecture" on factors causing vasopressin release, with a large section on emotional stressors which delay diuresis following a water load. These changes are in turn prevented by EP or tyramine.

Tyler, C.: "The effect of prolonged emotional disturbance on the vasopressor and oxytocic activities contained in the posterior pituitary glands of fallow deer." *Arch. Int. Pharmacodyn. Ther.* **131**: 301-308 (1961).

D86,848/61

In deer harried before being shot, the ratio of vasopressin to oxytocin progressively increased in the posterior pituitary, probably owing to a fall in oxytocin.

Moran, W. H. Jr., Miltenberger, F. W., Shuayb, W. A., Zimmermann, B.: "The relationship of antidiuretic hormone secretion to surgical stress." *Surgery* **56**: 99-108 (1964).

G17,607/64

Review of the literature and personal observations on increased vasopressin secretion after exposure to various stressors (19 refs.).

Taleisnik, S., Deis, R. P.: "Influence of cerebral cortex in inhibition of oxytocin release induced by stressful stimuli." *Am. J. Physiol.* **207**: 1394-1398 (1964).

F26,807/64

Fendler, K., Telegdy, G., Endrőczi, E.: "Effect of chronic stress on the oxytocic and antidiuretic activity of the hypophysis in the rat." *Acta Physiol. Acad. Sci. Hung.* **24**: 287-292 (1964).

G17,873/64

Fendler, K., "Endrőczi, E., Lissák, K.: "Changes in the oxytocin content of the posterior pituitary in the rat, following ovariectomy, thyroidectomy, oxytocin and thyroxine treatment." *Acta Physiol. Acad. Sci. Hung.* **25**: 21-25 (1964).

G22,784/64

In rats, the rise in the oxytocin content of the neurohypophysis normally elicited by the stress of swimming is inhibited by thyroxine, slightly diminished by thyroidectomy or exogenous oxytocin and not influenced by ovariectomy.

Fendler, K., Telegdy, G.: "Changes of pituitary oxytocin content on daily cooling in

the rat." *Acta Physiol. Acad. Sci. Hung.* **25**: 27-30 (1964). G22,782/64

In rats, exposure to cold for fourteen days increases the oxytocin content of the neurohypophysis.

Fendler, K., Endrőczi, E., Lissák, K.: "The effect of cervical sympathectomy on posterior pituitary oxytocic activity in rats under chronic stress." *Acta Physiol. Acad. Sci. Hung.* **27**: 275-278 (1965). G34,302/65

In rats, "exhaustive swimming daily for 18 days resulted in an increased pituitary oxytocic activity which was prevented by cervical sympathectomy."

Fendler, K., Rákóczi, I., Zibotics, H.: "Effect of daily electroshock treatment on neurohypophyseal hormone content in the rat." *Acta Physiol. Acad. Sci. Hung.* **29**: 41-46 (1966). G39,114/66

In rats, electroshocks (given daily for 16 days until a state of lethargy developed) significantly increased the oxytocin and vasopressin content of the neurohypophysis.

Ukai, M., Moran, W. H. Jr., Zimmermann, B.: "The role of visceral afferent pathways on vasopressin secretion and urinary excretory patterns during surgical stress." *Ann. Surg.* **168**: 16-28 (1968). G60,105/68

In dogs, partial gastrectomy increased vasopressin secretion about thirtyfold. This response was not modified by transection of the vagal pathways, but could be eliminated by cervical cordotomy or dorsal rhizotomy, "indicating that the ascending spinal pain pathways were serving as the predominant afferent pathway." The surgical trauma also decreased endogenous creatinine clearance, urinary flow and sodium secretion. The vasopressin discharge is ascribed to stress.

Takebe, K., Kunita, H., Sakakura, M., Horiuchi, Y.: "Effect of dexamethasone on ACTH release induced by lysine vasopressin in man; time interval between dexamethasone and vasopressin injection." *J. Clin. Endocrinol. Metab.* **28**: 644-650 (1968).

F98,960/68

Burlet, C.: "Variations des activités phosphatasiques acides du système hypothalamo-neurohypophysaire du lérot dans différentes conditions expérimentales" (Acid phosphatase in the hypothalamic-neurohypophyseal system of the lerot [garden dormouse] under experimental conditions). *C.R. Soc. Biol. (Paris)* **163**: 486-488 (1969).

H15,751/69

In the lerot (*Eliomys quercinus L.*), stress (sound, ether) increases the acid phosphatase activity in the ME and neurohypophysis, simultaneously enhancing ADH discharge.

Lutz, B., Koch, B., Mialhe, C.: "Sécrétion de l'hormone antidiurétique au cours de différents types d'agression chez le Rat" (Secretion of antidiuretic hormone during different types of aggression in the rat). *J. Physiol. (Paris)* **61** Supp. 1: 149-150 (1969).

J20,635/69

Konzett, H., Hörtnagl, H., Hörtnagl, H., Winkler, H.: "On the urinary output of vasopressin, epinephrine and norepinephrine during different stress situations." *Psychopharmacologia (Berlin)* **21**: 247-256 (1971).

J20,330/71

Narang, R. L., Chaudhury, R. R., Wig, N. N.: "Effect of electroconvulsive therapy on the antidiuretic hormone level in the plasma of schizophrenic patients." *Indian J. Med. Res.* **61**: 766-770 (1973).

J9,654/73

In schizophrenic patients, electroconvulsive therapy increased the vasopressin content of the plasma.

Soliman, M. G., Brindle, G. F.: "Plasma levels of anti-diuretic hormone during and after heart surgery with extra-corporeal circulation." *Can. Anaesth. Soc. J.* **21**: 195-204 (1974).

J10,760/74

Plasma vasopressin levels "increased in seven patients during cardiac surgery using extra-corporeal circulation, probably due to changes in serum osmolalities, surgical

trauma and the action of anaesthetic drugs." The literature on the effect of various stressors upon plasma vasopressin is discussed (25 refs.).

Fröhlich, H.: "Steuermechanismen der Motilität des nichtgraviden Uterus in situ" (Regulatory mechanisms of the motility of the non-pregnant uterus). *Wien Klin. Wochenschr.* **86** Supp. 24: 1-28 (1974).

H90,700/74

Extensive review on various mechanisms with a special section on psychogenic stressors regulating uterine motility (229 refs.).

Schrier, R. W.: "'Inappropriate' versus 'appropriate' antidiuretic hormone secretion." *West. J. Med.* **121**: 62-64 (1974).

H87,695/74

Review on "appropriate" and "inappropriate" vasopressin secretion during stress in man.

Maetz, J., Lahliou, B.: "Actions of neurohypophysial hormones in fishes." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. 4, Part 1, pp. 521-544. Washington, D.C.: American Physiological Society, 1974.

E10,739/74

Review on stress-induced changes in vasopressin secretion and the consequent alterations in water and electrolyte metabolism (140 refs.).

Shade, R. E., Share, L.: "Vasopressin release during nonhypotensive hemorrhage and angiotensin II infusion." *Am. J. Physiol.* **228**: 149-154 (1975).

H96,541/75

Insulin

(See also Diabetes Mellitus and Hyperinsulinism under Diseases of Adaptation)

The literature on the effect of stressors upon insulin secretion, and particularly, upon its plasma level is difficult to interpret. In some instances, rises, in others no change or drops, of insulinemia were noted.

These apparent contradictions are almost certainly due to the fact that insulin secretion during stress depends upon a variety of conditioning agents. EP, which is also released during stress, inhibits insulin discharge as does hypoglycemia, whereas glucagon and hyperglycemia augment its secretion, presumably acting as homeostatic mechanisms that help maintain a steady blood sugar level. Stress increases plasma glucagon and may either raise or depress blood sugar, depending mainly upon the availability of carbohydrate stores, the speed of their utilization, as well as the severity, duration and specific side-effects of the stressors applied. In addition, the gluco-

corticoids discharged during stress may cause pronounced changes in glycogen reserves and blood sugar.

In view of all these modifying factors, it is hardly surprising that the literature on the effect of stress upon the plasma insulin level is very contradictory and unsuitable for generalizations. Perhaps the only valid conclusion that can be drawn is that stress, either directly or through its effect on the conditioning agents just enumerated, can produce pronounced changes in the plasma insulin concentration.

The complexity of this situation is well illustrated by experiments on rats which showed that trauma can completely suppress the rise in plasma immunoreactive insulin, normally elicited by intravenous glucose. This blockade is in turn prevented by removal of the adrenal medulla, the main source of the inhibitory EP.

Insulin

(See also our earlier stress monographs, p. xiii)

Gellhorn, E., Feldman, J., Allen, A.: "Effect of emotional excitement on the insulin content of the blood. Contribution to physiology of the psychoses." *Arch. Neurol. Psychiatry* **47**: 234-244 (1942).

A37,798/42

In psychotic patients, emotional excitement considerably increases the blood insulin level, although blood sugar usually remains unaffected. In normal persons, excitement causes a rise in blood sugar but not in plasma insulin. "The experiments are interpreted to mean that the balance of the autonomic centers in psychotic patients under emotional stress is shifted toward the vagoinsulin side whereas in normal persons the sympatheticoadrenal system greatly predominates."

Schalch, D. S.: "The effect of physical stress and exercise in the human on growth hormone and insulin secretion." *Clin. Res.* **13**: 334 (1965).

F61,179/65

In man, various stressors (muscular exercise, electroconvulsive therapy, major surgery) increased plasma STH (radioimmunoassay) and FFA levels without affecting plasma insulin. It is possible that STH discharge "may be at least in part responsible for the mobilization of the readily oxidizable FFA which takes place during periods of increased energy requirements."

Baumann, R.: "Die Bedeutung des Stress für die Regulation des Kohlenhydratstoffwechsels und den Insulineffekt" (The effect of stress on insulin hypoglycemia, and the metabolism of carbohydrates in general). *Zentralbl. Chir.* **92**: 1324-1334 (1967).

F91,158/67

In rats, psychogenic stress increases the

blood sugar level and makes insulin hypoglycemia and the associated shock phenomena more intense and acute, although the latter are not directly dependent upon the dose of insulin or the blood sugar level.

Schalch, D. S.: "The influence of physical stress and exercise on growth hormone and insulin secretion in man." *J. Lab. Clin. Med.* **69**: 256-269 (1967).

G44,274/67

In man, plasma STH often rose during periods of physical stress or exercise, while insulin values remained unchanged or decreased. EP did not reproduce the release of STH. The failure of plasma insulin levels to rise in response to stress-induced hyperglycemia is consistent with the finding that EP infusion impairs insulin discharge. Plasma glucose and FFA levels rose as expected during physical exercise. Presumably, certain stressors are diabetogenic not only because of EP and corticoid release but also because of a discharge of STH on the one hand and an EP-induced suppression of insulin secretion on the other.

Mason, J. W., Wherry, F. E., Brady, J. V., Beer, B.: "Plasma insulin response to 72-hr. avoidance sessions in the monkey." *Psychosom. Med.* **30**: 746-759 (1968).

H6,462/68

"Emotional reactions to venipuncture may also elicit a decrease in plasma immunoreactive insulin levels with associated elevations in plasma 17-OHCS and glucose levels."

Wright, P. H., Malaisse, W. J.: "Effects of epinephrine, stress, and exercise on insulin secretion by the rat." *Am. J. Physiol.* **214**: 1031-1034 (1968).

F97,956/68

In rats, various stressors (EP, swimming, electroshock) diminish insulin secretion. "It is suggested that endogenous epinephrine released during stress or exercise is sufficient to

suppress insulin secretion even under conditions of hyperglycemia" (29 refs.).

Carey, L. C., Lowery, B. D., Cloutier, C. T.: "Blood sugar and insulin response of humans in shock." *Ann. Surg.* **172**: 342-350 (1970). G77,785/70

Within minutes, patients in traumatic hypovolemic shock develop severe hyperglycemia which falls gradually as resuscitation progresses, but which is still high after five hours. The serum insulin is unresponsive to the hyperglycemia of shock.

Bottger, I., Faloona, G. R., Unger, R. H.: "The effect of intensive physical exercise on pancreatic glucagon secretion." *Diabetes* **20** Supp. 1: 339 (1971). J10,799/71

In the dog and in man the blood glucagon level rose during physical exercise, probably contributing to the associated hyperglycemia. Blood insulin concentrations varied less regularly.

Hartley, L. H., Mason, J. W., Hogan, R. P., Jones, L. G., Kotchen, T. A., Mougey, E. H., Wherry, F. E., Pennington, L. L., Ricketts, P. T.: "Multiple hormonal responses to graded exercise in relation to physical training." *J. Appl. Physiol.* **33**: 602-606 (1972).

H79,757/72

In man the stress of heavy bicycle exercise increased plasma STH, cortisol and EP values, but decreased insulin concentration.

Hoffmann, H. D., Fiedler, H., Gürtler, H., Kibittel, W.: "Der Einfluss von Fahrradergometerarbeit, Sparring und Wettkampf auf die Plasmainsulinkonzentration und den Blutzuckerspiegel bei Boxern" (The influence of muscular exercise [bicycle ergometer], sparring, and competition on the plasma insulin concentration and blood sugar level in boxers). *Med. Sport (Berl.)* **12**: 119-123 (1972). H90,857/72

Fekete, M., Milner, R. D. G., Soltész, G., Assan, R., Mestyán, J.: "Plasma glucagon, thyrotropin, growth hormone and insulin response to cold exposure in the human newborn." *Acta Paediatr. Scand.* **61**: 435-441 (1972). G92,222/72

In full-term and premature babies, exposure to cold caused no significant change in plasma insulin, glucagon, STH or TTH concentration.

Meguid, M. M., Brennan, M. F., Muller, W. A., Aoki, T. T.: "Glucagon and trauma." *Lancet* November 25, 1972, p. 1145.

H62,755/72

In six patients who sustained major trauma, plasma glucagon rose considerably within eighteen hours. Plasma insulin levels did not change significantly, but maximal hyperglycemia preceded the glucagon peak. Literature is cited to show that hypoglycemia, starvation, diabetic ketoacidosis and exercise likewise caused hyperglucagonemia. Hence, glucagon appears to play a role in the pathophysiology of severe trauma.

Bloom, S. R., Daniel, P. M., Johnston, D. I., Ogawa, O., Pratt, O. E.: "Release of glucagon, induced by stress." *Q. J. Exp. Psychol.* **58**: 99-108 (1973). G99,793/73

In both conscious and lightly anesthetized (pentobarbital) rhesus monkeys startled by noise, plasma glucagon rose rapidly, followed by elevation of blood glucose but not of plasma insulin. Similar effects were produced in anesthetized animals by rectal distension, drilling a burr hole in the skull, and passage of an electric current through the head. "These experiments show that glucagon is rapidly released in response to various types of stress."

Vigaš, M., Németh, Š., Jurčovičová, J.: "Stress-induced inhibition of insulin release in non-conditioned and conditioned rats." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 143-150. Bratislava: Slovak Academy of Sciences, 1973.

E10,464/73

Whereas normal rats respond to 1 gm. per kg. intravenous glucose by a prompt rise in plasma immunoreactive insulin, this reaction is completely suppressed after traumatization in the Noble-Collip drum. The blockade is prevented by bilateral adrenomedulllectomy or by repeating the injury daily for seven days (13 refs.).

Wolf, S.: "The challenge of methodology in psychosomatic research with notes on the 'psychic' secretion of insulin." *Tex. Rep. Biol. Med.* **31**: 431-440 (1973).

J9,407/73

In man, "not only was a sense of appetite on viewing breakfast associated with an increase in acid and in insulin secretion, but an increase was also observed in those experiments in which anxiety was aroused because of difficulty with the intravenous needle." It must be kept in mind that hypoglycemia automatically enhances insulin secretion, and since the rise in blood sugar is characteristic of stress, an associated discharge of insulin is not unexpected.

Porte, D. Jr., Robertson, R. P.: "Control of insulin secretion by catecholamines, stress, and the sympathetic nervous system." *Fed. Proc.* **32**: 1792-1796 (1973). H71,915/73

Catecholamines inhibit insulin release by stimulation of pancreatic α -receptors and enhance it by excitation of β -receptors. "Activation of the sympathetic nervous system causes inhibition of glucose-stimulated insulin secretion via the α -receptor, but insulin output is maintained, probably via simultaneous β -receptor stimulation.... Pathological stress states may induce a metabolic state similar to diabetes with hyperglycemia and poor insulin responses to glucose challenge" (68 refs.).

Meguid, M. M., Brennan, M. F., Aoki, T. T., Muller, W. A., Ball, M. R., Moore, F. D.: "Hormone-substrate interrelationships following trauma." *Arch. Surg.* **109**: 776-783 (1974). J19,976/74

Observations in man lead the authors to the conclusion that "in trauma, the gradual rise in glucagon contributes to the increase in concentration of glucose and FFA, and that the cortisol rise synergizes with the elevated glucagon concentration to favor gluconeogenesis from muscle amino acids. Relatively low circulating insulin levels favor these metabolic changes" (62 refs.).

Koch, G.: "Vergleichende Untersuchungen über das Blutglukose- und Plasmainsulinverhalten am traumatisierten Kaninchen" (Blood glucose and plasma insulin levels of traumatized rabbits, an experimental study). *Brunn Beitr. Klin. Chir.* **221**: 158-163 (1974). J17,605/74

In rabbits, surgical trauma causes hyperglycemia and an increase in plasma insulin, both of which are ascribed to the G.A.S.

Singh, A. K., Chansouria, J. P. N., Singh, R. K., Wahi, R. S., Udupa, K. N.: "Hormonal and metabolic alterations following surgical trauma." *5th Asia and Oceania Congr. Endocr.*, pp. 50-51. Chandigarh, India, 1974. H82,068/74

In patients the stress of major surgery caused an increase in plasma STH, cortisol and FFA, with a decrease in plasma insulin.

Ivanova, I. I., Lapshina, V. F., Tsaplin, V. M.: "Corticosterone content in the peripheral blood and adrenal glands during stress in rats with alloxan diabetes." *Probl. Endokrinol.* **20** No. 3: 94-97 (1974) (Russian).

In rats, alloxan diabetes did not significantly influence the typical stress reaction to sian). H92,322/74

trauma. They showed adrenal enlargement, thymus involution and elevated corticosterone levels in the plasma and adrenals.

Demael-Suard, A., Garin, D., Brichon, G., Mure, M., Peres, G.: "Neoglycogenèse à partir de la glycine ^{14}C chez la tanche (*Tinca vulgaris* L.) au cours de l'asphyxie" (Neoglycogenesis from glycine ^{14}C in the tench [*Tinca vulgaris* L.] during asphyxia). *Comp. Biochem. Physiol. [A]* **47**: 1023-1033 (1974). H82,645/74

In the tench, increased cortisol, catecholamine and insulin secretions produce changes in carbohydrate metabolism which are ascribed to the stress of handling and asphyxia.

Unger, R. H.: "Alpha- and beta-cell interrelationships in health and disease." *Metabolism* **23**: 581-593 (1974). H86,900/74

"An inappropriately low concentration of insulin and/or high level of glucagon relative to fuel availability are observed in genetic diabetes, and in a variety of stressful illnesses such as severe infection, trauma, burns, fetal distress, and other conditions, all of which are characterized by a negative nitrogen balance" (88 refs.).

Wright, P. D., Henderson, K., Johnston, I. D. A.: "Glucose utilization and insulin secretion during surgery in man." *Br. J. Surg.* **61**: 5-8 (1974). H86,335/74

In man, various surgical operations depress glucose utilization, thereby decreasing resistance. "Suppression of insulin secretion was observed during operation together with increased plasma cortisol levels and an increased urinary catecholamine excretion. It is suggested that a failure of cellular glucose utilisation is the primary event in the metabolic response to injury which initiates cellular catabolism and urinary nitrogen loss."

Woods, S. C., Porte, D. Jr.: "Neural control of the endocrine pancreas." *Physiol. Rev.* **54**: 596-619 (1974). H89,399/74

Extensive review on factors influencing the endocrine activity of the pancreas with a special section on "stress states."

Vigaš, M., Németh, Š., Jurčovičová, J.: "Posttraumatic regulation of insulin secretion in adapted rats." *Physiol. Bohemoslov.* **23**: 245-249 (1974). J14,698/74

In rats, there is a rapid increase in the plasma immunoreactive insulin level after intravenous glucose, but not if this is preceded by traumatization in the Noble-Collip

drum. EP blocks the postglucose insulin secretion in nonadapted rats, but not in those adapted to trauma. "It is assumed that the posttraumatic change in insulin secretion in

adapted rats is caused by greater degradation of catecholamines, or by lower adrenaline sensitivity of the beta cells in the islets of Langerhans."

Glucagon

In man, both starvation and posttraumatic stress induce a characteristic catabolic response. Here, the discharge of glucagon probably plays a very important role in that it antagonizes stress-produced insulin resistance and supplies glucose as a readily available source of energy. Of course, catecholamines and glucocorticoids undoubtedly also contribute to the development of stress-induced hyperglycemia.

The plasma level of glucagon is regularly raised by various stressors, such as diverse forms of traumatic injuries, noise, muscular effort, fasting, infections, burns, cardiac infarctions and so on, both in experimental animals and in man. Hence, glucagon has been designated as a "stress hormone."

Despite the associated hyperglycemia, the stress-induced glucagon secretion is usually not accompanied by any significant change in plasma insulin, but it may lead to some degree of insulin resistance and aggravate pre-existent or latent diabetes. Its discharge has been suspected of being predominantly under sympathetic control.

The few available data concerning glucagon discharge in fetal and earliest postnatal life are somewhat contradictory.

Glucagon

(See also our earlier stress monographs, p. xiii)

Aguilar-Parada, E., Eisentraut, A. M., Unger, R. H.: "Effects of starvation on plasma pancreatic glucagon in normal man." *Diabetes* 18: 717-723 (1969). H18,441/69

Through the use of a relatively specific antiserum for pancreatic glucagon, the blood level of the latter was found to rise considerably during starvation in man. Literature is cited showing that insulin, phlorhizin, certain sulfonylurea derivatives, arginine and various other amino acids likewise cause hyperglucagonemia, and apparently the hormone is secreted in excess whenever a glucose need arises (23 refs.).

Carlo, P. E.: "Nutritional therapy in surgery and trauma. Metabolic consequences of nutritional restriction and stress." *Agrestologie* 12: 303-324 (1971). H51,864/71

Review on the effects of nutritional therapy upon the metabolic consequences of trauma and other forms of stress. The so-called "obligatory, post-traumatic nitrogen loss" is part of the G.A.S., facilitated by but not entirely dependent upon glucocorticoids. In acute stress, glycogenesis becomes es-

sential, at the expense of proteins, to furnish a rapidly available source of energy. Lysosomes supply the enzymes required to catabolize proteins or synthesize sugar. Glucagon probably plays a very important role here as it depresses insulin and stimulates lysosomal activity, thereby combatting stress-induced, post-traumatic insulin resistance, since insulin inhibits glycogenesis. The main pertinent questions are answered as follows: "a) post-traumatic nitrogen loss is due to starvation and stress; b) it is harmful because of the protein loss and metabolic imbalances it induces; c) it can be prevented or considerably limited by preventing the development of intense glycogenesis before surgery, and pharmacological control of adrenergic reactions; d) it helps the patient because it decreases the chances and severity of complications and speeds up recovery." In severe surgical stress, parenteral nutrition is advocated.

Bottger, I., Falonna, G. R., Unger, R. H.: "The effect of intensive physical exercise on pancreatic glucagon secretion." *Diabetes* 20 Supp. 1: 339 (1971). J10,799/71

In the dog and in man the blood glucagon level rose during physical exercise, probably contributing to the associated hyperglycemia.

Blood insulin concentrations varied less regularly.

Felig, P., Wahren, J., Handler, R., Ahlborg, G.: "Plasma glucagon levels in exercising man." *N. Engl. J. Med.* **287**: 184-185 (1972). H57,196/72

In man, plasma glucagon levels rise following forty minutes of exercise on a bicycle ergometer.

Bloom, S. R., Daniel, P. M., Johnston, D. I., Ogawa, O., Pratt, O. E.: "Changes in glucagon level associated with anxiety or stress." *Psychol. Med.* **2**: 426-427 (1972). G98,403/72

In monkeys [kind not mentioned (H.S.)] a sudden loud noise produced a large and rapid rise in plasma glucagon, even during ether anesthesia.

Meguid, M. M., Brennan, M. F., Muller, W. A., Aoki, T. T.: "Glucagon and trauma." *Lancet* November 25, 1972, p. 1145.

H62,755/72

In six patients who sustained major trauma, plasma glucagon rose considerably within eighteen hours. Plasma insulin levels did not change significantly, but maximal hyperglycemia preceded the glucagon peak. Literature is cited to show that hypoglycemia, starvation, diabetic ketoacidosis and exercise likewise caused hyperglucagonemia. Hence, glucagon appears to play a role in the pathophysiology of severe trauma.

Fekete, M., Milner, R. D. G., Soltész, G., Assan, R., Mestyán, J.: "Plasma glucagon, thyrotropin, growth hormone and insulin response to cold exposure in the human newborn." *Acta Paediatr. Scand.* **61**: 435-441 (1972). G92,222/72

In full-term and premature babies, exposure to cold caused no significant change in plasma insulin, glucagon, STH or TTH concentration.

"Glucagon and diabetes." *Br. Med. J.* August 11, 1973, pp. 310-311. H74,266/73

Letter to the editor summarizing evidence showing that "in a variety of stressful conditions the secretion of glucagon may be stimulated by the sympathetic nervous system." It is of clinical importance that stress-induced hyperglucagonemia contributes to the deterioration of diabetic control in patients kept on standard dosages of insulin.

Bloom, S. R., Daniel, P. M., Johnston, D. I., Ogawa, O., Pratt, O. E.: "Release of glucagon, induced by stress." *Q. J. Exp. Psychol.* **58**: 99-108 (1973). G99,793/73

In both conscious and lightly anesthetized (pentobarbital) rhesus monkeys startled by noise, plasma glucagon rose rapidly, followed by elevation of blood glucose but not of plasma insulin. Similar effects were produced in anesthetized animals by rectal distension, drilling a burr hole in the skull and passage of an electric current through the head. "These experiments show that glucagon is rapidly released in response to various types of stress."

Bloom, S. R.: "Glucagon, a stress hormone." *Postgrad. Med. J.* **49** Supp.: 607-611 (1973). J6,093/73

Glucagon is designated a "stress hormone." Its plasma level rises sharply in different species following exposure to various stressors. Presumably, its usefulness lies in the fact that it releases glucose from hepatic glycogen stores and activates hepatic glycogenesis, thereby supplying energy to satisfy increased requirements during stress.

Laniado, S., Segal, P., Esrig, B.: "The role of glucagon hypersecretion in the pathogenesis of hyperglycemia following acute myocardial infarction." *Circulation* **48** Supp. 4, 797-800 (1973). J6,374/73

In nondiabetic patients, postinfarction hyperglycemia tends to be associated with an increase in plasma glucagon concentration. Presumably, in "certain cases, hyperglycemia following acute myocardial infarction may be related to a temporary and uninhibited rise in plasma glucagon levels, probably stimulated by the major stress of acute myocardial infarction."

Lindsey, A., Santeusonio, F., Braaten, J., Falloona, G. R., Unger, R. H.: "Pancreatic alpha-cell function in trauma." *J.A.M.A.* **227**: 757-761 (1974). H82,359/74

In patients with traumatic shock, plasma glucagon levels rose far above normal and blood glucose averaged 188 mg. per 100 ml., whereas insulin levels remained unchanged. "In three patients undergoing major surgery without associated hypotension, glucagon concentrations did not rise comparably. Hyperglucagonemia without a proportional rise in insulin may be the usual islet cell response to severe trauma and possibly could contribute to survival."

Unger, R. H.: "Alpha- and beta-cell interrelationships in health and disease." *Metabolism* **23**: 581-593 (1974). H86,900/74

"An inappropriately low concentration of insulin and/or high level of glucagon relative to fuel availability are observed in genetic

diabetes, and in a variety of stressful illnesses such as severe infection, trauma, burns, fetal distress, and other conditions, all of which are characterized by a negative nitrogen balance" (88 refs.).

Harvey, W. D., Faloona, G. R., Unger, R. H.: "The effect of adrenergic blockade on exercise-induced hyperglucagonemia." *Endocrinology* **94**: 1254-1258 (1974).

H85,696/74

In rats, forced swimming increases the plasma glucagon level. This response can be prevented by pretreatment with the α -adrenergic blocker phentolamine, but not by propranolol. Presumably, exercise-induced hyperglucagonemia is largely mediated by α -adrenergic stimulation.

Schwiller, P.O., Schellerer, W., Reitzenstein, M., Hermanek, P.: "Hyperglucagonemia, hypocalcemia and diminished gastric blood flow—evidence for an etiological role in stress ulcer of rat." *Experientia* **30**: 824-826 (1974).

H90,543/74

In both intact and adrenalectomized rats, restraint causes gastric ulcers with a considerable rise in glucagon and a decrease in gastrin which are attributed to stress.

Thorner, M. O., Bloom, S. R.: "Rapid glucagon release in artificial fever." *Lancet*

September 14, 1974, p. 654. H91,868/74

In men, artificial fever produced by bacterial endotoxin causes a rapid increase in plasma glucagon, interpreted as "part of the primary pyrexial stress response."

Drucker, M. R., Pinsky, F., Brown, R. S., Elwyn, D. H.: "The interaction of glucagon and glucose on cardiorespiratory variables in the critically ill patient." *Surgery* **75**: 487-495 (1974). J11,745/74

Meguid, M. M., Brennan, M. F., Aoki, T. T., Muller, W. A., Ball, M. R., Moore, F. D.: "Hormone-substrate interrelationships following trauma." *Arch. Surg.* **109**: 776-783 (1974).

J19,976/74

Observations in man lead the authors to the conclusion that "in trauma, the gradual rise in glucagon contributes to the increase in concentration of glucose and FFA, and that the cortisol rise synergizes with the elevated glucagon concentration to favor gluconeogenesis from muscle amino acids. Relatively low circulating insulin levels favor these metabolic changes" (62 refs.).

Russell, R. C. G., Walker, C. J., Bloom, S. R.: "Hyperglucagonaemia in the surgical patient." *Br. Med. J.* January 4, 1975, pp. 10-12.

H97,996/75

Catecholamines and Their Derivatives

Ever since 1911, when Cannon showed that asphyxia or electric stimulation of the sciatic nerve increases EP secretion in the cat (even under anesthesia), the release of catecholamines and their metabolites has been found to be one of the most reliable indicators of acute stress reactions. This phenomenon, occurring after exposure to the most diverse stressors, in man as in virtually every experimental animal, has been studied by innumerable investigators. Hence, it would require a special monograph to survey the entire pertinent literature and particularly to offer a meaningful résumé of all these studies. The interested reader will find at least brief summaries of the highlights in the following abstract section, but here we shall have to limit ourselves to a few of the most striking generalizations that appear to be justified.

There can be no doubt that the catecholamine discharge is a nonspecific consequence of exposure to the most diverse acute stressors (emotional arousal, pain, hemorrhage, trauma, anesthesia, burns and so on) but it appears to play a much less significant, or even negligible, role during later phases of the G.A.S.

The discharges of EP and NEP do not necessarily run parallel. It has been claimed that aggression is likely to be associated with increased excretion of NEP, whereas tense, anxious, but passive emotional display is related to enhanced excretion of EP, often without any significant concomitant rise in the elimination of NEP.

In young men exposed to the "gravitational stress" of centrifugation, increased

secretion of EP has been ascribed primarily to emotional factors, whereas NEP release is allegedly more closely related to physical changes, such as hemodynamic disturbances. Increased release of either of these catecholamines is associated with a commensurate rise in their common urinary metabolite, vanillylmandelic acid (VMA).

Gravitational stress (centrifugation) increased EP but not NEP excretion or the pulse rate of medical students. Furthermore, gravitational, cold and psychogenic stress involving exhilarating or aggressive reactions caused a predominant excretion of NEP, whereas apprehension, anxiety, pain or discomfort was accompanied by an increase in EP discharge (Euler).

In patients undergoing cardiac catheterization, elevated plasma levels of EP and NEP were associated with decreased insulin concentrations.

Extensive studies have been published comparing the effects of various everyday stressors on catecholamine excretion in man.

The viewing of films causing sexual arousal elicited more pronounced EP and NEP excretion in male than in female students. These changes paralleled self-rating scores in emotional reactions.

It appears to be possible to dissociate the two types of catecholamines produced, even by pharmacologic means. In students the psychogenic stress of examinations increased EP and NEP excretion, but treatment with meprobamate selectively inhibited NEP discharge.

In medical students, various intellectual tests increased urinary EP excretion, which could be suppressed by amphetamine and pentobarbital.

In students carrying out a choice-reaction task and receiving electric shocks either at random or for poor performance, punishment raised both EP and NEP release. By increasing their control over the situation, it was possible to counteract the EP but not the NEP release. On the whole, subjects with high as compared to low rates of EP and NEP excretion performed more efficiently.

In policemen, both understimulation and overstimulation increased NEP release. Subjects excreting more EP performed better during understimulation; those excreting less EP showed better performance during overstimulation.

In men undergoing exacting vigilance tests, the plasma EP and NEP levels were inversely related to glycemia. EP was initially increased but later dropped in proportion to the efficiency of performance, whereas NEP was unrelated to it.

In young men, exposure to cold raised the urinary excretion of both EP and NEP, roughly paralleling the increased oxygen consumption. Presumably, here catecholamines assist in heat regulation.

In man, intense bicycle exercise raised the plasma EP concentration.

In pilots on over-water missions, urinary EP and NEP values were both considerably increased.

In city drivers and their passengers, VMA excretion rises considerably.

Racing driving caused a predominant increase in NEP secretion. Here, plasma NEP values were more constantly elevated than the EP concentration immediately after the race.

In the lamprey, there is a large accumulation of chromaffin cells in the heart which appears to act like the mammalian adrenal medulla. Exposure to cold diminishes its EP content, while the NEP concentration in the liver rises.

In cockerels, immobilization and ACTH increased plasma EP and NEP with a corresponding decrease in adrenal catecholamine levels. It will be recalled that, in birds, the cortical and medullary cells of the adrenal are intermixed.

The role of catecholamines in the regulation of stress responses within the nervous system will be discussed conjointly with other neurohumoral mediators in the section, Theories.

Catecholamines and Their Derivatives

(See also our earlier stress monographs, p. xiii)

Cannon, W. B., Hoskins, R. G.: "The effects of asphyxia, hyperpnoea, and sensory stimulation on adrenal secretion." *Am. J. Physiol.* **29**: 274-279 (1911). 57,883/11

In the cat, asphyxia and electric stimulation of the sciatic nerve, even under anesthesia, caused increased EP secretion.

Humphreys, R. J., Raab, W.: "Response of circulating eosinophils to norepinephrine, epinephrine and emotional stress in humans." *Proc. Soc. Exp. Biol. Med.* **74**: 302-303 (1950). B49,646/50

In medical students the stress of sitting for an examination caused a profound eosinopenia that was much more readily duplicated by EP than by NEP.

Meyer, R. J.: "Relative insensitivity of the hypothalamic-pituitary-adrenal system to activation by epinephrine." *J. Clin. Endocrinol. Metab.* **13**: 123-125 (1953). B77,155/53

Review of previously published and personal observations suggesting that in man the EP test is not a very sensitive indicator of ACTH release. Actually, "epinephrine is quantitatively a poor stimulant of the hypothalamic-pituitary-adrenal system" and hence cannot be accepted as a valid test.

Elmadjian, F., Hope, J. M., Lamson, E. T.: "Excretion of epinephrine and norepinephrine under stress." *Rec. Prog. Horm. Res.* **14**: 513-553 (1958). C57,735/58

Observations on people exposed to various types of stressors "support the hypothesis that active aggressive emotional displays are related to increased excretion of NE, whereas tense, anxious, but passive, emotional displays are related to increased excretion of E in association with normal excretion of NE."

Birke, G., Dunér, H., Liljedahl, S. O., Pernow, B., Plantin, L. O., Troell, L.: "Histamine, catechol amines and adrenocortical steroids in burns." *Acta Chir. Scand.* **114**: 87-98 (1958). J10,862/58

In severely burned patients the blood and urinary histamine, as well as the excretion of EP, NEP and corticoids (17-KGS), were

considerably increased during the first twenty-four hours, but the duration of the rise varied according to the substances examined. Their role in the genesis of burn shock is discussed.

Euler, U. S. von, Gemzell, C. A., Levi, L., Ström, G.: "Cortical and medullary adrenal activity in emotional stress." *Acta Endocrinol. (Kbh.)* **30**: 567-573 (1959).

C66,890/59

Brief technical note on adrenal cortical and medullary activity during emotional stress, based on new techniques of corticoid and catecholamine determinations.

Meehan, J. P., Jacobs, E.: "Venous plasma levels of catechol amines in several physical stresses." *Aerosp. Med.* **31**: 733-738 (1960).

C92,818/60

Berman, M. L., Pettitt, J. A.: "Urinary excretion of 3-methoxy-4-hydroxymandelic acid after several stress situations." *J. Lab. Clin. Med.* **57**: 126-135 (1961). J23,520/61

In healthy subjects, urinary VMA excretion is remarkably stable, but in certain stress situations it rises considerably.

Frankenhaeuser, M., Kareby, S.: "Effect of meprobamate on catecholamine excretion during mental stress." *Percept. Mot. Skills* **15**: 571-577 (1962). E30,225/62

In students, psychogenic stress (problem solving and to a lesser extent even anticipation of such tests) augmented EP and NEP excretion. After simultaneous administration of meprobamate, EP output increased but NEP decreased during stress. Thus, "meprobamate in moderate doses counteracted the increase in the catecholamine response of normal individuals subjected to mental stress in a laboratory situation."

Elmadjian, F.: "Epinephrine, norepinephrine, and aldosterone: release and excretion." In: Schaefer, K. E., *Man's Dependence on the Earthly Atmosphere*, pp. 100-116. New York and London: Macmillan, 1962.

D30,946/62

Studies on EP and NEP secretion during stressful life situations in normal people and psychiatric patients "support the hypothesis that active, aggressive, emotional displays are related to increased excretion of norepineph-

rine, whereas tense, anxious, but passive emotional displays are related to increased excretion of epinephrine." Aldosterone elimination was elevated in certain anxiety states without demonstrable increases in catecholamine excretion. The stressors examined were manipulation of the Hoagland-Werthessen pursuit meter, hockey, boxing, basketball, baseball and anxiety-inducing interviews.

Frankenhaeuser, M., Sterky, K., Jaerpe, G.: "Psychophysiological relations in habituation to gravitational stress." *Percept. Mot. Skills* 15: 63-72 (1962). D46,292/62

In male medical students, gravitational stress (centrifugation) increased EP excretion without causing any pronounced change in NEP elimination or heart rate. After repeated centrifugation, adaptation occurred.

Frankenhaeuser, M., Post, B.: "Catecholamine excretion during mental work as modified by centrally acting drugs." *Acta Physiol. Scand.* 55: 74-81 (1962). D35,589/62

In medical students the stress of various "intellectual tests" caused increased urinary excretion of EP which could be suppressed by methamphetamine and pentobarbital. It appears that "urinary excretion of adrenaline provides a sensitive measure of reactions to mental stress, and that centrally acting drugs may influence adrenaline excretion during mental work."

Levi, L.: "The urinary output of adrenalin and noradrenalin during experimentally induced emotional stress in clinically different groups. A preliminary report." *Acta Psychother. (Basel)* 11: 218-227 (1963).

E37,966/63

Healthy young soldiers were exposed to "industrial stress" simulating actual working conditions in a factory or workshop, or to "film stress" (viewing scenes of cruelty, violence and military surgery). Both caused increased catecholamine excretion.

Euler, U. S. von: "Adrenergic neurohormones." In: Euler, U.S. von and Heller, H., *Comparative Endocrinology. II. Tissue Hormones*, pp. 209-238. New York and London: Academic Press, 1963. E4,175/63

Review on catecholamines, with special reference to their distribution in the tissues of various species, biosynthesis, storage, release and excretion. The effect of stressors and of drugs specifically affecting the release of adrenergic transmitters is only briefly considered.

Marchbanks, V. H. Jr., Hale, H. B., Ellis, J. P. Jr.: "Stress responses of pilots flying 6-hour overwater missions in F-100 and F-104 aircraft." *Aerosp. Med.* 34: 15-18 (1963). G2,360/63

In navy pilots flying six-hour overwater missions in F-100 and F-104 aircraft, corticoid levels were increased in the plasma but not in the urine. Urinary EP and NEP values were considerably above normal as were the excretion rates of urea and uric acid, while phosphate levels were not altered. The total reaction depended very much upon airplane characteristics and pilot experience.

Weiner, N.: "The catecholamines: biosynthesis, storage and release, metabolism and metabolic effects." In: Pincus, G., Thimann, K. V. et al., *The Hormones. Physiology, Chemistry and Applications*, Vol. 4, pp. 403-479. New York and London: Academic Press, 1964. E4,436/64

Review on the catecholamines in the adrenal medulla, brain and other peripheral tissues, their biosynthesis, storage and release under normal conditions and after treatment with various agents (500 refs.).

Euler, U. S. von: "Quantitation of stress by catecholamine analysis." *Clin. Pharmacol. Ther.* 5: 398-404 (1964). G18,238/64

Review of the literature and personal observations on man suggest that "gravitational stress and exposure to cold are mainly associated with an increase in the norepinephrine excretion, indicating the importance of this hormone in circulatory and temperature-controlling homeostatic mechanisms. Mental stress involving exhilarating or aggressive reactions is also associated with an increase in the norepinephrine excretion. The types of emotional stress which are mainly characterized by apprehension, anxiety, pain, or general discomfort are regularly accompanied by an increase in the epinephrine excretion." Special sections are devoted to the catecholamine discharge associated with flying, mental work and exposure to cold.

Schmid, E., Meythaler, C.: "Untersuchungen über die sympathico-adrenale Reaktion bei Autofahrern mit Hilfe der Vanillinmandelsäure-Bestimmung im Harn" (Examination of the sympathetic-adrenal reaction in drivers. Urinary vanillylmandelic acid excretion). *Klin. Wochenschr.* 42: 139-140 (1964). F2,669/64

In city drivers and even in their passengers, VMA excretion increases considerably, imply-

ing raised catecholamine production during stress.

Frankenhaeuser, M., Patkai, P.: "Catecholamine excretion and performance during stress." *Percept. Mot. Skills* **19**: 13-14 (1964). F45,033/64

In college students exposed to various stressors, "the amount of noradrenaline excreted was positively correlated with improvement in performance during stress."

Petrásek, J.: "Stress and catecholamines." *Cas. Lék. Česk.* **103**: 772-778 (1964) (Czech). J24,602/64

Frankenhaeuser, M., Pátka, P.: "Interindividual differences in catecholamine excretion during stress." *Scand. J. Psychol.* **6**: 117-123 (1965). F72,211/65

Gillis, C. N.: "Altered cardiac retention of exogenous noradrenaline produced by stress in young rabbits." *Nature* **207**: 1302-1304 (1965). F50,830/65

The retention of radio-marked NEP during stress is inhibited by ACTH or cortisol in the rabbit heart.

D'Amelio, G., Marchiori, C., Busonera, G., Celon, E.: "Modificazioni della eliminazione urinaria delle catecolamine dei 17-idrossicorticoidi e dei 17-chetosteroidi, nello stress da stimolazione vestibolare" (Changes in urinary elimination of catecholamines, 17-hydroxycorticosteroids and 17-ketosteroids in stress caused by vestibular stimulation). *Endocrinol. Sci. Cost.* **29**: 57-63 (1966). J24,555/66

Zubek, J. P., Schutte, W.: "Urinary excretion of adrenaline and noradrenaline during prolonged perceptual deprivation." *J. Abnorm. Psychol.* **71**: 328-334 (1966). J24,049/66

In young men who successfully completed a week of perceptual isolation, there was no significant change in urinary EP or NEP excretion. However "quitters" had a significantly lower baseline of EP even months after the isolation experiment, but exhibited an increased excretion during isolation. "These results seem to suggest that isolation quitters may be biochemically or 'constitutionally' different from volunteers who can successfully complete a prolonged period of perceptual isolation."

Schmid, E.: "Untersuchungen über Physiologie und Pathophysiologie des sympathikos-

adrenalen Systems durch Bestimmung der Vanillin-Mandelsäure-Ausscheidung im Harn mit dünnenschichtchromatographischer Technik" (Studies on the physiology and physiopathology of the sympathico-adrenal system by determination of vanillylmandelic acid excretion in the urine by thin-layer chromatography). *Arch. Kreislaufforsch.* **49**: 83-116 (1966). F62,295/66

Clinical observations suggest that "emotional and bodily stress increases the turnover of catecholamines and the urinary excretion of vanilmandelic acid in healthy persons."

Peterfy, G., Pinter, E. J., Cleghorn, J. M., Pattee, C. J.: "Observations on the adrenergic mechanism of hyperadiopinesis of emotional stress." *Proc. Can. Fed. Biol. Soc.* **9**: 64 (1966). F66,182/66

In men and women the emotional stress of threatening suggestions leads to hyperadiopinesis. "The primary factor appears to be the adrenergic nervous system." This response, associated with marked increases in plasma FFA and catecholamine levels, is prevented by a β -adrenergic blocking agent (propranolol).

Glowinski, J., Baldessarini, R. J.: "Metabolism of norepinephrine in the central nervous system." *Pharmacol. Rev.* **18**: 1201-1238 (1966). F74,390/66

Review on the role of NEP in CNS activity, with a brief section on the effect of stress upon brain NEP.

Goldstein, M., Nakajima, K.: "The effect of disulfiram on the biosynthesis of catecholamines during exposure of rats to cold." *Life Sci.* **5**: 175-179 (1966). G36,828/66

In rats, enhanced catecholamine excretion during exposure to cold suggests increased activity of the sympatho-adrenal system. Disulfiram, a potent inhibitor of dopamine- β -hydroxylase, causes only a slight decrease in the cardiac NEP concentration of adrenalectomized rats at room temperature, but the levels in animals kept at 2°C for one hour show a .50 percent drop as compared with NEP values in the corresponding controls. The fact that cold decreases the cardiac NEP content following inhibition of dopamine- β -hydroxylase by disulfiram "suggests an increase in cardiac norepinephrine utilization during cold exposure." In otherwise untreated animals the cardiac NEP levels after cold exposure are sustained by an increase in the biosynthesis of these catecholamines. Pos-

sibly, the increase in NEP biosynthesis during cold is due to excess dopamine formation.

Rosecrans, J. A., Watzman, N., Buckley, J. P.: "The production of hypertension in male albino rats subjected to experimental stress." *Biochem. Pharmacol.* **15**: 1707-1718 (1966). G42,049/66

In rats subjected "to a chronic variable stress program consisting of flashing lights, audiogenic stimulation, and oscillation," hypertension developed after several months. This was associated with an increase in catecholamine excretion which disappeared after several weeks, and a rise in plasma corticosterone which tended to persist. "These results suggest that the adrenal glands had become more efficient in the rate of synthesis and release of steroids after chronic exposure to the stressors."

Balestra, V., Buonvino, M., Canepa, R.: "Sulla valutazione statistica ed epidemiologica degli stress psico-fisici. Ricerche effettuate mediante il dosaggio dell'acido vanilmandelico nell'urina e mediante questionari" (On the statistical and epidemiologic evaluation of psycho-physical stress. Research based on determinations of urinary vanilmandelic acid and on questionnaires). *G. It. Med. Prev.* **8**: 139-166 (1967).

J22,349/67

Extensive review and personal observations indicating that VMA excretion has only moderate value in determining psychogenic or somatic stress which may predispose to CHD (21 refs.).

Ehrentheil, O. F., Reyna, L. J., Adams, C. J., Giovanniello, T. J., Chen, E. T.: "Studies in stress glycosuria. II. Glycosuria and blood sugar elevation in alloxanized sub-diabetic white rats subjected to electric shock stress." *Diabetes* **16**: 319-324 (1967).

F81,456/67

Chang, C. C., Su, C. Y.: "Effect of cold stress on the subcellular distribution of noradrenaline in the rat heart." *J. Pharm. Pharmacol.* **19**: 73-77 (1967). G44,503/67

Stabrowskii, E. M.: "The distribution of adrenaline and noradrenaline in the organs of the baltic lamprey *Lampetra fluviatilis* at rest and under various functional stresses." *Zh. Evol. Biokhim. Fiziol.* **3** No. 3: 216-221 (1967). J11,822/67

In the lamprey, chromaffin cells containing EP and NEP are found in various organs, particularly the heart. The stress of hypoxia

diminishes the EP content in the heart, skeletal muscle and liver, whereas the NEP increases in liver tissue. "It is suggested that the chromaffin tissue of the lamprey heart acts as the medulla of mammalian suprarenals."

Euler, U. S. von: "Adrenal medullary secretion and its neural control." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 283-333. New York and London: Academic Press, 1967. E6,914/67

An extensive chapter on the neural control of adrenal medullary secretion within a treatise on neuroendocrinology in general. Special attention is given to comparing the ability of various stressors to stimulate EP secretion, as summarized in the following table:

Epinephrine excretion in urine during various kinds of stress

Situation	Epinephrine (nanograms per minute)
Normal, resting	4-8 ¹
Mental work	11-15 ²
Examinations	6.5-21 ³
Routine work under stressful conditions (industrial stress)	18 ⁴
Exciting films	11 ⁵
Air transportation	24 ⁶
Centrifugation mock run	31 ⁷
Centrifugation first run	38 ⁸
Centrifugation sixth run	9 ⁸
Suborbital space flight	
Preflight 4 days	25
Postflight 30 minutes	33 ⁹
Postflight 45 hours	6
Parachute jumping	18 ¹⁰

References

- ¹ U. S. von Euler, Hellner-Björkman and Orwen (1955)
- ² Frankenhaeuser and Post (1962)
- ³ Pekkarinen *et al.* (1961)
- ⁴ Levi (1963)
- ⁵ Levi (1964)
- ⁶ U. S. von Euler and Lundberg (1954)
- ⁷ Goodall and Berman (1960)
- ⁸ Frankenhaeuser *et al.* (1962)
- ⁹ Jackson *et al.* (1961)
- ¹⁰ Bloom *et al.* (1963)

Adapted, by permission, from L. Martini and W. F. Ganong, *Neuroendocrinology*, Vol. 2. New York and London: Academic Press, 1967.

The effects of numerous other stressors (cold, heat, hypoxia, hemorrhage, physical and emotional exertion, hypo- and hypergly-

cemia and so on) are separately discussed (several hundred refs.).

Roessler, R., Burch, N. R., Mefferd, R. B.: "Personality correlates of catecholamine excretion under stress." *J. Psychosom. Res.* **11**: 181-185 (1967). G49,965/67

Male students with low and high scores of ego strength (as determined by the MMPI) were compared regarding their catecholamine excretion upon exposure to different intensities of sound and light. In high ego strength subjects, catecholamine excretion was increased, whereas it was decreased in the other group.

Levi, L.: "Sympatho-adrenomedullary responses to emotional stimuli: methodologic, physiologic and pathologic considerations." In: Bajusz, E., *An Introduction to Clinical Neuroendocrinology*, p. 78. Basel and New York: S. Karger, 1967. E6,577/67

Brief review of personal observations and literature on the influence of everyday stressors upon catecholamine production.

Franzen, F., Friedrich, G., Gross, H.: "Normabweichendes Auftreten proteinogener Amine bei Verbrennungskranken" (Abnormal activities of proteinogenic amines in burned patients). *Z. Gesamte. Inn. Med.* **22**: 401-404 (1967). F87,778/67

In severely burned patients, the plasma and urinary concentrations of EP, NEP, 5-HT, histamine and other amines derived from protein decomposition are greatly increased. No evidence is given that these changes are due to stress rather than to the specific effect of burns.

Levi, L.: "Sympatho-adrenomedullary activity, diuresis, and emotional reactions during visual sexual stimulation in females and males." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 3: 1-33 (1968). G63,782/68

The viewing of films causing sexual arousal elicited more pronounced EP and NEP excretion in male than in female students. This difference paralleled self-rating scores in emotional reactions.

Taggart, P., Gibbons, D., Somerville, W.: "Some effects of motor-car driving on the normal and abnormal heart." *Br. Med. J.* October 18, 1969, pp. 130-134. H18,098/69

"Little or no change in the plasma catecholamine levels was noted in three coronary subjects immediately after a city drive compared with resting levels. All the racing drivers showed a considerable increase in

noradrenaline, and in one instance adrenaline, immediately after racing."

McDonald, L., Baker, C., Bray, C., McDonald, A.: "Plasma-catecholamines after cardiac infarction." *Lancet* November 15, 1969, pp. 1021-1023. H18,916/69

In racing drivers, plasma NEP levels were greatly raised immediately after the race. Following cardiac infarction, "patients with atrial dysrhythmias or early ventricular dysrhythmias had higher noradrenaline concentrations in their plasma. There was no such difference for patients with late ventricular dysrhythmias, and adrenaline levels were unremarkable. The raised noradrenaline levels are not thought to be related to stress because six other patients undergoing the stressful procedure of cardiac catheterisation had low levels."

Sharma, V. N., Godhwani, J. L.: "Stress-induced changes in catecholamine, glycogen and blood glucose levels and their modification by antiadrenergic drugs." *Indian J. Med. Res.* **58**: 1063-1072 (1970). G82,559/70

Frankenhaeuser, M., Rissler, A.: "Effects of punishment on catecholamine release and efficiency of performance." *Psychopharmacologia* **17**: 378-390 (1970). G77,863/70

Male university students were asked to accomplish a choice-reaction task, and some received electric shocks either at random or as punishment for slow performance. Others were not punished irrespective of performance. "Punishment produced a rise in both adrenaline and noradrenaline release. By increasing the subject's control over the situation it was possible to counteract the adrenaline increase, while noradrenaline release appeared unaffected. On the whole, subjects with high as compared with low rates of adrenaline and noradrenaline excretion were more efficient in terms of both speed and accuracy of performance."

Kvetňanský, R., Weise, V. K., Gewirtz, G. P., Kopin, I. J.: "Synthesis of adrenal catecholamines in rats during and after immobilization stress." *Endocrinology* **89**: 46-49 (1971). H43,006/71

Immobilization is known to augment tyrosine hydroxylase in rat adrenals. It could now be shown that "the increased levels of enzymes result in enhanced synthesis of epinephrine-¹⁴C from tyrosine-¹⁴C but not from dopa-³H. During immobilization, conversion of tyrosine-¹⁴C to catecholamines is further increased and may exceed the capacity of

even the elevated levels of dopamine- β -hydroxylase to convert dopamine to norepinephrine."

Konczett, H., Hörtnagl, H., Hörtnagl, H., Winkler, H.: "On the urinary output of vasopressin, epinephrine and norepinephrine during different stress situations." *Psychopharmacologia* (Berlin) **21**: 247-256 (1971).
J20,330/71

Shum, A., Johnson, G. E., Flattery, K. V.: "Catecholamine and metabolite excretion in cold-stressed immunosympathectomized rats." *Am. J. Physiol.* **221**: 64-68 (1971).

H41,823/71

Immunosympathectomy did not prevent the increase in NEP secretion produced in the rat by exposure to cold. However, when compared with untreated littermates, the immunosympathectomized rats excreted slightly less NEP and normetanephrine, and considerably less 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). "It is postulated that a decreased sympathetic reserve in these animals caused a higher percentage of norepinephrine synthesized to be secreted as such, causing the lower MHPG excretion."

Pátkai, P.: "Catecholamine excretion in pleasant and unpleasant situations." *Acta Psychol. (Amst.)* **35**: 352-363 (1971).
J20,641/71

Maas, J. W., Dekirmenjian, H., Fawcett, J.: "Catecholamine metabolism, depression and stress." *Nature* **230**: 330-331 (1971).

H35,227/71

Klepping, J., Escousse, A., Didier, J. P.: "Système adrénnergique et stress" (Adrenergic system and stress). *Sem. Hôp. (Paris)* **47**: 116-132 (1971).
G81,581/71

Extensive review on the G.A.S. with special emphasis on the sympathetic system and adrenergic responses to various stressors (46 refs.).

Taggart, P., Carruthers, M.: "Endogenous hyperlipidaemia induced by emotional stress of racing driving." *Lancet* February 20, 1971, pp. 363-366.
H35,851/71

During racing driving, "the total-catecholamine levels were grossly elevated, the increase being largely due to noradrenaline. The free-fatty-acid levels were also elevated one to three minutes before the start while the drivers were on the starting grid, and up to one hour after the race. The triglyceride levels were slightly elevated after the event, continued to increase, and reached a

peak at one hour." The blood cholesterol level showed no significant changes.

Frankenhaeuser, M., Nordheden, B., Myrsten, A. L., Post, B.: "Psychophysiological reactions to understimulation and overstimulation." *Acta Psychol. (Amst.)* **35**: 298-308 (1971).
G99,743/71

In student policemen subjected to understimulation (vigilance test) and overstimulation (complex sensorimotor test), NEP releases were increased in comparison to their levels during the control condition with a medium amount of stimulation. Subjects excreting relatively more EP performed better during understimulation, whereas those excreting small amounts of EP performed more efficiently during overstimulation.

Lamke, L. O., Lennquist, S., Liljedahl, S. O., Wedin, B.: "The influence of cold stress on catecholamine excretion and oxygen uptake of normal persons." *Scand. J. Clin. Lab. Invest.* **30**: 57-62 (1972).
H61,015/72

In young men, exposure to cold greatly increased urinary excretion of EP and NEP with a concurrent rise in oxygen uptake. "This indicates that the catecholamines play an important part in the regulation of the heat balance."

Hartley, L. H., Mason, J. W., Hogan, R. P., Jones, L. G., Kotchen, T. A., Mougey, E. H., Wherry, F. E., Pennington, L. L., Ricketts, P. T.: "Multiple hormonal responses to graded exercise in relation to physical training." *J. Appl. Physiol.* **33**: 602-606 (1972).
H79,757/72

In man the stress of heavy bicycle exercise increased plasma STH, cortisol and EP values, but decreased insulin concentration.

Devlin, J. G., Varma, M. P. S., Kuti, J., O'Boyle, A.: "Studies on growth hormone release and cortisol with intravenous glucose loading." *Ir. J. Med. Sci.* **141**: 69-78 (1972).
J19,599/72

Data on patients under extreme stress following myocardial infarction or major surgical interventions. 1. Growth hormone release is not readily suppressible by glucose in the stress situation studied. 2. Circulating catecholamines are probably not primarily involved in releasing excess growth hormone, as insulin release is more frequently elevated at the same time. 3. The paradoxical rise in glucose which can occur in extreme stress, appears to be a reversion to a primitive pattern of growth hormone secretion which is observed in the newborn infant. 4. The effect

of glucose in adequately suppressing A.C.T.H. while producing statistically insignificant suppression of growth hormone releases, suggests either that the A.C.T.H. secreting cell is more sensitive to the direct effect of glucose, or that extra-pituitary factors, either neuronal or hormonal, may be of more significance in controlling growth hormone release."

Nikki, P., Takki, S., Tammisto, T., Jäättelä, A.: "Effect of operative stress on plasma catecholamine levels." *Ann. Clin. Res.* **4**: 146-151 (1972). G92,448/72

Kvetňanský, R., Kopin, I. J.: "Activity of adrenal catecholamine-producing enzymes and their regulation after stress." *Adv. Exp. Med. Biol.* **33**: 517-533 (1972).

J23,807/72

Observations on rats suggest that tyrosine hydroxylase activity increases in the adrenals during stress. This response is "most probably mediated by a direct effect of ACTH on the adrenal medulla or by an unknown factor (not cyclic-AMP) released from the adrenal cortex following ACTH administration" (37 refs.).

Kvetňanský, R.: "Biosynthesis of adrenal catecholamines during adaptation of rats to immobilization stress." *Adv. Exp. Med. Biol.* **33**: 603-617 (1972) (31 refs.).

J23,808/72

Solov'ev, G. M., Mashlina, E. S.: "Cardiac catecholamines in stress situations." *Kardiologija* **13** No. 1: 140-152 (1973) (Russian).

J22,759/73

Smith, G. P.: "Adrenal hormones and emotional behavior." *Prog. Physiol. Psychol.* **5**: 299-351 (1973). J11,271/73

Review concerned mainly with the production of catecholamines and corticoids by psychogenic stress, and the effect of these hormones on this type of stress (about 120 refs.).

O'Hanlon, J. F., Horvath, S. M.: "Interrelationships among performance, circulating concentrations of adrenaline, noradrenaline, glucose, and the free fatty acids in men performing a monitoring task." *Psychophysiology* **10**: 251-259 (1973). J3,116/73

In young men performing an exacting vigilance test, basal levels of blood EP and NEP were inversely related to glucose. EP initially increased during the test but later returned to its basal level in proportion to per-

formance of the task. NEP was not related to performance. Glucose and FFA were elevated, both during the tasks and throughout a control period spent watching slide projections.

Harrison, M. H.: "Comparison of the metabolic effects of centrifugation and heat stress in man." *Aerospace Med.* **44**: 299-303 (1973). H80,109/73

In fasted men the stress of centrifugation and exposure to heat produced increased blood lactate, glucose, FFA, glycerol and catecholamine levels, but these changes did not always parallel each other (30 refs.).

Åstrand, I., Fugelli, P., Karlsson, C. G., Rodahl, K., Vokac, Z.: "Energy output and work stress in coastal fishing." *Scand. J. Clin. Lab. Invest.* **31**: 105-113 (1973).

H65,774/73

Among fishermen, "about a tenfold increase in epinephrine and a four-fold increase in norepinephrine excretion were observed during work as compared to resting night values."

Turton, M. B., Deegan, T.: "Central and peripheral levels of plasma catecholamines, cortisol, insulin and non-esterified fatty acids." *Clin. Chim. Acta* **48**: 347-352 (1973). J8,031/73

In patients undergoing cardiac catheterization, elevations of EP, NEP, FFA and cortisol, with lowered levels of insulin, are ascribed to stress. However, certain differences are noted in the concentration of these substances in various vascular territories.

Johansson, G.: "Activation, adjustment and sympathetic-adrenal medullary activity. Field and laboratory studies of adults and children." *Rep. Psychol. Lab. University Stockholm*, Supp. 21: 1-25 (1973).

J10,479/73

Brief monograph on the value of catecholamine excretion as an indicator of psychogenic stress responses.

Halawani, M. E. el, Waibel, P. E., Appel, J. R., Good, A. L.: "Effects of temperature stress on catecholamines and corticosterone of male turkeys." *Am. J. Physiol.* **224**: 384-388 (1973). H65,841/73

In male turkeys, neither heat nor stress had any pronounced effect upon adrenal, brain or heart catecholamine concentrations; however, plasma corticosterone levels rose. When α -MT (an inhibitor of catecholamine synthesis) was given prior to stress exposure,

catecholamine concentrations fell markedly unless the birds had been previously adapted in hot or cold environments. "These findings indicate that an increased rate of catecholamine and corticosterone release seems to be required during the initial response to temperature stress, and may be associated with the adaptive changes leading to temperature acclimation" (20 refs.).

Neil-Dwyer, G., Cruickshank, J., Stott, A., Brice, J.: "The urinary catecholamine and plasma cortisol levels in patients with subarachnoid haemorrhage." *J. Neurol. Sci.* **22**: 375-382 (1974). J13,673/74

Normetanephrine and metanephrine are urinary metabolites of NEP and EP, respectively. In patients with subarachnoid hemorrhages, urinary excretion of these compounds and the plasma cortisol levels remain increased for fourteen days, after other evidence of stress has subsided.

Ortiz, G. A., Argüelles, A. E., Crespin, H. A., Sposari, G., Villafañe, C. T.: "Modifications of epinephrine, norepinephrine, blood lipid fractions and the cardiovascular system produced by noise in an industrial medium." *Horm. Res.* **5**: 57-64 (1974).

H81,167/74

In aircraft factory workers exposed to turbine noise for three hours, there was generally a marked elevation of catecholamine excretion as well as of blood cholesterol levels, FFA values, blood pressure and pulse frequency. Unexpectedly, the plasma corticoid concentrations were slightly subnormal, but this may have been due to circadian variations.

Zachariasen, R. D., Newcomer, W. S.: "Phenylethanolamine-N-methyl transferase activity in the avian adrenal following immobilization or adrenocorticotropin." *Gen. Comp. Endocrinol.* **23**: 193-198 (1974).

H88,608/74

In cockerels, ACTH and immobilization resulted in an increase in plasma EP and NEP with an accompanying decrease in the adrenal levels of these catecholamines; plasma corticosterone rose, as did the phenylethanolamine-N-methyl transferase (PNMT) content of the adrenals, without affecting adrenal corticosterone. "It is suggested that the rapid increase in PNMT activity, occurring with the acute application of stressors in chickens, may provide a means of sustaining an increased outflow of EP in times of 'stress'." Corticosterone may play a role in

the elevation of PNMT during the avian stress response.

Melton, C. E., McKenzie, J. M., Saldivar, J. T. Jr., Hoffmann, S. M.: "Comparison of Opa Locka Tower with other ATC facilities by means of a biochemical stress index." *Federal Aviation Administration, Aviat. Med.*, p. 11. Washington, D.C., 1974.

J22,333/74

Among ATCs, catecholamine excretion is greatest at airports with the heaviest traffic.

Ancona, L., Capoleoni, M.: "L'aggressione giustificata e non giustificata attraverso il dosaggio catecolaminico" (Justified and unjustified aggression through dosage of catecholamines). *Totus Homo* **5**: 17-26 (1974).

H97,091/74

In man, "stress produced by a stimulus set on film representing a sadistic scene induces diverse biochemical and psychodynamic reactions depending on whether the subject thinks that the stressing action seen by him is justified or not. When the subject watches an action that he judges socially and normally deplorable, the ratio of noradrenaline/adrenaline excreted in the urine varies in favor of the adrenaline and there is a significant increase in the projected aggressiveness."

Friedman, M., Byers, S. O., Diamant, J., Rosenman, R. H.: "Plasma catecholamine response of coronary-prone subjects (Type A) to a specific challenge." *Metabolism* **24**: 205-210 (1975).

H98,918/75

In a nonphysical competitive struggle (puzzle solving), the plasma NEP content of Type-A persons rises 30 percent above that of Type-B individuals, whereas plasma EP remains essentially unchanged in both groups.

Brooks, Ch. McC., Koizumi, K., Pinkston, J. O. (eds.): "The Life and Contributions of Walter Bradford Cannon 1871-1945." *Papers at a Centennial Symposium at State University of New York Downstate Medical Center 1972*, p. 264. New York: SUNY Downstate Medical Center, 1975.

E10,898/75

Symposium in which all surviving students and associates of W. B. Cannon have summarized his major contributions, especially regarding the understanding of homeostasis in relation to catecholamine secretion, as well as the manner in which their own work was stimulated by this great master of physiology. Contains articles by H. W. Davenport, J. Farman, Ch. McC. Brooks, Z. M. Bacq, H. Selye, K. Lissák, Ph. Bard and R. Gerard.

Corticotropin Releasing Factor (CRF)

The role of CRF in the mediation of stress responses from the hypothalamus to the pituitary will be discussed in the section, Theories.

Here, let us merely point out that in hypophysectomized, unlike in intact rats, CRF could be demonstrated in the peripheral blood, even after adrenalectomy or treatment with large doses of cortisol, but not after appropriate hypothalamic lesions. It was concluded that CRF is a specific hypothalamic neurohumor regulating ACTH discharge.

However, even under conditions of maximal secretion, CRF is too labile to be demonstrable in the peripheral blood, except during a short period after its release.

For abstracts relating to this section, see CRF under Theories (Nervous Mechanisms).

5-HT (5-Hydroxytryptamine or Serotonin) and Related Compounds

In man, the corticoid and indole excretion patterns showed similar circadian variations and rises after exposure to ACTH or stressors.

Sleep deprivation and other stressful experiences, like ACTH, result in the appearance of a "stress-responsive indole substance" (SRIS) in the urine of man. The physicochemical characteristics of this material were carefully described but it could not be definitely identified. It may be related to 5-HT.

Among white-collar workers, excretion of 5-HIAA, corticoids and catecholamines was increased during work days as compared to weekends, but excessive individual variations make interpretation of these data difficult.

In various species of animals travelling on satellite spaceships, exposure to ionizing rays, acceleration and vibration considerably diminished the blood 5-HT content.

The bulk of the literature on 5-HT metabolism will be found in Chapter V, Theories, as it relates to neurohumoral mechanisms within the CNS during stress.

5-HT and Related Compounds

(See also our earlier stress monographs, p. xiii, as well as 5-HT under Other Hormones and Hormone-like Substances in the section on Hormonal Mechanisms, and cf. EP and NEP in abstracts, where these catecholamines are mentioned, for comparison with 5-HT)

Blackman, J. G., Campion, D. S., Fastier, F. N.: "Mechanism of action of reserpine in producing gastric haemorrhage and erosion in the mouse." *Br. J. Pharmacol.* **14**: 112-116 (1959).

C68,958/59

In mice, gastric hemorrhage and erosion are produced by reserpine through a mechanism involving liberation of 5-HT.

Mandell, A. J., Slater, G. G., Mersol, I.: "An indole stress reactant. A preliminary report." *Arch. Gen. Psychiatry* **5**: 42-44 (1961). E56,435/61

Indole and 17-OHCS excretion varied simultaneously in patients under stress or after injection of ACTH. The indole discharge (and its possible relationship to 5-HT) could not be clarified; yet it was concluded "that this indole might serve as another interesting

dependent variable in studies of stress and stress diseases."

Mandell, A. J., Slater, G. G., Mersol, I.: "Indole-like urinary stress reactant in man." *Science* **133**: 1832-1833 (1961).

D6,807/61

Shore, P. A.: "Release of serotonin and catecholamines by drugs." *Pharmacol. Rev.* **14**: 531-550 (1962). D52,037/62

Review on the effects of various drugs upon brain serotonin and catecholamines. Data on the ability of stressors to influence these drug effects are contradictory.

Mandell, A. J., Slater, G., Geertsma, R. H., Mersol, I.: "Stress-responsive indole substance." *Arch. Gen. Psychiatry* **9**: 89-95 (1963). D69,236/63

Previous reports on a "stress-responsive indole substance" (SRIS) are confirmed in patients receiving an indole-free diet. The rise in the urinary excretion of this substance is associated with increased 17-OHCS excretion during stress and after ACTH injection (17 refs.).

Mandell, A. J., Kollar, E. J., Sabbot, I. M.: "Starvation, sleep deprivation, and the stress responsive indole substance." *Rec. Adv. Biol. Psychiatry* **6**: 96-104 (1963) (28 refs.). E58,533/63

Mandell, A. J.: "Some determinants of indole excretion in man." *Rec. Adv. Biol. Psychiatry* **5**: 237-256 (1963). D68,081/63

Indole and corticoid excretion showed similar circadian variations and rises after ACTH or exposure to stressors (70 refs.).

Mandell, A. J., Sabbot, I. M., Mandell, M. P., Kollar, E. J.: "The stress responsive indole substance in sleep deprivation." *Arch. Gen. Psychiatry* **10**: 299-305 (1964). G2,556/64

In man, sleep deprivation and other stressors as well as ACTH and functioning adrenocortical tumors produce the appearance in the urine of a "stress-responsive indole substance" (SRIS) whose physiochemical characteristics are described, although it could not yet be definitely identified.

Parin, V. V., Antipov, V. V., Raushenbakh, M. O., Saksonov, P. P., Shashkov, V. S., Chernov, G. A.: "Changes in blood serotonin level in animals exposed to ionizing radiation and dynamic factors of space flight." *Fed.*

Proc. **25**: T103-T106 (1966). F60,935/66

In various species of animals traveling on satellite spaceships, exposure to x-rays, acceleration and vibration considerably diminished the blood 5-HT content.

Anthony, M., Hinterberger, H., Lance, J. W.: "Plasma serotonin in migraine and stress." *Arch. Neurol.* **16**: 544-552 (1967). G46,944/67

Gál, E. M., Heater, R. D., Millard, S. A.: "Studies on the metabolism of 5-hydroxytryptamine (serotonin). VI. Hydroxylation and amines in cold-stressed reserpined rats." *Proc. Soc. Exp. Biol. Med.* **128**: 412-415 (1968). H2,154/68

Vaccarezza, J. R., Loro-Marchese, J. H., Ruiz, D. C.: "The effect of stress on the urinary secretion of serotonin." *Rev. Allergy* **23**: 304-309 (1969). J21,911/69

Sharma, V. N., Khanna, N. K.: "Effect of cold stress on acetylcholine and 5-HT contents of rat myocardium and its modification by eserine, mecamylamine and reserpine." *Indian J. Med. Res.* **57**: 1563-1572 (1969). G71,369/69

Markiewicz, L., Jankowski, K., Grzesiuk, L., Szadkowski, S.: "Excretion of catecholamines, corticosteroids and 5-HIAA as related to the testing conditions, physical fitness and psychological variables of healthy subjects." *Acta Med. Pol.* **14**: 51-68 (1973). J3,838/73

Among white-collar workers living in Warsaw, excretion of 5-HIAA, corticoids and catecholamines was higher during work days than on weekends, although individual variations were very wide.

Chernukh, A. M., Gorizontova, M. P., Alexeyev, O. V.: "The mechanism of participation of the mast cells in regulation of the vascular permeability." *Biochem. Exp. Biol.* **11**: 105-110 (1974). H96,177/74

In rats, restraint causes degranulation of mast cells with liberation of histamine, 5-HT and heparin. These substances may have a role in the mechanism of vascular reactions during stress.

Vaccari, A., Maura, G.: "Effects of chronic environmental stress on 5-hydroxytryptamine receptors in smooth muscle of rats." *Environ. Physiol. Biochem.* **4**: 259-262 (1974). J22,265/74

Histamine

Even in our first publications on the alarm reaction, we expressed the suspicion that liberation of some histamine-like substance may act as the "first mediator." However, this hypothesis still cannot be adequately proven.

It has been shown that, in severely burned patients, blood and urinary histamine, EP, NEP and corticoid excretion products are concurrently increased during the first twenty-four hours. However, their role in the pathogenesis of burn shock cannot be defined exactly.

In rats depleted of histamine by compound 48/80, adrenal ascorbic acid discharge by stressors (formalin, cold) or chlorpromazine is significantly suppressed. Such pre-treatment also significantly blocked adrenal ascorbic acid depletion and plasma corticosterone elevation, but did not change the effect of exogenous histamine. Under various other circumstances, the plasma corticosterone rise and adrenal ascorbic acid loss were also frequently dissociated. Hence, histamine release may play some role in the mediation of adrenal ascorbic acid depletion during stress, but there is no strict correlation between this change and the elevation of plasma corticosterone.

In rats and guinea pigs kept on vitamin C-deficient diets, a great variety of stressors increased histamine formation and urinary excretion. This effect could be inhibited by large doses of exogenous vitamin C, allegedly suggesting endogenous detoxication of histamine by ascorbic acid.

In rats, cold markedly reduced brain histamine but augmented its formation in the hypothalamus. Furthermore, the ME is conspicuously rich in histamine, a fact that raised a question as to "whether histamine is an active stimulant of pituitary secretion." However, in rats pretreated with phenergan and exposed to a great variety of stressors, only histamine became incapable of causing adrenal ascorbic acid discharge, which suggested that it cannot be the only humoral agent responsible for ACTH secretion during stress. Yet histidine decarboxylase is considered to be an adaptive enzyme, because its activity increases in various tissues under the influence of stressors, and even if it is not the only first mediator of ACTH discharge, it may act as one of the first mediators transmitting the stress message from directly damaged tissues throughout the organism, even after hypophysectomy.

Histamine

(See also our earlier stress monographs, p. xiii, and cf. Histamine under Other Hormones and Hormone-like Substances in the section on Hormonal Mechanisms)

Selye, H.: "A syndrome produced by diverse nocuous agents." *Nature* **138**: 32 (1936). 36,031/36

Brief letter to the editor describing the most characteristic signs of what is now known as the stress syndrome, particularly the thymicolymphatic involution, gastroduodenal ulcers, lipid discharge from the adrenal cortex and loss of chromaffinity in the medulla. The three stages are discussed. "We consider the first stage to be the expression

of a general alarm of the organism when suddenly confronted with a critical situation, and therefore term it the 'general alarm reaction.' Since the syndrome as a whole seems to represent a generalised effort of the organism to adapt itself to new conditions, it might be termed the 'general adaptation syndrome'." The reaction is regarded as a non-specific adaptive response to various kinds of agents and in view of its stereotypical appearance is ascribed to the liberation of some common initiating substance, possibly histamine.

Selye, H.: "Further evidence in support of the alarm reaction theory of adrenal insufficiency." *Am. J. Physiol.* **119**: 400-401 (1937). 68,414/37

Brief description of observations which "lead us to assume that the liberation from the tissues of certain toxic metabolites with histamine-like pharmacological effects is the primary cause both of the alarm reaction and of adrenal insufficiency."

Selye, H.: "Experimental production and prevention of appendicitis with histamine." *Can. Med. Assoc. J.* **36**: 462-464 (1937).

68,819/37

In certain strains of rats, intravenous injection of histamine causes acute phlegmonous appendicitis which may be prevented by pretreatment with smaller doses of the same substance. Other stressors may also produce similar appendicular lesions.

Tepperman, J., Rakieten, N., Birnie, J. H., Diermeier, H. F.: "Effect of antihistamine drugs on the adrenal cortical response to histamine and to stress." *J. Pharmacol. Exp. Ther.* **101**: 144-152 (1951). B59,242/51

In rats, various antihistamines (Phenoxyadrine, Benadryl, Pyribenzamine) did not significantly alter the adrenal ascorbic acid concentration, but intraperitoneal injection of histamine reduced it remarkably. On the other hand, "pretreatment with an antihistamine drug did not prevent or modify the adrenal ascorbic acid response to the stress of intraperitoneal carbon tetrachloride administration."

Harris, G. W., Jacobsohn, D., Kahlson, G.: "The occurrence of histamine in cerebral regions related to the hypophysis." In: Wolstenholme, G. E. W., *Ciba Foundation. Colloquia on Endocrinology*, Vol. 4, pp. 186-193. London: J and A Churchill, 1952.

B76,078/52

In rats, "the median eminence is conspicuously rich in histamine." It remains to be shown whether histamine is an active stimulant of pituitary secretion.

Guillemin, R., Fortier, C.: "Role of histamine in the hypothalamo-hypophyseal response to stress." *Trans. N.Y. Acad. Sci.* **15**: 138-140 (1953). B80,534/53

In rats pretreated with Phenergan and exposed to various "neurotropic" (sound, restraint) and "systemic" (cold, histamine) stressors, only histamine became incapable of causing adrenal ascorbic acid discharge. "These results do not support the view that histamine may be an important factor and, in no way, an indispensable link in hypothalamo-pituitary alteration due to neurotropic stress." They also show that histamine

cannot be the only humoral agent responsible for pituitary stimulation during stress.

Nasmyth, P. A.: "Histamine release and the 'stress phenomenon.'" *Br. J. Pharmacol.* **10**: 51-55 (1955). C4,608/55

From experiments in rats, "it is concluded that released histamine plays some part in the effect of 48/80 on the adrenal cortex."

Birke, G., Dunér, H., Liljedahl, S. O., Persnow, B., Plantin, L. O., Troell, L.: "Histamine, catechol amines and adrenocortical steroids in burns." *Acta Chir. Scand.* **114**: 87-98 (1958). J10,862/58

In severely burned patients, blood and urinary histamine, as well as the excretion of EP, NEP and corticoids (17-KGS) were considerably increased during the first twenty-four hours, but the duration of the rise varied according to the substances examined. Their role in the genesis of burn shock is discussed.

Schayer, R. W.: "Relationship of stress-induced histidine decarboxylase to circulatory homeostasis and shock." *Science* **131**: 226-227 (1960). C79,680/60

Histidine decarboxylase is considered to be an adaptive enzyme. Its activity in various tissues of the mouse increases under the influence of stressors (burns, delayed allergy, vaccines, cold, bacterial toxins and so on) and EP. Histamine may be a shock toxin or mediator of the stress reaction.

Schayer, R. W.: "Evidence that induced histamine is an intrinsic regulator of the microcirculatory system." *Am. J. Physiol.* **202**: 66-72 (1962). D17,063/62

In various species, "such diverse stimuli as increased room temperature, infection and injection of reticuloendothelial system activators elicit changes in histidine decarboxylase activity consistent with microcirculatory homeostasis." The fact that augmented amounts of glucocorticoids are needed during inflammation is "compatible with the existence of a vasodilator substance associated with small blood vessels, which may be produced at an increased rate either locally or systemically."

Schayer, R. W.: "Role of induced histamine in tourniquet shock in mice." *Am. J. Physiol.* **203**: 412-416 (1962). D32,955/62

Observations on mice traumatized with a tourniquet "suggest that the fundamental process leading to shock after fluid loss is activation of histamine synthesis in or near

cells of the capillaries to restore an adequate supply of blood to the tissues. Since induced histamine synthesis is controlled by local conditions, opening of the capillary beds proceeds independently of the over-all circulatory picture; finally, homeostasis can no longer be maintained."

Thayer, W. R., Toffler, A. H., Chapo, G., Spiro, H. M.: "Inhibition of restraint ulcers in the rat by pyridoxine deficiency." *Yale J. Biol. Med.* **38**: 257-264 (1965).

G37,375/65

In rats, pyridoxine deficiency decreases the incidence of restraint ulcers and depresses gastric secretion. "It is suggested that since pyridoxine deficiency lowers histamine-forming capacity, this reduction in endogenous histamine leads to a decrease in acid production which then protects against restraint ulcers.... Selye has shown that prior restraint markedly diminishes an animal's general response to a histamine liberator, 48-80. Selye suggested that this was the result of protection by endogenous corticoids, but an alternative explanation suggested by the present experiments is that restraint so exhausted the histamine stores that there could be no further response to a histamine liberator."

Garden, J. W.: "Plasma and sweat histamine concentrations after heat exposure and physical exercise." *J. Appl. Physiol.* **21**: 631-635 (1966).

F73,240/66

Bousquet, W. F., Miya, T. S., Sanchez, C.: "Modification of stress responses in histamine-depleted rats." *Br. J. Pharmacol.* **27**: 177-184 (1966).

G40,225/66

In rats, depletion of histamine by compound 48/80 significantly inhibited adrenal ascorbic acid diminution by formaldehyde, cold or chlorpromazine. Such pretreatment also blocked adrenal ascorbic acid depletion and plasma corticosterone elevation by compound 48/80, but did not affect that caused by exogenous histamine. Under various other circumstances, adrenal ascorbic acid depletion and plasma corticosterone elevation were also often dissociated. Histamine release may be of significance in mediating the ascorbic acid depletion produced by stressors, but there is no strict correlation between plasma corticosterone and adrenal ascorbic acid levels during stress. "The measurement of stress by a single parameter is thus not an absolute indication that a complete re-

sponse to stimulation of the pituitary-adrenal axis has taken place."

Filipp, G.: *Pathogenese und Therapie allergischer Reaktionen. Grundlagenforschung und Klinik* (Pathogenesis and therapy of allergic reactions. Theory and practice), p. 767. Stuttgart: Ferdinand Enke Verlag, 1966.

E6,824/66

Monograph on the pathogenesis of allergic reactions, with several sections on the G.A.S. Stress influences the immune system in various ways, since activation of the hypothalamus-pituitary-adrenocortical axis mobilizes corticoids and catecholamines, causes involution of the thymic lymphatic apparatus and brings about "anamnestic reactions" which reactivate preexistent immune responses. Furthermore, histamine metabolism is largely dependent upon the above-mentioned stress hormones; and cortisone as well as catecholamines have long been known to affect allergies of various kinds. Presumably, the so-called "nonspecific irritation therapy" (injection of foreign proteins, bacterial polysaccharides and so on) also plays a role in this respect.

Ritchie, W. P. Jr., Breen, J. J., Grigg, D. I.: "Prevention of stress ulcer by reducing gastric tissue histamine." *Surgery* **62**: 596-600 (1967).

G59,906/67

Ritchie, W. P. Jr., Breen, J. J., Grigg, D. I., Wangensteen, O. H.: "Effect of decreased levels of endogenous gastric tissue histamine on acid secretion and stress ulcer formation in the rat." *Gut* **8**: 32-35 (1967).

G44,746/67

"Decreased levels of tissue histamine were found to afford significant protection against the development of restraint-induced ulceration in the glandular portion of the rat's stomach."

Schayer, R. W.: "Histamine and stress responses of lymphoid tissues." *Endocrinology* **81**: 1357-1361 (1967).

F91,671/67

Levine, R. J., Senay, E. C.: "Histamine in the pathogenesis of stress ulcers in the rat." *Am. J. Physiol.* **214**: 892-896 (1968).

F96,913/68

Studies with brocresine (a potent inhibitor of histidine decarboxylase) and aminoguanidine (an inhibitor of diamine oxidase activity) "support the hypothesis that histamine plays an essential role in the pathogenesis of stress ulcers" produced in the rat by restraint and cooling.

Kahlson, G., Rosengren, E.: "New approaches to the physiology of histamine." *Physiol. Rev.* **48**: 155-196 (1968).

F93,235/68

Review on the physiology of histamine, with several sections on histamine formation under the influence of various stressors and hormones (155 refs.).

Nowara, M.: "Histamine concentration in blood, plasma, and sweat of humans under thermal stress." *Acta Physiol. Pol.* **20**: 967-970 (1969) (Polish).

H22,361/69

Taylor, K. M., Snyder, S. H.: "Brain histamine: rapid apparent turnover altered by restraint and cold stress." *Science* **172**: 1037-1039 (1971).

H41,123/71

In rats, cold markedly reduced brain histamine levels but augmented its formation in the hypothalamus.

Makarov, I. A.: "Role of histaminemia in changes of the eosinophil count during stress." *Vrach. Delo* No. 1: 77-79 (1971) (Russian).

J19,053/71

Observations on the rat and man suggest that "histamin may be the cause of eosinopenia and eosinophilia. Local histaminemia is accompanied by eosinopenia, total by eosinophilia. It is concluded that poststress eosinopenia develops due to prevailing migration of eosinophils into tissues with an increased histamin content as compared with their mobilization from the bone marrow. Blocking of endogenous histamin leads only to mobilization of cells from the bone marrow causing [the] paradoxical character of the reaction."

Makarov, I. A.: "Role of the adrenals in the development of post-stress eosinopenia." *Ter. Arkh.* **44** No. 11: 53-58 (1972) (Russian)

H91,719/72

There is no evidence of a direct destruction of blood eosinophils by glucocorticoids. Observations in rats and patients suggest that stress eosinopenia is produced by "local freeing of endogenic histamin in a number of organs. Glucocorticoids play the auxiliary role of a creator of an appropriate gradient of histamin concentration in the blood and tissues causing migration of eosinophils in the tissue. This confirmed the fact of blocking eosinopenia by dimedrol premedication. A regular drop in the markedness of eosinopenia observed in stress in patients with considerable hypercorticism can be attributed to the increase of the level of natural antagonist of

histamin-heparin in patients of such kind."

Seidel, W., Lorenz, W., Doenicke, A., Mann, G., Uhlig, R., Rohde, H.: "Histamin-freisetzung beim Menschen und Stressulkus-Pathogenese" (Histamine liberation in man and the pathogenesis of stress ulcers). *Z. Gastroenterol.* **11**: 297-300 (1973).

J24,571/73

In man, the plasma histamine content rises under the influence of various stressors and may play an important role in the pathogenesis of stress ulcers.

Chernukh, A. M., Gorizontova, M. P., Alexeyev, O. V.: "The mechanism of participation of the mast cells in regulation of the vascular permeability." *Biochem. Exp. Biol.* **11**: 105-110 (1974).

H96,177/74

In rats, restraint causes degranulation of mast cells with liberation of histamine, 5-HT and heparin. These substances may have a role in the mechanism of vascular reactions during stress.

Kakihana, R., Blum, S., Kessler, S.: "Developmental study of pituitary-adrenocortical response in mice: plasma and brain corticosterone determination after histamine stress." *J. Endocrinol.* **60**: 353-358 (1974).

H83,418/74

In newborn mice, histamine caused a rise in plasma corticosterone between the sixteenth and twenty-first day of life, but not between the third and eleventh day. In the younger group the corticosterone levels of the brains of nonstressed controls were much higher than those of the older animals. Histamine significantly increased brain corticosterone during both periods, particularly in the stress-responsive older mice.

Galvin, M. J. Jr., Reichard, S. M.: "Hemoglobin and enzyme changes in stress." *Fed. Proc.* **33**: 317 (1974).

H84,077/74

In rats, histidine decarboxylase activity in the lung increases immediately after mechanical trauma. The "correlation of histamine production with the onset of hemoconcentration may be important in the pathophysiological changes leading to ultimate failure of the cardiovascular system."

Lorenz, W., Seidel, W., Doenicke, A., Tauber, R., Reimann, H.-J., Uhlig, R., Mann, G., Dormann, P., Schmal, A., Häfner, G., Hamelmann, H.: "Elevated plasma histamine concentrations in surgery: causes and clinical significance." *Klin. Wochenschr.* **52**: 419-425 (1974).

H86,774/74

In various animal species as well as in man, surgical interventions caused a discharge of histamine from diverse tissues, often accompanied by a rise in plasma histamine concentration. This response may account at least in part for hypotension, peptic ulcer formation and various other classic manifestations of stress. Unexpectedly, pre-operative medications may cause even more pronounced rises in plasma histamine than does the surgical intervention itself.

Kobayashi, R. M., Kopin, I. J.: "The effects of stress and environmental lighting on histamine in the rat brain." *Brain Res.* **74**: 356-359 (1974). J13,853/74

Review and personal observations on the effect of cold, restraint and various types of

illumination upon the histamine content of different regions in the rat brain.

Nandi, B. K., Subramanian, N., Majumder, A. K., Chatterjee, I. B.: "Effect of ascorbic acid on detoxification of histamine under stress conditions." *Biochem. Pharmacol.* **23**: 643-647 (1974). H81,833/74

In both rats and guinea pigs kept on an ascorbic acid-free diet, a variety of stressors (vaccines, toxoids, malnutrition, cold, heat, pregnancy) increased histamine formation and excretion into the urine. "Administration of large doses of ascorbic acid in any of the stressful situations resulted in a marked decrease in the urinary histamine level indicating detoxification of histamine in vivo."

Renin, Angiotensin

The renal pressor mechanism is undoubtedly also influenced during stress. In patients, operations under deep anesthesia raise renin secretion, presumably as a consequence of catecholamine release. The response is also modified by blood volume changes.

In severely burned patients, plasma renin and angiotensin II were usually extremely high, and the elevation persisted for days or weeks.

In healthy young men, exposure to high altitudes decreased plasma renin activity conjointly with urinary aldosterone excretion, roughly in proportion to the intensity of the mountain sickness that they developed. It remains to be shown whether this change is to be ascribed to lowered barometric pressure.

Rises in plasma renin were observed in patients undergoing various types of surgery or even anesthesia in preparation for surgery.

In rats, chronic exposure to stressors (sound, light, vibration) caused hypertension with increased turnover of NEP in the CNS. The chronic phase of this response was associated "with an action of angiotensin II on central receptors." In rats exposed to repeated electroshocks, the marked rises in the plasma concentrations of renin and corticosterone coincided. Hypophysectomy did not inhibit the increased plasma renin activity, which was blocked by dexamethasone and propranolol. Phentolamine increased it. Possibly, stress-induced renin release is mediated via β -adrenergic receptors, and corticoids modify this response.

Renin, Angiotensin

(See also our earlier stress monographs, p. xiii)

Lantos, C. P., Dahl, V., Basso, N., Cordeiro-Funes, J. R., Wassermann, G. F.: "A correlative study between adrenal function and the duration and intensity of an experi-

mentally produced disease of adaptation." *J. Steroid Biochem.* **2**: 335-347 (1971).

G88,441/71

In rats, stress produced by repeated intramuscular injections of formaldehyde caused a particularly pronounced increase in the secretion of aldosterone, and to a lesser extent of corticosterone, into the adrenal vein blood.

18-OH-DOC discharge was less markedly raised, and was not as clearly correlated with the intensity and duration of stress as were the other two corticoids. Plasma renin concentrations diminished during stress. The authors believe that "the present results exclude the possibility that the increased aldosterone secretion was secondary to an augmented plasma angiotensin concentration."

Pettinger, W. A., Augusto, L., Leon, A. S.: "Alteration of renin release by stress and adrenergic receptor and related drugs in unanesthetized rats." *Adv. Exp. Med. Biol.* **22**: 105-117 (1972). G94,419/72

Renin release noted after exposure to various stressors can be influenced by diverse drugs. "The beta-adrenergic blocking drug propranolol suppressed endogenous release of renin and inhibited renin release induced by stresses of swimming and anesthesia.... Suppression of endogenous renin release by propranolol could play a role in the antihypertensive properties of this drug in man."

Bailey, R. E., Bartos, D., Bartos, F., Castro, A., Dobson, R. L., Gretie, D. P., Kramer, R., Macfarlane, D., Sato, K.: "Activation of aldosterone and renin secretion by thermal stress." *Experientia* **28**: 159-160 (1972). H54,154/72

Robertson, D., Michelakis, A. M.: "Effect of anesthesia and surgery on plasma renin activity in man." *J. Clin. Endocrinol. Metab.* **34**: 831-836 (1972). H54,882/72

During surgery under deep anesthesia, plasma renin activity increases in patients. "Although catecholamine release and sympathetic discharge undoubtedly play a role in raising renin secretion during surgical stress, the results of the present study suggest that renin secretion during such stress is modified by blood volume changes."

Doleček, R., Závada, M., Adámková, M., Leikep, K.: "Plasma renin like activity (RLA) and angiotensin II levels after major burns. A preliminary report." *Acta Chir. Plast. (Praha)* **15**: 166-169 (1973). J9,675/73

In severely burned patients, plasma renin and angiotensin II were usually very high, and the rise persisted for days or weeks.

Buckley, J. P.: "Biochemical and physiological effects of intermittent neurogenic stress." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 165-177. Bratislava: Slovak

Academy of Sciences, 1973. E10,466/73

Various stressors (sound, light, vibration) chronically applied to rats caused hypertension, with an increased NEP turnover in the CNS. Possibly, "the chronic phase of the response is associated with an action of angiotensin II on central receptors."

Hogan, R. P., Kotchen, T. A., Boyd, A. E., Hartley, L. H.: "Effect of altitude on renin-aldosterone system and metabolism of water and electrolytes." *J. Appl. Physiol.* **35**: 385-390 (1973). J5,657/73

In healthy young males, exposure to a simulated altitude of 12,000 ft. decreased plasma renin activity and urinary aldosterone excretion in proportion to the symptoms of acute mountain sickness that were manifested. It remains to be proven whether these changes are due to stress or to the specific effects of anoxia (45 refs.).

Tsukiyama, H., Otsuka, K., Kyuno, S., Fujishima, S., Kijima, F.: "Influence of immobilization stress on blood pressure, plasma renin activity and biosynthesis of adrenocorticoid." *Jap. Circ. J.* **37**: 1265-1270 (1973). H81,677/73

In rabbits, "shortly after the beginning of immobilization stress a remarkable elevation in the arterial pressure, a significant increase in plasma renin levels and plasma corticosterone concentrations were observed." However, the changes in plasma renin and corticosterone activity did not parallel one another, and hence there would appear to be different mechanisms activating the renin-angiotensin and pituitary-adrenocortical systems. EEG studies suggest that the homeostatic mechanisms mediated by the mesencephalic reticular formation and grey matter regulate blood pressure and renin release, while the hippocampus, amygdala and anterior hypothalamic area are less effective in this respect. The results of selective electric stimulation of various brain areas substantiate this interpretation.

Leon, A. S., Pettinger, W. A., Saviano, M. A.: "Enhancement of serum renin activity by exercise in the rat." *Med. Sci. Sports* **5**: 40-43 (1973). J11,490/73

In rats, serum renin activity was enhanced during stress caused by swimming, but this rise was "blocked by propranolol, suggesting that beta-adrenergic mechanisms are involved in increased renin release induced by exercise stress."

Leenen, F. H., Shapiro, A. P.: "Effect of

intermittent electric shock on plasma renin activity in rats." *Proc. Soc. Exp. Biol. Med.* **146**: 534-538 (1974). H87,670/74

In rats, repeated electroshocks caused a marked increase in both the renin and corticosterone concentrations of the plasma. Hypophysectomy did not inhibit the rise in plasma renin activity, which was blocked by dexamethasone and propranolol but potentiated by phentolamine. Presumably, the "stress-induced release of renin is mediated via β -adrenergic receptors and endogenous corticosteroids modify this response."

Gál, T. J., Cooperman, L. H., Berkowitz, H. D.: "Plasma renin activity in patients undergoing surgery of the abdominal aorta." *Ann. Surg.* **179**: 65-69 (1974). J9,433/74

Surgical anesthesia sufficed to increase plasma renin activity, but a further rise was noted following subsequent insertion of an aortic bifurcation graft and release of the cross-clamped aorta. [The observations do not permit differentiation between the role of stress and of the specific operative procedure (H.S.).]

Molteni, A., Zakheim, R. M., Mullis, K. B., Mattioli, L.: "The effect of chronic alveolar hypoxia on lung and serum angiotensin I converting enzyme activity." *Proc. Soc. Exp. Biol. Med.* **147**: 263-265 (1974). H95,543/74

In mice, hypoxia caused elevations in serum and lung angiotensin I converting enzyme, closely related to renal renin granules. "The significance of the stimulation of the renin angiotensin aldosterone system in the response to hypoxia remains unknown. It may be an adjustment to the stress of hypoxia or be necessary to the erythropoietic response."

Finberg, J. P. M., Katz, M., Gazit, H., Berlyne, G. M.: "Plasma renin activity after acute heat exposure in nonacclimatized and naturally acclimatized man." *J. Appl. Physiol.* **36**: 519-523 (1974). J12,804/74

Baumann, R.: "Theoretische und klinische Aspekte der zerebro-viszeralen Regulationskrankheit arterielle essentielle Hypertonie. I. Zu Problemen der Adaptations-Maladaptionsprozesse und der pathogenetischen Effizienz des psycho-emotionalen Stresses" (Theoretical and chemical analyses of cerebro-visceral regulation of essential arterial hypertension. I. Problems of adaptation-maladaptation processes and the pathogenetic efficiency of psycho-emotional stress). *Dtsch. Gesundheitsw.* **29**: 673-676 (1974).

J15,328/74

Baumann, R.: "II. Hämodynamische und biochemische Regulationsstörungen des jugendlichen Hypertoniens unter Stressexposition" (II. Hemodynamic and biochemical disturbances in young male hypertensive patients under stress). *Dtsch. Gesundheitsw.* **29**: 721-733 (1974).

J15,329/74

In young hypertensive patients with or without latent diabetes, emotional stress produced a rise in plasma FFA, NEP and renin (63 refs.).

Carvalho, J. S., Shapiro, R., Hopper, P., Page, L. B.: "Methods for serial study of renin-angiotensin system in the unanesthetized rat." *Am. J. Physiol.* **228**: 369-375 (1975).

H99,301/75

"In the rat, most methods of blood collection involve stress of emotion, pain, or anesthesia. All these stimuli are known to increase the rate of renin secretion." The authors' findings were confirmed by an improved technique.

Acetylcholine

Neither cholinergic, adrenergic nor histaminergic blocking agents prevented ACTH secretion in the rat; hence, it was concluded that catecholamines, acetylcholine and histamine do not play an important role in activating the hypothalamus-pituitary system during stress in this species.

On the other hand, carbaminoylecholine and eserine injected into the septum, preoptic region, anterolateral hypothalamus or the dorsal tegmental area did inhibit pituitary-adrenal activity. Furthermore, ACTH secretion was increased by cholinergic stimulation of the medial and caudal hypothalamus as well as of the posterior hypothalamus and ventral tegmentum.

The acetylcholine content of various regions of the rat brain was not consistently

influenced by stress. However, implantation of atropine crystals into the anterior hypothalamus greatly inhibited ACTH secretion following exposure to various stressors, whereas similar implantations of other materials were ineffective. It was concluded that "the hypothalamic control of pituitary corticotropin may have a cholinergic component" which may regulate CRF discharge.

The deposition of small amounts of acetylcholine in the immediate extracellular environment of single cells in the CNS showed that some neurons are particularly sensitive to the direct effect of acetylcholine; these may be involved in ACTH discharge.

Acetylcholine

(See also our earlier stress monographs, p. xiii)

Guillemin, R.: "A re-evaluation of acetylcholine, adrenaline, nor-adrenaline and histamine as possible mediators of the pituitary adrenocortotropic activation by stress." *Endocrinology* **56**: 248-255 (1955).

C2,756/55

In rats, it was impossible to inhibit the ACTH release following stress (formalin, restraint) by pretreatment with adrenergic or cholinergic-blocking agents or antihistamines. It is concluded that EP, NEP and histamine are not indispensable or even important mediators of hypothalamus-pituitary activation by stress.

Endrőczi, E., Schreiberg, G., Lissák, K.: "The role of central nervous activating and inhibitory structures in the control of pituitary-adrenocortical function. Effects of intracerebral cholinergic and adrenergic stimulation." *Acta Physiol. Acad. Sci. Hung.* **24**: 211-212 (1963). G12,029/63

In the cat, pituitary-adrenocortical activation evoked by cholinergic and adrenergic drugs injected into various areas of the CNS has been examined. "Carbaminoylecholine and eserine injected into the septum, preoptic region, anterolateral hypothalamus or into the dorsal tegmental area, were found to inhibit pituitary-adrenal activity. Cholinergic chemical stimulation of the medial and caudal hypothalamus, as well as of the posterior hypothalamus and ventral tegmentum resulted in an increase of ACTH secretion. Adrenaline, nor-adrenaline and ephedrine increased ACTH secretion only when injected into the area of the posterior hypothalamus and ventral tegmentum. The suppression of adrenocortical activity in response to the cholinergic stimulation of the inhibitory structures of the forebrain could be blocked by the adrenergic stimulation of the posterior

hypothalamus." Apparently, chemical stimulation of the diencephalon and brain stem makes it possible to separate endocrine regulatory activities from complex behavioral reactions.

Bowers, M. B. Jr., Hartmann, E. L., Freedman, D. X.: "Sleep deprivation and brain acetylcholine." *Science* **153**: 1416-1417 (1966). F70,358/66

In rats, sleep deprivation caused "a significant fall in brain acetylcholine in the telencephalon; there were no significant changes in the diencephalon and brain stem. Restraint stress and activity wheel stress produced no significant change in acetylcholine levels in any of these regions; the telencephalic response to sleep deprivation, therefore, cannot be attributed to nonspecific stress."

Khanna, N. K., Madan, B. R.: "Effect of beta adrenergic blocking agents on stress induced changes in acetylcholine content of rat's myocardium." *Arch. Int. Pharmacodyn. Ther.* **175**: 136-140 (1968). H6,739/68

The cold stress-induced increase in the acetylcholine content of the rat myocardium is prevented by pretreatment with β -adrenergic blockers.

Hedge, G. A., Smelik, P. G.: "Corticotropin release: inhibition by intrahypothalamic implantation of atropine." *Science* **159**: 891-892 (1968). J11,294/68

In rats, implantation of atropine crystals in the anterior hypothalamus greatly inhibits ACTH secretion following surgical trauma, ether anesthesia and arginine vasopressin. Similar implantations in other nearby brain regions are ineffective. Presumably, "the hypothalamic control of pituitary corticotropin may have a cholinergic component" which may regulate the discharge of CRF.

Steiner, F. A., Ruf, K., Akert, K.:

"Steroid-sensitive neurones in rat brain: anatomical localization and responses to neurohumours and ACTH." *Brain Res.* **12**: 74-85 (1969). H28,002/69

Microelectrophoresis allows the deposition of minute amounts of soluble compounds in the immediate extracellular environment of single cells in the CNS, and a direct monitoring of the local response by recording single unit action potentials. With this technique it has been shown that in rats dexamethasone-sensitive cells scattered over wide areas can be identified and localized in the hypothalamus and midbrain. The majority of these cells are clearly inhibited, but some are activated. No steroid-sensitive neurons were found in the cortex, dorsal hippocampus or thalamus. The steroid-sensitive neurons were also responsive to microelectrophoretically-applied NEP and acetylcholine. The predominant action of the former was inhibition while that of the latter was stimulation. ACTH activated the steroid-sensitive neurons. Presumably, "specific nerve cells in the hypothalamus and midbrain are sensitive to both hormonal and humoral factors and involved in negative and positive feedback actions of the hormones."

Sharma, V. N., Khanna, N. K.: "Effect of cold stress on acetylcholine and 5-HT contents of rat myocardium and its modification

by eserine, mecamylamine and reserpine." *Indian J. Med. Res.* **57**: 1563-1572 (1969). G71,369/69

Godhwani, J. L., Sharma, V. N.: "Stress-induced changes in myocardial acetylcholine cholinesterase and 5-hydroxytryptamine and their modification by antiadrenergic drugs." *Indian J. Med. Res.* **58**: 1729-1735 (1970). G84,767/70

Khanna, N. K.: "Effect of cold stress on acetylcholine content of rat myocardium and its modification by atropine." *Jap. J. Pharmacol.* **21**: 425-426 (1971). H47,274/71

Khanna, N. K., Lauria, P., Sharma, V. N.: "Effect of electroshock stress on the glycogen and acetylcholine content of the myocardium of the dog." *Indian J. Med. Sci.* **26**: 380-382 (1972). G94,705/72

Electroshock stress produced an increase in acetylcholine and a decrease in glycogen in the myocardium of the dog.

Allikmets, L. H.: "Cholinergic mechanisms in aggressive behaviour." *Med. Biol.* **52**: 19-30 (1974). J14,512/74

A review on brain 5-HT and catecholaminergic systems in aggressive behavior. It is suggested that the cholinergic trigger mechanism of aggressive behavior depends on brain 5-HT and catecholaminergic processes (75 refs.).

Pheromones

Pheromone has been considered as a possible stress hormone because, in fish, this substance (secreted by specialized cells in the epidermis) causes not only peculiar "fright and alarm behavior" but also flight or withdrawal. It has been designated as "alarm pheromone" and can allegedly enhance avoidance conditioning. Through all these effects, it appears to exert a protective, adaptive action.

Some similar compound may also exist in mammals. Mice exposed to the odor of an animal for which they expressed preference are repulsed by it upon application of stress to the "communicator." Removal of the olfactory mucosa abolished the odor aversion, indicating the presence of a "true pheromone." Possibly, the glands which secrete the pheromone are near the urethra; hence, the odor can be conveyed either by the urine or by direct excretion.

Pheromones

(See also our earlier stress monographs, p. xiii)

Skinner, W. A., Mathews, R. D., Parkhurst, R. M.: "Alarm reaction of the top smelt, *Atherinops affinis* (Ayres)." *Science* **138**: 681-682 (1962). D38,493/62

Thomson, D. A.: "Ostracitoxin: an ichthyotoxic stress secretion of the boxfish, *Ostracion lentiginosus*." *Science* **146**: 244-245 (1964). F21,880/64

Under conditions of stress, the boxfish exudes a nonprotein hemolytic poison designated as "ostracitoxin." Introduction of a newly captured, highly excited specimen into

an aquarium can cause the death of all other fish within a few minutes. Partial purification of the toxin suggests that it may be a steroid saponin. It is poisonous also for vertebrates. [Its possible relationship to pheromones is not mentioned (H.S.).]

Thines, G., Vandenbussche, E.: "The effects of alarm substance on the schooling behaviour of *Rasbora heteromorpha duncker* in day and night conditions." *Anim. Behav.* **14**: 296-302 (1966). J23,194/66

Rosenblatt, R. H., Losey, G. S. Jr.: "Alarm reaction of the top smelt, *Atherinops affinis*: reexamination." *Science* **158**: 671-672 (1967). J22,282/67

Review of the literature on the "alarm substance" in the skin of the minnow *Phoxinus laevis L.*, which alters the behavior of some species of fish in that they refuse food and dash toward cover. This "alarm reaction" in fishes is restricted to members of the order *Cypriniformes*. Contrary to other reports in the literature, the authors did not observe the alarm reaction in the top smelt *Atherinops affinis* (Ayres) when it was exposed to a methanol extract of whole top smelt; they regard this response as an experimental artifact (10 refs.).

Valenta, J. C., Rigby, M. K.: "Discrimination of the odor of stressed rats." *Science* **161**: 599-601 (1968).

F98,695/68

Rats can distinguish between the odor of stressed and nonstressed rats. "Five animals learned to interrupt an ongoing response when air from the cages of stressed rats was introduced into the test compartment, and to continue responding when air from unstressed rats was introduced. The discrimination does not seem to depend on recognition of odors of individual rats." This is tentatively ascribed to the production of pheromones.

Kimbrell, G. M., Weinrott, M. R., Morris, E. K. Jr., Scheid, J., Sangston, D.: "Alarm pheromone and avoidance conditioning in goldfish, *Carassius auratus*." *Nature* **225**: 754 (1970). H21,093/70

"The alarm reaction in fish is believed

to be produced by a chemical substance (pheromone) secreted by specialized cells in the epidermis." A crude preparation of "alarm pheromone" dropped into an aquarium, causes "not only 'fright' and 'alarm' behaviour but also flight or withdrawal." Presumably, the pheromone can even enhance avoidance conditioning. [It is not clear whether the "alarm reaction" described here is equivalent to the first phase of the G.A.S. (H.S.).]

Carr, W. J., Martorano, R. D., Krames, L.: "Responses of mice to odors associated with stress." *J. Comp. Physiol. Psychol.* **71**: 223-228 (1970). G75,361/70

"Male mice respond to an olfactory signal emitted by stressed mice."

Stevens, D. A., Köster, E. P.: "Open-field responses of rats to odors from stressed and nonstressed predecessors." *Behav. Biol.* **7**: 519-525 (1972). J21,339/72

"While stressing may not evoke an *alarm* pheromone, it seems likely that stressed rats do produce an odor with pheromonal qualities."

Rottman, S. J., Snowdon, C. T.: "Demonstration and analysis of an alarm pheromone in mice." *J. Comp. Physiol. Psychol.* **81**: 483-490 (1972). H79,754/72

"Mice exposed to the odor of a stressed nonspecific communicator demonstrated an aversion to the source of the odor, although prior to the stress they had demonstrated a preference for the source of the communicator's odor.... Mice that were socially isolated for 12 wk. after weaning could emit the odor when stressed but responded inappropriately. Subsequently, 15 wk. of social experience improved, but did not restore to normal, the odor aversion of the isolates. Removal of the olfactory mucosa abolished the odor aversion, indicating the presence of a true pheromone." Intense stress induced the mice to excrete an "alarm pheromone" that brings about avoidance behavior by the recipient. Possibly, the glands that secrete the pheromone are located either in or near the urethra. Hence, the odor can be conveyed either by the urine or by direct excretion.

Kinins

Blood kinin concentrations are increased by muscular stress in man, whereas emotional stress has an opposite effect. It has been suspected that blood kinin represents a humoral mechanism regulating adaptation of the cardiovascular system.

In rats exposed to endotoxin shock, inactivation of bradykinin by kininase is considerably diminished and this has been held responsible for the raised level of circulating bradykinin.

Kinins

(See also our earlier stress monographs, p. xiii)

Lantsberg, L. A., Nekrasova, A. A., Tsepko, N. K.: "Changes in blood kinin system in various physiological states." *Cor vasa (Praha)* **15**: 190-198 (1973).

J9,744/73

In man, muscular stress increases, whereas emotional stress decreases, blood kinin concentrations. "Evidently, the blood kinin system represents one of the humoral mechanisms governing the adaptation of the cardiovascular system to various conditions."

Herman, C. M., Oshima, G., Erdös, E. G.: "The effect of adrenocorticosteroid pretreatment on kinin system and coagulation response to septic shock in the baboon." *J. Lab. Clin. Med.* **84**: 731-739 (1974) (40 refs.).

J18,036/74

Hirsch, E. F., Nakajima, T., Oshima, G., Erdös, E. G., Herman, C. M.: "Kininsystem responses in sepsis after trauma in man." *J. Surg. Res.* **17**: 147-153 (1974).

J16,838/74

Observations on previously healthy young soldiers with combat wounds "suggest the liberation of bradykinin in septic shock."

Sardesai, V. M., Rosenberg, J. C.: "Proteolysis and bradykinin turnover in endotoxin shock." *J. Trauma* **14**: 945-949 (1974).

J18,604/74

Experiments on dogs and rats "suggest that in endotoxin shock the inactivation of bradykinin by kininase is considerably lessened, and that the extremely high level of circulating bradykinin is the result of its elaboration by increased proteolysis as well as its decreased inactivation by kininases."

Prostaglandins

Since patients with peptic ulcers have a deficient prostaglandin E concentration in plasma and gastric juice, and since such ulcers are related to stress, the possible participation of prostaglandins in the stress response must also be considered. During hemorrhagic stress, arterial prostaglandin levels are high. In this connection, the E and F types may be of the greatest importance.

Additional data concerning this subject will be found in the section on peptic ulcers, in which prostaglandins have been considered to play a major pathogenic role and are consequently recommended for treatment.

Prostaglandins

(See also our earlier stress monographs, p. xiii)

Horrobin, D. F., Manku, M. S., Karmali, R. A., Nassar, B. A., Greaves, M. W.: "Pro-lactin and prostaglandin synthesis." *Lancet* November 9, 1974, p. 1154. H95,470/74

Observations on rats suggest that increased LTH production during stress may stimulate prostaglandin synthesis.

Hinsdale, J. G., Engel, J. J., Wilson, D. E.: "Prostaglandin E in peptic ulcer disease." *Prostaglandins* **6**: 495-500 (1974).

J13,965/74

Patients with peptic ulcers have a deficiency in the prostaglandin E concentration of plasma and gastric juice. This may indicate that treatment of peptic ulcers by prostaglandin E represents a substitute type of therapy (12 refs.).

Flynn, J. T., Reed, E. A.: "Arterial prostaglandin levels following hemorrhagic shock in the dog." *Fed. Proc.* **33**: 317 (1974). H84,078/74

"During hemorrhagic stress, it appears that arterial pg [prostaglandin] levels are elevated, and that the E and F types may be of greatest physiological importance."

Various Other Hormones and Hormone-like Substances

Little is known about the participation of other hormones and hormone-like substances in the stress response.

Various Other Hormones and Hormone-like Substances

(See also our earlier stress monographs, p. xiii)

Orr, W. H.: *Hormones, Health and Happiness*, p. 322. New York and London: Macmillan, 1954. B97,161/54

Popular description of the role of endocrine glands in disease, with a special chapter on the alarm reaction.

Unoza, A.: "Fluctuation of adrenal cholesterol and corticosterone [as well as *parotin*] levels during stress induced by histamine." *Shikwa Gaku* **68**: 1650-1659 (1968) (Japanese). J24,735/68

Schwille, P. O., Schellerer, W., Reitzenstein, M., Hermanek, P.: "Hyperglucagonemia, hypocalcemia and diminished gastric blood flow—evidence for an etiological role in stress

ulcer of rat." *Experientia* **30**: 824-826 (1974). H90,543/74

In both intact and adrenalectomized rats, restraint causes gastric ulcers with a considerable rise in glucagon and a decrease in gastrin which are attributed to stress.

Goldstein, A. L., Hooper, J. A., Schulof, R. S., Cohen, G. H., Thurman, G. B., McDaniel, M. C., White, A., Dardenne, M.: "Thymosin and the immunopathology of aging." *Fed. Proc.* **33**: 2053-2056 (1974). H92,570/74

Thymosin, a low molecular weight acidic polypeptide isolated from thymus tissue, is probably a hormone. Its blood concentration is high in young and low in old people. Probably the thymus through secretion of thymosin and perhaps other hormones, can act at a distance and influence the function and development of lymphoid cells involved in cell-mediated immunity, thereby participating in the aging process.

OTHER METABOLITES

Lipids in General

Several review articles and monographs deal with lipid changes during stress. The most striking and constant alterations in lipid metabolism are an increase in blood cholesterol, FFA, lipid phosphorus and lipoproteins. Presumably, lipid mobilization is necessary to cope with heightened metabolic requirements during emergencies.

Since in most publications various lipid constituents are discussed conjointly, it would lead to countless unnecessary repetitions to cite each communication under every type of lipid constituent mentioned. Hence, with very few exceptions, we shall classify the literature according to that lipid metabolite which has received the greatest attention in a particular communication.

Lipids in General

(See also our earlier stress monographs, p. xiii)

Beischer, D. E.: "Effect of simulated flight stresses on the concentration of serum cholesterol, phospholipid and lipoprotein." *J.*

Aviat. Med. **27**: 260-266 (1956) (24 refs.). J13,199/56

Zarafonetis, C. J. D., Seifter, J., Baeder, D., Kalas, J. P.: "Lipid mobilization as a consequence of surgical stress." *Am. J. Med. Sci.* **237**: 418-433 (1959). C67,041/59

Horwitz, C., Bronte-Stewart, B.: "Mental stress and serum lipid variation in ischemic heart disease." *Am. J. Med. Sci.* **244**: 272-281 (1962). E44,952/62

Allison, J. B.: "Stress diseases in relation to nutrition." *Rev. Invest. Clin.* **14**: 139-154 (1962). D29,232/62

Protein malnutrition, tumor growth and hypertension cause hyperlipemia in the dog and rat. They are considered to be stress diseases treatable by adequate protein intake.

Leites, S. M., Su, C.: "On some features of lipid metabolism in stress." *Vopr. Med. Khim.* **8** No. 3: 289-293 (1962) (Russian). D69,390/62

Leites, S. M., Su, C.: "The role of the adrenal glands and the sympathetic nervous system in fat mobilization in stress condition." *Probl. Endokrinol. Gormonoter.* **9** No. 5: 30-35 (1963) (Russian). E27,396/63

Leites, F. L.: "Affection of the coronary heart arteries in repeated stress states." *Patol. Fiziol. Éksp. Biol.* **8** No. 5: 27-31 (1964) (Russian). J25,188/64

"Morphological and histochemical methods were used to study changes in the coronary heart arteries in rats subjected to a repeated stress (provoked after Selye), as well as to a combination of stresses with food cholesterol loads. In a proportion of the animals it was already after a lapse of one month that there occurred lipoidosis of the coronary arteries, no such phenomenon being noted in controls. In pathogenesis of these changes a definite role is evidently played by reduction of the lipolytic enzyme activity in the walls of coronary arteries revealed in stress by histochemical methods."

Leites, S. M., Lempert, B. L.: "Effect of stress on some patterns of lipid metabolism in alimentary loading by fat and cholesterol." *Vopr. Med. Khim.* **11** Nos. 11-12: 25-30 (1965) (Russian). J23,803/65

Wolf, S.: "Cardiovascular adjustments and serum lipid concentration in relation to the integrative functions of the nervous system." In: Blumenthal, H. T., *Cowdry's Arteriosclerosis. A Survey of the Problem*, pp. 679-685. Springfield, Ill.: Charles C Thomas, 2nd ed., 1967. E7,740/67

Handbook chapter on cardiovascular and metabolic adjustments in relation to nervous coordination during stress. The increase in

blood cholesterol, FFA, lipid phosphorous and lipoproteins is rather constant after exposure to various stressors, presumably reflecting a great need for lipid mobilization to cope with metabolic requirements during emergencies (36 refs.).

Friedman, M., Byers, S. O., Brown, A. E.: "Plasma lipid responses of rats and rabbits to an auditory stimulus." *Am. J. Physiol.* **212**: 1174-1178 (1967). F83,722/67

"Rats exposed to a continuous sound stimulus having an intensity of 102 db and an intermittent sound stimulus (200-cycle square wave with a duration of about 1 sec and having an intensity of 114 db) exhibited marked elevation and prolongation of clearing of postprandial plasma triglyceride for a period of approximately 21 days. . . . Cholesterol-fed rabbits exposed to similar sound stimulus for 10 weeks exhibited a higher blood cholesterol and more intense atherosclerosis than similarly fed control animals."

Friedman, M., Byers, S. O.: "Effect of environmental influences on alimentary lipemia of the rat." *Am. J. Physiol.* **213**: 1359-1364 (1967). F92,202/67

Klain, G. J., Whitten, B. K.: "The effect of orotic acid and cold stress on lipogenesis in white adipose tissue." *Biochim. Biophys. Acta (Amst.)* **144**: 174-176 (1967). G46,938/67

Saddler, J. B., Cardwell, R.: "The effect of tagging upon the fatty acid metabolism of juvenile pink salmon." *Comp. Biochem. Physiol. [A]* **39**: 709-721 (1971). J19,852/71

In tagged salmon, excessive fatty acid transfer from muscle to liver was ascribed to the stressor effect of the operation itself. The literature on other stress manifestations (particularly increased cortisol production) in salmons, following exposure to various stressors, is reviewed.

Prioux-Guyonneau, M., Buchel, L.: "Métabolisme des lipides et des glucides chez le rat blanc au cours de deux agressions, immobilisation forcée et variations thermiques" (Lipid and carbohydrate metabolism in white rats in the course of two stresses, forced immobilization and thermal variations). *C.R. Soc. Biol. (Paris)* **166**: 1277-1283 (1972). H66,183/72

Kissebah, A. H.: "'Stress' hormones and lipid metabolism." *Proc. R. Soc. Med.* **67**: 665-667 (1974). J21,224/74

Cholesterol

Since cholesterol is a precursor of steroid hormones, its metabolism quickly attracted the attention of early investigators of the stress response. Virtually every acute stressor (anoxia, cold, fasting, hemorrhage, trauma, restraint and so on) produces a pronounced depletion of cholesterol stores in the adrenal and an increase in plasma cholesterol, usually associated with similar changes in vitamin C levels.

This has been amply confirmed by experiments, first in the rat, but also in other species including man, and it is generally regarded as one of the most characteristic features of the alarm reaction. It is usually accompanied by other typical manifestations of acute stress such as thymicolumphatic involution, peptic ulcers, eosinopenia, a discharge of ACTH, corticoids and catecholamines. However, all these changes do not necessarily run parallel, and the mechanism of their interdependence is far from being clarified.

In fact, some observations in this field are difficult to reconcile. For example, in normal people, large amounts of ACTH cause a decrease in serum cholesterol with the esterified fraction falling sooner than the free fraction. This response does not occur in Addisonians, and hence it was thought that the fall may be induced by the discharged corticoids, or that the blood cholesterol does not disappear if there is no adrenocortical tissue to use it for corticoid synthesis.

Furthermore, in normal dogs, inanition decreased plasma cholesterol, especially the esterified fraction. In rats, this plasma cholesterol change was inversely proportional to the size and cholesterol content of the adrenals. From this, it was actually concluded "that a physiological response to stress is a reduction of the total serum cholesterol." Even in rats, a week of exposure to mild restraint increased the cholesterol and ascorbic acid levels of the adrenals, whereas severe restraint produced inverse changes.

In general, the depletion of adrenal cholesterol is most pronounced in the acute alarm reaction elicited by severe stress, and disappears or increases during the stage of resistance.

On the other hand, among survivors of myocardial infarction, serum cholesterol values almost invariably rose during periods of life judged subjectively as being particularly stressful.

In a group of accountants, the highest serum cholesterol values were noted at periods of severe occupational stress, when income tax declarations became due, and this was associated with an acceleration of blood clotting. Similarly, the serum cholesterol values rose in medical students during examinations. Striking increases in serum cholesterol and triglycerides were also noted in people kept on a strictly constant diet, at times of anxiety, including difficulties in the family or the job, as well as during "stress interviews." Rises in serum cholesterol were observed in underwater demolition crews during periods of great stress; these again paralleled other manifestations of the alarm reaction, such as rises in serum uric acid and cortisol and so on.

Although, as we have said, a rise in serum cholesterol is considered one of the most typical manifestations of the alarm reaction, it appears to be influenced by a variety of hitherto unclarified conditioning factors (such as genetics, nutrition), which may account for some of the observations seemingly incompatible with this interpretation. Even in patients, one group of investigators quite regularly found decreased serum cholesterol levels as a result of surgical operations or presurgical anxiety. The decrease in adrenal and the increase in serum cholesterol are most manifest during acute intense

stress, and may be reversed when the stressor is mild or when adaptation to it diminishes the intensity of the demands made upon the body. These observations agree with our concept according to which the adrenal cortex is most indispensable for the acquisition, and much less for the maintenance of nonspecific resistance.

Although exposure to severe cold produced a significant decrease of adrenal ascorbic acid in the opossum and dog, it failed to do so in frogs, toads, chickens, mice, hamsters, rabbits and cats. Adrenal cholesterol concentrations remained unchanged in most of these species, and actual increases were observed in rabbits exposed to cold and in frogs treated with ACTH.

In closing this survey, it should be clearly stated that the typical stress-induced pattern of cholesterol changes consists of a decrease in the adrenal and an increase in the blood content of this compound. This is the reaction obtained in most cases; the occasional exceptions are not fully understood. In surveying the literature, the impression is gained that usually adrenal cholesterol is unchanged or above normal during moderate chronic stress, and an atypical fall in serum cholesterol occurs in patients whose cholesterol stores are depleted, for example, by chronic undernutrition or loss of appetite.

Cholesterol

(See also our earlier stress monographs, p. xiii)

Sayers, G., Sayers, M. A., Liang, T. Y., Long, C. N. H.: "The cholesterol and ascorbic acid content of the adrenal, liver, brain and plasma following hemorrhage." *Endocrinology* 37: 96-110 (1945). B512/45

In rats, severe hemorrhage decreases the cholesterol and ascorbic acid content of the adrenals, presumably as a consequence of its stressor effect. Hypophysectomy prevents these changes, whereas they are duplicated by ACTH. The cholesterol content of the liver and brain is unaffected by nonfatal hemorrhage, and plasma cholesterol falls during shock due to severe hemorrhage. The ascorbic acid content of the liver and plasma rises after mild, and falls after fatal hemorrhage. Brain ascorbic acid levels are unaffected.

Levin, L.: "The effects of several varieties of stress on the cholesterol content of the adrenal glands and of the serum of rats." *Endocrinology* 37: 34-43 (1945).

B364/45

In rats, various stressors (anoxia, cold, fasting) caused a depletion of adrenal cholesterol considered to be characteristic of the alarm reaction. The blood cholesterol levels were much more variable.

Long, C. N. H.: "The relation of cholesterol and ascorbic acid to the secretion of the

adrenal cortex." *Rec. Prog. Horm. Res.* 1: 99-122 (1947). A53,620/47

Conn, J. W., Vogel, W. C., Louis, L. H., Fajans, S. S.: "Serum cholesterol: a probable precursor of adrenal cortical hormones." *J. Lab. Clin. Med.* 35: 504-517 (1950).

B53,036/50

Normal people given large amounts of ACTH develop pronounced drops in serum cholesterol after several days. The esterified fraction falls sooner than the free fraction. This effect of ACTH does not occur in those with Addison's disease. The fall may be induced by the discharged corticoids or by the utilization of blood cholesterol for the synthesis of corticoids under the influence of ACTH.

Kuhl, W. J. Jr., Ralli, E. P.: "Effect of acute stress upon blood constituents, white cells, and urine constituents in normal individuals." *Proc. Assoc. for the Study of Internal Secretions—33rd. Meet.*, p. 51. Atlantic City, N. J., 1951. Also in: *J. Clin. Endocrinol. Metab.* 11: 776 (1951).

B58,505/51

Normal men immersed in cold water (9.5°C) for eight minutes showed: 1—A decrease in temperature (immediate, 1 and 2 hours); 2—An increase in systolic and diastolic blood pressure (immediate) and a decrease (2 hours); 3—A decrease in heart rate (1, 2 and 4 hours); 4—An increase in neutrophiles (immediate); 5—A decrease in lymphocytes (2 hours); 6—A decrease in

eosinophiles (2 hours); 7—A decrease in serum chloride (immediate); 8—An increase in total proteins (immediate and 4 hours); 9—A decrease in serum water (immediate); 10—An increase in total cholesterol (4 hours); 11—An increase in the urine uric acid/creatinine ratio (2 and 4 hours)." All of these changes were significant and ascribed to stress, but no one indicator gave uniformly positive results.

Kyle, L. H., Hess, W. C., Walsh, W. P.: "The effect of ACTH, cortisone, and operative stress upon blood cholesterol levels." *J. Lab. Clin. Med.* **39**: 605-617 (1952).

B79,256/52

Mann, G. V., White, H. S.: "The influence of stress on plasma cholesterol levels." *Metabolism* **2**: 47-58 (1953). B76,678/53

"In normal dogs treatment with an environmental stress such as inanition produced a marked fall in the plasma cholesterol with a disproportionate reduction of the esterified fraction." In rats, this plasma cholesterol change was inversely proportional to the size and cholesterol content of the adrenals. Similar cholesterol alterations were produced in dogs by ACTH, whereas cortisone allowed a stabilization and rise of serum cholesterol to normal levels in human beings suffering from the stressor effect of disease. "It is proposed that a physiological response to stress is a reduction of the total serum cholesterol."

Bartlett, R. G. Jr., Miller, M. A.: "The adrenal cortex in restraint hypothermia and in adaptation to the stress of restraint." *J. Endocrinol.* **14**: 181-187 (1956).

C25,043/56

In rats, one week of exposure to mild restraint increased the ascorbic acid and to a lesser extent the cholesterol content of the adrenals. Restraint sufficiently severe to reduce body temperature produced inverse changes. Loss of cholesterol and ascorbic acid from the adrenals was particularly marked in animals restrained while exposed to cold.

Hammarsten, J. F., Cathey, C. W., Redmond, R. F., Wolf, S.: "Serum cholesterol, diet and stress in patients with coronary artery disease." *J. Clin. Invest.* **36**: 897 (1957). D32,061/57

In survivors of myocardial infarction, serum cholesterol values were routinely taken and stressful events in their lives registered. "It was striking that 19 of the 20 occasions of high cholesterol corresponded with periods

that had been separately judged as particularly stressful for the individuals concerned."

Friedman, M., Rosenman, R. H., Carroll, V.: "Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress." *Circulation* **17**: 852-861 (1958). C56,083/58

In a large group of accountants, "each subject's highest serum cholesterol consistently occurred during severe occupational or other stress, and his lowest at times of minimal stress. The results could not be ascribed to any changes of weight, exercise, or diet. Marked acceleration of blood clotting time consistently occurred at the time of maximum occupational stress, in contrast to normal blood clotting during periods of respite."

Wertlake, P. T., Wilcox, A. A., Haley, M. I., Peterson, J. E.: "Relationship of mental and emotional stress to serum cholesterol levels." *Proc. Soc. Exp. Biol. Med.* **97**: 163-165 (1958). C47,228/58

In male medical students the mental stress of examinations caused a considerable increase in serum cholesterol values, considered to reflect manifestations of the G.A.S.

Grundy, S. M., Griffin, A. C.: "Effects of periodic mental stress on serum cholesterol levels." *Circulation* **19**: 496-498 (1959).

C66,837/59

In male medical students the blood cholesterol levels rose significantly during final examinations.

Elton, R. L., Zarrow, I. G., Zarrow, M. X.: "Depletion of adrenal ascorbic acid and cholesterol: a comparative study." *Endocrinology* **65**: 152-157 (1959). C71,402/59

"Exposure to severe cold produced significant depression of adrenal ascorbic acid in opossums and dogs, but failed to do so in frogs, toads, chickens, mice, hamsters, rabbits, and cats. ACTH failed to produce such a depletion in frogs, toads, chickens, rabbits, cats, or dogs; significant depressions were observed in opossums, mice and hamsters. Adrenal cholesterol concentrations remained unchanged in most species tested, however, increases were observed in rabbits, following cold exposure, and in frogs, following ACTH treatment" (24 refs.).

Rose, K. D., Maca, R., Pace, D. M.: "Sterol synthesis by cells cultured on serum from heat-stressed chickens." *Proc. Soc. Exp. Biol. Med.* **108**: 282-285 (1961).

D89,507/61

"Young chickens subjected to heat stress at 102°F for 24 hours elaborate a stress factor into their blood stream. When serum from these animals is used as an adjuvant in a serum-balanced salt solution medium, cells grown on this medium accumulate large numbers of small lipid droplets within their cytoplasm." Possibly, this factor may account for the hypercholesterolemia characteristic of stress in vivo.

Klein, P. D., Dahl, R. M.: "The sensitivity of cholesterol esterification to environmental stress." *J. Biol. Chem.* **236**: 1658-1660 (1961). J12,255/61

Goodman, J. R., Kellogg, F., Porter, R. W., Liechti, R.: "Decrease in serum cholesterol with surgical stress." *Calif. Med.* **97**: 278-280 (1962). D55,584/62

In patients, serum cholesterol decreased as a result of the stress of surgery, both before and after operations. "A presurgical drop was noted and considered to be related to psychological stress."

Wolf, S., McCabe, W. R., Yamamoto, J., Adsett, C. A., Schottstaedt, W. W.: "Changes in serum lipids in relation to emotional stress during rigid control of diet and exercise." *Circulation* **26**: 379-387 (1962).

J10,367/62

Striking increases in serum cholesterol and triglycerides occurred in people kept on a constant diet and exposed to various situations inducing anxiety, including difficulties in the family, on the job and so on. Stressful interviews caused such changes within sixty minutes. "No inferences are drawn with respect to the significance of emotional stress in the pathogenesis of coronary atherosclerosis or myocardial infarction, but it is clear that the mechanisms that govern the serum concentration of certain lipids are connected with and capable of responding to impulses from the higher centers of the brain."

Peterson, J. E., Keith, R. A., Wilcox, A. A.: "Hourly changes in serum cholesterol concentration. Effects of the anticipation of stress." *Circulation* **25**: 798-803 (1962).

J22,953/62

"Environmental stress and cholesterol esterification in plasma and liver." *Nutr. Rev.* **20**: 88-90 (1962). D20,596/62

Brief review on changes in hepatic cholesterol metabolism induced by restraint in the rat.

Sarai, K.: "On the relationship of the

blood cholesterol level in emotional stress to the personality pattern." *J. Yomago Med. Assoc.* **14**: 138-141 (1963). J24,617/63

Thomas, C. B., Ross, D. C.: "Observations on some possible precursors of essential hypertension and coronary artery disease. VIII. Relationship of cholesterol level to certain habit patterns under stress." *Bull. Johns Hopkins Hosp.* **113**: 225-238 (1963).

E29,405/63

Among medical students, "subjects in the lower cholesterol group more often reported loss of appetite, exhaustion, nausea and anxiety when under [psychogenic] stress; in addition, urge to be alone, tremulousness and depression were more frequent than expected, although these items only approached significance. The only item with a significant positive relationship to higher cholesterol levels was urge to eat" (35 refs.).

Meier, R. M., Greenhoot, J. H., Shonley, I., Goodman, J. R., Porter, R. W.: "Sex differences in the serum cholesterol response to stress in monkeys." *Nature* **199**: 812-813 (1963).

E24,291/63

Stress caused by restraint decreased serum cholesterol in rhesus monkeys of both sexes, but particularly in males. A review of earlier data shows that some researchers found an increase, others a decrease, in plasma cholesterol levels in both animals and man, but the reasons for these discrepancies are not investigated (11 refs.).

Khomulo, P. S.: "Changes in serum cholesterol and lipoprotein content in dogs on application of prolonged functional stress to the nervous system." *Biull. Éksp. Biol. Med.* **58** No. 10: 44-47 (1964) (Russian). English trans.: *Bull. Exp. Biol. Med.* **58**: 1176-1179 (1964).

J25,040/64

Thiesen, J. W., Brown, K. D., Forgas, R. H., Evans, S. M., Williams, G. M., Taylor, J.: "Further data on a stress syndrome related to achievement motivation: relationships with age and basal serum cholesterol level." *Percept. Mot. Skills* **20**: 1277-1292 (1965).

G35,812/65

Verification of a multifactorial stress test based on heart rate acceleration. "While a tendency toward higher over-all heart rates with increased age was observed, the principal specific finding was a positive association of basal serum cholesterol level with post-stress heart rate, independent of age. Individuals with higher serum cholesterol levels showed less complete recovery fol-

lowing stress and higher initial heart rates, but they did not necessarily show a stronger immediate response to the stressors."

Greco, A.: "On relationships between blood cholesterol and stress." *Med. Sport (Roma)* **5**: 399-405 (1965). J23,784/65

Sarai, K.: "The relation of the blood cholesterol in emotional stress to the character pattern." *Yonago Acta Med.* **10**: 34-37 (1966). J23,238/66

Geber, W. F., Anderson, T. A., Dyne, B. van: "Physiologic responses of the albino rat to chronic noise stress." *Arch. Environ. Health* **12**: 751-754 (1966). G39,248/66

In rats, exposure to a variety of sounds (gongs, horns, loudspeakers, bells, vibrators) caused roughly parallel decreases in blood eosinophil and ascorbic acid concentrations in the adrenal and other tissues. On the other hand, chronic audiogenic stress led to increases in adrenal weight, ascorbic acid concentration and serum cholesterol.

Rahe, R. H., Arthur, R. J.: "Stressful underwater demolition training. Serum urate and cholesterol variability." *J.A.M.A.* **202**: 1052-1054 (1967). F91,967/67

In men training for underwater demolition work the serum urate concentration was elevated during anticipation of a demanding task, and "cholesterol levels rose concomitant with a period of particular psychological stress. Serum urate concentration demonstrated a significant fall during a period of quite intense psychological stress."

Symbas, P. N., Abbott, O. A., Ende, N.: "Surgical stress and its effects on serum cholesterol." *Surgery* **61**: 221-227 (1967).

G44,339/67

In opposition to most of the literature, the authors find that, after surgical stress, the serum cholesterol level is usually decreased in man, although sometimes an initial rise may be noted (19 refs.).

Iroshnikova, G. P.: "The blood cholesterol level and bile acids excretion depending on the degree and duration of functional stress of the nervous system." *Kardiologija* **8** No. 4: 48-54 (1968) (Russian). J23,895/68

"Prolonged functional stress of the nervous activity, not leading to the development of neurosis, may cause in rabbits an alteration of the cholesterol metabolism, this being manifested by an increased excretion of bile acids and wave-like fluctuation of the blood cholesterol level. The blood cholesterol con-

tent manifests a tendency to rise with increase of the functional stress."

Rahe, R. H., Rubin, R. T., Arthur, R. J., Clark, B. R.: "Serum uric acid and cholesterol variability. A comprehensive view of Underwater Demolition Team training." *J.A.M.A.* **206**: 2875-2880 (1968).

G63,836/68

Steigrad, A.: "Kleine Blutdruckamplitude bei Hypercholesterinämie. Beobachtungen über den Einfluss von Stress und Schilddrüsenfunktion" (Small blood pressure amplitude in hypercholesterolemia. Studies on the influence of stress and thyroid function). *Praxis* **57**: 1225-1228 (1968). H14,750/68

In man, psychogenic stress increases the blood cholesterol level. At the same time, thyroid activity (blood PBI) is usually, but not always, diminished (26 refs.).

Kasl, S. V., Cobb, S., Brooks, G. W.: "Changes in serum uric acid and cholesterol levels in men undergoing job loss." *J.A.M.A.* **206**: 1500-1507 (1968). J13,893/68

In people who lose their job or anticipate loss of employment, blood cholesterol and uric acid levels tend to rise, with a return to normal following the stress period of economic uncertainty.

Rubin, R. T., Rahe, R. H., Clark, B. R., Arthur, R. J.: "Serum uric acid, cholesterol and cortisol levels. Interrelationships in normal men under stress." *Arch. Intern. Med.* **125**: 815-819 (1970). G74,760/70

In healthy young U.S. Navy divers undergoing underwater demolition training, the physical and psychologic stress is associated with increases in serum uric acid, cholesterol and cortisol concentrations (34 refs.).

Kato, M.: "Sensitivity of cholesterol turnover in rat liver to cold environmental stress." *Am. J. Physiol.* **221**: 1255-1259 (1971). J19,652/71

Taggart, P., Carruthers, M.: "Endogenous hyperlipidaemia induced by emotional stress of racing driving." *Lancet* February 20, 1971, pp. 363-366. H35,851/71

During racing driving, "the total-catecholamine levels were grossly elevated, the increase being largely due to noradrenaline. The free-fatty-acid levels were also elevated one to three minutes before the start while the drivers were on the starting grid, and up to one hour after the race. The triglyceride levels were slightly elevated after the event, continued to increase, and reached a peak at

one hour." Blood cholesterol values showed no significant changes.

Rahe, R. H., Rubin, R. T., Gunderson, E. K. E.: "Measures of subjects' motivation and affect correlated with their serum uric acid, cholesterol, and cortisol." *Arch. Gen. Psychiatry* **26**: 357-359 (1972).

G90,674/72

Among trainees in a U.S. Navy underwater demolition team, "predominantly positive correlations were seen between the subjects' serum uric acid levels and their estimates of their own motivation. Their serum cholesterol concentrations demonstrated consistently negative correlations with their motivational and pleasant affect scores. Highest correlations were positive ones found between the subjects' serum cholesterol levels and their unpleasant affect scores. Serum cortisol correlations with the three psychological criteria demonstrated wide variability around a zero correlation baseline."

Kaatzsch, H.: "Endogene Cholesterinbildung bei Kraftfahrern, Akkord- und Schichtarbeitern" (Endogenous cholesterol synthesis in truck drivers, piece-workers and shiftworkers). *Med. Klin.* **67**: 262-266 (1972).

J16,980/72

In truck drivers and shiftworkers the increase in blood cholesterol roughly paralleled the elevation of blood catecholamines, and reflected the severity of the stress associated with work.

Rothfeld, B., Paré, W. P., Varady, A. Jr., Isom, K. E., Karmen, A.: "The effects of environmental stress on cholesterol synthesis and metabolism." *Biochem. Med.* **7**: 292-298 (1973).

J2,491/73

In rats, the stressor effect of sound or electroshock caused cholesterol deposition in the aorta and liver with a rise in blood cholesterol.

Rothfeld, B., Paré, W. P., Varady, A. Jr., Isom, K. E., Karmen, A.: "CPIB as a factor in stress-mediated effects on cholesterol syn-

thesis in metabolism." *Biochem. Med.* **8**: 324-328 (1973).

J21,509/73

When produced by electroshock or sound, "stress results in diminution if not disappearance of many previously noted effects of CPIB on cholesterol metabolism in the rat."

Fokin, A. S.: "The influence of a sustained functional stress of the central nervous system on cholesterol-lipoprotein metabolism, thyroid function, on the reaction of the adrenals in dogs with normal and suppressed function of the sexual glands." *Kardiologija* **13** No. 11: 69-73 (1973) (Russian).

J23,977/73

Rahe, R. H., Rubin, R. T., Arthur, R. J.: "The three investigators study. Serum uric acid, cholesterol, and cortisol variability during stresses of everyday life." *Psychosom. Med.* **36**: 258-268 (1974).

J21,223/74

The authors studied their own responses to various life events. "Marked elevations in serum cholesterol were seen in one investigator throughout an unpleasant residential move; repeated peaks in serum cortisol were seen in one investigator during times of anguish and anger over personal disappointments and work changes. Two of the three men showed uric acid elevations into the 'gout range' prior to eagerly taking on a physical change. Occasionally, serum uric acid and cortisol values reached magnitudes previously reported as characteristic of men entering underwater demolition training and jumping into the ocean from hovering helicopters."

Krekhova, M. A., Chekhranova, M. K.: "Cholesterol content in the venous blood of the adrenal glands and the peripheral blood of rats." *Probl. Endokrinol.* **20** No. 4: 81-83 (1974) (Russian).

H92,741/74

In rats, "surgical stress" decreased adrenal cholesterol 1.25 times more than would correspond to the secreted corticosterone. Corticosterone elimination coincided with the discharge of cholesterol esters from the adrenal cortex.

FFA, Triglycerides and Lipoproteins

A rise in plasma lipids and FFA is generally accepted as a characteristic manifestation of stress. In fact, extensive surveys have led to the conclusion that an elevated plasma FFA level is a particularly sensitive indicator of increased autonomic activities, such as occur during the alarm reaction, even during comparatively mild, emotionally-

induced stress situations caused by demanding social interrelations. The primary factor here appears to be the discharge of catecholamines, which are known for their lipolytic action.

This hyperlipidemia and elevation of blood FFA are usually associated with hyperlipoproteinemia; allegedly, these lipid changes can be selectively diminished by treatment with nicotinic acid.

Increased plasma FFA levels in man were also noted after excessive muscular exercise, hot baths, racing driving, exposure to gravity forces (centrifugation), exacting vigilance tests and so on.

In obese persons, exercise and perceptual judgment tasks elevated plasma FFA values very consistently, although the initial levels were low. Marked rises were also noted in a few obese patients exposed to heat.

FFA, Triglycerides and Lipoproteins

(See also our earlier stress monographs, p. xiii)

Kabal, J., Ramey, E. R.: "Effect of guanylic acid on plasma NEFA [FFA] response to stress." *Proc. Soc. Exp. Biol. Med.* **104**: 95-97 (1960). C90,828/60

Mallov, S., Witt, P. N.: "Effect of stress and tranquilization on plasma free fatty acid levels in the rat." *J. Pharmacol. Exp. Ther.* **132**: 126-130 (1961). D3,463/61

In rats, electroshocks raise the plasma FFA concentration. This in turn can be inhibited by tranquilizers (chlorpromazine, meprobamate), but only when given at certain dose levels at critical times.

Mayes, P. A.: "Blood glucose and plasma unesterified fatty acid changes induced by the stress of an emergency situation." *Experientia* **18**: 451-453 (1962). J23,455/62

Leites, S. M., Chou-Su: "Some features of fat metabolism during stress." *Vopr. Med. Khim.* **8**: 289-293 (1962) (Russian). Engl. trans.: *Fed. Proc.* **22**: 244-246 (1963). D60,206/62

Leites, S. M., Chou-Su: "Lipolytic activity of the aortic wall in certain experimental pathologic conditions." *Klin. Med. (Mosk.)* **40**: 15-21 (1962) (Russian). Engl. trans.: *Fed. Proc.* **22**: 466-469 (1963). G9,132/62

In rats, the stress of restraint increases both the blood FFA concentration and the lipolytic activity of adipose tissue. On the other hand, the lipolytic activity of the aorta and myocardium is diminished during stress.

This may be of pathogenic importance in cardiovascular disease.

Leonov, B. V., Lomova, M. A., Rudakov, I. A.: "Connection of radiosensitivity of rats with antioxidative activity of bone marrow and content of unesterified fatty acids in their blood under conditions of 'stress.'" *Radiobiologija* **3**: 518-522 (1963) (Russian). Engl. trans.: *Radiobiology* **3**: 43-49 (1963). J24,546/63

Experiments on rats "suggested that the increased expenditure of antioxidants under conditions of 'stress' may be connected with mobilization of fats from fat depots and that one of the mechanisms of the increase of radiosensitivity of animals in 'stress' can be the oxidation of mobilized lipids." It is assumed that crossed sensitization by stressors to x-rays may result from the loss of antioxidants during stress.

Back, K. W., Bogdonoff, M. D.: "Plasma lipid responses to leadership, conformity, and deviation." In: Leiderman, P. H. and Shapiro, D., *Psychobiological Approaches to Social Behavior*, pp. 24-42. Stanford, Cal.: Stanford University Press, 1964. J11,130/64

Detailed review on plasma FFA as an objective indicator of stress in man, particularly in social interrelations. Plasma FFA are very sensitive to changes in autonomic nervous activity, and are especially useful in assessing situational demands and group interactions.

Khan, A. U., Forney, R. B., Hughes, F. W.: "Stress of shocking stimulus on plasma free fatty acids in rats." *Arch. Int. Pharmacodyn. Ther.* **151**: 459-465 (1964). F26,604/64

Electroshock applied to rats for three minutes caused marked increases in blood FFA. However, repeated intermittent electric shocks were less effective or ineffective in this respect. "It is suggested that hyperglycemia resulting from the stress of electric shocks suppressed the plasma FFA response in the groups of rats in which no changes were observed."

Klein, R. F., Troyer, W. G., Back, K. W., Hood, T. C., Bogdonoff, M. D.: "Lipid mobilization in lean and obese subjects." *Ann. N. Y. Acad. Sci.* **131**: 662-672 (1965).
G8,825/65

Psychogenic and physical stresses were "inversely related to body size when the duration of fasting was held constant. Plasma FFA lability or variability was significantly greater in lean subjects, suggesting that their lipid mobilizing processes are more active than those of obese subjects."

Sapira, J. D., Lipman, R., Shapiro, A. P.: "Effect of restraint on free fatty acid mobilization in rats." *Psychosom. Med.* **27**: 165-170 (1965).
G28,050/65

Havel, R. J.: "Autonomic nervous system and adipose tissue." In: Renold, A. E. and Cahill, G. F., *Handbook of Physiology. Section 5. Adipose Tissue*, pp. 575-582. Washington, D.C.: American Physiological Society, 1965.
E7,291/65

Handbook article on the role of the ANS in the regulation of FFA, lipoproteins and other lipids, especially in connection with various stressors.

Carlson, L. A., Boberg, J., Höglstedt, B.: "Some physiological and clinical implications of lipid mobilization from adipose tissue." In: Renold, A. E. and Cahill, G. F., *Handbook of Physiology. Section 5. Adipose Tissue*, pp. 625-644. Washington, D.C.: American Physiological Society, 1965.
E7,294/65

Handbook article on the theoretical and practical applications of our knowledge concerning lipid, particularly FFA, metabolism as influenced by catecholamines, the ANS and stressors.

Klein, R. F., Troyer, W. G., Back, K. W., Hood, T. C., Bogdonoff, M. D.: "Experimental stress and fat mobilization in lean and obese subjects." *Metabolism* **14**: 17-25 (1965).
F26,728/65

Plasma FFA values in obese persons exposed to two stressors (exercise on a station-

ary bicycle, a difficult perceptual judgment task) revealed lower initial levels and diminished variability, as compared to those in nonobese subjects. "Insulin activity or adrenergic nervous system activity may be altered in obesity."

Schalch, D. S.: "The effect of physical stress and exercise in the human on growth hormone and insulin secretion." *Clin. Res.* **13**: 334 (1965).
F61,179/65

In man, various stressors (muscular exercise, electroconvulsive therapy, major surgery) increased plasma STH (radioimmunoassay) and FFA levels without affecting plasma insulin. The STH discharge "may be at least in part responsible for the mobilization of the readily oxidizable FFA which takes place during periods of increased energy requirements."

Peterfy, G., Pinter, E. J., Cleghorn, J. M., Pattee, C. J.: "Observations on the adrenergic mechanism of hyperadipokinesis of emotional stress." *Proc. Can. Fed. Biol. Soc.* **9**: 64 (1966).
F66,182/66

In men and women the emotional stress of threatening suggestions leads to hyperadipokinesis. "The primary factor appears to be the adrenergic nervous system." This response, associated with marked increases in plasma FFA and catecholamine levels, is prevented by a β -adrenergic blocking agent, propranolol.

Levi, L.: "Das Experiment am Menschen in der Psychosomatik" (Psychosomatic studies in man). *Verh. Dtsch. Ges. Inn. Med.* **73**: 58-70 (1967).
G85,102/67

In man, various psychic stressors cause hyperlipoproteinemia as well as increased blood FFA. Nicotinic acid treatment diminishes the blood lipids without influencing tachycardia, hypertension or catecholamine secretion. Hence it is assumed that nicotinic acid inhibits fatty acid mobilization within the adipose tissue itself.

Schalch, D. S.: "The influence of physical stress and exercise on growth hormone and insulin secretion in man." *J. Lab. Clin. Med.* **69**: 256-269 (1967).
G44,274/67

In man, plasma STH often rose during periods of physical stress or exercise, while insulin values remained unchanged or decreased. EP did not reproduce the release of STH. The failure of plasma insulin levels to rise in response to stress-induced hyperglycemia is consistent with the finding that EP infusion impairs insulin discharge. Plasma

glucose and FFA levels rose as expected during physical exercise. Presumably, certain stressors are diabetogenic not only because of EP and corticoid release, but also because of a discharge of STH on the one hand, and an EP-induced suppression of insulin secretion on the other.

Buchel, L., Guyonneau, M.: "Variations du taux plasmatique des acides gras libres et de la glycémie au cours de la contrainte du Rat blanc" (Changes in the plasma level of free fatty acids and blood glucose during restraint in white rats). *C. R. Soc. Biol. (Paris)* **161**: 289-292 (1967).

F85,806/67

Pinter, E. J., Peterfy, G., Cleghorn, J. M., Pattee, C. J.: "The influence of emotional stress on fat mobilization; the role of endogenous catecholamines and the β adrenergic receptors." *Am. J. Med. Sci.* **254**: 634-651 (1967). G52,170/67

Anxiety-inducing hypnotic suggestion increases catecholamine secretion and blood FFA. Pretreatment with β -adrenergic blocking agents inhibits the adipokinetic response.

Roux, J. F., Romney, S. L.: "Plasma free fatty acids and glucose concentrations in the human fetus and newborn exposed to various environmental conditions." *Am. J. Obstet. Gynecol.* **97**: 268-276 (1967).

J22,838/67

Observations on women exposed to various stressors show that "the regulation of fetal plasma FFA is controlled by the same mechanisms as those of the pregnant adult. The fetus is however, unable to respond to a high plasma glucose concentration as the pregnant woman does (i.e., by a decrease in plasma FFA concentration). This difference is probably due to a limited supply of fetal insulin and/or to the saturation of the enzyme systems synthesizing lipids in fetal tissues. Pathologic conditions of gestation and stresses in utero have no effect on the fetal plasma FFA concentrations. This is considered as an expression of fetomaternal homeostatic ability. Increase in fetal plasma FFA concentrations takes place after birth."

Hrubeš, V., Beneš, V.: "The plasma level of non-esterified fatty acids as an indicator of stress." *Activ. Nerv. Sup. (Praha)* **9**: 241-244 (1967) (Czech). J23,105/67

Gittleman, B., Shatin, L., Bierenbaum, M. L., Fleischman, A. I., Hayton, T.: "Effects of quantified stressful stimuli on blood lipids

in man." *J. Nerv. Ment. Dis.* **147**: 196-201 (1968). G60,448/68

In man, a variety of stressors increase plasma FFA levels (24 refs.).

Hrubeš, V., Beneš, V.: "The time course of nicotinic acid on stress-induced changes in serum non-esterified fatty acids in rats." *Activ. Nerv. Sup. (Praha)* **10**: 45-48 (1968). J23,115/68

Back, K. W., Wilson, S. R., Bogdonoff, M. D., Troyer, W. G.: "Racial environment, cohesion, conformity and stress." *J. Psychosom. Res.* **13**: 27-36 (1969).

J22,201/69

Comparative studies on stress responses—especially the elevations of plasma FFA—in various groups, particularly blacks and whites.

Buchel, L., Liblau, L., Murawsky, M., Prioux-Guyonneau, M.: "Influence de substances psychotropes sur les variations du taux plasmatique des acides gras libres chez le rat contraint" (Influence of psychotropic substances on variations of total plasma free fatty acids in restrained rats). *Arch. Sci. Physiol.* **23**: 407-414 (1969).

G68,704/69

In rats, restraint severe enough to cause gastric ulcers diminishes the FFA content of the plasma, contrary to most other stressors.

Geisen, K., Meder, R.: "Effekt von Wärme auf das Wachstumshormon beim Menschen" (The effect of heat on growth hormone secretion in man). *Z. Kinderheilkd.* **106**: 308-313 (1969). H17,060/69

In four men taking hot baths, plasma STH and to a lesser extent FFA values rose, whereas plasma cortisol levels remained constant. Literature is cited to show that other stressors (pyrogens, physical exercise, heat) likewise raise the plasma STH levels.

Mays, E. T.: "The effect of surgical stress on plasma free fatty acids." *J. Surg. Res.* **10**: 315-319 (1970). J21,337/70

Jage, J., Olthoff, D., Kunze, D.: "Das Verhalten der freien Fettsäuren des Serums als Indikator sympatho-adrenaler Aktivität während Narkose und Operation" (The composition of serum free fatty acids as an indicator of sympatho-adrenal activity during anesthesia and surgery). *Dtsch. Gesundheitsw.* **26**: 488-492 (1971). H63,313/71

In man, anesthetics increased serum FFA levels, except for halothane, probably because it has a sympatheticolytic action. Among oper-

ations performed during anesthesia, intra-abdominal interventions caused the greatest FFA elevations. For inexplicable reasons, only mitral commissurotomy elicited a decrease in serum FFA.

Taggart, P., Carruthers, M.: "Endogenous hyperlipidaemia induced by emotional stress of racing driving." *Lancet* February 20, 1971, pp. 363-366. H35,851/71

During racing driving, "the total-catecholamine levels were grossly elevated, the increase being largely due to noradrenaline. The free-fatty-acid levels were also elevated one to three minutes before the start while the drivers were on the starting grid, and up to one hour after the race. The triglyceride levels were slightly elevated after the event, continued to increase, and reached a peak at one hour." The blood cholesterol values showed no significant changes.

Ruxin, R. L., Bidder, T. G., Agle, D. P.: "The influence of autonomic arousal on blood clotting time in patients receiving electroconvulsive treatments." *J. Psychosom. Res.* **16**: 185-192 (1972). J19,669/72

In patients, electroconvulsive treatments raised plasma FFA, but the observations "do not support previous reports demonstrating a direct relationship between arousal and decreased clotting time. Furthermore, they provide no evidence for the hypothesis that emotional factors may influence the pathogenesis of vascular disease or play a part in hemostasis during stress through changes in blood coagulability" (37 refs.).

Okada, Y., Matsuoka, T., Kumahara, Y.: "Human growth hormone secretion during exposure to hot air in normal adult male subjects." *J. Clin. Endocrinol. Metab.* **34**: 759-763 (1972). H54,871/72

In four obese adult males exposed to hot air (48°C) for one hour after an overnight fast, elevation of body temperature was associated with increased plasma STH and FFA levels. No significant changes in cortisol, total thyroxine-iodine, blood glucose or hematocrit were noted. In two subjects, administration of glucose before heat exposure prevented the rise in plasma STH.

Sarviharju, P. J., Vihko, V.: "Plasma FFA during psychophysical loading and endurance training." *J. Sports Med. Phys. Fitness* **12**: 250-257 (1972). H81,647/72

Stress produced in male students by intense work on a bicycle ergometer or a difficult mental choice situation greatly increased

catecholamine excretion. Plasma FFA elevations were noted only after the physical work.

Harrison, M. H.: "Comparison of the metabolic effects of centrifugation and heat stress in man." *Aerosp. Med.* **44**: 299-303 (1973). H80,109/73

In fasted men the stress of centrifugation or exposure to heat increased blood lactate, glucose, FFA, glycerol and catecholamine levels, but these changes did not always parallel each other (30 refs.).

Turton, M. B., Deegan, T.: "Central and peripheral levels of plasma catecholamines, cortisol, insulin and non-esterified fatty acids." *Clin. Chim. Acta* **48**: 347-352 (1973). J8,031/73

In patients undergoing cardiac catheterization, elevations of EP, NEP, FFA and cortisol, and lowered levels of insulin, are ascribed to stress. However, certain differences are noted in the concentration of these substances in various vascular territories.

O'Hanlon, J. F., Horvath, S. M.: "Interrelationships among performance, circulating concentrations of adrenaline, noradrenaline, glucose, and the free fatty acids in men performing a monitoring task." *Psychophysiology* **10**: 251-259 (1973). J3,116/73

In young men performing an exacting vigilance test, basal blood, EP and NEP levels were inversely related to glucose. EP initially increased during the test but later returned to its basal level in proportion to performance. NEP was not related to performance. Glucose and FFA were elevated both during the task and throughout a control period spent watching slide projections.

Somerville, W.: "Emotions, catecholamines and coronary heart disease." *Adv. Cardiol.* **8**: 162-173 (1973). J16,987/73

A statistical study shows that "certain experienced motor-car drivers with a history of coronary heart disease when driving in busy traffic develop angina, sinus tachycardia, ectopic beats and various arrhythmias. Healthy racing drivers, stimulated by the emotions of competition and danger, develop high-grade sinus tachycardia, raised plasma catecholamines and free fatty acids immediately before and after a race. Public speaking induces in normal persons similar changes in heart rate and rhythm and elevations in plasma catecholamines and free fatty acids. In both drivers and public speakers, triglycerides show a peak elevation 1-2 h after the event. Oxprenolol inhibits the increase in

heart rate, plasma catecholamines, free fatty acids and triglycerides."

Numano, F., Kobayashi, M., Moriya, K., Numan, F., Shimamoto, T.: "Plasma free fatty acid and acute vascular injury." *Acta Pathol. Jap.* **23**: 769-777 (1973).

J10,126/73

In rabbits, various types of chemically induced vascular injury are associated with a marked increase in plasma FFA.

Paul, P., Holmes, W. L.: "Free fatty acid metabolism during stress: exercise, acute cold exposure, and anaphylactic shock." *Lipids* **8**: 142-150 (1973). J19,554/73

Baumann, R.: "Theoretische und klinische Aspekte der zerebro-viszeralen Regulationskrankheit arterielle essentielle Hypertonie. I. Zu Problemen der Adaptations-Maladaptionsprozesse und der pathogenetischen Effizienz des psycho-emotionalen Stresses" (Theoretical and chemical analyses of cerebro-visceral regulation of essential arterial hypertension. I. Problems of adaptation-maladaptation processes and the pathogenetic efficiency of psycho-emotional stress). *Dtsch. Gesundheitsw.* **29**: 673-676 (1974). J15,328/74

Baumann, R.: "II. Hämodynamische und

biochemische Regulationsstörungen des jugendlichen Hypertoniens unter Stressexposition" (II. Hemodynamic and biochemical disturbances in young male hypertensive patients under stress). *Dtsch. Gesundheitsw.* **29**: 721-733 (1974). J15,329/74

In young hypertensive patients with or without latent diabetes, emotional stress produced a rise in plasma FFA, NEP and renin (63 refs.).

Michailov, M. L., Gnüchtel, U., Nitschkoff, S., Baumann, R., Gnauck, G.: "Verhalten von Fettsäuren im Blutplasma von Affen nach Einwirkung kurzfristiger Stressoren" (The behavior of fatty acids in blood plasma of monkeys following exposure to short-time stressors). *Acta Biol. Med. Ger.* **32**: 675-680 (1974). J16,605/74

In baboons (*Papio hamadryas*), various stressors (restraint, jealousy) cause a rise in unsaturated plasma FFA, especially oleic acid, and a relative decrease in saturated FFA, particularly palmitinic acid.

Ferguson, J. H., Shultz, T. D.: "Plasma free fatty acid composition before and after cold exposure in the white rat." *Int. J. Biochem.* **6**: 69-72 (1975). J22,458/75

Phospholipids

In naval aviators during combat, the plasma phospholipid fractions allegedly behaved differently than in individuals exposed to other stressors in that phosphatidylglycerol "responded to this type of stress more markedly and consistently than other fractions."

In rats, ionizing radiation or acceleration stress consistently increased plasma phosphatidylglycerol. Similar rises in this fraction were also noted in people stressed by acceleration to grayout, sleep deprivation, combat, schizophrenia and so on, suggesting that the response is nonspecific. In rats, it can be prevented by hypophysectomy.

Phospholipids

(See also our earlier stress monographs, p. xiii)

Austin, F. H. Jr.: "A review of stress and fatigue monitoring of naval aviators during aircraft carrier combat operations: blood and urine biochemical studies." In: Bourne, P. G., *The Psychology and Physiology of Stress: With Reference to Special Studies of the Viet Nam War*, pp. 197-218. New York and London: Academic Press, 1969.

E8,568/69

Review on stress and fatigue monitoring in naval aviators during combat operations on a U.S. Navy aircraft carrier in North Vietnam. Plasma phospholipid fractions behaved differently than in normal individuals or in those exposed to other stressors. "The phosphatidylglycerol responded to this type of stress more markedly and consistently than the other fractions. A discriminant functions formula has been developed which may facilitate identification of the stress type and degree of subject response up to and includ-

ing psychophysiological exhaustion and collapse." Variations in typical stress hormone levels are also reported.

Polis, B. D., Polis, E., Cani, J. de, Schwarz, H. P., Dreisbach, L.: "Effect of physical and psychic stress on phosphatidyl glycerol and related phospholipids." *Biochem. Med.* 2: 286-312 (1969). G65,013/69

In rats exposed to ionizing radiation or "acceleration stress," the plasma concentration of phosphatidylglycerol was consistently increased. "Extension of the studies to humans stressed by acceleration to grayout, sleep deprivation, schizophrenia, combat, etc., revealed that all stresses were accompanied by significant increments in plasma

phosphatidyl glycerol." In rats, hypophysectomy prevented the increase in phosphatidylglycerol induced by acceleration stress; yet a rise in the brain level of this compound was shown even in the absence of the pituitary.

Polis, B. D., Polis, E., Schwarz, H. P., Dreisbach, L.: "The effect of cold on the composition of the phospholipids of the blood plasma of healthy athletes." *Proc. Soc. Exp. Biol. Med.* 145: 70-73 (1974).

J21,416/74

In athletes, the phosphatidylglycerol content of plasma was very significantly elevated immediately after and for seven minutes following exposure to cold.

Proteins and Amino Acids

The fact that stress causes catabolism and loss of body weight is so well known that it need not be discussed here in detail. Of course, stress-induced catabolism is not due exclusively to degradation of body proteins. Increased utilization of lipid and carbohydrate reserves is equally important, but since an initial loss and subsequent restoration of structure proteins is most characteristic of the stress response, body weight changes have been discussed at the very beginning of this section on metabolism.

Such an arbitrary classification has been adopted to avoid unnecessary repetitions, although separate sections deal with lipid and carbohydrate as well as with electrolyte and water metabolism, all of which can cause important modifications in total body weight.

In man, mere discussion of stressful subjects for one hour elicits diuresis with increased electrolyte and nitrogen elimination, concurrently with the typical rise in 17-OHCS excretion.

Additional observations in man showed that both emotional and physical stressors cause alterations in blood proteins, including the "acute phase reaction" accelerated blood clotting time and a particularly pronounced rise in the 4S and 19S class of serum proteins. (See also Blood Clotting under Functional Changes.)

Several monographs deal with the complex changes in protein metabolism and the protein constitution of various tissues under stress.

Proteins and Amino Acids

(See also our earlier stress monographs, p. xiii)

Hetzel, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man." *J. Clin. Endocrinol. Metab.* 15: 1057-1068 (1955).

C8,424/55

In patients a one-hour discussion of

"stressful subjects" caused diuresis with increased 17-OHCS, nitrogen, sodium and potassium elimination.

Hetzel, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary nitrogen and electrolyte excretion during stressful life experiences, and their relation to thyroid function." *J. Psychosom. Res.* 1: 177-185 (1956).

E83,418/56

Studies on serum PBI, urine flow, total

nitrogen, sodium and potassium "suggest that the thyroid may be participating in a rapid metabolic adjustment, but the mechanism involved is not clear from existing knowledge of the thyroid hormone."

Fessel, W. J.: "Mental stress, blood proteins, and the hypothalamus." *Arch. Gen. Psychiatry* 7: 427-435 (1962).

D69,380/62

"The word stress is used according to Selye's definition: Stress is a non-specific deviation from the normal resting state; it is caused by function or damage and it stimulates repair." Review of the literature on alterations of blood proteins and accelerated blood clotting time in man, due to the influence of various emotional and physical stressors. The diencephalon and hypothalamus affect blood proteins through immunologic mechanisms. In the present experiments on man, severe mental stress was noted to cause a rise in 4S and 19S class serum proteins. "It is speculated that functional behavior disturbances are but one expression of a general metabolic disorder which is contributed to by the effects of both stress and hypothalamic-hypophyseal action" (61 refs.).

Jayle, M. F.: "Rôle du métabolisme des glycoprotéines dans la biogénèse de l'athérosclérose. Concept sur le 'syndrome général de l'agression'" (Role of the metabolism of glycoproteins in the biogenesis of atherosclerosis. Concept of the "general stress syndrome"). *Ann. Thér.* 14: 11-22 (1963).

G63,439/63

Under various stress conditions, the plasma levels of fibrinogen and of the glycoproteins haptoglobin and seromucoid are characteristically increased; this may play an important part in stress-induced atherosclerosis. The common denominator of the diseases of adaptation and of stress responses may be a rise in these compounds which might thus correspond to the "first mediator." This interpretation might act as a valid focal point of Selye's "unitary concept" although the claims concerning the central role of the pituitary-adrenal axis are rejected.

Braksh, T. A., Popova, A. V.: "Tryptophan requirements under nervous stress." *Vopr. Pitani.* 23 No. 6: 21-25 (1964) (Russian).
J24,926/64

Munro, H. N.: "A general survey of pathological changes in protein metabolism." In: Munro, H. N. and Allison, J. B., *Mammalian Protein Metabolism*, Vol. 2, pp. 267-319.

New York and London: Academic Press, 1964. G79,177/64

Monograph on protein metabolism with an extensive section on the effects of stressors, including infection, trauma, undernutrition, heat, cold, muscular exercise and psychologic overstimulation.

Weimer, H. E., Godfrey, J. F.: "Effects of inanition, semistarvation, and protein-free diets on serum proteins." *Amer. J. Physiol.* 206: 331-334 (1964). F1,697/64

Lombart, C.: Thesis, Université de Paris, 1965. J11,880/65

Strong inflammatory processes with a pronounced stressor effect increase the secretion of haptoglobin in the rat.

Schumer, W.: "Metabolic considerations in the preoperative evaluation of the surgical patient." *Surg. Gynecol. Obstet.* 121: 611-620 (1965). F48,023/65

"The organism in stress has a dual function in relation to protein metabolism. Its duality lies in the fact that it will catabolize the protein pool of lean tissue mass in order to promote healing.... It is this shrinking of the protein stores that causes the marked catabolic wastage of the patient in surgical stress which is reinforced by lessened activity. The latter results in diminished food and water intake producing protein degradation for energy production. These factors emphasize the importance of preoperative, transoperative, and postoperative nutrition to avoid any increase in the catabolic nature of stress" (58 refs.).

Agostino, D., Girolami, A.: "Influenza dello stress sul fibrinogeno e sulla fibrinolisi ematica. [Nota sperimentale.]" (Influence of stress on fibrinogen and hematic fibrinolysis [Experimental note]). *Arch. Maragliano Patol. Clin.* 21: 137-141 (1965).

J25,102/65

Nitrogen metabolism in rats undergoing the stress of various surgical operations is associated with a pronounced hyperfibrinogenemia. These changes in the blood coagulation mechanism after stress can be considered as part of the first phase (alarm reaction) of the general adaptation syndrome of Selye.

Leon, H. A., Feller, D. D., Neville, E. D., Daligcon, B.: "Stress induced stimulation of liver protein synthesis independent of adrenal or pituitary action." *Life Sci.* 4: 737-741 (1965). G28,287/65

In vitro observations using labeled valine suggest that "the large increases in incorporation seen with adrenalectomized or hypophysectomized rats show that a mechanism independent of hormones released by the adrenal or pituitary glands is rapidly invoked by centrifugation stress and exerts a considerable influence over the rate of liver protein synthesis."

Weimer, H. E., Godfrey, J. F.: "Nutritional stress and the acute-phase reactants of rat serum in experimental inflammation." *Can. J. Physiol. Pharmacol.* **43**: 925-935 (1965). F53,959/65

Observations suggesting "that the response of the acute-phase reactants of rat serum to tissue injury is of such magnitude that it is not suppressed by several types of severe nutritional stress." In man as well as in other animals, the "characteristic changes are a decreased albumin level and increased levels of protein-bound carbohydrates, α_2 -globulin, fibrinogen, and the seromucoid fraction. In man, a new serum protein, C-reactive protein, appears and erythrocyte sedimentation rates are elevated. The components involved have been generally classified as acute-phase reactants since they usually exhibit a degree of parallelism toward each other in their deviation from normal during an inflammatory reaction." The authors do not discuss to what extent stressors not causing inflammation would affect acute-phase reactants.

Beauge, L. A., Palma, J. A.: "Modificacion del proteinograma en el 'stress' por inmovilizacion de la rata. Accion de la piridoxina" (Change in the proteinogram in "stress" caused by immobilization of the rat. Action of pyridoxine). *Rev. Soc. Argent. Biol.* **41**: 31-35 (1965). F63,084/65

Crockson, R. A., Payne, C. J., Ratcliff, A. P., Soothill, J. F.: "Time sequence of acute phase reactive proteins following surgical trauma." *Clin. Chim. Acta* **14**: 435-441 (1966). J22,863/66

Acute stress situations cause characteristic changes, especially in a group of plasma proteins referred to as "acute phase reactive proteins." Among these are C-reactive protein, orosomucoid, haptoglobin, the α_1 -acid glycoprotein of Schultze, fibrinogen, ceruloplasmin and α_2 -macroglobulin; the latter fails to rise following surgical interventions. "C-reactive protein, unique in being undetectable in normal sera, is most consistent in response and is therefore probably the most

satisfactory single screening test of an 'acute phase' reaction" (16 refs.).

Rao, V. V. S., Gupta, M. L.: "Effect of heat and cold stress on brain glutamic acid." *Fed. Proc.* **25**: 1185-1186 (1966).

F69,403/66

In rats, exposure to either cold or heat reduced the glutamic acid content of the brain.

Majumdar, C., Tsukada, K., Lieberman, I.: "Liver protein synthesis after partial hepatectomy and acute stress." *J. Biol. Chem.* **242**: 700-704 (1967). J21,396/67

In partially hepatectomized rats, stress caused by intraperitoneal Celite increases serum albumin and fibrinogen synthesis, presumably because the ability of liver polyribosomes to form protein is enhanced.

Clay, M. M., Adler, M. W.: "Alterations in hyaluronidase activity and serum protein electrophoretic patterns after chronic heat stress." *J. Pharm. Sci.* **56**: 756-767 (1967). F80,259/67

Muto, K., Koyama, M., Kazabuchi, M., et al.: "Effect of operative stress on protein metabolism." *Jap. J. Clin. Med.* **25**: 2654-2656 (1967). J24,398/67

Pereyra, B.: "Urinary excretion of hydroxyproline and proline during surgical stress." *Am. J. Surg.* **115**: 777-781 (1968). G58,338/68

During the postoperative period, the excretion of proline and hydroxyproline is increased in man, presumably as a consequence of the catabolic response.

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Conditions of work and their influence on psychological and endocrine stress reactions." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 8: 1-19 (1969).

G69,180/69

In Swedish officers deprived of sleep for seventy-five hours and performing on an electronic shooting range or engaged in military staff work, EP and NEP excretion was increased, as were erythrocyte sedimentation and the amount of PBI, whereas serum iron was decreased. Some subjects developed ECG anomalies, particularly ST-T depression, and it took several days of rest for the ECG patterns to return towards normal. Stressors recreating situations in civilian life produced essentially similar changes proportional to their severity.

Banceni, D., Gonin, J.: "Le titrage immunologique de l' α_2 -macroglobuline sérique

dans les états de stress et d'inflammation chez le rat" (The immunologic assay of serum α -2-macroglobulin in stress and inflammation in rats). *Rev. Franç. Étud. Clin. Biol.* **14**: 754-761 (1969). G71,638/69

Jayle, M. F., Engler, R., Degrelle, H.: "Les sialoglycoprotéines plasmatiques dans le syndrome d'agression et la croissance tissulaire" (Plasma sialoglycoproteins in the stress syndrome and during tissue growth). *Expos. Annu. Biochim. Méd.* **30**: 149-172 (1970). J20,529/70

A rise in plasma sialoglycoproteins is particularly characteristic of stress which necessitates wound healing and tissue regeneration.

Tayeau, F., Jouzier, E., Tixier, M.: "II. Isolement et étude 'in vitro' d'un inhibiteur naturel du facteur clarifiant" (II. Isolation and "in vitro" study of a natural inhibitor of the clearing factor). *Bordeaux Méd.* **3**: 1999-2008 (1970). H32,022/70

Tayeau, F., Jouzier, E., Tixier, M.: "III. Action 'in vivo' de l'inhibiteur du facteur clarifiant" (III. "In vivo" action of the inhibitor of the clearing factor). *Bordeaux Méd.* **3**: 2011-2014 (1970). H32,023/70

Observations on man and on various experimental animals have shown that the mucoprotein that appears in the blood and urine during stress (physical effort, intoxications, infections, serious diseases) constitutes a natural inhibitor of the lipoprotein lipase or "clearing factor" (22 refs.).

Jakoubek, B., Semiginovsky, B., Kraus, M., Erdossová, R.: "The alterations of protein metabolism of the brain cortex induced by anticipation stress and ACTH." *Life Sci. [I]* **9**: 1169-1179 (1970). G80,011/70

Szantay, I., Acalovschi, I.: "Aspects du métabolisme de la ^{35}S -méthionine au cours du stress opératoire" (Aspects of ^{35}S -methionine metabolism during surgical stress). *Agressologie* **11**: 389-394 (1970). H32,849/70

Studies with ^{35}S -methionine revealed an increased metabolism in patients following various operations.

Stanosek, J., Krzoska, K., Lewandowska-Tokarz, A., Józkiewicz, S.: "Die Einwirkung von Stress-Stimuli auf den Metabolismus bei Versuchstieren. 1. Mitteilung. Über den Einfluss von Betriebslärm auf das Verhalten von DNA, RNA und Eluateiweiß in der Leber, sowie das relative Gewicht dieses Organs bei

Meerschweinchen" (The influence of stress stimuli on metabolic changes in laboratory animals. I. Communication. The effect of industrial noise on the behavior of RNA, DNA and soluble proteins of the liver, as well as on the relative weight of this organ in guinea pigs). *Int. Arch. Arbeitsmed.* **26**: 216-223 (1970). H48,369/70

Leise, E. M., Morita, T. N., Gray, I., Le-Sane, F.: "Lymphocyte and polymorphonuclear enzymes in stress. II. Effect of the stress of restraint on rabbit leukocyte protein, aldolase, and lactate dehydrogenases." *Biochem. Med.* **4**: 336-346 (1970). H62,674/70

In rabbits, the stressor effect of restraint caused extensive metabolic alterations. "Some enzyme and protein changes in leukocytes were demonstrable 24 hours after the applied stress. Differences in the quantitative distribution of LDH isozymes in repeatedly bled and restrained rabbits were noted."

Heath, D. F., George, D. R., Rose, J. G.: "The effects of the stress caused by experimental procedures on alanine, aspartate, glutamate and glutamine in rat liver." *Biochem. J.* **125**: 765-771 (1971). G87,544/71

Kurochkin, V. I.: "Properdin concentration and protein composition of the lymph and blood in stress." *Biull. Èksp. Biol. Med.* **71**: 12-13 (1971) (Russian). Engl. trans.: *Bull. Èksp. Biol. Med.* **71**: 10-11 (1971).

"After fractures of the tibia and fibula in rabbits the properdin concentration in the lymph draining from the injured limb is reduced, while the total protein concentration is increased. The properdin, total protein, and albumin levels in the blood are lowered under these circumstances."

Jakoubek, B., Semiginovsky, B., Dědičová, A.: "The influence of stress and ACTH on the protein synthesis in brain." *Activ. Nerv. Suppl. (Praha)* **13**: 140 (1971). H65,267/71

Kraft, W.: "Das Verhalten von Na, K, Ca, anorganischem Phosphat, Chlorid, Gesamt-Eiweiss, GOT, GPT, LDH und alkalischer Phosphatase im Plasma von Schlachschweinen vor dem Transport zum Schlachthof, nach dem Transport und während der Entblutung" (Sodium, potassium, calcium, inorganic phosphate, chloride, total serum proteins, GOT, GPT, LDH, and alkaline phosphatase in the plasma of pigs for slaughter before and after transportation to the slaughterhouse and dur-

ing bleeding). *Berl. Münch. Tierärztl. Wochenschr.* **84**: 349-351 (1971).

J21,217/71

Árvay, A., Takács, I., Ladányi, P., Balogh, Á., Benkő, K.: "The effect of intensive nervous stimulation on certain physico-chemical properties of rat tail tendon and uterus collagen." *Gerontologia* **17**: 157-169 (1971).

J16,955/71

The physico-chemical properties of rat tail tendon (quantity of labile hydroxyproline, changes in thermo-isometric tension) and uterine collagen during biologic aging and exposure to various stressors are essentially similar. These findings and EM studies led the authors to suggest that "long-lasting intensive stress, therefore, produced changes of such a degree and character which exceeded the physiological changes characteristic of and accompanying biological ageing."

Wohler, W. H. Jr.: "Shipping stress in cattle: blood chemistry." *Mod. Vet. Pract.* **53**: 39-40 (1972).

J20,550/72

Wannemacher, R. W. Jr.: "Ribosomal RNA synthesis and function as influenced by amino acid supply and stress." *Proc. Nutr. Soc.* **31**: 281-290 (1972).

H80,192/72

Earlier observations showed that various stressors influence amino acid distribution in tissues. The present experiments on rats used mineralocorticoid hypertension to produce cardiac hypertrophy, and Walker tumor or infection to induce liver enlargement. The associated influx of amino acids and the increase in RNA and protein synthesis in the enlarged organs were ascribed to a "stress-related flux of amino acids." [The reason for this interpretation is not quite clear (H.S.).]

Tiplady, B.: "Brain protein metabolism and environmental stimulation, effects of forced exercise." *Brain Res.* **43**: 215-225 (1972).

J20,139/72

In rats, changes in the rate of cerebral protein synthesis induced by exercise may be due either specifically to motor activity or to stress (21 refs.).

Toader, C., Acalovschi, I., Szantay, I.: "Protein metabolism following surgical stress. Pre- and postoperative [⁷⁵S]methionine incorporation in serum albumin." *Clin. Chim. Acta* **37**: 189-192 (1972).

G89,576/72

Knott, P. J., Joseph, M. H., Curzon, G.: "Effects of food deprivation and immobiliza-

tion on tryptophan and other amino acids in rat brain." *J. Neurochem.* **20**: 249-251 (1973).

G99,781/73

Chvapil, M., Bartos, D., Bartos, F.: "Effect of long-term physical stress on collagen growth in the lung, heart, and femur of young and adult rats." *Gerontologia* **19**: 263-270 (1973).

J24,105/73

Observations on rats suggest that "collagen in every organ reacts differently to physical stress in relation to age."

Jakoubek, B., Pavlík, A., Semiginovský, B.: "Effect of activation of the hypophyseal-adrenal axis on the synthesis of brain macromolecules." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 79-88. Bratislava: Slovak Academy of Sciences, 1973.

E10,459/73

In rats, both the anticipation and the actual stress of restraint increase the uptake of labeled leucine into brain cortical slices. This uptake is not reflected by enhanced incorporation into proteins. The phenomenon appears to be due to activation of the hypothalamus-hypophyseal-adrenal axis, since it is prevented by adrenalectomy.

Völker, H., Furcht, G., Stolpe, J., Bauer, U.: "Zur Stressproblematik des Kälbertransports unter den Anforderungen industriemässiger Tierproduktion. Die Stresssituation und Stressreaktion transportierter Kälber" (Problems of transport stress in calves under conditions of intensive husbandry. The stress situation and reaction to stress in calves). *Arch. Exp. Veterinaemed.* **27**: 555-569 (1973).

J25,395/73

In calves, shipping over long distances elicits a typical stress reaction with increased glucocorticoid production and characteristic biochemical and hematologic changes. Special emphasis is placed upon the associated alterations in serum proteins and general protein loss which are of considerable commercial importance.

Addis, P. B., Nelson, D. A., Ma, R. T. I., Burroughs, J. R.: "Blood enzymes in relation to porcine muscle properties." *J. Anim. Sci.* **38**: 279-286 (1974).

J22,026/74

Studies on changes in protein metabolism that developed in porcine muscle during the stress of shipping.

Bressler, R., Huxtable, R.: "Increased concentration of taurine in congestive heart failure and hypertension" (abstracted). *Clin.*

Res. **22:** 552A (1974). H90,424/74

Observations on spontaneously hypertensive rats suggest that increased taurine levels in the myocardium are the immediate cause of hypertension and congestive heart failure during exposure to stress.

O'Keefe, S. J. D., Sender, P. M., James, W. P. T.: "Catabolic" loss of body nitrogen in response to surgery." *Lancet* November 2, 1974, pp. 1035-1038. H95,481/74

Observations on patients who received infusions of ¹⁴C-leucine before and after abdominal surgery "suggest that the 'catabolic'

response to operative stress involves a fall in protein synthesis without an acute rise in breakdown-rate of body protein."

Hale, H. B., Garcia, J. B. Jr., Ellis, J. P. Jr., Storm, W. F.: "Human amino acid excretion patterns during and following prolonged multistressor tests." *Aviat. Space Environ. Med.* **46:** 173-178 (1975). J22,135/75

Sherman, A. D., Gebhart, G. F.: "Pain-induced alteration of glutamate in periaqueductal central gray and its reversal by morphine." *Life Sci.* **16:** 673-681 (1975).

J23,618/75

Carbohydrates, Lactic Acid

It was repeatedly noted during the early years of this century that emotional glycosuria or "Fesselungsdiabetes" occurs during restraint in various species, particularly in cats. Considerable importance was attached to this finding, since a temporary "diabetes" was also noted in patients following severe emotional upset. These observations were probably the first indications of some relationship between stress and diabetes. They also represented an early clearcut example of an objective, quantitatively measurable psychosomatic change. However, since in cats this response could be abolished by adrenalectomy, and EP was the only known adrenal hormone, emotional glycosuria had been ascribed exclusively to EP discharge. The mobilization of sugar into the blood was considered to be helpful for supplying energy to muscles during the "fight or flight" emergency response of Cannon.

However, by 1940 it was evident that, during stress, hyperglycemia is not the only blood sugar response, and emotional excitement not its sole cause. Many other stressors were found to induce transient hyperglycemia in various species, but they could also elicit hypoglycemia. It became clear, furthermore, that blood sugar regulation during stress is not exclusively under the control of EP.

For example, during a particularly pronounced alarm reaction, produced by severe formaldehyde intoxication in the rat, hypoglycemia developed and this could be at least partially inhibited by a crude adrenocortical extract ("cortin").

A great deal has been written about the clinical syndrome of "functional hypoglycemia," which is allegedly closely related to stress, especially in neuropsychiatric patients. The mechanism and even the existence of this condition as a special syndrome have not yet been established with sufficient precision to permit discussion here. It has often been observed, however, that patients with neuropsychiatric disease suffer from anomalies in carbohydrate metabolism, although it is usually difficult to establish whether these are the cause or the consequence of the nervous manifestations.

It has long been known that a pure mineralocorticoid, such as DOC, can diminish stress-induced hyperglycemia, presumably owing to the inhibition of glucocorticoid secretion. This was the first observation showing that "overdosage with one of the compounds, produced by an endocrine cell, can interfere with the production by the same cell of other hormonal compounds." In this case, a mineralocorticoid can inhibit the production and the effect of a glucocorticoid.

In any event, the action of stress upon glucose metabolism depends upon so many conditioning factors that these will have to be consulted in the individual studies listed in the abstract section. This is easily understandable if we keep in mind that stress influences the production and activity of virtually every hormone that regulates carbohydrate metabolism, particularly catecholamines, ACTH, corticoids, STH, glucagon and insulin.

It is worth mentioning here, however, that serum hexosamine levels increase under the influence of various stressors in man, although the rise of blood hexosamine, unlike that of glucose, is independent of the adrenal cortex.

In man, as well as in various other mammals, serum and urinary lactic acid also rise under the influence of stress. These changes, as well as the depletion of glycogen stores, are similarly of great importance in regulating carbohydrate and energy metabolism during emergencies.

Carbohydrates, Lactic Acid

(See also our earlier stress monographs, p. xiii)

Cannon, W. B., Shohl, A. T., Wright, W. S.: "Emotional glycosuria." *Am. J. Physiol.* **29**: 280-287 (1912). B26,719/12

Personal observations on emotional glycosuria in cats separately caged next to a barking dog, and review of earlier literature dealing with "Fesselungsdiabetes" elicited by restraint in cats, and the appearance of diabetes in patients following severe emotional upset. In cats, emotional glycosuria after restraint is abolished by adrenalectomy, presumably as a consequence of EP-induced hyperglycemia. "A mobilization of sugar in the blood under these circumstances might be of signal service to the laboring muscles."

Selye, H., Dosne, C., Bassett, L., Whitaker, J.: "On the therapeutic value of adrenal cortical hormones in traumatic shock and allied conditions." *Can. Med. Assoc. J.* **43**: 1-8 (1940). A32,768/40

During the shock phase of the alarm reaction produced by heavy formaldehyde dosage in the rat, there is hypochloremia, hypoglycemia and hemoconcentration, all of which can be at least partially inhibited by a crude cortical extract (cortin). This is even more obvious in surgical shock produced by partial hepatectomy, but here a specific effect of hepatic insufficiency could not be excluded.

Gellhorn, E., Feldman, J., Allen, A.: "Effect of emotional excitement on the insulin content of the blood. Contribution to physiology of the psychoses." *Arch. Neurol. Psychiatry* **47**: 234-244 (1942). A37,798/42

In psychotic patients, emotional excitement

considerably increases the blood insulin level, although the blood sugar usually remains unaffected. In normal persons, excitement causes a rise in blood sugar but not in plasma insulin. "The experiments are interpreted to mean that the balance of the autonomic centers in psychotic patients under emotional stress is shifted toward the vagoinsulin side whereas in normal persons the sympathetic-adrenocortical system greatly predominates."

Rennie, T. A. C., Howard, J. E.: "Hypoglycemia and tension-depression." *Psychosom. Med.* **4**: 273-282 (1942). B19,676/42

Description of a syndrome designated as "functional hypoglycemia," which can occur in a predisposed patient when any one of the many factors of blood sugar homeostasis is interfered with. It is especially common among patients with a variety of neuropsychiatric disturbances, and appears to be the result of these, since it disappears when the latter are successfully treated. This syndrome is often difficult to distinguish from adrenocortical deficiency or hyperinsulinism.

Selye, H., Dosne, C.: "Physiological significance of compensatory adrenal atrophy." *Endocrinology* **30**: 581-584 (1942).

A37,249/42

In rats, large doses of DOC inhibit but do not prevent the adrenal enlargement characteristic of the alarm reaction following treatment with such stressors as cold, formaldehyde, atropine, trauma or forced muscular exercise. As a result of this inhibition the resistance of the DOC-treated animals to stressors is actually subnormal, since they are unable to produce optimal amounts of glucocorticoids. The hyperglycemia of the alarm reaction (presumably useful in providing en-

ergy during stress) is likewise diminished by DOC pretreatment. It is apparent that "overdosage with one of the compounds produced by an endocrine cell can interfere with the production by the same cell of other hormonal compounds (in this case corticoids, such as corticosterone, active in carbohydrate metabolism). As a result of this interference symptoms of overdosage with hormones produced by a certain endocrine cell type may coexist with signs of deficiency in the hormone production of that same cell."

Pincus, G.: "Adrenal cortex function in stress." *Ann. N.Y. Acad. Sci.* **50**: 635-645 (1949). B37,780/49

General review on changes in adrenocortical function during stress and psychiatric illness. Special emphasis is placed upon blood sugar, blood lymphocytes, corticoids and 17-KS.

Hinkle, L. E. Jr., Wolf, S.: "The effects of stressful life situations on the concentration of blood glucose in diabetic and non-diabetic humans." *Diabetes* **1**: 383-392 (1952).

B75,041/52

In healthy people, stressful life experiences usually cause a fall in the postabsorptive blood glucose concentration, often to definitely hypoglycemic levels, and a rise in circulating ketone bodies. In diabetics, definite ketoacidosis sometimes ensues in association with hyperglycemia (26 refs.).

Burns, T. W., Engel, F. L., Viau, A., Scott, J. L. Jr., Hollingsworth, D. R., Werk, E.: "Studies on the interdependent effects of stress and the adrenal cortex on carbohydrate metabolism in man." *J. Clin. Invest.* **32**: 781-791 (1953). B84,911/53

Observations on the effect of cortisone on carbohydrate metabolism during stress as well as after insulin or glucose administration "are considered to be compatible with the concept that there is an interaction between stress and adrenal hormone in modifying carbohydrate metabolism. They are not reconcilable with the view that the metabolic alterations during stress are direct consequences of adrenal cortical hypersecretion."

Stullken, D. E., Hiestand, W. A.: "Hematological changes influenced by short and long exposure to cold." *Proc. Soc. Exp. Biol. Med.* **86**: 253-255 (1954). B95,324/54

In mice, brief or prolonged exposure to cold produced no significant change in blood hemoglobin or red cell count but in the acute

state it raised the blood sugar level. These findings are discussed in relation to the G.A.S.

Merrick, A. W.: "Cardiac glycogen following fulminating anoxia." *Am. J. Physiol.* **176**: 83-85 (1954). G62,149/54

In the goldfish, cardiac glycogen stores are extremely high and difficult to exhaust, even by fulminating anoxia. "Cardiac glycogen is an emergency stand-by used by the heart during periods of anoxic stress." However, complete removal of cardiac glycogen is not necessary for the induction of cardiovascular and respiratory failure, and the observations do not prove any particular resistance of this fish to other stressors.

Boas, N. F., Bollet, A. J., Bunim, J. J.: "Effect of acute clinical stress on the levels of hexosamine in serum and its excretion in urine." *J. Clin. Invest.* **34**: 782-789 (1955).

C5,708/55

In man, serum hexosamine increased under the influence of various stressors (myocardial infarction, surgical operations, acute attacks of gout). ACTH or cortisone administration reduced the elevated serum hexosamine levels in rheumatic fever, rheumatoid arthritis and lupus erythematosus. ACTH had no effect when the urinary excretion and the serum levels of hexosamine were normal before treatment. In a patient with Addison's disease, the serum hexosamine still rose during stress. "Stress-hexosamine response in the serum and urine does not appear to be mediated by the adrenal cortex" (20 refs.).

Rice, C. O., Strickler, J. H., Tzeris, H.: "The relationship of an elevated blood sugar to an electrolyte imbalance." *Arch. Surg.* **72**: 508-513 (1956). D92,510/56

In man, stress-induced hyperglycemia is associated with electrolyte imbalance.

Manes, P. A.: "Blood glucose and plasma unesterified fatty acid changes induced by the stress of an emergency situation." *Experientia* **18**: 451-453 (1962). J23,455/62

Fedday, Z., Clay, M. M.: "Acid mucopolysaccharide content of dermal connective tissue of normal and stressed rats." *Nature* **202**: 907-908 (1964). F12,108/64

Various stressors caused an elevation of hyaluronic acid and chondroitin sulphate in rat skin.

Ehrentheil, O. F., Reyna, L. J., Yerganian, G., Chen, E. T.: "Studies in stress glycosuria.

I. Prolonged glycosuria in Chinese hamsters after repeated stress." *Diabetes* **13**: 83-86 (1964). F1,978/64

Chinese hamsters unfamiliar with each other started fighting when placed together. This resulted in glycosuria, which continued for two weeks after daily repeated fights. Both catecholamine and corticoid discharge during the G.A.S. may be of etiologic significance. The findings could be pertinent to the development of stress-induced diabetes.

Oyama, J., Medina, R., Platt, W. T.: "Influence of age on liver glycogenesis in rats exposed to acceleration stress." *Endocrinology* **78**: 556-560 (1966). F62,885/66

"Significant increases in liver glycogen deposition occurred in centrifuged rats 18 days or older but not in younger rats. The unresponsiveness of the younger rats was attributed to their limited ability to elaborate increased amounts of adrenal corticosterone during centrifugation."

Oyama, J., Daligcon, B. C.: "Liver glycogenesis, glycogen synthetase and adrenal responsiveness of rats exposed to acceleration stress." *Endocrinology* **80**: 707-713 (1967).

F81,569/67

As indicated by changes observed after centrifugation, "increased liver glycogenesis in stressed rats was always preceded by an increase in total synthetase activity due to an increase in the G-6-P independent form of the enzyme. No increase in liver glycogenesis or synthetase activity occurred in 14-day-old rats, in rats treated with actinomycin D or Metopirone, or in adrenalectomized rats."

Buchel, L., Guyonneau, M.: "Variations du taux plasmatique des acides gras libres et de la glycémie au cours de la contrainte du Rat blanc" (Changes in the plasma level of free fatty acids and blood glucose during restraint in white rats). *C.R. Soc. Biol. (Paris)* **161**: 289-292 (1967). F85,806/67

Wegman, H. M., Klein, K. E., Brüner, H.: "Die Auswirkung fliegerischer Belastung auf einige Blutkomponenten" (Effects of flying stress on certain components of the blood). *Int. Z. Angew. Physiol.* **23**: 293-304 (1967). G45,957/67

Among the indicators examined in jet pilots training for Starfighter F-104 G flights, corticoids and certain enzyme activities in the blood proved most sensitive to stress, whereas other enzyme and blood sugar variations were unreliable (24 refs.).

Danilova, L. Y.: "The role of adrenal glands in the regulation of carbohydrate metabolism of undercooled animals having different degrees of thermoregulation." *Acta Biol. Med. Ger.* **21**: 625-634 (1968).

H7,143/68

In various premature, but not in mature, newborn mammals, cooling is not accompanied by glycogenolysis because of an insufficient EP secretion. Glucocorticoids raise the hepatic glycogen reserves in newborns, but fail to increase their resistance to hypothermia.

Mason, J. W., Wherry, F. E., Brady, J. V., Beer, B.: "Plasma insulin response to 72-hr. avoidance sessions in the monkey." *Psychosom. Med.* **30**: 746-759 (1968).

H6,462/68

"Emotional reactions to venipuncture may also elicit a decrease in plasma immunoreactive insulin levels with associated elevations in plasma 17-OHCS and glucose levels."

Brahmachari, H. D., Joseph, S.: "Carbohydrate metabolism under environmental stress. Part I—Blood sugar response of albino rats under heat, cold and hypoxic stress." *Indian J. Exp. Biol.* **7**: 23-25 (1969).

J24,130/69

In rats exposed to hypoxia, cold or heat, "hyperglycemia is the general response to all the stress conditions and it is highest for hypoxic stress. Starvation for 24 and 48 hr prior to exposure produces hypoglycemia in hypoxic stress while heat and cold stimulate normal response."

Sharma, V. N., Godhwani, J. L.: "Stress-induced changes in catecholamine, glycogen and blood glucose levels and their modification by antiadrenergic drugs." *Indian J. Med. Res.* **58**: 1063-1072 (1970).

G82,559/70

Carey, L. C., Lowery, B. D., Cloutier, C. T.: "Blood sugar and insulin response of humans in shock." *Ann. Surg.* **172**: 342-350 (1970).

G77,785/70

Within minutes, patients in traumatic hypovolemic shock develop severe hyperglycemia, which falls gradually as resuscitation progresses, but is still high after five hours. The serum insulin is unresponsive to the hyperglycemia of shock.

Bottger, I., Falloona, G. R., Unger, R. H.: "The effect of intensive physical exercise on pancreatic glucagon secretion." *Diabetes* **20** Supp. 1: 339 (1971).

J10,799/71

In the dog and in man, blood glucagon levels rose during physical exercise, probably

contributing to the associated hyperglycemia. Blood insulin concentrations varied less regularly.

Joseph, S., Brahmachari, H. D.: "Carbohydrate metabolism under environmental stress. Part II—Glucose tolerance under heat, cold and hypoxic stress." *Indian J. Exp. Biol.* **10**: 272-273 (1972). J20,224/72

Exposure to heat, cold, or hypoxia decreases glucose tolerance in the rat, presumably as a consequence of stress.

Raichle, M. E., King, W. H.: "Functional hypoglycemia: a potential cause of unconsciousness in flight." *Aerosp. Med.* **43**: 76-78 (1972). J20,017/72

In a student pilot, functional hypoglycemia with unconsciousness developed during acceleration a few hours after a high carbohydrate meal.

Prioux-Guyonneau, M., Buchel, L.: "Métabolisme des lipides et des glucides chez le rat blanc au cours de deux agressions, immobilisation forcée et variations thermiques" (Lipid and carbohydrate metabolism in white rats in the course of 2 stresses, forced immobilization and thermal variations). *C.R. Soc. Biol. (Paris)* **166**: 1277-1283 (1972). H66,183/72

Khanna, N. K., Lauria, P., Sharma, V. N.: "Effect of electroshock stress on the glycogen and acetylcholine content of the myocardium of the dog." *Indian J. Med. Sci.* **26**: 380-382 (1972). G94,705/72

Electroshock stress produced an increase in acetylcholine and a decrease in glycogen in the myocardium of the dog.

Németh, Š., Vigaš, M., Lichardus, B.: "Indirect proofs for true metabolization of glucose disappearing from the blood of rats during trauma." *J. Trauma* **12**: 891-897 (1972). H78,475/72

In rats subjected to trauma in the Noble-Collip drum, the glucose concentration in small bowel irrigation effluents dropped, even after glucose pretreatment. In alloxan diabetic rats, the injury caused a significant decrease in blood sugar. From this and other experiments, it is concluded that true metabolic disappearance of blood glucose occurs during the first period of trauma (21 refs.).

Rahe, R. H., McHugh, W., Kaplan, N., Rimon, R., Arthur, R. J.: "Serum lactic acid variability in subjects experiencing stressful training." *Dis. Nerv. Syst.* **33**: 403-408 (1972). H79,743/72

In a U. S. Navy underwater demolition team undergoing a psychologically and physically stressful underwater training swim, serum lactic acid rose considerably. "In contrast to reports by other authors, no significant correlation was seen between subjects' serum lactic acid levels and a psychological questionnaire's indices of psychoneurotic symptomatology. A significant correlation was seen between a measure of physical fitness of the men and their serum lactic acid concentrations."

Stremmel, W.: "Die Bedeutung des Blutglykogens nach stressinduzierten Stoffwechselstörungen" (The importance of blood glycogen concentration after stress-induced metabolic disturbances). *Brunn's Beitr. Klin. Chir.* **220**: 297-305 (1973). J3,874/73

In patients the stress of surgical interventions raises blood glycogen. A similar change is seen after exposure to various stressors and may be responsible for increased platelet adhesiveness and stress-induced thrombosis.

Németh, Š., Vigaš, M.: "Hypercatabolism of glycide compounds during trauma: possible mechanisms." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 295-306. Bratislava: Slovak Academy of Sciences, 1973.

E10,477/73

In rats, trauma in the Noble-Collip drum increases the degradation of carbohydrates via the Embden-Meyerhof pathway. Much of the increased glycolysis during stress may serve for "fight or flight" necessitating muscular work. In fasted animals, the resulting hypoglycemia threatens damage to the CNS, whereas in fed rats hyperlactacidemia may be a symptom of hypoxia, and can contribute to fatal acidosis.

Heath, D. F., Corney, P. L.: "The effects of starvation, environmental temperature and injury on the rate of disposal of glucose by the rat." *Biochem. J.* **136**: 519-530 (1973).

J8,004/73

The disposal rate of intravenous glucose among rats was not very predictably influenced by exposure to various stressors such as burns, surgical trauma, fasting, cold, heat or hind-limb ischemia.

Harrison, M. H.: "Comparison of the metabolic effects of centrifugation and heat stress in man." *Aerosp. Med.* **44**: 299-303 (1973).

H80,109/73

In fasted men the stress of centrifugation

or exposure to heat increased blood lactate, glucose, FFA, glycerol and catecholamine levels, but these changes did not always parallel each other (30 refs.).

O'Hanlon, J. F., Horvath, S. M.: "Interrelationships among performance, circulating concentrations of adrenaline, noradrenaline, glucose, and the free fatty acids in men performing a monitoring task." *Psychophysiology* **10**: 251-259 (1973). J3,116/73

In young men performing an exacting vigilance test, basal blood EP and NEP were inversely related to glucose. EP initially increased during the test but later returned to its basal level in proportion to performance. NEP was not related to performance. Glucose and FFA were elevated, both during the task and throughout a control period spent watching slide projections.

White, J. A., Bolsteidge, M., Downing, H. J., et al.: "Effects of stress on the results of glucose tolerance tests performed on vervet monkeys (*Ceropithecus pygerythrus* F. Cuvier)." *J. S. Afr. Vet. Med. Assoc.* **44**: 379-381 (1973). J24,393/73

Myles, W. S., Radomski, M. W.: "Excretion of lactic acid by rats exposed to simulated high altitude." *Aerospace Med.* **45**: 422-424 (1974). J12,121/74

In rats, hypoxia, like EP injections, increased the urinary lactate level. This may furnish us with "an indicator of the severity of hypoxic stress at altitude."

Silbergeld, E. K.: "Blood glucose: a sensitive indicator of environmental stress in fish." *Bull. Environ. Contam. Toxicol.* **11**: 20-25 (1974). J9,883/74

In the freshwater fish johnny darter (*Etheostoma nigrum Rafinesque*) a rise in blood glucose is a sensitive indicator of stress (for example, handling, capture, insecticide).

Wiener, R., Spitzer, J. J.: "Glucose metabolism following severe hemorrhage in the conscious dog." *Am. J. Physiol.* **227**: 63-66 (1974). H89,534/74

Robertson, R. P., Porte, D. Jr.: "Plasma catecholamine responses to intravenous glucose in normal man." *J. Clin. Endocrinol. Metab.* **39**: 403-405 (1974). H89,331/74

In man, glucose-stimulated insulin secretion is inhibited during stress. This effect can be reversed by α -adrenergic blockade which raises insulin discharge and augments insulin responses to glucose. Presumably, endogenous

catecholamine secretion exerts an inhibitory effect upon insulin production.

Dechezleprêtre, S., Lechat, P.: "Effets comparés de l'adrénaline et d'un stress aigu sur la glycémie, la lactacidémie et la corticostérone plasmatique et surrénalienne du rat" (Comparison of the effects of epinephrine and acute stress on glycemia, lactacidemia, and the plasma and adrenal corticosterone levels in the rat). *Agressologie* **15**: 117-123 (1974). H93,830/74

In rats, acute exposure to cold causes marked hyperlactacidemia and mild hyperglycemia, with a considerable increase in plasma and adrenal corticosterone levels. These changes reach their maximum within ten minutes. EP exerts a similar effect due to the stressor action of the injection procedure, since it is also produced by injection of the solvent alone. The changes elicited by combined treatment with cold and EP are not greater than those caused by the two agents separately.

Äärimaa, M., Slätis, P., Haapaniemi, L., Jeglinsky, B.: "Glucose tolerance and insulin response during and after elective skeletal surgery." *Ann. Surg.* **179**: 926-929 (1974). J13,288/74

In patients undergoing surgery the glucose tolerance curves assumed a diabetic pattern. Insulin secretion was suppressed on the day of operation but rose above preoperative values in the postoperative period. "The hyperglycemia occurring after hemorrhage and after tissue injury is presumably a purposeful metabolic alarm reaction tending to maintain an adequate supply of fuel to the brain and peripheral nerves during stress conditions."

Giddings, A. E. B.: "The control of plasma glucose in the surgical patient." *Br. J. Surg.* **61**: 787-792 (1974). H95,487/74

On the basis of studies on surgical patients, "it is suggested that insulin resistance is an adaptive feature which permits an augmented supply of energy substrate to meet the demands of injury. In adequate amounts intravenous carbohydrate spares tissue protein and fat during recovery."

Struck, P. J., Tipton, C. M.: "Effect of acute exercise on glycogen levels in adrenalectomized rats." *Endocrinology* **95**: 1385-1391 (1974). H94,156/74

Follenius, M., Brandenberger, G.: "Influence de l'exercice musculaire sur l'évolution

de la cortisolémie et de la glycémie chez l'homme" (Effect of muscular exercise on diurnal variations of plasma cortisol and glucose in normal men). *Eur. J. Appl. Physiol.* **33**: 23-33 (1974).

J16,058/74

In man, exercise on a bicycle ergometer raises plasma cortisol within ten minutes. Blood glucose decreases at first but is elevated to the initial level twenty minutes after cessation of work.

Electrolytes, Water, Osmotic Pressure, Diuresis, pH

Acute stress, especially if conducive to shock, undoubtedly exerts a pronounced influence upon water and salt metabolism, and consequently alters osmotic pressure in blood and tissues.

In this connection, the first studies directly related to the G.A.S. revealed that in rats an alarm reaction produced by heavy formaldehyde intoxication caused hypochloremia concurrently with hemoconcentration and hypoglycemia, all of which could be inhibited by the crude cortical extracts (cortin) then available.

It has also been shown that stress caused by prolonged swimming reduces the potassium concentration in brain and muscle, and elicits many other alterations in electrolyte metabolism. However, these are not always strictly correlated with other manifestations characteristic of stress, presumably because each parameter has its own time-curve and is subject to different special conditioning influences.

Attention has been called to the fact that patients with head injuries develop hypochloremia and hypochloruria reminiscent of the drop in blood chloride produced by DOC in the rat, but the latter is unassociated with hypochloruria; hence, a close relationship between the two remains highly problematic. In any event, various stressors can elicit hypochloremia in man as well as in other mammals. The increased diuresis associated with stress in man is similar to that seen during early starvation. It can even be elicited by discussion of "stressful subjects," and is then associated with enhanced corticoid, nitrogen, sodium and potassium elimination.

A particularly interesting manifestation of stress-induced alterations in water and electrolyte metabolism is the so-called "distress edema." At times of emotional crisis, a patient may gain as much as 20 pounds in a single day, owing to fluid and electrolyte retention.

Several investigators have also examined the blood pH variations and calcium metabolism changes during stress. However, apart from the well-known hyperlactacidemia that contributes to acidosis and the loss of calcium in astronauts on long voyages (which may be more specifically related to the effect upon bones in an environment deprived of gravity), no definitely established regularities have been revealed.

Electrolytes, Water, Osmotic Pressure, Diuresis, pH

(See also our earlier stress monographs, p. xiii)

Rydin, H., Verney, E. B.: "The inhibition of water-diuresis by emotional stress and by muscular exercise." *Q. J. Exp. Physiol.* **27**: 343-374 (1938).

A14,575/38

In dogs, emotional excitement and muscular exercise inhibit diuresis. This response

is unaltered by transection of the renal nerves, by extirpation of one adrenal and denervation of the other or by decentralization of the whole abdominal sympathetic system with removal of ganglia L₂ to S₁ inclusive. The course of this inhibition is matched by intravenous vasopressin. "The post-pituitary equivalent of this stress in terms of the standard powder is of the order of 1 µg."

Selye, H., Dosne, C., Bassett, L., Whit-

taker, J.: "On the therapeutic value of adrenal cortical hormones in traumatic shock and allied conditions." *Can. Med. Assoc. J.* **43**: 1-8 (1940). A32,768/40

During the shock phase of the alarm reaction produced by heavy formaldehyde dosage in the rat, there is hypochloremia, hypoglycemia and hemoconcentration, all of which can be at least partially inhibited by a crude cortical extract (cortin). This is even more obvious in surgical shock produced by partial hepatectomy, but here a specific effect of hepatic insufficiency could not be excluded.

O'Connor, W. J., Verney, E. B.: "The effect of increased activity of the sympathetic system in the inhibition of water-diuresis by emotional stress." *Q. J. Exp. Physiol.* **33**: 77-90 (1945). 95,009/45

Hoagland, H., Stone, D.: "Brain and muscle potassium in relation to stressful activities and adrenal cortex function." *Am. J. Physiol.* **152**: 423-435 (1948) (31 refs.). B19,300/48

Hoagland, H.: "Stress and the adrenal cortex with special reference to potassium metabolism." *Psychosom. Med.* **12**: 142-148 (1950). B51,612/50

In rats, stress caused by prolonged swimming reduced the potassium concentration of the brain and muscle.

Hinkle, L. E. Jr., Wolf, S.: "Studies in diabetes mellitus: changes in glucose, ketone, and water metabolism during stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 338-389. Baltimore: Williams & Wilkins, 1950.

B51,913/50

During stress, polyuria may occur in both diabetic and nondiabetic persons. However, in the former a massive loss of glucose and electrolytes contributes to the development of dehydration and coma. "The life history of one diabetic person was presented; and a brief formulation of a possible meaning of diabetes mellitus as the inappropriate use of a normal adaptive mechanism to starvation because of early conditioning, and perhaps of constitutional predisposition, has been suggested" (76 refs.).

Pfeiffer, J. B. Jr., Wolff, H. G.: "Studies in renal circulation during periods of life stress and accompanying emotional reactions in subjects with and without essential hypertension; observations on the role of neural

activity in regulation of renal blood flow." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 929-953. Baltimore: Williams & Wilkins, 1950.

B51,951/50

Kuhl, W. J. Jr., Ralli, E. P.: "Effect of acute stress upon blood constituents, white cells, and urine constituents in normal individuals." *Proc. Assoc. for the Study of Internal Secretions—33rd. Meet.*, p. 51. Atlantic City, N.J., 1951. Also in: *J. Clin. Endocrinol. Metab.* **11**: 776 (1951).

B58,505/51

Normal men immersed in cold water (9.5°C) for eight minutes showed: 1—A decrease in temperature (immediate, 1 and 2 hours); 2—An increase in systolic and diastolic blood pressure (immediate) and a decrease (2 hours); 3—A decrease in heart rate (1, 2 and 4 hours); 4—An increase in neutrophiles (immediate); 5—A decrease in lymphocytes (2 hours); 6—A decrease in eosinophiles (2 hours); 7—A decrease in serum chloride (immediate); 8—An increase in total proteins (immediate and 4 hours); 9—A decrease in serum water (immediate); 10—An increase in total cholesterol (4 hours); 11—An increase in the urine uric acid/creatinine ratio (2 and 4 hours)." All of these changes were significant and ascribed to stress, but no one indicator gave uniformly positive results.

Blake, W. D.: "Effect of exercise and emotional stress on renal hemodynamics, water and sodium excretion in the dog." *Am. J. Physiol.* **165**: 149-157 (1951).

B58,156/51

In dogs, "emotional stress" associated with exercise increased the reabsorptive rate of sodium, since the excretion did not correlate with a similar change in the glomerular filtration rate.

Higgins, G., Lewin, W., O'Brien, J. R. P., Taylor, W. H.: "Metabolic disorders in head injury. Hyperchloraemia and hypochloururia." *Lancet* June 16, 1951, pp. 1295-1300.

J12,252/51

In patients with serious head injuries, hyperchloraemia with hypochloururia occurs as it does after DOC treatment. Hyperchloraemia has previously been described as characteristic of the G.A.S. in rats, but this was unassociated with hypochloururia, and hence it remains questionable whether the present clinical observations can be ascribed to stress as such.

Faurbye, A., Vestergaard, P., Kobbernagel, F., Nielsen, A.: "Adrenal cortical function in chronic schizophrenia (stress, adrenaline-test, ACTH-test)." *Acta Endocrinol.* (Kbh.) **8**: 215-246 (1951). B63,996/51

In man, EP treatment and the production of fever by injections of killed *B. faecalis* *alcaligenes* are regarded as adequate "stress tests" as indicated by the increase in uric acid and potassium excretion, as well as the hematologic changes that result.

Hinkle, L. E. Jr., Edwards, C. J., Wolf, S.: "The occurrence of diuresis in humans in stressful situations and its possible relation to the diuresis of early starvation." *J. Clin. Invest.* **30**: 809-817 (1951) (35 refs.).

B61,252/51

Kuhl, W. J. Jr., Wilson, H., Ralli, E. P.: "Measurements of adrenal cortical activity in young men subjected to acute stress." *J. Clin. Endocrinol. Metab.* **12**: 393-406 (1952).

B69,085/52

Normal men immersed in cold water for eight minutes exhibited significant eosinopenia, lymphopenia and hypochloremia, with increased urinary ascorbic acid and uric acid excretion. Serum sodium, potassium, blood sugar and ascorbic acid were not significantly altered.

Levine, J., Luby, E., Rauch, A., Yesner, R.: "Blood viscosity of psychotics and non-psychotics under stress." *Psychosom. Med.* **16**: 398-403 (1954). C3,539/54

Increased blood viscosity is a characteristic consequence of psychologic stress in man, and may be related to emotionally-induced thromboembolic diseases.

Hetzl, B. A., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man." *J. Clin. Endocrinol. Metab.* **15**: 1057-1068 (1955). C8,424/55

In patients a one-hour discussion of "stressful subjects" caused diuresis, with increased 17-OHCS, nitrogen, sodium, and potassium elimination.

Nicholls, D., Rossiter, R. J.: "The role of the pituitary and thyroid glands in the phosphorus metabolism of the adrenal gland during cold stress." *Endocrinology* **56**: 547-559 (1955). C4,483/55

Rice, C. O., Stickler, J. H., Azeris, H.: "The relationship of an elevated blood sugar

to an electrolyte imbalance." *Arch. Surg.* **72**: 508-513 (1956). D92,510/56

In man, stress-induced hyperglycemia is associated with electrolyte imbalance.

Hetzl, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary nitrogen and electrolyte excretion during stressful life experiences, and their relation to thyroid function." *J. Psychosom. Res.* **1**: 177-185 (1956). E83,418/56

Studies on serum PBI, urine flow, total nitrogen, sodium and potassium "suggest that the thyroid may be participating in a rapid metabolic adjustment, but the mechanism involved is not clear from existing knowledge of the thyroid hormone."

Hale, H. B., Ellis, J. P. Jr., Kratochvil, C. H.: "Effects of piloting supersonic aircraft on plasma corticosteroids and bicarbonate." *J. Appl. Physiol.* **14**: 629-631 (1959).

J11,140/59

In pilots flying supersonic military aircraft, no significant correlation was found between the fall in plasma bicarbonate and the rise in corticoids.

Gold, A. J., Barry, J. Q., Ferguson, F. P.: "Early effect of moderate altitude stress on plasma potassium in the dog." *J. Appl. Physiol.* **15**: 37-39 (1960). C80,876/60

Munday, K. A., Blane, G. F.: "Changes in electrolytes and 17-oxosteroids in the rat subjected to cold environment." *J. Endocrinol.* **20**: 266-275 (1960). C86,538/60

Sodium, potassium and 17-OHCS determinations suggest "early adrenal hyperactivity with release of hormones of the 'mineralocorticoid-type' during the acute stress caused by cold."

Gupta, S., Kumar, S.: "Studies in anaemia of infection. Part VI. Relation of plasma iron with stress and adreno-cortical function." *Indian J. Med. Res.* **48**: 140-145 (1960).

C99,744/60

In rabbits and man, since various divergent stimuli, including infections, produce a common state of distress, "it is postulated that 'stress' caused by these stimuli may be concerned in some way with the production of hypoferraemia."

Wiancko, K. B.: "Serum magnesium and peripheral blood counts in rats fed high and low magnesium diet." *Arch. Int. Pharmacodyn. Ther.* **132**: 91-96 (1961).

J23,521/61

"During stress the rat is able to rapidly mobilize magnesium."

Benjamin, F. B., Anastasi, J. N., Helvey, W. M.: "Effect of stress on potassium content of rat brain." *Proc. Soc. Exp. Biol. Med.* **107**: 972-973 (1961). D12,860/61

Benjamin, F. B., Anastasi, J. N., Helvey, W. M.: "Effect of stress on potassium release from surviving rat brain." *Proc. Soc. Exp. Biol. Med.* **107**: 973-974 (1961).

D12,861/61

Prioreschi, P., Gabbiani, G.: "Action of various damaging agents on myocardial potassium." *Can. J. Physiol. Pharmacol.* **42**: 763-767 (1964). G19,432/64

Some stressors increase the potassium content of the rat myocardium while others do not.

Valtin, H., Schroeder, H. A.: "Familial hypothalamic diabetes insipidus in rats (Brattleboro strain)." *Am. J. Physiol.* **206**: 425-430 (1964). F1,711/64

In rats with familial hypothalamic diabetes insipidus, which can be corrected by vasopressin, the ability to concentrate urine in response to stress, dehydration, hypertonic saline or nicotine is greatly impeded.

Maniey, J.: "Aggressions et hypokaliémie chez le rat. II. Rôle de l'hypophyse et de la surrénales dans l'hypokaliémie provoquée par une agression non spécifique" (Stress and hypokalemia in the rat. II. Role of the hypophysis and adrenals in the hypokalemia induced by nonspecific stress). *J. Physiol. (Paris)* **57**: 447-456 (1965). G34,801/65

Weltman, A. S., Sackler, A. M.: "Timidity and metabolic elimination patterns in audiogenic-seizure susceptible and resistant female rats." *Experientia* **22**: 627-629 (1966). G16,051/66

There is a positive relationship between timidity and seizure susceptibility in rats exposed to "auditory stress." At the same time, there is an increase in diuresis and the quantity of feces.

Robert, A., Phillips, J. P., Nezamis, J. E.: "Production, by restraint, of gastric ulcers and of hydrothorax in the rat." *Gastroenterology* **51**: 75-81 (1966). G40,473/66

In rats, restraint produced gastric ulcers and hydrothorax within four to six hours. Overnight fasting prevented the hydrothorax and reduced the gastric ulcerations (contrary to previous reports). Restraint ulcers and hy-

drothorax "were also inhibited by crowding of the animals, a rise in ambient temperature, or administration of prednisolone."

Zlody, R. L.: "Changes in three blood components as a result of a stress situation." *Psychosomatics* **7**: 14-18 (1966).

F61,990/66

In male graduate students, a stressful examination causes a shift of the blood acid base level in the alkaline direction, an increase in red cell count and leukocytosis (21 refs.).

Paré, W. P., McCarthy, T. E.: "Urinary sodium and potassium and prolonged environmental stress." *J. Genet. Psychol.* **108**: 135-142 (1966). J21,567/66

Rats exposed to stressors (sound, electroshock) "manifest a significant eosinopenia and adrenal hypertrophy. Estimates of Na and K during the stress period do not manifest a shift in electrolyte balance for stress animals. The authors conclude that the adrenal mineralocorticoids do not participate in the physiological response to chronic environmental stress."

Gordon, R. S. Jr., Andrews, H. L.: "Potassium depletion under heat stress." *Fed. Proc.* **25**: 1372-1374 (1966). F69,424/66

Malm, J. R., Manger, W. M., Sullivan, S. F., Papper, E. M., Nahas, G. G.: "The effect of acidosis on sympatho-adrenal stimulation. Particular reference to cardiopulmonary bypass." *J.A.M.A.* **197**: 121-125 (1966).

F67,945/66

Acidosis accompanying hemorrhagic shock, apneic oxygenation and retransfusion of stored blood is associated with a rise in catecholamine production and plays a decisive role in cardiopulmonary bypass operations. "Control of arterial pH is of prime importance in modifying the sympatho-adrenal stress response of extracorporeal circulation."

Maniey, J.: "Influence des agressions sur la teneur en potassium et en sodium du plasma chez la ratte gestante ou non gestante et chez le foetus" (Influence of stresses on plasma potassium and sodium levels in the pregnant and nonpregnant rat and in the fetus). *Ann. Endocrinol. (Paris)* **28** Suppl.: 63 (1967). H61,543/67

Pospíšil, M.: "Oscillations of urine electrolyte excretion in mice and its significance for evaluating interindividual differences in the reaction to stress." *Physiol. Bohemoslov.* **16**: 172-177 (1967). G48,158/67

Gairard, A., Marnay-Gulat, C., Raoul, Y.: "Essai d'analyse de la contrainte ulcérogène du Rat par l'étude de l'élimination urinaire de divers ions" (Experimental analysis of restraint ulcerogenesis in the rat by study of the urinary elimination of various ions). *C.R. Soc. Biol. (Paris)* **161**: 2132-2136 (1967).

F98,979/67

In rats, restraint ulcers are associated with a decrease in creatinine, chlorine, sodium and calcium excretion. Phosphaturia is increased, whereas potassium elimination does not change.

Power, L.: "Distress edema." *Postgrad. Med.* **42**: 14-18 (1967).

G48,510/67

In a female patient, "weight fluctuations and edema were found to be a response to emotional stress and family tension. At times of emotional crisis the patient was capable of gaining as much as 20 lb in a single day." Probably, many cases of so-called "idiopathic edema" are due to stress.

Pride, L. F.: "An adrenal stress index as a criterion measure for nursing." *Nurs. Res.* **17**: 292-303 (1968).

J23,742/68

Shoemaker, W. C.: "The action of epinephrine and other hormones associated with the stress response on potassium movements with special reference to the development of postoperative depletion states." *Rev. Surg.* **25**: 9-24 (1968).

J23,680/68

Wheeler, T. E., New, A. E.: "A study of blood serum potassium concentration and stress in the squirrel monkey (*Saimiri sciuereus*). NAMI-1041. *U.S. Naval Aerospace Med. Inst.* 1-8 (1968).

J23,751/68

Kay, R. G.: "The effect of an aldosterone antagonist upon the electrolyte response to surgical trauma." *Br. J. Surg.* **55**: 266-272 (1968).

F97,873/68

In patients following surgical interventions, there is diminished urinary excretion of sodium and early postpotassium-diuresis. These changes are not much influenced by the aldosterone antagonist SC-11927. The finding "obviously challenges the accepted role of aldosterone in post-traumatic sodium metabolism and an alternative explanation must be sought for the diminished urinary excretion of sodium observed at this time." Literature is cited to show that the characteristic post-traumatic electrolyte changes are also present in adrenalectomized patients on constant corticoid intake.

Leo, P. di: "Rapporto tra modificazioni

della potassiemia e tasso di magnesio plasmatico nello stress" (Relationship between the changes of potassium and the plasmatic magnesium level in stress). *Boll. Soc. Ital. Biol. Sper.* **44**: 850-852 (1968).

J22,411/68

Leo, P. di, Onorato, A.: "Rapporto tra modificazioni della calcemia e tasso di magnesio plasmatico nello stress" (Relationship between the changes of calcemia and plasmatic magnesium levels in stress). *Boll. Soc. Ital. Biol. Sper.* **44**: 847-850 (1968).

G61,205/68

Raab, W., Bajusz, E., Kimura, H., Herrlich, H. C.: "Isolation-stress, myocardial electrolytes and epinephrine cardiotoxicity in rats." *Proc. Soc. Exp. Biol. Med.* **127**: 142-147 (1968).

F96,287/68

Lambert, R., André, C., Martin, M. S., Martin, F.: "Incorporation du radiosulfate dans les tissus du rat normal ou soumis à la contrainte" (Incorporation of radiosulfate in the tissues of normal rats and of rats under restraint). *Biol. Gastroentérol. (Paris)* **1**: 35-44 (1969).

J20,822/69

Spigel, I. M., Ramsay, A.: "Excretory electrolytes and response to stress in a reptile." *J. Comp. Physiol. Psychol.* **68**: 18-21 (1969).

G67,129/69

"Elevated urinary alkali metal (combined Na^+ and K^+) was observed in electrically shocked turtles."

Tashima, C. K.: "Metabolic acidosis after stress." *N. Engl. J. Med.* **280**: 671 (1969).

J21,993/69

Winkler, G., Graef, V.: "Nachwirkungen einmaliger Nebennierenrindenstimulierung auf den Verlauf der Aldosteronausscheidung im Harn" (The effect of a single stimulation of the adrenal cortex on the course of urinary aldosterone excretion). *Z. Klin. Chem. Klin. Biochem.* **7**: 179-180 (1969).

J22,932/69

In man, the stress of exhaustive muscular exercise causes an increase in aldosterone and potassium excretion as well as sodium retention, followed by a decrease in aldosterone and potassium elimination, which in turn initiates a rebound phenomenon. This cyclicity must be taken into account in evaluating pertinent information.

Majle, T.: "Studies on the influence of stress factors, external irradiation and selected pharmacologic agents on the retention of radioactive caesium ^{137}Cs in rat body."

Roczn. Zak. Hig. (Warsz.) **21**: 497-508 (1970) (Polish). H64,378/70

Kaffarnik, H., Gross, W., Dawid, E., Deibert, K., Juchems, R.: "Verhalten der Adenylatkinase (Myokinase), des Adenosintriphosphats (ATP) und der K- und Na-Ionen im Serum bzw. Blut unter standardisierter körperlicher Belastung" (Behavior of adenylate kinase [myokinase], adenosine triphosphate [ATP] and K and Na ions in the serum or blood under standardized physical stress). *Z. Gesamte Exp. Med.* **153**: 324-330 (1970). H36,724/70

In man, muscular work increases the serum concentration of adenylate kinase and ATP, but does not change potassium or sodium levels. "The results are discussed with respect to the turnover of the phosphates during physical stress" (25 refs.).

Hadynoń, B.: "Influence of stress on potassium and calcium content of the myocardium in guinea pigs." *Pathol. Pol.* **22**: 633-639 (1971) (Polish). J20,494/71

Flynn, A., Pories, W. J., Strain, W. H., Hill, O. A. Jr.: "Mineral element correlation with adrenohypophyseal-adrenal cortex function and stress." *Science* **173**: 1035-1036 (1971). H44,997/71

In rats stressed by hemorrhage, "serum calcium, copper, and magnesium demonstrated little correlation with ACTH changes. The strong ACTH-zinc correlation points to an as yet undefined interaction between ACTH and zinc."

Classen, H.-G., Marquardt, P., Späth, M., Schumacher, K.-A.: "Hypermagnesemia following exposure to acute stress." *Pharmacology (Basel)* **5**: 287-294 (1971).

H44,498/71

In the cat, the "hypermagnesemia produced by withdrawal of blood, asphyxia, infusions of catecholamines or poisoning with potassium cannot be prevented by reserpine, phentolamine or Kö 592."

Sevy, S.: "Acute emotional stress and sodium in breast milk." *Am. J. Dis. Child.* **122**: 459 (1971). J20,192/71

Viru, A., Körge, P.: "Metabolic processes and adrenocortical activity during marathon races." *Int. Z. Angew. Physiol.* **29**: 173-183 (1971). G84,664/71

Among fourteen first-class marathon runners, all but the two best showed lowering of blood cortisol levels during the race. Urinary sodium decreased and potassium increased.

In most cases, GPT activity and NPN rose in plasma, and the excretion of nitrogen and creatinine was reduced. "It was suggested that before the end of the marathon race the protein catabolism is diminished due to a decrease of the glucocorticoid function of the adrenal gland."

Rothschild, H. C., Shaw, S. M.: "Urinary sodium-potassium ratio determination by tracer methodology for the detection of stress caused by noise." *Environ. Lett.* **1**: 277-285 (1971). J11,082/71

In rats, sound causes a marked depletion of adrenal ascorbic acid associated with significant alterations of sodium/potassium ratios in the urine. The sodium/potassium ratio "should prove valuable in the identification of various environmental stimuli as possible stressors."

Newton, W. M.: "An evaluation of the effects of various degrees of long-term confinement on adult beagle dogs." *Lab. Anim. Sci.* **22**: 860-864 (1972). H79,341/72

In adult beagles confined to cages for long periods, no evidence of musculoskeletal rearrangement of calcium metabolism could be detected.

Sabbot, I. M., McNew, J. J., Hoshizaki, T., Sedgwick, C. J., Adey, W. R.: "Effect of a 30 day isolation stress on calcium, phosphorus and other excretory products in an unrestrained chimpanzee." *Aerosp. Med.* **43**: 142-148 (1972). H73,921/72

Observations on chimpanzees kept in isolation for thirty days suggest that "the calcium to phosphorus excretion ratio might serve as a physiological stress indicator of Selye's adaptation syndrome (period of resistance)."

Wessels, F., Losse, H.: "Untersuchungen des Natriumtransports und -gehaltes der Erythrozyten unter Stresseinwirkung" (Studies on the sodium transport and content of erythrocytes under the effects of stress). *Med. Welt (Stuttg.)* **23**: 1394-1395 (1972). H60,857/72

Moore Ede, M. C., Burr, R. G.: "Circadian rhythm of urinary calcium excretion during immobilization." *Aerosp. Med.* **44**: 495-498 (1973). H91,935/73

Wegner, T. N., Ray, D. E., Lox, C. D., Stott, G. H.: "Effect of stress on serum zinc and plasma corticoids in dairy cattle." *J. Dairy Sci.* **56**: 748-752 (1973).

J19,913/73

In cattle, various stressors produced inconsistent changes in serum zinc, which were not clearly related to the plasma corticoid levels.

Umminger, B. L., Gist, D. H.: "Effects of thermal acclimation on physiological responses to handling stress, cortisol and aldosterone injections in the goldfish, *Carassius auratus*." *Comp. Biochem. Physiol. [A]* **44**: 967-977 (1973). H64,677/73

"Goldfish subjected to stressful handling and sham injection procedures responded with a hyperglycemia and a decline in serum chloride and sodium concentrations. Carcass water content was not affected."

Németh, S., Vigaš, M.: "Hypercatabolism of glycidic compounds during trauma: possible mechanisms." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 295-306. Bratislava: Slovak Academy of Sciences, 1973. E10,477/73

In rats, trauma in the Noble-Collip drum increases the degradation of carbohydrates via the Embden-Meyerhof pathway. Much of the increased glycolysis during stress may serve for "fight or flight" necessitating muscular work. In fasted animals, the resulting hypoglycemia threatens damage to the CNS, whereas in fed rats hyperlactacidemia may be a symptom of hypoxia and can contribute to fatal acidosis.

Smith, D. F.: "The effect of exercise and pain-stress on the renal clearance of lithium, sodium, potassium and creatinine in the rat." *Int. Pharmacopsychiatry* **8**: 217-220 (1973).

J9,657/73

Forced exercise increases the renal lithium clearance in rats but fails to alter sodium and potassium excretion. Pain stress does not affect electrolyte elimination. "The possibility of a decreased lithium clearance during strenuous exercise in psychiatric patients taking lithium is discussed."

Mullane, J. F., Wilfong, R. G., Phelps, T. O., Fischer, R. P.: "Metabolic acidosis, stress and gastric lesions in the rat." *Arch. Surg.* **107**: 456-459 (1973). J5,966/73

In rats the acidosis induced by restraint and ingestion of ammonium chloride was compared with that in patients with renal failure. "These studies suggest that metabolic acidosis may account in part for gastric lesions associated with renal failure."

Sobocinska, J.: "The effect of prolonged immobilization on diuresis and water intake

in rats." *Space Life Sci.* **4**: 200-203 (1973). H79,375/73

In rats immobilized in their natural position for many weeks, there was an increase in diuresis but no change in sodium or potassium excretion.

Avioli, L. V.: "The therapeutic approach to hypoparathyroidism." *Am. J. Med.* **57**: 34-42 (1974). J13,992/74

Review of the literature on the effects of stressors, particularly emotional arousal, upon calcium metabolism (103 refs.).

Perault-Staub, A. M., Staub, J. F., Milhaud, G.: "A new concept of plasma calcium homeostasis in the rat." *Endocrinology* **95**: 480-484 (1974). H88,418/74

Review of the literature and personal observations on the maintenance of calcium homeostasis during stress, especially in the rat.

Sabbot, I., Costin, A.: "Effect of stress on the uptake of radiolabelled calcium in the pituitary gland and the brain of the rat." *J. Neurochem.* **22**: 731-734 (1974).

J13,461/74

In rats, cold stress induces a change in the permeability of the blood-brain and blood-pituitary barriers for calcium uptake.

Sabbot, I., Costin, A.: "Cold stress induced changes in the uptake and distribution of radiolabelled magnesium in the brain and pituitary of the rat." *Experientia* **30**: 905-906 (1974). H92,909/74

Hafner, R. J.: "Relationships between personality and autonomic nervous reactions to stress." *J. Psychosom. Res.* **18**: 181-185 (1974). J15,136/74

Salivary secretion and particularly the sodium/potassium ratios correlate well with psychogenic stress in man. In subjects who react defensively, the response is essentially different from that of subjects who react aggressively (16 refs.).

Durakovic, A., Hollins, J. G., Storr, M. C.: "The retention of americium and plutonium by rat bone under stress" (abstracted). *Proc. Can. Fed. Biol. Soc.* **17**: 176 (1974).

H92,190/74

Various stressors reduce the retention of americium and plutonium by the bones of the rat.

Harnoncourt, K., Gaisl, G.: "Stress acidosis as a criterion for work capacity in 11-

year-old school children." *Acta Paediatr. Belg.* **28** Supp.: 266-273 (1974).

J21,516/74

Foster, S. B.: "An adrenal measure for evaluating nursing effectiveness." *Nurs. Res.* **23**: 118-124 (1974). J24,583/74

Urinary potassium and sodium ratios are

used to evaluate nursing effectiveness in patients.

H97,155/75

Schrier, R. W., Berl, T.: "Nonosmolar factors affecting renal water excretion (First of two parts)." *N. Engl. J. Med.* **292**: 81-88 (1975) (102 refs.).

Enzymes

Countless investigations have dealt with enzymatic changes characteristic of stress, but often the techniques used have not been sufficiently well described to permit any definitive interpretation. Hence, in order to promote research along these lines, we have to limit ourselves to a classification of the data as reported by the authors, merely reproducing their own conclusions in the abstract section. Thus the reader will at least be provided with a classified index of data on the enzyme systems studied, which will enable him to consult the abstracts (and, if necessary, the original publications) cited under each heading.

Review articles, as well as those dealing conjointly with many enzymatic activities in the blood or in certain tissues, are discussed under Generalities. The same is true of publications concerned with poorly characterized or very rarely examined enzymes that do not require separate sections.

However, the following are recognized as special categories and are arranged alphabetically in the abstract sections:

Amylase

ATPase and related enzymes

Catecholamine synthetases

Decarboxylases (e.g., histidine and ornithine decarboxylases)

Dehydrogenases (e.g., succinic dehydrogenase, lactate dehydrogenase)

Esterases (e.g., cholinesterase, arylesterases)

Glucuronidase

Hyaluronidase

Hydroxylases (e.g., dopamine- β -hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, cholesterol-7 α -hydroxylase)

Lipases, including "clearing factor lipase" and other lipoprotein lipases

Lysozyme

Monoamine oxidase (MAO)

Methyl transferases (e.g., phenylethanolamine-N-methyl transferase)

Oxidases, peroxidases and oxygenases (except MAO which, because of its importance in stress, has been dealt with in a separate section)

Phosphatases

Phosphokinases (e.g., creatine phosphokinase)

Plasmin and fibrinolysin (see also Blood Coagulation under Functional Changes)

Transaminases (e.g., GOT, GPT, tyrosine aminotransferase)

Tryptophan pyrolase

Uropepsin and pepsinogen

Drug-metabolizing enzymes. Because they partly overlap with previously mentioned groups, these are discussed separately in the final part of this section. They play an especially important role in stress by inactivating endogenous or exogenous toxicants, as a consequence of hepatic microsomal activity.

Enzymes

(See also our earlier stress monographs, p. xiii)

Generalities. Knox, W. E., Auerbach, V. H., Lin, E. C. C.: "Enzymatic and metabolic adaptations in animals." *Physiol. Rev.* **36**: 164-254 (1956). E83,471/56

Excellent review of the literature on enzymatic adaptations to the most diverse stimuli, including sections on the regulation of these adaptations by hormones and the nervous system (752 refs.).

Knox, W. E.: "Adaptive enzymes in animals." In: Mongar, J. L. and de Reuck, A. V. S., *Ciba Foundation Symposium on Enzymes and Drug Action*, pp. 245-275. London: J and A Churchill, 1962. G51,969/62

Review on adaptive enzyme production with special reference to the stimulating effect of glucocorticoids. Stress as such receives no detailed attention, but it is noted that a great variety of agents can increase the activity of certain hepatic enzymes. "The recognition of the adrenal hormone-induced adaptation of the tryptophan pyrrolase has provided the unified explanation for a large number of different stressful stimuli which increase the enzyme level."

Rosen, F., Nichol, C. A.: "Corticosteroids and enzyme activity." *Vitam. Horm.* **21**: 135-214 (1963). E3,837/63

Review based mainly on observations concerning glucocorticoid-induced alterations in hepatic enzymes. It is postulated that "the ability of man or animals to respond to stress depends essentially on changes in the activity of particular enzymes in peripheral tissues and in the liver. Such changes in metabolism are selective and are of importance in relation to survival when the stress is severe" (several hundred refs.).

Beard, E. L., Hampton, J. K. Jr.: "Effect of trauma on rat serum proteolytic activity." *Am. J. Physiol.* **204**: 405-407 (1963). D58,955/63

Belenkii, M. L., Bliuger, A. F., Shuster, I. I.: "Changes in the activity of some blood

serum enzymes during the action of strong stimuli on the body." *Biull. Èksp. Biol. Med.* **55** No. 5: 67-69 (1963) (Russian).

G57,360/63

Review of blood enzyme changes during the G.A.S.

Jonek, J., Stanosek, J., Krauze, M., Wacławczyk, H.: "Histochemische Untersuchungen über das Verhalten einiger Enzyme in Nebennieren bei Meerschweinchen nach chronischer Lärmeinwirkung" (Histochemical examinations of various enzymes in the adrenals of guinea pigs after chronic exposure to noise). *Z. Mikrosk. Anat. Forsch.* **73**: 174-186 (1965). G38,514/65

In guinea pigs, chronic exposure to noise (kind not clearly described) produced characteristic histochemical changes in various enzyme activities which gradually tended to disappear. These changes were ascribed to the alarm and resistance stages of the G.A.S.

Wegman, H. M., Brüner, H., Jovy, D., Klein, K. E.: "Änderung von Enzymaktivitäten im Serum als Ausdruck unspezifischer Anpassung" (Plasma enzyme changes as a result of nonspecific adaptation). *D.V.L.* No. **431**: 11-17 (1965). F61,311/65

Brief report on plasma enzyme changes under the influence of hypoxia and other stressors.

Wegman, H. M., Klein, K. E., Brüner, H.: "Die Auswirkung fliegerischer Belastung auf einige Blutkomponenten" (Effects of flying stress on certain components of the blood). *Int. Z. Angew. Physiol.* **23**: 293-304 (1967). G45,957/67

Among the indicators examined in jet pilots training for Starfighter F-104 G flights, corticoids and certain enzyme activities in the blood proved most sensitive to stress, whereas other enzyme and blood sugar variations were unreliable (24 refs.).

Rasmussen, R. A., Rasmussen, L. E.: "Some observations on the protein and enzyme levels and fractions in normal and stressed elasmobranchs." *Trans. N.Y. Acad. Sci.* **29**: 397-413 (1967). J10,798/67

In various elasmobranchs, stressors (mus-

cular fatigue, hypoxia, confinement, osmotic and temperature shock) produced serum and brain enzyme changes interpreted as characteristic of stress.

Reddy, M. V. V., Kastenschmidt, L. L., Cassens, R. G., Briskey, E. J.: "Studies on stress-susceptibility: the relationship between serum enzyme changes and the degree of stress-susceptibility." *Life Sci. [II]* **10**: 1381-1391 (1971). *G88,453/71*

Stress-susceptible pigs exhibit a particularly pronounced increase in certain plasma enzymes when exposed to various stressors.

Tollersrud, S., Baustad, B., Flatlandsmo, K.: "Effects of physical stress on serum enzymes and other blood constituents in sheep." *Acta Vet. Scand.* **12**: 220-229 (1971) (Norwegian). *J20,894/71*

Raby, C.: "Enzymes et agressions" (Enzymes and stresses). *Cah. Anesth.* **20**: 131-145 (1972). *J20,133/72*

Klain, G. J.: "Acute high altitude stress and enzyme activities in the rat adrenal medulla." *Endocrinology* **91**: 1447-1449 (1972). *H62,369/72*

Welch, B. L., Goldberg, A. M.: "Adrenal choline acetyltransferase activity: sustained effects of chronic intermittent psychological and psychosocial stimulation." *Int. J. Neurosci.* **5**: 95-99 (1973). *H80,352/73*

When mice were caged together and allowed to fight for ten to fifteen minutes on ten consecutive days, choline acetyltransferase in their adrenals increased. A decrease in enzyme activity appeared to precede this adaptive rise.

Wyndham, C. H., Kew, M. C., Kok, R., Bersohn, I., Strydom, N. B.: "Serum enzyme changes in unacclimatized and acclimatized men under severe heat stress." *J. Appl. Physiol.* **37**: 695-698 (1974) (25 refs.). *J18,802/74*

Oyama, J.: "Drug alteration of brain biogenic amines and effect of acceleration stress-induced hypothermia." *Fed. Proc.* **33**: 287 (1974). *H84,041/74*

Németh, Š.: "The physiologic importance of the stimulating effect of glucocorticoids on the activity of some liver enzymes." *Lék. Obz.* **23**: 359-364 (1974) (Czech). *H93,183/74*

Description of the effect of restraint upon plasma corticoids and hepatic enzymes in the rat.

Teshima, H., Inoue, S., Ago, Y., Ikemi, Y.: "Plasminic activity and emotional stress." *Psychother. Psychosom.* **23**: 218-228 (1974). *J16,685/74*

Angioneurotic or Quincke's edema often occurs immediately after psychogenic stress. This may be related to the increased plasmin activity which is found in animals following exposure to various stressors or EP.

Miller, N. E.: "Effects of learning and enzyme induction on emotional stress and visceral functions." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 36-39. Baku, USSR, 1974 (Russian, with extensive English summary). *J17,532/74*

Critz, J. B.: "The effect of the mental stress of examination writing on plasma enzyme activity" (abstracted). *Physiologist* **17**: 203 (1974). *H89,885/74*

Leise, E. M., LeSane, F., Gray, I.: "Lymphocyte and polymorphonuclear enzymes in stress. IV. Changes associated with an acute bacterial infection with *Diplococcus pneumoniae*." *Biochem. Med.* **9**: 206-213 (1974). *J11,685/74*

Leise, E. M., LeSane, F., Gray, I.: "V. Changes associated with a viral infection: herpes simplex." *Biochem. Med.* **9**: 214-224 (1974). *J11,686/74*

Aldolase. Blüger, A. F., Belenkii, M. L., Shuster, I. I.: "On the mechanism of increase in some blood serum enzymes activity under the influence of strong stressors." *Vopr. Med. Khim.* **10** No. 1: 12-15 (1964). *G59,822/64*

Amylase. Gültzow, M., Klemm, G.: "Einfluss der Nebennierenhemmung auf die Plasmapolyamylaseaktivität von gefesselten Ratten" (Effect of adrenal inhibition on plasma amylase activity in captive rats). *Z. Gesamte Inn. Med.* **19**: 234-235 (1964). *F8,091/64*

Groza, P., Zamfir, V., Lungu, D.: "Post-operative salivary amylase changes in children." *Rev. Roum. Physiol.* **8**: 307-312 (1971). *J20,219/71*

In children, surgical trauma decreases secretion of saliva and induces an "elevation of the concentration and output of salivary amylase, seemingly by the interference of glucocorticoid hormones."

Arginase. Angelis, W. de Barsantini, C.: "Acción del stress sobre la actividad de la

arginasa hepática en la rata" (Effect of stress on hepatic arginase activity in the rat). *Arch. Soc. Biol. Montevideo* 21: 25-29 (1954).

C38,038/54

K.: "Adenyl cyclase activities in rat erythrocytes during stress erythropoiesis: localization of the enzyme in the reticulocytes." *Life Sci.* 13: 31-40 (1973). J4,726/73

ATPase and Related Enzymes. Hilf, R., Breuer, C., Borman, A.: "The effect of Sarcoma 180 and other stressing agents upon adrenal adenine nucleotide-metabolizing enzymes." *Cancer Res.* 21: 1439-1444 (1961).

D15,008/61

In mice, Sarcoma 180 transplants caused typical stress reactions, with a rise in blood corticoids and an increase in adrenal ATPase activity. "Liver 5'-nucleotidase activity was elevated by tumor growth but not altered by the other stresses studied."

Kaffarnik, H., Gross, W., Dawid, E., Deibert, K., Juchems, R.: "Verhalten der Adenylatkinase (Myokinase), des Adenosintriphosphats (ATP) und der K- und Na-Ionen im Serum bzw. Blut unter standardisierter körperlicher Belastung" (Behavior of adenylate kinase [myokinase], adenosine triphosphate [ATP] and K and Na ions in the serum or blood under standardized physical stress). *Z. Gesamte Exp. Med.* 153: 324-330 (1970). H36,724/70

In man, muscular work increases the serum concentration of adenylate kinase and ATP, but does not change potassium or sodium levels. "The results are discussed with respect to the turnover of the phosphates during physical stress" (25 refs.).

Levin, K.: "Influence of stress, adrenalectomy and age on the stimulation in vitro of rat kidney ATPase by angiotensin." *Acta Physiol. Scand.* 79: 50-57 (1970).

G77,380/70

Rothman, I. K., Zanjani, E. D., Gordon, A. S., Silber, R.: "Nucleoside deaminase: an enzymatic marker for stress erythropoiesis in the mouse." *J. Clin. Invest.* 49: 2051-2067 (1970). H31,285/70

Hypoxia, hemorrhage, and phenylhydrazine were used as stressors. "The persistence of high levels of nucleoside deaminase for the full life span of a generation of erythrocytes formed during stress, viewed in contrast to the virtual absence of the enzyme from normal erythrocytes of all ages, represents an enzymatic difference between the normal red blood cell and the cell produced under conditions of accelerated erythropoiesis" (87 refs.).

Gauger, D., Palm, D., Kaiser, G., Quiring,

Catecholamine Synthetases. Stanton, H. C., Mueller, R. L., Bailey, C. L.: "Adrenal catecholamine levels and synthesizing enzyme activities in newborn swine exposed to cold and 6-hydroxydopamine." *Proc. Soc. Exp. Biol. Med.* 141: 991-995 (1972).

H64,032/72

Goldstein, M., Anagnosse, B., Freedman, L. S., Roffman, M., Ebstein, R. P., Fuxe, K., Hokfelt, T.: "Characterization, localization and regulation of dopamine- β -hydroxylase and of other catecholamine synthesizing enzymes." *Life. Sci.* 13: LIII-LV (1973).

J7,884/73

Diez, J. A., Sze, P. Y., Ginsburg, B. E.: "Brain biogenic amine synthesis: genetic and hormonal regulation." *Fed. Proc.* 33: 287 (1974).

H84,040/74

In mice, genetic factors, glucocorticoids and stress exert a considerable influence upon enzymes involved in the synthesis of biogenic amines in the brain. [The brief abstract does not lend itself to evaluation (H.S.).]

Ciaranello, R. D., Lipsky, A., Axelrod, J.: "Association between fighting behavior and catecholamine biosynthetic enzyme activity in two inbred mouse sublines." *Proc. Natl. Acad. Sci. USA* 71: 3006-3008 (1974).

J16,804/74

Fighting behavior after isolation is genetically determined and associated with characteristic changes in the catecholamine biosynthetic enzyme activity of the adrenals.

Decarboxylases. Schayer, R. W.: "Relationship of induced histidine decarboxylase activity and histamine synthesis to shock from stress and from endotoxin." *Am. J. Physiol.* 198: 1187-1192 (1960).

C90,163/60

Schayer, R. W.: "Relationship of stress-induced histidine decarboxylase to circulatory homeostasis and shock." *Science* 131: 226-227 (1960). C79,680/60

Histidine decarboxylase is considered to be an adaptive enzyme. Its activity in various tissues of the mouse increases under the influence of stressors (burns, delayed allergy, vaccines, cold, bacterial toxins and so on) and EP. Histamine may be a shock toxin or mediator of the stress reaction.

Schwartz, J. C., Cohen, Y., Valette, C.: "Histidine decarboxylase gastrique et ulcères expérimentaux chez le rat" (Gastric histidine decarboxylase and experimental ulcers in rats). *Biochem. Pharmacol.* **15**: 2122-2124 (1966). *J22,887/66*

Schrock, T. R., Oakman, N. J., Bucher, N. L. R.: "Ornithine decarboxylase activity in relation to growth of rat liver. Effects of partial hepatectomy, hypertonic infusions, celite injection or other stressful procedures." *Biochim. Biophys. Acta* **204**: 564-577 (1970). *G75,566/70*

Galvin, M. J. Jr., Reichard, S. M.: "Hemoglobin and enzyme changes in stress." *Fed. Proc.* **33**: 317 (1974). *H84,077/74*

In rats, histidine decarboxylase activity in the lung increases immediately after mechanical trauma. The "correlation of histamine production with the onset of hemoconcentration may be important in the pathophysiological changes leading to ultimate failure of the cardiovascular system."

Moore, T. C., Sinclair, M. C., McAlpin, C. D., Weber, G. A., Lemmi, C. A. E.: "Effect of aging, organ allografting, and surgical stress on rat thymus histidine decarboxylase activity." *Surgery* **76**: 733-740 (1974).

J17,862/74

Dehydrogenases. Ikeda, I., Kawaguchi, N., Ueda, Y.: "A histochemical study of the rabbit eye in stress with special reference to succinic dehydrogenase. DPN-diaphorase and TPN-diaphorase of the retina." *Folia Ophthalmol. Jap.* **18**: 61-67 (1967).

J24,397/67

Susheela, L., Ramasarma, T.: "Modulation of succinate dehydrogenase in response to environmental stress conditions of hypobaria and hypoxia." *Biochim. Biophys. Acta* **321**: 423-436 (1973). *J8,839/73*

"The results suggest that the modulation of the succinate dehydrogenase activity in hypobaria and hypoxia appears to be a compensatory mechanism invoked to overcome the effect of lowered O_2 tension prevalent in both the stress conditions."

York, J. W., Penney, D. G., Oscai, L. B.: "Glycolytic enzymes in exercised rat heart" (abstracted). *Physiologist* **17**: 393 (1974).

H89,991/74

Observations in rats "suggest that changes in heart LDH isozyme pattern and activity and PK activity in response to physical train-

ing are similar to those which occur as a result of certain other cardiac hypertrophic stresses."

Penney, D. G.: "Lactate dehydrogenase subunit and activity changes in hypertrophied heart of the hypoxically exposed rat." *Biochim. Biophys. Acta* **358**: 21-24 (1974). *J14,758/74*

Esterases. Gazzarrini, A.: "Influenze dell'anesthesia etera e dello stress operatorio sul tasso della tributirrinasi epatica e serica di ratte impuberi" (Effect of ether anesthesia and operative stress on hepatic and serum cholinesterase level in pubertal rats). *Minerva Anestesiolog.* **20**: 267-268 (1954).

C11,324/54

Bondarenko, I. I.: "The role of the adrenal glands in changes in the activity of blood serum cholinesterase in stress reactions caused by surgical trauma." *Patol. Fiziol. Éksp. Ter.* **11** Nos. 11-12: 70-71 (1967) (Russian). *J22,291/67*

Augustinsson, K. B., Henricson, B.: "Stress-induced alterations in arylesterase activity in the rat." *Biochim. Pharmacol.* **18**: 21-27 (1969). *G64,142/69*

In rats, emotional stress enhances plasma arylesterase activity, whereas muscular work has an inverse effect. The EP-induced increase in arylesterase activity is inhibited by ACTH.

Litvak, E. A.: "Cholinesterase activity in fatal cases of traumatic shock, craniocerebral injuries and stress." *Sud. Med. Ekspert.* **12** No. 2: 7-10 (1969) (Russian).

J24,150/69

Cholinesterase determinations in rabbits and rats under stress revealed a "considerable decrease of enzyme activity in the cortical regions of the large hemispheres, anterior and posterior hypothalamic parts, in the medulla oblongata and in the liver. . . . Immobilisatory stress proved that the enzymatic reaction is not specific but depends on the amount of the inflicted trauma."

Yordanova, L., Gotsev, T.: "Alterations in the enzyme activity of students with increased body temperature during examinations." *J. Physiol. (Paris)* **63**: 463-464 (1971). *J20,215/71*

Among students under "examination stress," the most outstanding objective changes were tachycardia, hypertension, dilatation of the pupils, increased intraocular

pressure, sweating, alterations in erythrocytes and platelets, a rise in body temperature and in the blood levels of carbonic anhydrase and cholinesterase.

Glucuronidase. Kendler, J., Harry, E. G.: "Systemic Escherichia coli infection as a physiological stress in chickens." *Res. Vet. Sci.* **8**: 212-218 (1967). J23,505/67

Coli-septicemia caused a characteristic stress syndrome with involution of the spleen and bursa, associated with increased bursal β -glucuronidase.

Hyaluronidase. Clay, M. M., Sinai, C. R.: "Stress effects on hyaluronidase activity." *J. Pharm. Sci.* **54**: 469-470 (1965).

F33,493/65

In rats, various stressors decreased the hyaluronidase spreading activity in the skin. Forced swimming did, whereas cold did not, cause adrenal hypertrophy.

Clay, M. M., Adler, M. W.: "Alterations in hyaluronidase activity and serum protein electrophoretic patterns after chronic heat stress." *J. Pharm. Sci.* **56**: 756-767 (1967).

F80,259/67

Hydroxylases. Akopian, I. I.: "Effect of some factors on the formation of induced enzymes involved in tyrosine oxidation in liver tissue." *Biokhimiia* **28**: 643-646 (1963) (Russian).

J24,999/63

Thoenen, H.: "Induction of tyrosine hydroxylase in peripheral and central adrenergic neurones by cold-exposure of rats." *Nature* **228**: 861-862 (1970). H32,295/70

Weinshilboum, R. M., Kvetňanský, R., Axelrod, J., Kopin, I. J.: "Elevation of serum dopamine- β -hydroxylase activity with forced immobilization." *Nature [New Biol.]* **230**: 287-288 (1971). J20,891/71

Restraint increases serum dopamine- β -hydroxylase activity in rats, even after adrenalectomy or adrenal demedullation. This is probably an index of elevated sympathetic nerve activity.

Kvetňanský, R., Weise, V. K., Gewirtz, G. P., Kopin, I. J.: "Synthesis of adrenal catecholamines in rats during and after immobilization stress." *Endocrinology* **89**: 46-49 (1971). H43,006/71

Immobilization is known to augment tyrosine hydroxylase in rat adrenals. It could now be shown that "the increased levels of enzymes result in enhanced synthesis of

epinephrine- ^{14}C from tyrosine- ^{14}C but not from dopa- ^3H . During immobilization, conversion of tyrosine- ^{14}C to catecholamines is further increased and may exceed the capacity of even the elevated levels of dopamine- β -hydroxylase to convert dopamine to norepinephrine."

Kvetňanský, R., Kopin, I. J.: "Activity of adrenal catecholamine-producing enzymes and their regulation after stress." *Adv. Exp. Med. Biol.* **33**: 517-533 (1972).

J23,807/72

Observations on rats suggest that tyrosine hydroxylase activity increases in the adrenals during stress. This response is "most probably mediated by a direct effect of ACTH on the adrenal medulla or by an unknown factor (not cyclic-AMP) released from the adrenal cortex following ACTH administration" (37 refs.).

Cantfort, J. van: "Influence du 'stress' sur l'activité de la cholestérol-7 α -hydroxylase" (Effect of stress on cholesterol-7 α -hydroxylase activity). *C.R. Acad. Sci. (Paris)* **277**: 345-348 (1973). J6,396/73

In normal animals the cholesterol-7 α -hydroxylase activity of the liver shows a circadian rhythm with a maximum at the beginning of the night. This is controlled by the hypothalamus-pituitary-adrenal axis and is abolished by adrenalectomy. Corticoids and various stressors increase the activity of the enzyme in the rat.

Thoenen, H., Otten, U., Oesch, F.: "Transsynaptic regulation of tyrosine hydroxylase." In: Usdin, E., *Frontiers in Catecholamine Research*, pp. 217-218. London: Pergamon Press, 1973. J16,138/73

Immediately after swimming stress, the cAMP content of the adrenal is not increased.

Otten, U., Oesch, F., Thoenen, H.: "Dissociation between changes in cyclic AMP and subsequent induction of TH in the rat superior cervical ganglion and adrenal medulla." *Naunyn Schmiedebergs Arch. Pharmacol.* **280**: 129-140 (1973). J9,378/73

In rats, various stressors (cold, swimming) cause changes in the cAMP and tyrosine hydroxylase activities of the superior cervical ganglion and adrenal medulla. Their significance in the production of stress reactions is not clear.

Leon, A. S., Thomas, P. E., Sernatinger, E., Canlas, A.: "Serum dopamine beta-hy-

droxylase activity as an index of sympathetic activity." *J. Clin. Pharmacol.* **14**: 354-362 (1974). H87,422/74

In rats and in man, elevation of dopamine β -hydroxylase activity is a less reliable indicator of stress than is measurement of circulating catecholamines.

Hoeldtke, R., Lloyd, T., Kaufman, S.: "An immunochemical study of the induction of tyrosine hydroxylase in the rat adrenal." *Biochem. Biophys. Res. Commun.* **57**: 1045-1053 (1974). J12,349/74

"Tyrosine hydroxylase-specific protein is increased in rat adrenal medulla by immobilization stress, cold exposure and 6-hydroxydopamine administration."

Lamprecht, F., Eichelman, B. S., Williams, R. B., Wooten, G. F., Kopin, I. J.: "Serum dopamine-beta-hydroxylase (DBH) activity and blood pressure response of rat strains to shock-induced fighting." *Psychosom. Med.* **36**: 298-303 (1974). J19,160/74

In rats, electroshock-induced fighting is associated with increased sympathetic nerve activity, reflected in serum dopamine- β -hydroxylase activity. The levels of this enzyme are "a useful index of sympathetic nerve function in that they are related to hemodynamic responses to stress."

Ogihara, T., Nugent, C. A.: "Serum DBH in three forms of acute stress." *Life Sci.* **15**: 923-930 (1974). J17,673/74

In man, various stressors cause no consistent changes in serum dopamine- β -hydroxylase. Hence, this enzyme is not a reliable indicator of stress.

Azmitia, E. C. Jr., McEwen, B. S.: "Adrenocortical influence on rat brain tryptophan hydroxylase activity." *Brain Res. (Amst.)* **78**: 291-302 (1974). J16,012/74

Naftchi, N. E., Wooten, G. F., Lowman, E. W., Axelrod, J.: "Relationship between serum dopamine- β -hydroxylase activity, catecholamine metabolism, and hemodynamic changes during paroxysmal hypertension in quadriplegia." *Circ. Res.* **35**: 850-861 (1974). H97,485/74

Observations on patients "indicate that hypertension in quadriplegia, whether spontaneous or induced, is caused by increased release of norepinephrine and that the half-life of dopamine- β -hydroxylase released during stress is shorter than that previously reported."

Chuang, D. M., Costa, E.: "Biosynthesis

of tyrosine hydroxylase in rat adrenal medulla after exposure to cold." *Proc. Natl. Acad. Sci. U.S.A.* **71**: 4570-4574 (1974) (22 refs.). J18,863/74

Goodwin, P. M., Harrop, J., Marks, V.: "Dopamine-beta-hydroxylase and sympathoadrenal activity." *Lancet* January 18, 1975, pp. 170-171. H97,468/75

In man, during various stress tests that considerably raised plasma catecholamines, plasma dopamine- β -hydroxylase levels did not prove to be a good indicator of sympathetic nervous activity.

Lipases and "Clearing factor." Seifter, J., Baeder, D. H.: "Lipemia clearing by hyaluronidase, hyaluronate and desoxycorticosterone, and its inhibition by cortisone, stress and nephrosis." *Proc. Soc. Exp. Biol. Med.* **86**: 709-713 (1954). B98,156/54

Observations in rats suggest that the "release of a lipemia clearing inhibitor appears to be another manifestation of the general adaptation syndrome."

Povoa, H. Jr., Callado, A. N. A., Pereira, J. M., Coutinho, J. M.: "Stress and clearing factor lipase in rat adipose tissue." *Acta Biol. Med. Ger.* **21**: 125-126 (1968).

H2,269/68

Following formalin- or cold-induced stress, the clearing factor lipase activity of adipose tissue decreases in the rat.

Ham, J. M., Slack, W. W.: "Lipoprotein lipase activity in patients before and after minor surgical operations." *Clin. Chim. Acta* **25**: 417-422 (1969). J22,519/69

The mean rise in lipoprotein lipase (clearing factor lipase) in the plasma of patients given a standard dose of heparin is diminished on the second day following surgical operations.

Tayeau, F., Jouzier, E., Tixier, M.: "II. Isolement et étude 'in vitro' d'un inhibiteur naturel du facteur clarifiant" (II. Isolation and "in vitro" study of a natural inhibitor of the clearing factor). *Bordeaux Méd.* **3**: 1999-2008 (1970). H32,022/70

Tayeau, F., Jouzier, E., Tixier, M.: "III. Action 'in vivo' de l'inhibiteur du facteur clarifiant" (III. "In vivo" action of the inhibitor of the clearing factor). *Bordeaux Méd.* **3**: 2011-2014 (1970). H32,023/70

Observations on man and various experimental animals have shown that the mucoprotein that appears in the blood and urine

during stress (physical effort, intoxications, infections, serious diseases and so on) constitutes a natural inhibitor of the lipoprotein lipase or "clearing factor" (22 refs.).

Bondarenko, M. F.: "The activity of lipoprotein lipase of the cardiac muscle in experimental diabetes in association with stress." *Probl. Endokrinol.* **16** Nos. 3-4: 92-95 (1970) (Russian). J23,974/70

Borbola, J., Gecse, A., Karady, S.: "The activity of lipoprotein lipase in rat heart after tourniquet stress." *Adv. Exp. Med. Biol.* **33**: 387-393 (1972). J23,805/72

Oehler, G., Wolf, H., Schmahl, F. W., Róka, L.: "Veränderungen der Lipoproteinkinase nach experimenteller Femurfraktur" (Changes in lipoprotein-lipase after experimental fracture of the femur). *Res. Exp. Med.* **163**: 31-38 (1974). H87,841/74

In rabbits, fracture of the femur caused a significant decrease in heparin-insoluble lipoprotein-lipase with a concurrent increase in serum glycerides and in the excretion of catecholamines during the first twenty-four hours. There was also histologic evidence of pulmonary fat embolism. It is concluded that "in addition to the increased synthesis of triglycerides during the post-traumatic phase (lipid mobilization syndrome) the elimination of blood lipids is impaired by decreased LPL activity. The elevated release of catecholamine is probably of essential significance for both effects."

Lysozyme. Luca, R. de, Caruso, P.: "Modificazioni del lisozima serico e della properdina dopo elettroshock" (Modifications of the serum lysozyme and properdin content after electroshock). *First Symp. Internaz. Lisozima*, April, 1959, pp. 3-5. Milan, 1959. D16,164/59

In five patients, the serum properdin values rose during the first two hours following electroshock and then returned to normal, whereas the lysozyme concentration increased up to twenty-four hours and longer.

MAO (Monoamine oxidase). Eleftheriou, B. E., Boehlke, K. W.: "Brain monoamine oxidase in mice after exposure to aggression and defeat." *Science* **155**: 1693-1694 (1967). F78,184/67

Shimmyo, T.: "Effects of stress on MAO activity in the brain and the ocular tissues of

rabbits." *Folia Ophthalmol. Jap.* **18**: 312-314 (1967). J24,622/67

Almeida, P. A. M., Kulay, L. Jr., Camano, L.: "Histochemical study of the monoamine oxidase (MAO) in the placenta of rats (*Rattus norvegicus albinus*, Rodentia mammalia) which were submitted to acute stress on the 15th and 18th days of pregnancy." *Ann. Histochem.* **16**: 265-272 (1971). G88,359/71

Maura, G., Vaccari, A., Gemignani, A., Cugurra, F.: "Development of monoamine oxidase activity after chronic environmental stress in the rat." *Environ. Physiol. Biochem.* **4**: 64-79 (1974). J13,612/74

In rats exposed to various stressors (auditory stimulation, flashing lights, cage oscillations), MAO activity was measured in the liver, brain, heart, stomach, adrenals and platelets. "The acute environmental stress was ineffective in all organs; chronic stress, however, caused variations in the enzyme activity in all organs, chiefly the heart, in both male and female rats. Liver, brain and cardiac MAO appeared to be more sensitive to stresses, as they were reduced by a shorter exposure than was required in the other organs studied. The environmental stress did not change significantly adrenal and platelet MAO. The variations appeared within the first 10 days after the termination of the stress period. This early effect may suggest an alteration of MAO turnover. The effects of chronic stress are reversible as there was an almost complete recovery of MAO activity one month after the stress."

Makarova, L. V., Bazarevich, G. I., Likhentshtein, A. O.: "Role played by the serotonin-monoaminoxidase system in the changes of functional condition of the adrenal cortex in traumatic shock." *Probl. Endokrinol.* **20** No. 5: 72-74 (1974) (Russian). H95,572/74

In dogs, stress induced by traumatic shock produces characteristic changes in 5-HT-MAO activity which are related to the secretion of corticoids.

Maura, G., Vaccari, A.: "Relationships between age of submission to environmental stress, and monoamine oxidase activity in rats." *Experientia* **31**: 191-193 (1975). K398/75

Young rats exposed to various stressors exhibit a drop in cerebral and hepatic MAO activity.

Mitro, A., Szetei, F., Kvetňanský, R.: "Stress-induced changes of monoamine oxidase activity (MAO) in different areas of the rat hypothalamus" (abstracted). *Physiol. Bohemoslov.* **24:** 71-72 (1975).

J22,935/75

Methyl transferases. Kvetňanský, R., Weise, V. K., Kopin, I. J.: "Elevation of adrenal tyrosine hydroxylase and phenylethanolamine-N-methyl transferase by repeated immobilization of rats." *Endocrinology* **87:** 744-749 (1970).

H30,287/70

Ciarenallo, R. D., Dornbusch, J. N., Barchas, J. D.: "Rapid increase of phenylethanolamine N-methyltransferase by environmental stress in an inbred mouse strain." *Science* **175:** 789-790 (1972).

H51,460/72

Zachariasen, R. D., Newcomer, W. S.: "Phenylethanolamine-N-methyl transferase activity in the avian adrenal following immobilization or adrenocorticotropin." *Gen. Comp. Endocrinol.* **23:** 193-198 (1974).

H88,608/74

In cockerels, ACTH or immobilization resulted in an increase in plasma EP and NEP with an accompanying decrease in the adrenal levels of these catecholamines; plasma corticosterone also rose as did the phenylethanolamine-N-methyl transferase (PNMT) content of the adrenals without affecting adrenal corticosterone. "It is suggested that the rapid increase in PNMT activity, occurring with the acute application of stressors in chickens, may provide a means of sustaining an increased outflow of EP in times of 'stress'." Corticosterone may play a role in the elevation of PNMT during the avian stress response.

Oxidases, Peroxidases, Oxygenases (except MAO). Maffei-Faccioli, A., Mortari, A., Ornesi, A., Scamazzo, T.: "Comportamento della triptofano perossidasi ossidasi epatica nel ratto in varie condizioni stressanti" (Behavior of hepatic tryptophan peroxidase oxidases in the rat in various stressful conditions). *Boll. Soc. Ital. Biol. Sper.* **37:** 1258-1261 (1961).

J22,944/61

Dewhurst, F.: "The effect of stress upon the metabolism of 2-naphthylamine in mice." *Experientia* **19:** 646-647 (1963).

E37,601/63

In mice, exposure to cold or noise accelerates the metabolism of 2-naphthylamine, pre-

sumably owing to activation of microsomal oxidases by the stressors.

Billewicz-Stankiewicz, J., Szczekala, Z.: "Studies on adrenaline oxidase of the blood plasma. III. Effect of stress on adrenaline oxidase activity." *Acta Physiol. Pol.* **16:** 695-699 (1965) (Polish). F59,654/65

Yuwiler, A., Geller, E.: "Rat liver tryptophan oxygenase induced by neonatal corticoid administration and its effect on brain serotonin." *Enzyme* **15:** 161-168 (1973).

J11,698/73

A single injection of cortisol in newborn rats prematurely induces tryptophan oxygenase in the liver, "with a concomitant reduction in serotonin concentration in the thalamic-hypothalamic and pontine areas of the brain. The ability of tryptophan to behave as a metabolic regulator may be important in the organism's response to stress."

Francesconi, R. P., Mager, M.: "Cold exposure: effect on hepatic tryptophan oxygenase and tyrosine aminotransferase, plasma tryptophan and tyrosine, and brain monoamines." *Experientia* **30:** 233-235 (1974).

H86,502/74

In mice, exposure to "cold stress" rapidly enhances the production of tryptophan oxygenase and tyrosine aminotransferase. However, "there are no general correlations between increased activity of these catabolic enzymes and reduced levels of plasma tryptophan, tyrosine and brain norepinephrine and serotonin. . . Our results indicate that if the rate limiting enzymes in serotonin and norepinephrine biosynthesis, tryptophan and tyrosine hydroxylases respectively, are stimulated by cold stress, then homeostatic conditions are maintained by increased levels of catabolic activity."

Phosphatases. Feustel, G., Pieper, K. S., Hübner, H. J., Lappa, H.: "Histochemische Untersuchung zum Verhalten der sauren Phosphatase in Schilddrüse, Nebennierenrinde, Adenohypophyse und hypothalamischen neurosekretorischen Kernen von Albinoratten nach lang dauernder körperlicher Belastung unter normalem und verminderter Sauerstoffpartialdruck" (Histochemical study on the behavior of acid phosphatase in the thyroid gland, adrenal cortex, adenohypophysis and hypothalamic neurosecretory nuclei of albino rats after long-term physical stress under normal and diminished partial pressure of oxygen). *Acta Histochem. (Jena)* **34:** 317-333 (1969). H21,129/69

Börnig, H., Horn, A., Müller, W.: "Zum Mechanismus der Aktivitätsänderung der alkalischen Phosphatase in Leber und Darm der Ratte nach Ligatur des Ductus choledochus" (Alkaline phosphatase changes in liver and intestine caused by choledochus ligation in the rat). *Acta Biol. Med. Ger.* **22**: 537-549 (1969). H15,664/69

In rats, choledochus ligation, laparotomy and other stressors increase hepatic alkaline phosphatase activity. This is not inhibited by adrenalectomy or by the effective steroid hormone, cortisol.

Choudhury, S. R., Lundy, A. M.: "Studies of acid phosphatase and nonspecific esterase activities in rat adrenal glands following operative stress." *J. Histochem. Cytochem.* **18**: 650-659 (1970). G78,540/70

Boyne, R., Fell, B. F.: "Observations on the alkaline phosphatase content of the neutrophil granulocytes of some laboratory and farm animals, with particular reference to the effects of intensive management and reproduction." *Res. Vet. Sci.* **13**: 347-355 (1972). J19,597/72

Alkaline phosphatase activity in circulating polymorphonuclears was raised "under relatively mild conditions of stress in cattle, pigs and rats. Marked increases occurred in association with pregnancy in pigs, sheep and rabbits." The effect is presumably caused by enhanced corticoid secretion.

Clermont, H. G., Williams, J. S., Adams, J. T.: "Steroid effect on the release of the lysosomal enzyme acid phosphatase in shock." *Ann. Surg.* **179**: 917-921 (1974).

J13,287/74

In dogs, various forms of shock and especially that elicited by endotoxin raised the serum acid phosphatase level but this change could be largely inhibited by glucocorticoids and prolonged survival. "Whether this salutary effect is due solely to the ability of steroids to stabilize cellular membranes or is in part secondary to promoting improved tissue hemodynamics could not be established."

Phosphokinases. Meltzer, H. Y.: "Plasma creatine phosphokinase activity, hypothermia, and stress." *Am. J. Physiol.* **221**: 896-901 (1971). H47,238/71

In rats, exposure to cold greatly increases plasma creatine phosphokinase activity, presumably as part of the stress reaction, although other stressors are less effective.

Adrenalectomy does not prevent this response.

Meltzer, H. Y., Holzman, P. S., Hassan, S. Z., Guschwan, A.: "Effects of phenacyclidine and stress on plasma creatine phosphokinase (CPK) and aldolase activities in man." *Psychopharmacologia* (Berlin) **26**: 44-53 (1972). G92,837/72

Meltzer, H. Y.: "Effects of phenacyclidine and restraint at 2°C on rat plasma creatine phosphokinase activity." *Res. Commun. Chem. Pathol. Pharmacol.* **5**: 117-127 (1973). H64,159/73

Misner, J. E., Massey, B. H., Williams, B. T.: "The effect of physical training on the response of serum enzymes to exercise stress." *Med. Sci. Sports* **5**: 86-88 (1973).

J11,491/73

In man, running increases the serum creatine phosphokinase and glutamic oxalacetic transaminase concentrations (17 refs.).

Blumöhr, T., Klöcking, R., Sprössig, M.: "Veränderungen der Plasmakreatinkinaseaktivität durch Coxsackievirusinfektion bei Mäusen" (Coxsackie virus infection causing plasma creatine kinase changes in mice). *Pathol. Microbiol.* (Basel) **40**: 241-250 (1974). H89,273/74

In mice, swimming (allegedly owing to its stressor effect) predisposes to Coxsackie virus infection and raises plasma creatine kinase activity. Causal connections between these changes are suspected but not proven.

Loegering, D. J.: "Effect of swimming and treadmill exercise on plasma enzyme levels in rats." *Proc. Soc. Exp. Biol. Med.* **147**: 177-180 (1974). H95,533/74

Swimming or treadmill exercise in the rat resulted in elevations of the plasma levels of aspartate aminotransferase, creatine phosphokinase and lactate dehydrogenase. These changes were ascribed to stress.

Plasmin and fibrinolysin. Beard, E. L., Carroll, G. F., Danos, G. T.: "Release of plasminogen activator from rat liver lysosomes induced by stress related enzymes." *Proc. Soc. Exp. Biol. Med.* **131**: 438-442 (1969). H14,082/69

Beard, E. L., Busuttil, R. W., Gottshalk, S. K.: "Stress induced release of plasminogen activator from lysosomes." *Thromb. Diath. Haemorrh.* **21**: 20-25 (1969).

H9,860/69

Engquist, A., Winther, O.: "Variations of plasma cortisol and blood fibrinolytic activity during anaesthetic and surgical stress." *Br. J. Anaesth.* **44**: 1291-1297 (1972). J672/72

In man, during thirty to ninety-three minutes of "surgical stress, enhancement of fibrinolysis was significantly correlated with an increase of plasma cortisol levels."

Teshima, H., Inoue, S., Ago, Y., Ikemi, Y.: "Plasminic activity and emotional stress." *Psychother. Psychosom.* **23**: 218-228 (1974).

J16,685/74

Angioneurotic or Quincke's edema often occurs immediately after psychogenic stress. This may be related to the increased plasmin activity found in animals following exposure to various stressors or EP.

Transaminases. Mandel, M. J., Robinson, F. R., Luce, E. A.: "SGOT levels in man and the monkey following physical and emotional exertion." *Aerosp. Med.* **33**: 1216-1223 (1962).

J23,454/62

In man, no clearcut relationship was found between SGOT and vibration, heat or static acceleration. "The marked lability of the SGOT levels in the monkey remains unexplained; however, the possibility of a less discrete mechanism for 'stress' may be responsible for the monkey values" (46 refs.).

Bliuger, A. F., Belenkii, M. L., Shuster, I. I.: "On the mechanism of increase in some blood serum enzymes activity under the influence of strong stressors." *Vopr. Med. Khim.* **10** No. 1: 12-15 (1964) (Russian).

G59,822/64

Geller, E., Yuwiler, A., Schapiro, S.: "Comparative effects of a stress and cortisol upon some enzymic activities." *Biochim. Biophys. Acta* **93**: 311-315 (1964).

G22,722/64

In rats, "although the activities of liver tyrosine- α -ketoglutarate transaminase (EC 2.6.1.5), tryptophan- α -ketoglutarate transaminase and tryptophan pyrolase (EC 1.11.1.4) are elevated by injection of cortisol, no such activation could be observed following imposition of a stress demonstrably effective in causing adrenal cortical hormone secretion." This apparent paradox might be due to differences in plasma cortisol levels.

Schapiro, S., Yuwiler, A., Geller, E.: "Stress-activated inhibition of the cortisol effect on hepatic transaminase." *Life Sci.* **3**: 1221-1226 (1964).

G21,848/64

Schapiro, S., Yuwiler, A., Geller, E.: "Maturation of a stress-activated mechanism inhibiting induction of tyrosine transaminase." *Science* **152**: 1642-1643 (1966).

F67,277/66

Matsubara, Y., Tahara, K., Kogure, T., et al.: "Effect of electroshock on serum transaminase (GOT, GPT) in rabbits." *J. Tokyo Med. Coll.* **24**: 513-521 (1966).

J23,776/66

Pearl, W., Balazs, T., Buyske, D. A.: "The effect of stress on serum transaminase activity in the rat." *Life Sci.* **5**: 67-74 (1966).

G36,694/66

"Myocardial damage was produced in rats by isoproterenol without elevating serum glutamic-oxalacetic transaminase or serum glutamic-pyruvic transaminase. However, restraint was followed by an increase in both of these enzymes without gross myocardial injury, while adrenalectomy suppressed this elevation. Neither ACTH nor corticosterone replacement elicited the enzyme response. Epinephrine induced a marked rise in serum transaminase, and this effect was potentiated by corticosterone."

Berry, L. J., Agarwal, M. K., Snyder, I. S.: "Comparative effect of endotoxin and reticuloendothelial 'blocking' colloids on selected inducible liver enzymes." In: Luzio, N. R. di and Paoletti, R., *The Reticuloendothelial System and Atherosclerosis*, pp. 266-274. New York: Plenum Press, 1967.

E7,069/67

In mice, stress induced by endotoxin lowers the activity of tryptophan pyrolase and increases that of tyrosine- α -ketoglutarate transaminase in the liver. Presumably, such enzyme responses are characteristic of stress.

Viru, A., Körge, P.: "Metabolic processes and adrenocortical activity during marathon races." *Int. Z. Angew. Physiol.* **29**: 173-183 (1971).

G84,664/71

Among fourteen first-class marathon runners, all but the two best showed lowering of blood cortisol levels during the race. Urinary sodium decreased and potassium increased. In most cases, GPT activity and NPN rose in plasma, and excretion of nitrogen and creatinine was reduced. "It was suggested that before the end of the marathon race the protein catabolism is diminished due to a decrease of the glucocorticoid function of the adrenal gland."

Chatterjee, A. K., Dighe, S. K., Naithani, R. C., Ghose, A., Balkrishna: "The role of

methylamphetamine on plasma transaminase level under altitude stress." *Jap. J. Pharmacol.* **22**: 871-873 (1972). H65,788/72

Chatterjee, A. K., Dighe, S. K., Naithani, R. C., Sachan, A. S., Krishna, B.: "The role of DL-dihydroxy phenyl alanine (DOPA) on plasma transaminase level under altitude stress." *Jap. J. Pharmacol.* **23**: 269-271 (1973). H85,774/73

A rise in plasma and tissue transaminase is considered to be characteristic of stress in the rat. These observations would indicate that DOPA is not a particularly effective "antistress drug."

Misner, J. E., Massey, B. H., Williams, B. T.: "The effect of physical training on the response of serum enzymes to exercise stress." *Med. Sci. Sports* **5**: 86-88 (1973). J11,491/73

In man, running increases the serum creatine phosphokinase and glutamic oxalacetic transaminase concentrations (17 refs.).

Németh, Š., Straková, A., Vigaš, M.: "The role played by adrenal hormones in the increase of liver tyrosine aminotransferase activity of rats subjected to trauma." *Horm. Metab. Res.* **5**: 204-207 (1973).

H71,682/73

Németh, Š., Vigaš, M., Straková, A.: "Time and level of increased plasma corticosterone necessary for induction of liver tyrosine aminotransferase in rats subjected to trauma." *Horm. Metab. Res.* **5**: 283-285 (1973). H74,982/73

Namboodiri, M. A. A., Ramasarma, T.: "Mechanism of induction of tyrosine aminotransferase during cold exposure." *Environ. Physiol. Biochem.* **3**: 255-262 (1973).

J11,453/73

Stefan, M., Gheorghe, N., Boerescu, J.: "L'activité de l'aminotransférase de la tyrosine dans diverses conditions de stress" (Tyrosine aminotransferase activity in various stress conditions). *Rev. Roum. Physiol.* **11**: 299-304 (1974). J16,281/74

In rats, various stressors (restraint, burns, noise, x-irradiation, hypoxia, hypothermia, ether, chloroform) increase the tyrosine aminotransferase activity of the liver, both in the presence and after extirpation of the adrenal. The effect is comparable to that produced by cortisol. "It is concluded that induction of tyrosine aminotransferase is characteristic of the alarm reaction in the rat."

Németh, Š., Juráni, M.: "Hepatic tyrosine aminotransferase (TAT) in stressed trouts and rats." *Gen. Comp. Endocrinol.* **22**: 388 (1974). H83,271/74

In trout living under crowded conditions and in rats traumatized by the Noble-Collip drum, plasma cortisol increased, but hepatic tyrosine aminotransferase activity was elevated only in the rats. This agrees with previous observations suggesting that the enzyme response is not observable in vertebrates below the evolutionary level of amphibians.

Loegering, D. J.: "Effect of swimming and treadmill exercise on plasma enzyme levels in rats." *Proc. Soc. Exp. Biol. Med.* **147**: 177-180 (1974). H95,533/74

Swimming or treadmill exercise in the rat resulted in elevations of the plasma levels of aspartate aminotransferase, creatine phosphokinase, and lactate dehydrogenase. These changes were ascribed to stress.

Tryptophan pyrolase. Knox, W. E.: "Adaptive enzymes in animals." In: Mongar, J. L. and de Reuck, A. V. S., *Ciba Foundation Symposium on Enzymes and Drug Action*, pp. 245-275. London: J and A Churchill, 1962. G51,969/62

Review on adaptive enzyme production with special reference to the stimulating effect of glucocorticoids. Stress as such receives no detailed attention, but it is noted that a great variety of agents can increase the activity of certain hepatic enzymes. "The recognition of the adrenal hormone-induced adaptation of the tryptophan pyrolase has provided the unified explanation for a large number of different stressful stimuli which increase the enzyme level."

Geller, E., Yuwiler, A., Schapiro, S.: "Comparative effects of a stress and cortisol upon some enzymic activities." *Biochim. Biophys. Acta* **93**: 311-315 (1964). G22,722/64

In rats, "although the activities of liver tyrosine- α -ketoglutarate transaminase (EC 2.6.1.5), tryptophan- α -ketoglutarate transaminase and tryptophan pyrolase (EC 1.11.1.4) are elevated by injection of cortisol, no such activation could be observed following imposition of a stress demonstrably effective in causing adrenal cortical hormone secretion." This apparent paradox might be due to differences in plasma cortisol levels.

Nomura, J.: "Effect of stress and psycho-

tropic drugs on rat liver tryptophan pyrrolase." *Endocrinology* **76**: 1190-1194 (1965).

F41,304/65

Various stressors and chlorpromazine increase tryptophan pyrrolase activity in the rat liver. Hypophysectomy does, whereas adrenalectomy does not, prevent this effect.

Berry, L. J., Agarwal, M. K., Snyder, I. S.: "Comparative effect of endotoxin and reticuloendothelial 'blocking' colloids on selected inducible liver enzymes." In: Luzio, N. R. di and Paoletti, R., *The Reticuloendothelial System and Atherosclerosis*, pp. 266-274. New York: Plenum Press, 1967.

E7,069/67

In mice, stress induced by endotoxin lowers the activity of tryptophan pyrrolase and increases that of tyrosine- α -ketoglutarate transaminase in the liver. Presumably, such enzyme responses are characteristic of stress.

Cabibbe, F., Paracchi, G., Lanzara, D.: "Azione di alcuni psicofarmaci sulla triptofano-pirrolasi epatica di ratti in stato di stress post-operatorio" (Action of some psychopharmacologic agents on hepatic tryptophan pyrrolase in rats during postoperative stress). *Boll. Soc. Ital. Biol. Sper.* **43**: 1183-1186 (1967).

G52,346/67

Nisticò, G., Preziosi, P.: "Brain and liver tryptophan pathways and adrenocortical activation during restraint stress." *Pharmacol. Res. Commun.* **1**: 363-368 (1969).

G80,145/69

In rats, the increase in plasma corticosterone produced by restraint is associated with a rise in tryptophan pyrrolase and a fall in brain 5-HT, which are not correlated with the duration of the stress. The decrease in 5-HIAA during the first hour is followed by a progressive increase. Apparently, during stress "the tryptophan shunt from the serotonin to the kynurenine pathway is almost abolished."

Golotin, V. G., Berdyshev, G. D., Brekhman, I. I.: "The activity of tryptophan pyrrolase in rat liver in health and in stress." *Vopr. Med. Khim.* **15** No. 1: 16-21 (1969) (Russian).

J15,869/69

In both intact and adrenalectomized rats, the tryptophan pyrrolase activity of the liver is increased by cortisol and the stress of restraint. Adrenalectomy in itself has a similar effect. Obviously, this enzyme system must be regulated during stress not only through corticoids, but also through extra-adrenal mechanisms (27 refs.).

Sitaramam, V., Ramasarma, T.: "Nature of induction of tryptophan pyrrolase in cold exposure." *J. Appl. Physiol.* **38**: 245-249 (1975).

J21,676/75

Exposure to cold increased the hepatic tryptophan pyrrolase of the rat presumably through the mediation of corticoids. "The changes in the enzyme obtained under cold stress with respect to the overshoot phenomenon, relationship to the degree of stress and reversibility on withdrawal from the stress indicate the 'adaptate' nature of the response."

Green, A. R., Curzon, G.: "Effects of hydrocortisone and immobilization on tryptophan metabolism in brain and liver of rats of different ages." *Biochem. Pharmacol.* **24**: 713-716 (1975).

H99,235/75

In rats, restraint or cortisol increased hepatic tryptophan pyrrolase activity and (in certain age groups) 5-HT and 5-HIAA concentrations in the brain.

Uropepsin and Pepsinogen. Gray, S. J., Ramsey, C., Reifenstein, R. W., Benson, J. A. Jr.: "The significance of hormonal factors in the pathogenesis of peptic ulcer." *Gastroenterology* **25**: 156-172 (1953).

B89,103/53

In man, ACTH and cortisone enhanced the basal nocturnal gastric hydrochloric acid and pepsin secretion with a concomitant increase in uropepsin elimination. Similar changes were seen during stress, but vagotomy and anticholinergic agents "do not appear to alter the gastric acid, pepsin and urinary uropepsin response to adrenal stimulation or stress.... Although the gastric response to stress is undoubtedly mediated through the vagus nerve, there appears to be an additional hormonal mechanism which is intimately associated with the adrenal gland and the general adaptation syndrome."

Gray, S. J., Ramsey, C. G., Reifenstein, R. W.: "Clinical use of the urinary uropepsin determination in medicine and surgery." *N. Engl. J. Med.* **251**: 835-843 (1954).

C1,309/54

Extensive studies in man "support the concept that acute and chronic stress stimulates the stomach and increases uropepsin excretion by way of a humoral mechanism involving the hypothalamic-pituitary-adrenal-gastric axis that is independent of the vagus nerve or the gastric antrum" (25 refs.).

Hill, S. R. Jr., Goetz, F. C., Fox, H. M.,

Murawski, B. J., Krakauer, L. J., Reifenstein, R. W., Gray, S. J., Reddy, W. J., Hedberg, S. E., St. Marc, J. R., Thorn, C. W.: "Studies on adrenocortical and psychological response to stress in man." *Arch. Intern. Med.* **97**: 269-298 (1956).

C35,720/56

The intense muscular and psychogenic stressor effect of crew racing caused eosinopenia with increased urinary elimination of 17-OHCS, 17-KS and uropepsin, but signs of adrenal hyperactivity were also obvious during the prerace tension. In earlier studies, it was found that eosinopenia developed in both the coxswain and coach during the race; hence "the physical exertion of rowing was not the only stress involved capable of inducing a marked eosinopenia."

Hunter, C. G.: "Uropepsinogen and uoreninogen; the estimation of adrenal cortical function in stress situations." *J. R. Nav. Med. Serv.* **42**: 13-22 (1956). C16,926/56

Siruala, M., Railo, J. E.: "Stress and stomach. The effect of various traumatic lesions upon uropepsin excretion and blood eosinophils." *Acta Med. Scand.* **166**: 43-50 (1960). J23,562/60

Mason, J. W., Brady, J. V., Polish, E., Bauer, J. A., Robinson, J. A., Rose, R. M., Taylor, E. D.: "Patterns of corticosteroid and pepsinogen change related to emotional stress in the monkey." *Science* **133**: 1596-1598 (1961). D4,949/61

In rhesus monkeys, conditioned avoidance sessions of seventy-two hours caused an increase in the 17-OHCS levels, and an initial drop followed by a prolonged, marked elevation in the pepsinogen concentration of the plasma.

Pahk, S. K.: "Studies on uropepsin. II. The effect of stress upon uropepsin excretion." *J. Korea Med. Assoc.* **5**: 47-58 (1962). J23,798/62

Simler, M., Schwartz, J.: "Effets de la contrainte sur l'élimination de l'uropepsine et les stéroïdes urinaires d'origine cortico-surrénaliennes chez le rat" (The effects of restraint on the elimination of uropepsin and the urinary steroids of adrenocortical origin in the rat). *Rev. Fr. Etudes Clin. Biol.* **7**: 962-966 (1962). Also in: *C.R. Soc. Biol. (Paris)* **156**: 494-498 (1962). D47,630/62

In rats, uropepsin excretion remains normal or drops during restraint, despite increased corticoid production.

Colehour, J. K., Graybiel, A.: "Excretion of 17-hydroxycorticosteroids, catecholamines, and uropepsin in the urine of normal persons and deaf subjects with bilateral vestibular defects following acrobatic flight stress." *Aerosp. Med.* **35**: 370-373 (1964).

G11,705/64

In subjects on acrobatic flights causing increases in 17-OHCS and catecholamine excretion, uropepsin values remained unchanged.

Kuttner, R. E., Mailander, J. C.: "Serum pepsinogen in migrant Mexicans and stressed Caucasians." *J. Nat'l. Med. Assoc.* **57**: 109-111 (1965).

G28,384/65

Serum pepsinogen values are higher in Mexican men than in Caucasians. "This difference did not appear to be due to migrancy and its unsettling influences. A study of a presumably stressed female Caucasian population showed no influence on pepsin secretion. It was concluded that the Indian racial element in the Mexican sample was the responsible factor behind the pepsinogen elevation."

Eigelsreiter, H.: "Zur Uropepsin-Ausscheidung nach sportlichen Anstrengungen" (Uropepsin excretion after athletic exertion). *Forsch. Forscher Tiroler Ärzteschule* **6**: 163-184 (1966).

G63,751/66

In athletes, uropepsin excretion is increased during the alarm reaction and decreased in the stage of exhaustion of the G.A.S.

Eigelsreiter, H., Schmid, H., Spielberger, M., Teichmann, W.: "Die Uropepsin-Ausscheidung bei hydrotherapeutischen Kuren (ohne und mit gleichzeitiger Bewegungstherapie)" (Uropepsin excretion during balneotherapy with and without simultaneous kinesiatrics). *Z. Angew. Bader- u. Klimather.* **15**: 58-71 (1968).

G58,525/68

Uropepsin elimination increases during balneotherapy possibly as a consequence of stimulation by corticoids produced under the stress of adaptation to this treatment. [The data do not lend themselves well to statistical evaluation (H.S.).]

Kitamura, R.: "On the influence of Kendo training or home study upon uropepsin excretion." *Jap. Arch. Intern. Med.* **15**: 55-60 (1968).

J24,355/68

Groza, P., Buzoianu, V., Ionescu, S., Bogatu, D.: "Uropepsinogen reaction in surgical stress in terms of age." *Rev. Roum. Physiol.* **6**: 203-206 (1969). H18,402/69

In elderly patients, operative stress causes a fall in uropepsinuria that is not obvious in younger subjects. "Uropepsin assay may represent a functional test for post-traumatic reactivity."

Lozinskii, V. S.: "Significance of uropepsin determination in pilots." *Voen. Med. Zh.* **10** No. 10: 65-66 (1970) (Russian).

J22,749/70

Komorowska, A.: "Evaluation of stress conditions after dental surgery by the uropepsin test." *Czas. Stomatol.* **24**: 1163-1170 (1971) (Polish).

J20,890/71

In patients, even minor dental interventions cause an increase in uropepsin excretion within three hours, which persists for four days. The change is regarded as characteristic of the alarm reaction.

Drug-Metabolizing Enzymes. Rupe, B. D., Bousquet, W. F., Miya, T. S.: "Stress modification of drug response." *Science* **141**: 1186-1187 (1963).

E26,910/63

In rats, tourniquet stress decreases the toxicity of various drugs that can be metabolized by hepatic enzymes. "The effect of stress on drug response is not noted with barbital, a compound which is not metabolized; this effect is inhibited by treatment of the animal with a drug metabolism inhibitor such as SKF 525-A." Similar actions are obtained with ACTH or corticosterone. "Compounds which can stimulate adrenocorticotropic hormone secretion or act directly on the adrenals to produce corticosteroids should thus be able to stimulate their own metabolism or that of other drugs."

Bousquet, W. F., Rupe, B. D., Miya, T. S.: "Endocrine modification of drug responses in the rat." *J. Pharmacol. Exp. Ther.* **147**: 376-379 (1965).

F35,073/65

In rats, the duration of the response to hexobarbital, pentobarbital, meprobamate and zoxazolamine was significantly reduced as a consequence of tourniquet stress. ACTH or corticosterone simulated these stress effects. "It is suggested that the pituitary-adrenal axis serves a regulatory function with respect to duration of drug responses which may be mediated by an alteration of drug metabolism."

Driever, C. W., Bousquet, W. F.: "Stress-drug interactions: evidence for rapid enzyme induction." *Life Sci.* **4**: 1449-1454 (1965).

G31,872/65

In rats, "the ability of stress situations to

stimulate drug metabolism and its dependence upon an intact pituitary-adrenal axis is suggestive of a regulatory function of the endocrine system in mediating a rapid induction of liver microsomal enzymes responsible for drug metabolism."

Driever, C. W., Bousquet, W. F., Miya, T. S.: "Stress stimulation of drug metabolism in the rat." *Int. J. Neuropharmacol.* **5**: 199-205 (1966).

F73,812/66

In rats, stress (tourniquet) accelerated the blood clearance of hexobarbital, pentobarbital and meprobamate but not that of phenobarbital; however, this occurred only in the presence of an intact pituitary-adrenal system. "The response could be stimulated in adrenalectomized animals by corticosterone, but not by ACTH, and in hypophysectomized animals by both corticosterone and ACTH."

Lee, N. H., Hospador, M. A., Manthei, R. W.: "Influence of age and dietary stress on hexobarbital activity in mice." *Proc. Soc. Exp. Biol. Med.* **125**: 153-156 (1967).

F80,166/67

On an 8 percent casein diet, mice can still synthesize drug-metabolizing enzymes despite rapid growth. However, hexobarbital sleeping time is prolonged, perhaps because of a less active TPNH generating system.

Stitzel, R. E., Furner, R. L.: "Stress-induced alterations in microsomal drug metabolism in the rat." *Biochem. Pharmacol.* **16**: 1489-1494 (1967).

G48,920/67

"Stress (cold) caused increases in the rate of p-hydroxylation of aniline, N-dealkylation of ethylmorphine, and increases in adrenal ascorbic acid content. The stimulatory actions of stress on microsomal metabolism and ascorbic acid levels are additive with those produced by phenobarbital. It is tentatively concluded that stress and phenobarbital appear to act through different mechanisms in inducing increases in enzyme activity, although each treatment may have a common final step, namely an increased net synthesis of enzyme protein."

"Effect of nutrition and stress upon the metabolism of some barbiturate anesthetics." *Nutr. Rev.* **25**: 51-53 (1967).

J23,104/67

Arrhenius, E.: "Effects on hepatic microsomal N- and C-oxygenation of aromatic amines by in vivo corticosteroid or amino-fluorene treatment, diet, or stress." *Cancer Res.* **28**: 264-273 (1968).

F95,955/68

Observations on hepatic microsomes of guinea pigs and rats showed that "stress

caused an increase in N-oxygenation accompanied by decreased N-demethylation" of various substrates.

Furner, R. L., Stitzel, R. E.: "Stress-induced alterations in microsomal drug metabolism in the adrenalectomized rat." *Biochem. Pharmacol.* **17**: 121-127 (1968).

G54,558/68

In rats, cold stress can bring about changes in drug metabolism independently of the presence of the adrenals.

Sethy, V. H., Naik, S. R., Sheth, U. K.: "Effect of stress on pentobarbital sleeping time in rats." *Indian J. Med. Res.* **58**: 352-357 (1970).

G77,511/70

In rats, pentobarbital sleeping time is significantly reduced by the stress of centrifugation.

Huff, J. E., Shaw, S. M., Christian, J. E.: "Effect of acute and chronic stress on amobarbital metabolism in the rat." *J. Pharm. Sci.* **59**: 126-128 (1970).

H19,999/70

By use of labeled amobarbital, it was found that the stress of hind leg tourniquets considerably alters the urinary excretion of amobarbital metabolites.

Wei, E., Wilson, J. T.: "Stress-mediated decrease in liver hexobarbital metabolism: the role of corticosterone and somatotropin." *J. Pharmacol. Exp. Ther.* **177**: 227-233 (1971).

H37,417/71

Coessens, R.: "La production de NADPH dans les surrénales de rat sous l'effet d'un stress, de l'administration d'ACTH ou d'un traitement cortisonique" (Production of NADPH in adrenal glands of rats under the effects of stress, of administration of ACTH, or corticoid therapy). *Ann. Endocrinol. (Paris)* **32**: 355-360 (1971).

H43,487/71

Stitzel, R. E., McCarthy, J. S.: "Stress and strain. Factors influencing drug metabolism." *Biochem. Pharmacol.* **21**: 755-760 (1972).

H46,352/72

Observations suggesting that "whether there is an effect on microsomal metabolism within a single rat strain depends upon the type of stress used, and the nature of that effect (i.e. increase or decrease) depends upon the animal strain used."

Benthe, H. F., Schmoldt, A., Schmidt, H.: "Induktion mikrosomaler Leberenzyme nach einmaliger Gabe von polychlorierten Biphenylen (PCB) und anschliessender Stress-Situation" (Induction of microsomal liver enzymes after polychlorinated biphenyls [PCB] and

following stress). *Arch. Toxikol.* **29**: 97-106 (1972).

G92,593/72

Gaskin, F., Clayton, R. B.: "Decreased availability of hepatic NADPH in stressed mice." *Biochem. Biophys. Res. Commun.* **46**: 861-865 (1972).

G89,976/72

Buchel, L., Prioux-Guyonneau, M., Liblau, L., Murawsky, M.: "Influence de la contrainte du rat blanc sur l'activité, la pénétration et le métabolisme de l'hexobarbital et du barbital" (Influence of restraint on the activity, penetration and metabolism of hexobarbital and barbital in white rats). *Thérapie* **27**: 609-625 (1972).

G92,849/72

"The potentiation of the hypnotic effects, increase of the sleeping time with hexobarbital, shortening of the latent period with barbital, in relation with short or long-lasting restraint in rats, are attributable to two different mechanisms: inhibition of hexobarbital metabolism; increase of barbital penetration into the brain."

Gayathri, A. K., Rao, M. R. S., Padmanabhan, G.: "Drug metabolism in cold-exposed animals." *Indian J. Biochem. Biophys.* **10**: 31-33 (1973).

J24,134/73

"Cold exposure (5-7°) of rats and mice for a week results in a significant increase in the levels of cytochrome P-450 and aniline hydroxylase activity in liver microsomes. There is no change in the activities of β -aminolaevulinate synthetase and aminopyrine demethylase. It is held that the availability of haem is not a rate-limiting step for the increased formation of cytochrome P-450 in cold-exposed animals."

Buchel, L., Murawsky, M.: "Métabolisme et activité de la zoxazolamine chez le rat blanc au cours de l'immobilisation forcée accompagnée ou non d'hypothermie" (Zoxazolamine metabolism and activity in white rats during restraint with or without hypothermia). *Arch. Sci. Physiol. (Paris)* **27**: 37-53 (1973).

J7,077/73

In rats the muscle-relaxing effect of zoxazolamine is considerably enhanced by the stress of restraint, especially in cold surroundings. This is ascribed mainly to increased sensitivity of the nervous system, and to a lesser extent, to impaired zoxazolamine metabolism during stress.

Campbell, T. C., Hayes, J. R.: "Role of nutrition in the drug-metabolizing enzyme system." *Pharmacol. Rev.* **26**: 171-197 (1974).

J21,011/74

Varia

Among other biochemical alterations that have been related to stress, the most important are changes in vitamin C, cAMP, creatinine and uric acid, hippuric acid, glutathione, DNA and RNA, as well as in the equilibrium between anabolic and catabolic responses, which largely determine body weight.

Vitamin C. One of the most characteristic consequences of exposure to acute stress is the loss of ascorbic acid from the adrenal cortex. This has been confirmed in man and in many other species. It is even employed as a standard stress test, particularly in connection with the verification of the functional efficiency of the hypothalamus-hypophysis-adrenocortical system. After hypophysectomy, stress no longer exerts this effect, but ACTH remains active, indicating that the stimulus travels to the adrenals and is mediated by ACTH through the hypophysis. Since this discharge of adrenal ascorbic acid runs roughly parallel to that of the corticoids, it represents a fairly reliable indicator of the latter; however, the biochemical relationship between ascorbic acid depletion and corticoid production is not yet clearly understood.

Following treatment with ACTH, the ascorbic acid depletion of the adrenal is associated with an increase in the concentration of this vitamin within the adrenal venous blood, but curiously, under stress, more ascorbic acid disappears from the cortex than can be found in its venous effluent.

Allegedly, adrenal cannulation raises the circulating ascorbic acid level, even after hypophysectomy and exclusion of the adrenal from the circulation. Hence, part of the ascorbic acid must have an extra-adrenal origin. This conclusion is supported by the loss of ascorbic acid from various tissues of the body and its greatly increased urinary elimination during stress.

Many independent studies have shown that animal species differ greatly in their ascorbic acid discharge from the adrenals and other tissues in the course of the alarm reaction. There is no strict correlation between adrenal cholesterol and asorbic acid release, although in general the two phenomena tend to coincide.

Unlike most other species, *Tupaia* exposed to various stressors show an increase in adrenocortical ascorbic acid content.

Varia

(See also our earlier stress monographs, p. xiii)

Vitamin C. Sayers, G., Sayers, M. A., Liang, T. Y., Long, C. N. H.: "The cholesterol and ascorbic acid content of the adrenal, liver, brain and plasma following hemorrhage." *Endocrinology* 37: 96-110 (1945).

B512/45

In rats, severe hemorrhage decreases the cholesterol and ascorbic acid content of the adrenals, presumably as a consequence of its stressor effect. Hypophysectomy prevents these changes, whereas they are duplicated by ACTH. The cholesterol content of the

liver and brain is unaffected by nonfatal hemorrhage, and plasma cholesterol falls during shock due to severe hemorrhage. Hepatic and plasma ascorbic acid levels rise after mild and fall after fatal hemorrhage. Brain ascorbic acid levels are unaffected.

Long, C. N. H.: "The relation of cholesterol and ascorbic acid to the secretion of the adrenal cortex." *Rec. Prog. Horm. Res.* 1: 99-122 (1947).
A53,620/47

Sayers, M. A., Sayers, G., Woodbury, L. A.: "The assay of adrenocorticotropic hormone by the adrenal ascorbic acid-depletion method." *Endocrinology* 42: 379-393 (1948).
B19,837/48

Kuhl, W. J. Jr., Wilson, H., Ralli, E. P.: "Measurements of adrenal cortical activity in young men subjected to acute stress." *J. Clin. Endocrinol. Metab.* **12**: 393-406 (1952). B69,085/52

Normal men immersed in cold water for eight minutes exhibited significant eosinopenia, lymphopenia and hypochloremia, with increased urinary ascorbic acid and uric acid excretion. Serum sodium, potassium, blood sugar and ascorbic acid were not significantly altered.

Kark, R. M.: "Ascorbic acid, stress, and the adrenal gland." *J. Clin. Nutr.* **1**: 306-308 (1953). B84,500/53

Bartlett, R. G., Miller, M. A.: "The adrenal cortex in restraint hypothermia and in adaptation to the stress of restraint." *J. Endocrinol.* **14**: 181-187 (1956).

C25,043/56

In rats, one week of exposure to mild restraint increased the ascorbic acid, and to a lesser extent, the cholesterol content of the adrenals. Restraint sufficiently severe to reduce body temperature produced inverse changes. Loss of cholesterol and ascorbic acid from the adrenals was particularly marked in animals restrained while exposed to cold.

Briggs, F. N., Toepel, W.: "The effect of ACTH on the ascorbic acid concentration of adrenal venous plasma of the rat." *Endocrinology* **62**: 24-29 (1958). C48,344/58

The ascorbic acid concentration of adrenal venous blood was increased by laparotomy in intact rats, and by ACTH in hypophysectomized rats. "Under the influence of ACTH, the amount of ascorbic acid found in adrenal venous blood could account for that which disappeared from the adrenal, but under 'stress' more ascorbic acid disappeared from the adrenal than could be found in the adrenal venous blood." Curiously, adrenal cannulation raised the circulating ascorbic acid level even after hypophysectomy and exclusion of the adrenal from the circulation. This ascorbic acid must have been of extra-adrenal origin.

Elton, R. L., Zarrow, I. G., Zarrow, M. X.: "Depletion of adrenal ascorbic acid and cholesterol: a comparative study." *Endocrinology* **65**: 152-157 (1959). C71,402/59

"Exposure to severe cold produced significant depression of adrenal ascorbic acid in opossums and dogs, but failed to do so in frogs, toads, chickens, mice, hamsters, rab-

bits, and cats. ACTH failed to produce such a depletion in frogs, toads, chickens, rabbits, cats, or dogs; significant depressions were observed in opossums, mice and hamsters. Adrenal cholesterol concentrations remained unchanged in most species tested, however, increases were observed in rabbits, following cold exposure, and in frogs, following ACTH treatment" (24 refs.).

Saiki, H., Ebe, T.: "Physiological role of ascorbic acid. I. Ascorbic acid metabolism under decompression stress." *J. Vitaminol.* **5**: 141-150 (1959). D93,035/59

Schwartz, N. B., Kling, A.: "Stress-induced adrenal ascorbic acid depletion in the cat." *Endocrinology* **66**: 308-310 (1960).

C80,679/60

In cats, unilateral adrenalectomy causes a depletion in the ascorbic acid content of the remaining adrenal. This response can be blocked by cortisol, the blockade in turn being overcome by ACTH injection. Compensatory hypertrophy after unilateral adrenalectomy is not as obvious in the cat as in other species.

Lahiri, S., Lloyd, B. B.: "The effect of stress and corticotrophin on the concentrations of vitamin C in blood and tissues of the rat." *Biochem. J.* **84**: 478-483 (1962). D35,013/62

Geber, W. F., Anderson, T. A., Dyne, B. van: "Physiologic responses of the albino rat to chronic noise stress." *Arch. Environ. Health* **12**: 751-754 (1966). G39,248/66

In rats, exposure to a variety of sounds (gongs, horns, loud speakers, bells, vibrators) caused roughly parallel decreases in blood eosinophil and ascorbic acid concentrations in the adrenal and other tissues. On the other hand, chronic audiogenic stress led to an increase in adrenal weight, ascorbic acid concentrations and serum cholesterol.

Sanchez, C., Miya, T. S., Bousquet, W. F.: "Effects of conditioning upon stress responses in the rat." *Proc. Soc. Exp. Biol. Med.* **123**: 615-618 (1966). F73,973/66

Pretreatment of rats with small amounts of intravenous sodium chloride for five days inhibited the marked elevation of plasma corticosterone induced by saline in unpretreated controls. Similar pretreatment offered no protection, however, against the more pronounced stressor effect of intravenous histamine. The resting plasma corticosterone and ascorbic acid levels did not show any

consistent seasonal variations, and there was no manifest relationship between the two values. This "suggests that caution be employed in relying upon adrenal ascorbic acid determinations as an index of adrenocortical activity or response to stressors."

Stitzel, R. E., Furner, R. L.: "Stress-induced alterations in microsomal drug metabolism in the rat." *Biochem. Pharmacol.* **16**: 1489-1494 (1967). G48,920/67

It is incidentally noted that exposure to cold raises adrenal ascorbic acid concentrations concurrently with an increase in adrenal weight and thymus atrophy. [The authors do not discuss the fact that most investigators consider a fall in adrenal ascorbic acid as characteristic of stress (H.S.).]

Blanc, B., Mühl, M. von der: "Interaction d'un facteur P (flavonoïde) et de la vitamine C, son influence sur le poids du cobaye et la teneur en vitamine C de ses organes; effets de variations thermiques" (Interaction of a P factor [flavonoid] and of vitamin C, its effects on guinea pig weight and the vitamin C content of its organs; effects of thermal variations). *Int. Z. Vitaminforsch.* **37**: 156-169 (1967). F86,545/67

Axt, J., Richter, W., Ott, W.: "Vitamin-C-Spiegel des Blutserums verschiedener Tierarten bei Belastungen. III. Mitteilung: Einfluss von Arbeitsbelastungen auf Serumaskorbinsäure- und Blutzuckerspiegel des Pferdes" (Vitamin C content in the blood serum of various animal species under stress. III. Effect of work stress on serum ascorbic acid and blood sugar in the horse). *Arch. Exp. Vet. Med.* **22**: 1165-1173 (1968). J25,390/68

Paré, W. P.: "Effect of duration of environmental stress on stomach ulceration and adrenal ascorbic acid." *Psychol. Rep.* **23**: 683-688 (1968). J19,594/68

In rats repeatedly exposed to electroshock over a twenty-four-day period, adrenal ascorbic acid showed an initial decline, followed by a rise far above normal by the end of the experiment [corresponding to the stage of adaptation (H.S.)]. In these animals, which were not deprived of food or water, gastric lesions developed only irregularly.

Asano, K.: "The influence of hypoxia and

exercise on ascorbic acid metabolism." *Jap. J. Phys. Fitness Sports Med.* **21**: 69-86 (1972). H91,964/72

Review and personal observations on rats and rabbits concerning changes in vitamin C metabolism during stress (hypoxia, swimming to exhaustion).

Holst, D. von: "Die Funktion der Nebennieren männlicher Tupaia belangeri. Nebentierengewicht, Ascorbinsäure und Glucocorticoids im Blut bei kurzem und andauerndem soziopsychischem Stress" (The function of the adrenals in male Tupaia belangeri. Adrenal weight, ascorbic acid and glucocorticoids in the blood after acute and prolonged psychosocial stress). *J. Comp. Physiol.* **78**: 289-306 (1972). G93,303/72

Male *Tupaias*, after being defeated by a trained fighter, were separated from him by a wire mesh so that they could continually see the victor without being attacked. The fight was repeated every one to two days. Under these conditions the defeated *Tupaias* died in less than twenty days owing to the "psychosocial stress" associated with adrenal enlargement and increased ascorbic acid concentration. Plasma glucocorticoid levels initially dropped and then rose above normal. An elevation of adrenal ascorbic acid also occurred in *Tupaias* exposed to various other stressors, in contrast to the characteristic depletion in most other species.

Litwornia, B. L., Brush, M. K.: "The effect of stress on the intestinal transport of ascorbic acid in the guinea pig and on the ascorbic acid concentration of various organs." *Fed. Proc.* **33**: 673 (1974). H84,512/74

Willis, R. J., Kratzing, C. C.: "Pulmonary ascorbic acid loss induced by catecholamines." *Biochem. Pharmacol.* **23**: 2705-2711 (1974). H93,874/74

In mice, both "hyperbaric stress" and NEP decreased the vitamin C content of the lung. Following treatment with NEP, EP and some of their derivatives, both the loss of lung ascorbic acid and the development of pulmonary edema depended on α -receptor activity and were potentiated by β -receptor activity. "The results suggest an association between the loss of lung ascorbate and the development of catecholamine-induced pulmonary edema in mice."

Other Vitamins. Among other vitamins, nicotinic acid appears to play a prominent role in human psychogenic stress responses in that it inhibits fatty acid mobilization

from adipose tissue and diminishes blood lipids without influencing tachycardia, hypertension or catecholamine secretion. Furthermore, thiamine requirements appear to be directly related to energy expenditure, and a variety of stressors augment the demand for thiamine in man.

Other Vitamins. Taketani, T.: "Variations of total vitamin B₂ content in the cornea, iris and ciliary body and the blood of rabbits in stress. (A preliminary report)." *Folia Ophthalmol. Jap.* **13**: 489-494 (1962).

J24,376/62

Phillips, W. E. J.: "Low-temperature environmental stress and the metabolism of vitamin A in the rat." *Can. J. Biochem.* **40**: 491-499 (1962).

D21,932/62

Blanc, B., Mühl, M. von der: "Interaction d'un facteur P (flavonoïde) et de la vitamine C, son influence sur le poids du cobaye et la teneur en vitamine C de ses organes; effets de variations thermiques" (Interaction of a P factor [flavonoid] and of vitamin C, its effects on guinea pig weight and the vitamin C content of its organs; effects of thermal variations). *Int. Z. Vitaminforsch.* **37**: 156-169 (1967).

F86,545/67

Horio, K.: "Studies on thiamine metabolism in the brain and liver under various en-

vironmental conditions." *Jap. J. Hyg.* **22**: 487-495 (1967).

J24,340/67

Chernov, M. S., Hale, H. W. Jr., Wood, M.: "Prevention of stress ulcers." *Am. J. Surg.* **122**: 674-677 (1971).

G86,818/71

Following severe surgical trauma or burns, serum vitamin A levels drop sharply in man. Allegedly, "treatment with high doses of parenteral vitamin A reduces the risk of gastroduodenal ulceration in these severely stressed patients" (23 refs.).

Frattali, V., Robertson, R.: "Nutritional evaluation of humans during an oxygen-helium dive to a simulated depth of 1000 feet." *Aerospace Med.* **44**: 14-21 (1973).

H79,775/73

In man, oxygen-helium dives to a simulated depth of 1000 ft. decreased thiamine excretion and erythrocyte transketolase activity. In one diver these changes persisted to the end of the decompression phase. "Since thiamin requirement is directly related to energy expenditure, it is possible that hyperbaric stress exacerbates exercise and cold stress, thereby creating a greater thiamin demand."

AMP, ADP, ATP and other Nucleotide Derivatives. In the rat brain, electro-shock decreases adenyl nucleotide concentration, and several investigators examined the details of this type of response. It has been suggested that ACTH alters kinase, making it more sensitive to dissociation after binding by cAMP. However, there are differences in the responses of various regions of the brain. Certain stressors increase cAMP in the septum and hippocampus of the rat brain, a phenomenon thought to be involved in the mediation of responses during emotionally-induced stress. These findings and many other investigations suggested that cAMP plays a role in the reaction of the hypothalamo-pituitary system to stressors.

In rats, cAMP and cGMP (cyclic guanosine monophosphate) could be separated to study their behavior during the induction of tyrosine hydroxylase by stress, in the chromaffin cells of the adrenals. When rats swim in cold water, it appears that enhancement of cAMP/cGMP concentration ratios may function as the second messenger for the induction of tyrosine hydroxylase in the adrenal medulla.

Observations on newborn rats showed that, apparently, the functional ACTH-sensitive adenylcyclase system is present by the sixth day, but the presumably hypothalamic mechanism that controls stress-induced ACTH release becomes operative only after about the fifteenth day.

Further studies on this undoubtedly highly important aspect of the stress response would certainly offer great promise.

AMP, ADP, ATP and Other Nucleotide Derivatives. Albaum, H. G., Milch, L. J.: "Adenosine triphosphate changes induced by cold, heat and crush injury." *Am. J. Physiol.* **178**: 293-295 (1954). B97,925/54

Yasin, R., Bergel, F.: "Effect of injection on nicotinamide adenine dinucleotide-levels." *Nature* **20**: 783-784 (1963). J23,199/63

Hollis, V. W. Jr., Ramey, E. R.: "Liver nucleotide patterns in stressed and unstressed intact and adrenalectomized rats." *Am. J. Physiol.* **211**: 1339-1344 (1966).

F75,204/66

In rats, tourniquet stress increased hepatic nucleotides whereas the reverse was true after adrenalectomy. "This may contribute to the stress sensitivity of these animals." Detailed data are given concerning the differential variations of individual nucleotides, including AMP, ADP, ATP, GMP, GDP, GTP, UMP and so on.

Hollis, V. W. Jr., Ramey, E. R.: "Effect of stress on blood levels of guanine nucleotides." *Proc. Soc. Exp. Biol. Med.* **121**: 104-106 (1966). F61,359/66

"Studies using C¹⁴-labelled guanylic acid demonstrated a rapid disappearance of these substances from the blood of intact and adrenalectomized rats. The application of tourniquets across the hind limbs of these animals produced a significantly decreased clearance of the label from the blood after the tourniquet was removed." Possibly, changes in hepatic function and increased release of intracellular nucleotides resulting from lymphatic involution or cell damage may raise the blood nucleotide pool and induce an apparent delay in the clearance of these substances.

Ove, P., Takai, S., Umeda, T., Lieberman, I.: "Adenosine triphosphate in liver after partial hepatectomy and acute stress." *J. Biol. Chem.* **242**: 4963-4971 (1967).

G51,398/67

Voskoboinikov, G. V.: "Changes in adenine nucleotides content in the liver and spleen of rats during starvation and painful irritation." *Vopr. Med. Khim.* **14**: 197-199 (1968).

J23,530/68

Starvation decreases the ATP but greatly increases the ADP and AMP content of the rat liver.

Kaffarnik, H., Gross, W., Dawid, E., Deibert, K., Juchems, R.: "Verhalten der Adenylatkinase (Myokinase), des Adenosin-

triphosphats (ATP) und der K- und Na-Ionen im Serum bzw. Blut unter standardisierter körperlicher Belastung" (Behavior of adenylate kinase [myokinase], adenosine triphosphate [ATP] and K and Na ions in the serum or blood under standardized physical stress). *Z. Gesamte Exp. Med.* **153**: 324-330 (1970). H36,724/70

In man, muscular work increases the serum concentration of adenylate kinase and ATP, but does not change potassium or sodium levels. "The results are discussed with respect to the turnover of the phosphates during physical stress" (25 refs.).

Camarda, R., D'Alessandro, F., Guarneri, R., Bonavita, V.: "Stress and brain nicotinamide adenine dinucleotides in normal and hypophysectomized rats." *Acta Neurol. (Napoli)* **26**: 501-510 (1971). J20,829/71

In rats, restraint or injection of saline modifies NAD, NADH, NADP and NADPH levels in the brain. Hypophysectomy prevents these changes.

Marton, J., Stark, E., Mihály, K.: "Effect of imidazole on the adrenal response to ACTH and to stress." *Acta Physiol. Acad. Sci. Hung.* **42**: 225-230 (1972). J6,599/72

In rats, "the in vivo antagonism of imidazole and ACTH or stressful stimuli supports the hypothesis that cAMP is the intracellular mediator of the steroidogenic effect of ACTH in the adrenal cortex."

Lee, C. J., Dubos, R.: "Lasting biological effects of early environmental influences. VII. Metabolism of adenosine 3'-5'-monophosphate in mice exposed to early environmental stress." *J. Exp. Med.* **135**: 220-234 (1972). H50,727/72

Dickman, S. R., Harrison, J. F., Grosser, B. I.: "Decrease in adenylyl nucleotide concentrations in rat brain components after footshock stress." *Brain Res.* **53**: 483-487 (1973). H80,354/73

Shima, S., Mitsunaga, M., Kawashima, Y., Taguchi, S., Nakao, T.: "Studies on cyclic nucleotides in the adrenal gland. IV. Effect of ACTH on cyclic nucleotides-dependent protein kinases in the adrenal gland." *Endocrinology* **94**: 650-654 (1974). H85,334/74

Experiments on rats "indicate that the rapid increase in adrenal protein kinase activity following ACTH administration is not solely dependent on the increased cAMP levels or binding of cyclic nucleotides to the kinase. It is suggested that ACTH alters the

kinase making it more sensitive to dissociation after binding cAMP."

Paz, R. L. de la, Dickman, S. R., Grosser, B. I.: "Effects of stress on rat brain adenosine cyclic 3',5'-monophosphate (cAMP) in vivo." *Clin. Res.* **22**: 190A (1974).

H84,811/74

Various stressors (electric shock, restraint) increase the cAMP in the septum and hippocampus of the rat brain. This may be of special importance, since these components of the limbic system might be involved in the mediation of responses during emotionally-induced stress.

Chowers, I., Siegel, A., Conforti, N., Feldman, S.: "Effects of neurogenic and systemic stress on hypothalamic and pituitary cyclic AMP." *Isr. J. Med. Sci.* **10**: 572 (1974).

H89,688/74

Siegel, R., Conforti, N., Feldman, S., Chowers, I.: "Effects of neurogenic and systemic stresses on hypothalamic and adenohypophyseal cAMP content." *Neuroendocrinology* **14**: 24-33 (1974). H83,083/74

Various systemic and neurogenic stressors produced similar but not identical changes in the cAMP content of the rat hypothalamus and adenohypophysis. In any event, presumably, "cAMP plays a role in the response of the hypothalamo-pituitary system to stress."

Strange, R. C., Vetter, N., Rowe, M. J., Oliver, M. F.: "Plasma cyclic AMP and total catecholamines during acute myocardial infarction in man." *Eur. J. Clin. Invest.* **4**: 115-119 (1974). J15,219/74

There is a marked elevation of plasma cAMP during the first hours after myocardial infarction in man. "Patients with the worst prognosis had the highest plasma concentrations of cyclic AMP and total catecholamines."

Guidotti, A., Costa, E.: "Association between increase in cyclic AMP and subsequent induction of tyrosine hydroxylase in rat adrenal medulla. Experiments with swimming stress." *Naunyn Schmiedebergs Arch. Pharmacol.* **282**: 217-221 (1974). J12,854/74

cAMP and cGMP (cyclic guanosine monophosphate) were separated from the medulla to determine the relationship between them, because from the literature cited it is clear that the induction of tyrosine hydroxylase activity in the chromaffin cells is preceded by changes in these compounds. When rats are placed in cold water, "the swimming stress

experiments are in agreement with the view that the enhancement of cyclic AMP/cGMP concentration ratios may function as the second messengers for the induction of tyrosine hydroxylase in adrenal medulla" (12 refs.).

Cote, T. E., Yasumura, S.: "Fluctuations in adrenal cyclic AMP levels in immature rats in response to ACTH and histamine stress." *Fed. Proc.* **33**: 205 (1974).

H83,812/74

Adrenal cAMP levels were studied in rats subjected to treatment with either ACTH (50 mU/rat) or histamine dihydrochloride (0.2 mg/g body wt.). Untreated rats were used as controls in order to preclude the stress of vehicle injections. In 6-day-old rats, the values for adrenal cyclic AMP were: 3.35 pmol/mg in the untreated group; 4.35 pmol/mg in the histamine-treated group; and 37.03 pmol/mg 25 min. after injection of ACTH. The corresponding plasma corticosterone levels were 4.55 µg/100 ml in the untreated group; 5.13 µg/100 ml in the histamine-treated group; and 7.27 µg/100 ml in the ACTH-treated group. In 15-day-old rats, the values for adrenal cyclic AMP were: 4.60 pmol/mg in the untreated group; 45.1 pmol/mg in the histamine-stressed group; and 47.3 pmol/mg in the ACTH-treated group. The corresponding plasma corticosterone levels were: 4.58 µg/100 ml in the untreated group; 14.25 µg/100 ml in the histamine-stressed group; and 14.05 µg/100 ml in the ACTH-treated group." Apparently, the functional ACTH-sensitive adenyl cyclase system is present in rats by the sixth day after birth, but the presumably hypothalamic mechanism which controls stress-induced ACTH release is inoperative until the fifteenth day.

Meerson, F. Z.: "Role of synthesis of nucleic acids and protein in adaptation to the external environment." *Physiol. Rev.* **55**: 79-123 (1975). H81,616/75

Review on the role of nucleic acids in adaptation to various stressors (220 refs.).

Francesconi, R., Cymerman, A.: "Adrenocortical activity and urinary cyclic AMP levels: effects of hypobaric hypoxia." *Aviat. Space Environ. Med.* **46**: 50-54 (1975). J20,384/75

Delapaz, R. L., Dickman, S. R., Grosser, B. I.: "Effects of stress on rat brain adenosine 3',5'-monophosphate in vivo." *Brain Res. (Amst.)* **85**: 171-175 (1975). J20,677/75

Observations showing "a relationship between stress and increases in the level of cAMP in several regions of the rat brain. A marked rise is seen in the septum after stress from electric shock or restraint. Smaller increases are seen in hippocampus and brain stem in animals stressed by electric shock. These changes in septum and hippocampus are of interest since these regions are components of the limbic system and, therefore,

might be involved in the mediation of emotional responses during stress."

Terrier, M., Perrier, H.: "Cyclic 3',5'-adenosine monophosphate level in the plasma of the rainbow trout (*Salmo gairdnerii* Richardson) following adrenaline administration and constrained exercise." *Experientia* 31: 196 (1975). K400/75

Creatinine. An increase in urinary creatinine output was noted in submarine personnel undergoing stressful training in underwater tanks, as well as in dogs after surgical trauma, but the change is not considered to be a reliable indicator of stress.

Creatinine. Cook, E. B., Wherry, R. J.: "The urinary 17-ketosteroid output of naval submarine enlisted candidates during two stressful situations." *Hum. Biol.* 22: 104-124 (1950). B48,615/50

In submarine enlisted candidates, stress-producing training in tanks evokes typical manifestations of the G.A.S., including an increase in 17-KS and creatinine output, although the two parameters are not strictly related.

Kuhl, W. J. Jr., Ralli, E. P.: "Effect of acute stress upon blood constituents, white cells, and urine constituents in normal individuals." *Proc. Assoc. for the Study of Internal Secretions—33rd. Meeting*, p. 51. Atlantic City, N.J., 1951. Also in: *J. Clin. Endocrinol. Metab.* 11: 776 (1951).

B58,505/51

Normal men immersed in cold water (9.5°C) for eight minutes showed: "1—A decrease in temperature (immediate, 1 and 2 hours); 2—An increase in systolic and diastolic blood pressure (immediate) and a decrease (2 hours); 3—A decrease in heart rate (1, 2 and 4 hours); 4—An increase in neutrophiles (immediate); 5—A decrease in lymphocytes (2 hours); 6—A decrease in eosinophiles (2 hours); 7—A decrease in serum chloride (immediate); 8—An increase in total proteins (immediate and 4 hours); 9—A decrease in serum water (immediate); 10—An increase in total cholesterol (4 hours); 11—An increase in the urine uric acid/creatinine ratio (2 and 4 hours)." All of these changes were significant and ascribed to stress, but no one indicator gave uniformly positive results.

Schwartz, T. B., Shields, D. R.: "Urinary excretion of formaldehydogenic steroids and

creatinine. A reflection of emotion tension." *Psychosom. Med.* 18: 159-172 (1956).

C25,345/56

In students undergoing stressful final examinations, increased urinary corticoid excretion occurs fairly regularly, but urinary volume and creatinine elimination are not clearly related to the stress of the examinations.

Gairard, A., Marnay-Gulat, C., Raoul, Y.: "Essai d'analyse de la contrainte ulcérogène du Rat par l'étude de l'élimination urinaire de divers ions" (Experimental analysis of restraint ulcerogenesis in the rat by study of the urinary elimination of various ions). *C.R. Soc. Biol. (Paris)* 161: 2132-2136 (1967).

F98,979/67

In rats, restraint ulcers are associated with a decrease in creatinine, chlorine, sodium and calcium excretion. Phosphaturia is increased, whereas potassium elimination does not change.

Ukai, M., Moran, W. H. Jr., Zimmermann, B.: "The role of visceral afferent pathways on vasopressin secretion and urinary excretory patterns during surgical stress." *Ann. Surg.* 168: 16-28 (1968). G60,105/68

In dogs, partial gastrectomy increased vasopressin secretion about thirty-fold. This response was not modified by transection of the vagal pathways, but could be eliminated by cervical cordotomy or dorsal rhizotomy, "indicating that the ascending spinal pain pathways were serving as the predominant afferent pathway." The surgical trauma also decreased endogenous creatinine and osmolal clearance, urinary flow and sodium secretion. The vasopressin discharge is ascribed to stress.

Uric Acid. A rise in uric acid excretion is allegedly an invariable result of ACTH secretion in man, and has even been used as a test for cortical activity. EP, killed bacteria, immersion in cold water, flying overwater missions in military planes, underwater demolition work and other stressors likewise augment the serum and/or urinary concentration of uric acid in man.

Uric Acid. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., Hills, A. G.: "A test for adrenal cortical insufficiency." *J.A.M.A.* **137**: 1005-1009 (1948). D98,669/48

Eosinopenia and a rise in uric acid excretion consistently follow ACTH injection in man, and may be used as a test of adrenocortical activity.

Faurbye, A., Vestergaard, P., Kobbernagel, F., Nielsen, A.: "Adrenal cortical function in chronic schizophrenia (stress, adrenaline-test, ACTH-test)." *Acta Endocrinol. (Kbh.)* **8**: 215-246 (1951). B63,996/51

In man, EP treatment and the production of fever by injections of killed *B. faecalis alcaligenes* are both regarded as adequate "stress tests," as indicated by the increase in uric acid and potassium excretion as well as the hematologic changes that result.

Kuhl, W. J. Jr., Ralli, E. P.: "Effect of acute stress upon blood constituents, white cells, and urine constituents in normal individuals." *Proc. Assoc. for the Study of Internal Secretions—33rd. Meeting*, p. 51. Atlantic City, N.J., 1951. Also in: *J. Clin. Endocrinol. Metab.* **11**: 776 (1951).

B58,505/51

Normal men immersed in cold water (9.5°C) for eight minutes showed: "1—A decrease in temperature (immediate, 1 and 2 hours); 2—An increase in systolic and diastolic blood pressure (immediate) and a decrease (2 hours); 3—A decrease in heart rate (1, 2 and 4 hours); 4—An increase in neutrophiles (immediate); 5—A decrease in lymphocytes (2 hours); 6—A decrease in eosinophiles (2 hours); 7—A decrease in serum chloride (immediate); 8—An increase in total proteins (immediate and 4 hours); 9—A decrease in serum water (immediate); 10—An increase in total cholesterol (4 hours); 11—An increase in the urine uric acid/creatinine ratio (2 and 4 hours)." All of these changes were significant and ascribed to stress, but no one indicator gave uniformly positive results.

Kuhl, W. J. Jr., Wilson, H., Ralli, E. P.: "Measurements of adrenal cortical activity

in young men subjected to acute stress." *J. Clin. Endocrinol. Metab.* **12**: 393-406 (1952). B69,085/52

Normal men immersed in cold water for eight minutes exhibited significant eosinopenia, lymphopenia and hypochloremia with increased urinary ascorbic acid and uric acid excretion. Serum sodium, potassium, blood sugar and ascorbic acid were not significantly altered.

Marchbanks, V. H. Jr., Hale, H. B., Ellis, J. P. Jr.: "Stress responses of pilots flying 6-hour overwater missions in F-100 and F-104 aircraft." *Aerosp. Med.* **34**: 15-18 (1963). G2,360/63

In navy pilots flying six-hour overwater missions in F-100 and F-104 aircraft, corticoid levels were increased in the plasma but not in urine. Urinary EP and NEP values were considerably above normal, as were excretions of urea and uric acid, while phosphate levels were not altered. The total reaction depended very much on airplane characteristics and pilot experience.

Rahe, R. H., Arthur, R. J.: "Stressful underwater demolition training. Serum urate and cholesterol variability." *J.A.M.A.* **202**: 1052-1054 (1967). F91,967/67

In men training for underwater demolition work, the serum urate concentration was elevated during anticipation of a demanding task and "cholesterol levels rose concomitant with a period of particular psychological stress. Serum urate concentration demonstrated a significant fall during a period of quite intense psychological stress."

Kasl, S. V., Cobb, S., Brooks, G. W.: "Changes in serum uric acid and cholesterol levels in men undergoing job loss." *J.A.M.A.* **206**: 1500-1507 (1968). J13,893/68

In people who lose their job or anticipate loss of employment, blood cholesterol and uric acid levels tend to rise, with a return to normal following the stress period of economic uncertainty.

Rahe, R. H., Rubin, R. T., Arthur, R. J., Clark, B. R.: "Serum uric acid and cholesterol variability. A comprehensive view of

Underwater Demolition Team training." *J.A.M.A.* **206**: 2875-2880 (1968).

G63,836/68

Pfeiffer, C. C., Iliev, V., Nichols, R. E., Sugerman, A. A.: "The serum urate level reflects degree of stress." *J. Clin. Pharmacol.* **9**: 384-392 (1969). H18,436/69

"The level of serum urate may reflect the degree of stress in the schizophrenic since serum urate usually decreases with antipsychotic therapy."

Mueller, E. F., Kasl, S. V., Brooks, G. W., Cobb, S.: "Psychosocial correlates of serum urate levels." *Psychol. Bull.* **73**: 238-257 (1970). J21,403/70

An extensive review of the literature and personal observations suggest "that serum uric acid levels change in response to socially and psychologically stressful situations" (about 100 refs.).

Rahe, R. H., Rubin, R. T., Gunderson, E. K. E.: "Measures of subjects' motivation and affect correlated with their serum uric acid, cholesterol, and cortisol." *Arch. Gen. Psychiatry* **26**: 357-359 (1972).

G90,674/72

Among trainees of a U.S. Navy underwater demolition team, "predominantly positive correlations were seen between the subjects' serum uric acid levels and their estimates of their own motivation. Their serum cholesterol concentrations demonstrated consistently negative correlations with their motivational and pleasant affect scores. Highest correlations were positive ones found between the subjects' serum cholesterol levels and their unpleasant affect scores."

Hippuric Acid. Patients who react to psychic or drug-induced stress with free anxiety usually show an elevated hippuric acid excretion following administration of benzoic acid. The reverse is true of those reacting with catatonic withdrawal. However, comparative studies under different conditions showed that hippuric acid excretion is not a particularly reliable indicator of stress.

Hippuric Acid. Persky, H., Grinker, R. R., Mirsky, I. A., Gamm, S. R.: "Life situations, emotions and the excretion of hippuric acid in anxiety states." In: Wolff, H. G., Wolf, S. G. Jr. *et al.*, *Life Stress and Bodily Disease*, pp. 297-306. Baltimore: Williams & Wilkins, 1950. B51,575/50

Patients who react to psychic or drug-induced stress with free anxiety usually show elevated hippuric acid excretion, while a diminution of this acid occurs in those react-

Serum cortisol correlations with the three psychological criteria demonstrated wide variability around a zero correlation baseline."

Machtey, I., Meer, A.: "In certain physiological stress conditions on the problem of hyperuricemia." *Adv. Exp. Med. Biol.* **41**: 419-421 (1974). J24,476/74

Blood levels of uric acid remained essentially constant during menstruation and ovulation but rose considerably during labor and following delivery. "It is therefore an attractive assumption, that the marked stress connected with labour is the possible cause of the hyperuricemia found in the reported cases."

Rahe, R. H., Rubin, R. T., Arthur, R. J.: "The three investigators study. Serum uric acid, cholesterol, and cortisol variability during stresses of everyday life." *Psychosom. Med.* **36**: 258-268 (1974). J21,223/74

The authors studied their own responses to various life events. "Marked elevations in serum cholesterol were seen in one investigator throughout an unpleasant residential move; repeated peaks in serum cortisol were seen in one investigator during times of anguish and anger over personal disappointments and work changes. Two of the three men showed uric acid elevations into the 'gout range' prior to eagerly taking on a physical change. Occasionally, serum uric acid and cortisol values reached magnitudes previously reported as characteristic of men entering underwater demolition training and jumping into the ocean from hovering helicopters."

ing with catatonic withdrawal. "Hippuric acid is a detoxification product of benzoic acid and it is conceivable that alteration in detoxification may represent a homeostatic defense of the organism to stress."

Persky, H., Grinker, R. R., Mirsky, I. A.: "The excretion of hippuric acid in subjects with free anxiety." *J. Clin. Invest.* **29**: 110-114 (1950). J13,730/50

In patients with free anxiety, hippuric acid

excretion is abnormally high after administration of sodium benzoate.

Persky, H., Gamm, S. R., Grinker, R. R.: "Correlation between fluctuation of free anxiety and quantity of hippuric acid excretion." *Psychosom. Med.* **14**: 34-40 (1952). B54,166/52

In patients with manifest anxiety and in individuals exposed to the mild stressors of daily life, hippuric acid excretion increases, but it is subnormal in catatonic schizophrenics.

Persky, H.: "Response to a life stress: evaluation of some biochemical indices." *J. Appl. Physiol.* **6**: 369-374 (1953).

J11,917/53

Pilots under training were subjected to various stressors (parachute jumps, physical exercise and so on) which caused a significant diminution in blood eosinophil and glutathione levels but did not affect the synthesis of hippuric acid from administered sodium benzoate. "These findings are taken to indicate that airborne training focal stresses are of intermediate severity on a scale whose poles are fear of failure and fear of bodily injury."

Basowitz, H., Korchin, S. J., Grinker, R. R.: "Anxiety in a life stress." *J. Psychol.* **38**: 503-510 (1954). B29,178/54

Earlier research has shown that subjects having free anxiety (a feeling of intense

dread and foreboding with generalized apprehensiveness not directed toward any specific object) exhibit an elevated hippuric acid tolerance in the absence of other evidence of liver dysfunction. Moreover, as anxiety is reduced, hippuric acid synthesis is lowered. In the present study, persons with initially elevated hippuric acid tolerance developed higher levels of anxiety under the stress of paratroop training than those with initially low values of this biochemical index, although prior to training the two groups were indistinguishable in their self-ratings of anxiety. Hippuric acid excretion not only distinguishes between neurotics with free anxiety and normal people, but even "normal individuals whose excretion values are very high, although still below levels typifying the condition of free anxiety, are prone toward heightened anxiety in a life stress."

Korchin, S. J., Basowitz, H.: "Perceptual adequacy in a life stress." *J. Psychol.* **38**: 495-502 (1954). J13,189/54

Earlier observations had shown that stress with free anxiety elevates hippuric acid excretion following administration of a standard dose of sodium benzoate. During paratroop training, men with a low hippuric acid discharge prior to the test are uniformly superior in performance, and proneness to stress responses is reflected in the prestressed hippuric acid excretion level.

Glutathione and other -SH compounds. In man, blood levels of glutathione and other -SH compounds are considerably lowered after parachute jumping. The same is true in rats after intense auditory stimulation and other stressors, but this parameter likewise fails to reflect stress with any degree of accuracy and consistency.

Glutathione and other -SH Compounds. Hess, W. C., Kyle, L. H., Doolan, P. D.: "Effect of administration of ACTH and cortisone upon blood glutathione levels." *Proc. Soc. Exp. Biol. Med.* **76**: 418-422 (1951).

B57,533/51

In man, ACTH and cortisone decrease the blood-reduced glutathione levels without significantly altering the total blood glutathione values. [It remains to be shown whether endogenous ACTH and glucocorticoids liberated during stress act similarly (H.S.).]

Persky, H.: "Response to a life stress: evaluation of some biochemical indices." *J. Appl. Physiol.* **6**: 369-374 (1953).

J11,917/53

Pilots under training were subjected to various stressors (parachute jumps, physical exercise and so on) which caused a significant diminution in blood eosinophil and glutathione levels, but did not affect the synthesis of hippuric acid from administered sodium benzoate. "These findings are taken to indicate that airborne training focal stresses are of intermediate severity on a scale whose poles are fear of failure and fear of bodily injury."

Persky, H.: "Glutathione metabolism in men under psychological stress." *Psychosom. Med.* **16**: 489-495 (1954). J13,307/54

In man, blood-reduced glutathione is considerably lowered five to ten hours after parachute jumping, but not after severe

physical exercise. Despite this apparent lack of nonspecificity, "it is postulated that severe psychological stress operating over long periods may produce irreversible depression of the blood glutathione level and its associated metabolic dysfunctions."

Beck, L. V., Linkenheimer, W. H., Marraccini, A.: "Effects of tumbling trauma, scalding and hemorrhage on rat tissue non-protein sulphydryl." *Proc. Soc. Exp. Biol. Med.* **86**: 823-827 (1954). J24,111/54

"Significant decreases in concentration of non-protein -SH were noted in rat liver following tumbling trauma, and in rat liver and kidney following severe scalding. In analyses confined to the liver, a significant decrease in liver non-protein -SH was noted following severe hemorrhage."

Register, U. D., Bartlett, R. G. Jr.: "Regeneration of tissue nonprotein sulphydryl compounds in rats after exposure to cold and restraint." *Proc. Soc. Exp. Biol. Med.* **86**: 836-838 (1954). B98,154/54

Rats exposed to cold or restraint stress exhibited "a lowering of concentration of the total nonprotein sulphydryl compounds (NPSH) in the liver. . . . Recovery was completed in fasting and nonfasting animals in less than 8 hours, with a transient overcompensation in both categories."

Register, U. D., Sorsa, A. M. Ia, Katsuyama, D. M., Smith, H. M.: "Soluble sulphydryl changes in dietary and environmental stress." *Am. J. Physiol.* **197**: 1353-1356 (1959). C79,673/59

Jurtshuk, P. Jr., Weltman, A. S., Sackler, A. M.: "Biochemical responses of rats to auditory stress." *Science* **129**: 1424-1425 (1959). C68,703/59

In rats, prolonged intense auditory stimulation reduced the glutathione level of the blood simultaneously with an increase in the weight, ascorbic acid and cholesterol content of the adrenals.

Stout, D. A., McCartney, R. L., Lewis, B. M., Smith, H. M., Register, U. D.: "Effect of cold and restraint on intracellular distribution of glutathione in rat liver." *Proc. Soc. Exp. Biol. Med.* **112**: 334-335 (1963). D58,524/63

Ellman, G. L., Sullivan, C. V.: "Sulphydryl reactivity in the central nervous system: effects of electro-shock." *Exp. Neurol.* **13**: 191-197 (1965). J22,996/65

In the rat brain, reactive SH groups are normally found in neuroglia cells, but after electroshock the number of these cells increases. In addition, neurons also show SH reactivity.

Murdoch, J. L., Hoenes, R. L., Ekkens, D. A., Russell, C. A., Register, U. D.: "Role of the pituitary and adrenals in cold and restraint induced liver nonprotein sulphydryl depletion." *Proc. Soc. Exp. Biol. Med.* **124**: 274-276 (1967). F76,099/67

"A significant decrease in liver nonprotein sulphydryl levels (LNPSH) was demonstrated in intact, hypophysectomized and adrenalectomized female rats in response to cold and restraint. A similar response was demonstrated following epinephrine injection. Neither ACTH nor cortisol replacement was necessary for this response. It is concluded that maximum LNPSH depletion during cold and restraint can be effected through stimulation of the sympathetic nervous system although other mechanisms are operative in intact animals."

Varma, R. R., Khuteta, K. P., Dandiya, P. C.: "The effect of some psychopharmacological agents on heat stress-induced changes in the glutathione levels of brain and blood in rats." *Psychopharmacologia* (Berlin) **12**: 170-175 (1968). G54,762/68

Khuteta, K. P., Mathur, K. N., Mali, S. L.: "Effect of exposure to heat on total blood sulphydryl (SH) groups in human beings." *Indian J. Med. Res.* **57**: 1767-1768 (1969). G73,777/69

In man, "heat stress" causes a decrease in blood sulphydryl groups.

Gupta, M. L., Khuteta, K. P., Mathur, K. N.: "Blood total sulphydryl groups in human beings after surgery." *J. Indian Med. Assoc.* **55**: 199-201 (1970). G80,624/70

In man, the total sulphydryl content of the blood decreased significantly after various types of stress. Similar results have been observed by earlier investigators following other stressors.

DNA, RNA. In rats, thymus involution induced by cortisol or stressors is associated with a considerable decrease in DNA and RNA, but systematic studies on the

effect of the G.A.S. upon the nucleic acid metabolism of the thymus have not yet been undertaken.

A so-called "stress satellite DNA" appears in seedlings of certain plants upon exposure to stress, but this is probably of bacterial origin and does not signify an amplification of ribosomal RNA genes as a consequence of stress.

DNA, RNA. Macchitella, E., Crucitti, F.: "Modificazioni surrenaliche in corso di ustioni sperimentali. Azione dello stress sull'attività mitotica e sul comportamento degli acidi nucleinici" (Adrenal modifications during experimental burns; effect of stress on mitosis and nucleic acids). *Chir. Patol. Sper.* **4**: 655-673 (1956). C41,613/56

Kerckhove, D. van de: "Variation de la teneur en acide désoxyribonucléique dans les cellules de la granulosa chez le rat lors du stress par le froid" (Variation in the desoxyribonucleic acid content of the granulosa cells of rats during cold-induced stress). *Ann. Endocrinol. (Paris)* **20**: 893-896 (1959). C85,242/59

Leeman, L.: "La tenur en ADN des noyaux de la médullosurrénale du rat blanc splanchnicotomisé au cours du stress" (DNA content of adrenal medulla nuclei in the splanchnicotomized white rat during stress). *Exp. Cell. Res.* **20**: 596-597 (1960).

C95,510/60

Gindin, A. P., Ogienko, N. M., Ushakova, A. V.: "Ribonucleic acid in the lymphocytes during adrenal lymphocytosis. (Data relating to the mechanisms of the general adaptation syndrome)." *Biull. Éksp. Biol. Med.* **54** No. 9: 62-64 (1962) (Russian). Engl. Trans.: *Bull. Exp. Biol. Med.* **54**: 998-1000 (1962). J25,032/62

In horses in which stress was produced by EP injections, "the number of RNA-saturated lymphocytes doubled in 4 minutes and increased 2.5-fold in 2 hours, 3-fold in 24 hours, but in 48 hours it dropped almost to the normal level. Adrenal lymphocytosis occurred mainly at the expense of RNA-rich lymphocytes."

Thorn, W., Busch, E. W.: "RNS- und Metabolitgehalte in Warmblüterorganen nach unterschiedlicher akuter oder chronischer Belastung" (RNA- and metabolic content in mammalian organs after various acute and chronic loading tests). *Biochem. Z.* **339**: 112-124 (1963). E81,153/63

Verwoerd, C. D. A., Verwoerd-Verhoef, H. L., Fautrez, J.: "Evolution de la teneur en

acide désoxyribonucléique des noyaux de la medullo-surrénale de rat pendant et après un stress chronique au froid" (Evolution of desoxyribonucleic acid content of nuclei of the rat adrenal medulla during and after chronic cold stress). *Arch. Biol. (Liège)* **74**: 51-61 (1963). J23,539/63

Lahtiharju, A., Rytömaa, T.: "DNA synthesis in fore and glandular stomach and in skin after nonspecific stress in mice." *Exp. Cell Res.* **46**: 593-596 (1967).

G48,366/67

Sagisaka, K.: "Behavior of the thymus DNA in formalin stress." *Med. Biol. (Tokyo)* **74**: 80-84 (1967). J24,615/67

Šimek, J., Erbenová, Z., Deml, F., Dvořáčková, I.: "Liver regeneration after partial hepatectomy in rats exposed before the operation to the stress stimulus." *Experientia* **24**: 1166-1167 (1968). H13,837/68

In partially hepatectomized rats, exposure to various stressors or treatment with ACTH enhances DNA synthesis in the liver remnant as well as hepatic regeneration and triglyceride storage.

Imondi, A. R., Balis, M. E., Lipkin, M.: "Effects of restraint-stress on enzymes involved in DNA synthesis." *Proc. Soc. Exp. Biol. Med.* **131**: 376-379 (1969).

H14,077/69

Bozhko, H. K.: "Renewal of ribonucleic acids in the rat brain under conditions of emotional stress." *Ukr. Biokhim. Zh.* **42**: 590-595 (1970) (Russian). J25,147/70

Stringfellow, C., Brachfeld, N.: "A study of transfer RNA and protein interrelationships in control and stressed isolated perfused rat hearts." *J. Mol. Cell Cardiol.* **1**: 221-223 (1970). H31,093/70

Moolten, F. L., Oakman, N. J., Bucher, N. L. R.: "Accelerated response of hepatic DNA synthesis to partial hepatectomy in rats pretreated with growth hormone or surgical stress." *Cancer Res.* **30**: 2353-2357 (1970) (13 refs.). H30,606/70

Hayasaki, N., Hosaka, K., Tsukada, K.: "Studies on the function of deoxyribonuclease

inhibitor after partial hepatectomy." *Biochim. Biophys. Acta* **238**: 75-81 (1971).

G83,224/71

Toma, V., Abraham, A. D., Pora, E. A.: "Nucleic acids in thymus involution and regeneration." *Rev. Roum. Biol.* **16**: 185-188 (1971). J10,495/71

In rats, the thymus involution produced by cortisol is associated with a considerable decrease in DNA and RNA. The values return to normal after several weeks and probably reflect similar changes caused by stressors through glucocorticoid liberation.

Wannemacher, R. W. Jr.: "Ribosomal RNA synthesis and function as influenced by RNA supply and stress." *Proc. Nutr. Soc.* **31**: 281-290 (1972). H80,192/72

Earlier observations showed that various stressors influence amino acid distribution in tissues. The present experiments on rats used mineralocorticoid hypertension to produce cardiac hypertrophy, and Walker tumor or infection to induce liver enlargement. The associated influx of amino acids and increase in RNA and protein synthesis in the enlarged organs were ascribed to a "stress-related flux of amino acids." [The reason for this interpretation is not quite clear (H.S.).]

Pearson, G. G., Ingle, J.: "The origin of stress-induced satellite DNA in plant tissues." *Cell Different.* **1**: 43-51 (1972).

G90,501/72

A so-called "stress-satellite DNA" is induced in growing seedlings of various *Cu-*

curbitaceae exposed to darkness, trauma and other stressors. The present observations suggest that in response to cold storage, the appearance of the stress-satellite is of bacterial origin and therefore cannot be "taken as evidence for the amplification of the ribosomal-RNA genes under this condition of physiological stress."

Baskin, F., Masiarz, F. R., Agranoff, B. W.: "Effect of various stresses on the incorporation of [³H]orotic acid into goldfish brain RNA." *Brain Res. (Amst.)* **39**: 151-162 (1972). J20,141/72

Earp, H. S.: "Glucocorticoid regulation of transcription: the role of physiologic concentrations of adrenal glucocorticoids in the diurnal variation of rat liver chromatin template availability." *Biochim. Biophys. Acta* **340**: 95-107 (1974) (53 refs.).

J12,596/74

Kontaratos, A. N.: "Hypothesis on the significance of RNA-directed DNA synthesis for evolution." *Pav. J. Biol. Sci.* **9**: 51-59 (1974). H83,050/74

The hypothesis is advanced that stress may influence evolution through protoviruses transmitted to germ cells. "Protopviruses are produced in response to environmentally-induced stress and via the RNA → DNA feedback loop are inserted into the genome of recipient cells. Once inserted there, they confer new biochemical properties to the host cell which are normally of selective value." [Highly speculative paper (H.S.).]

Other Compounds. Among other compounds whose metabolism and tissue concentration have been examined following exposure to stressors, data will be found in the abstract section on: amyloid, carnitine, ceruloplasmin, GABA, haptoglobin, heparin, hexosamine, histidine, interferon, 3-methoxy-4-hydroxyphenylglycol, neuraminic acid, orotic acid, orosomucoid, peroxide, phenols, polyuronide, pyruvic acid, serum mucoid, sialic acid, taurine, ubiquinone, uroporphyrin, and various unidentified stress metabolites.

Other Compounds. Gitelson, S., Tiberin, P.: "Effect of emotional stress on the blood pyruvic acid level." *Acta Endocrinol. (Kh.)* **11**: 345-350 (1952). B76,933/52

In patients showing obvious signs of anxiety before surgery, the blood pyruvic acid level rises. Hence, "it is suggested that hyperpyruvicemia occurring in these cases is the result of emotional stress caused by fear of operation and is part of the general 'alarm reaction'."

Rohdenburg, G. L., Manheims, P. J.: "A clinical laboratory procedure for the study of the General Adaptation Syndrome." *J. Clin. Endocrinol. Metab.* **12**: 1031-1039 (1952). B72,657/52

A turbidity test "applicable to blood and urine, which renders it possible to evaluate the General Adaptation Syndrome of Selye, is reported. A series of cases is presented illustrating the clinical application of the procedure."

Robinson, R., Smith, P.: "Urinary phenols in stress." *Nature* **186**: 240 (1960).
C84,573/60

Marconi, R., Cravero, D.: "Il test del Tween 80. Un indice della reattività organica al trauma operatorio" (The tween 80 test. An index of organic reactivity to surgical trauma). *Minerva Chir.* **15**: 774-778 (1960).

J24,042/60

Some metabolite causing turbidity in human blood when mixed with tween 80 is considered to be indicative of stress.

Hall, C. E., Cross, E., Hall, O.: "Amyloidosis and other pathologic changes in mice exposed to chronic stress." *Tex. Rep. Biol. Med.* **18**: 205-213 (1960).
D93,919/60

Old mice repeatedly exposed to electric shocks for seventy-one days developed generalized amyloidosis, which was interpreted as a stress manifestation in this species (23 refs.).

Horgan, V. J., Philpot, J. S. L.: "Peroxide-like substance in alarmed mice." *Nature* **192**: 662-663 (1961).
D14,949/61

Aiyar, A. S., Sreenivasan, A.: "Intracellular distribution of ubiquinone in rat liver under certain stress conditions." *Nature* **190**: 344 (1961).
J22,942/61

Rose, K. D., Maca, R., Pace, D. M.: "Sterol synthesis by cells cultured on serum from heat-stressed chickens." *Proc. Soc. Exp. Biol. Med.* **108**: 282-285 (1961).
D89,507/61

"Young chickens subjected to heat stress at 102°F for 24 hours elaborate a stress factor into their blood stream. When serum from these animals is used as an adjuvant in a serum-balanced salt solution medium, cells grown on this medium accumulate large numbers of small lipid droplets within their cytoplasm." Possibly, this factor may account for the hypercholesterolemia characteristic of stress in vivo.

Gidron, E., Czaczkes, J. W., Yaron, E.: "Increased uroporphyrin excretion in response to stress." *Clin. Sci.* **22**: 409-412 (1962).
D27,276/62

Urinary uroporphyrin excretion rose after exposure to various stressors in man.

Brayer, F. T.: "Influence of plasma from a variety of stressed animals on I¹³¹ uptake in chick embryos." *J. Nucl. Med.* **4**: 312-319 (1963).
J23,190/63

"Plasma from rats, guinea pigs and rabbits exposed to whole-body x-irradiation when in-

jected into 15 day old chick embryos elicits a significant increase in the I¹³¹ uptake of the thyroid." The thyroid and pituitary appear to be essential to elicit this response, whereas the adrenal is not. This phenomenon is not produced by certain others stressors, such as violent exercise or abnormal environmental temperatures.

Leonov, B. V., Lomova, M. A., Rudakov, I. A.: "Connection of radiosensitivity of rats with antioxidative activity of bone marrow and content of unesterified fatty acids in their blood under conditions of 'stress.'" *Radiobiologia* **3**: 518-522 (1963) (Russian). Engl. trans.: *Radiobiology* **3**: 43-49 (1963).
J24,546/63

Experiments on rats "suggested that the increased expenditure of *antioxidants* under conditions of 'stress' may be connected with mobilization of fats from fat depots and that one of the mechanisms of the increase of radiosensitivity of animals in 'stress' can be the oxidation of mobilized lipids." It is assumed that cross-sensitization by stressors to x-rays may result from the loss of antioxidants during stress.

Dedichen, J., Laland, P., Laland, S. G.: "The effect of material prepared from ox blood on cold stress in mice." *Acta Pathol. Microbiol. Scand.* **58**: 219-224 (1963).
E22,664/63

High molecular material prepared from ox blood after exposure to stress significantly reduces the mortality of cold-stressed mice. "It is suggested that the material is related to a hypothetical *resistance factor* mentioned in the work of Raskova and Vanecek."

Schmid, K., Burke, J. F., Debray-Sachs, M., Tokita, K.: "Sialic acid-deficient α_1 -acid glycoprotein produced in certain pathological states." *Nature* **204**: 75-76 (1964).
F22,452/64

Horgan, V. J., Philpot, J. S. L.: "Apparent peroxide ('pro-blue') in organs of irradiated and alarmed mice." *Int. J. Radiat. Biol.* **8**: 165-176 (1964).
G23,405/64

"X-irradiation of mice, or mild alarm, produced a statistically-significant increase in apparent *peroxide*, or rather in an unidentified oxidant called 'pro-blue.'"

Therriault, D. G., Mehlman, M. A.: "Metabolism of *carnitine* in cold-acclimated rats." *Can. J. Biochem.* **43**: 1437-1443 (1965).
J22,857/65

Fessel, W. J.: "Dextran turbidity: acute

distress-phase reaction." *Nature* **205**: 771-773 (1965). F32,709/65

Among patients treated for various types of psychogenic stress, heavy turbidity in the plasma occurs after additional dextran therapy. This response can also be induced experimentally by exposing the subjects to stressful mental experiences. "The presence of so much fibrinogen in the precipitate suggests the possibility that the increased levels of *dextran turbidity* in mental disease and emotional stress result from activation of various serum enzyme systems which cause changes in the internal structure of blood proteins. Plasmin, which affects the fibrinogen molecule, is activated by various agents including emotional stress, physical stress, adrenal steroids, adrenaline, acetylcholine and histamine, and some evidence suggests that plasmin may be under reflex control. Other serum enzymes are also activated by stress, which is known to influence a variety of blood proteins" (20 refs.).

Rowell, L. B., Blackmon, J. R., Martin, R. H., Mazzarella, J. A., Bruce, R. A.: "Hepatic clearance of *indocyanine green* in man under thermal and exercise stresses." *J. Appl. Physiol.* **20**: 384-394 (1965). G30,112/65

Tokita, K., Burke, J. F., Yoshizaki, H., Fischer, S., Schmid, K.: "The constancy of the α_1 -acid glycoprotein variants of normal adults under conditions of severe stress." *J. Clin. Invest.* **45**: 1624-1630 (1966).

F71,312/66

The blood level of α_1 -acid glycoprotein (*orosomucoid*) is increased during various forms of stress, particularly major surgical interventions and pregnancy.

Solomon, G. F., Merigan, T. C., Levine, S.: "Variation in adrenal cortical hormones within physiologic ranges, stress and interferon production in mice." *Proc. Soc. Exp. Biol. Med.* **126**: 74-79 (1967).

F90,260/67

Review of earlier literature and conflicting data suggesting that stress and large amounts of corticoids suppressed the synthesis of *interferon*. Observations on mice failed to show any significant change in interferon production after infection with NDV, although electric shocks administered five hours prior to virus inoculation significantly enhanced interferon production.

Klain, G. J., Whitten, B. K.: "The effect of *orotic acid* and cold stress on lipogenesis in

white adipose tissue." *Biochim. Biophys. Acta* **144**: 174-176 (1967). G49,938/67

Stern, I. J., Cosmas, F., Smith, L.: "Urinary *polyuronide* excretion in man after enzymic dissolution of the chondromucoprotein of the intervertebral disc or surgical stress." *Clin. Chim. Acta* **21**: 181-190 (1968). G60,108/68

Salama, A. I., Goldberg, M. E.: "Effect of several models of stress and amphetamine on brain levels of amphetamine and certain monoamines." *Arch. Int. Pharmacodyn. Ther.* **181**: 474-483 (1969). H19,863/69

Pretreatment with various stressors (cold, trauma, electroshock) greatly increased the sensitivity of rats to *amphetamine*. The stressors did not alter the MAO, NEP, 5-HT or amphetamine levels of the brain, but when amphetamine preceded electroshock its brain concentration was significantly raised. Yet, even then, the change could not account for the increased toxicity of the stimulant (18 refs.).

Irwin, L. N.: "Protein and *N-acetylneurameric acid* changes in subcellular fractions of brains of stimulated rats." *Brain Res. (Amst.)* **15**: 518-521 (1969). J21,245/69

Evans, G. W., Myron, D. R., Wiederanders, R. E.: "Effect of protein synthesis inhibitors on plasma ceruloplasmin in the rat." *Am. J. Physiol.* **216**: 340-342 (1969). H7,807/69

"During a stress reaction, there is an accelerated protein synthesis within the *ceruloplasmin*-synthesizing mechanism."

Osborne, J. C., Meredith, J. H.: "The influence of environmental and surgical stressors on susceptibility to bacterial endotoxin." *Exp. Med. Surg.* **28**: 39-44 (1970).

H39,299/70

In young piglets, "stress associated with transport, weaning, sunburn and a new environment appeared to be responsible for a state of decreased susceptibility to bacterial endotoxin."

Chatterjee, A. K., Ghose, A.: "The role of methylamphetamine on plasma *hexosamine* level under stress." *Jap. J. Pharmacol.* **20**: 439-441 (1970). H46,847/70

Rubin, R. T., Miller, R. G., Clark, B. R., Poland, R. E., Arthur, R. J.: "The stress of aircraft carrier landings. II. 3-Methoxy-4-hydroxyphenylglycol excretion in naval avia-

tors." *Psychosom. Med.* **32**: 589-597 (1970).
G80,364/70

In naval aviators practicing landing on aircraft carriers (which causes considerable stress), the urinary excretion of *3-methoxy-4-hydroxyphenylglycol* (MHPG, a catecholamine metabolite) was increased considerably. "These findings suggest that there may be an accelerated metabolism of brain norepinephrine under conditions of heightened arousal and concentration compared to the normal waking state."

Kudriashov, B. A., Bazazian, G. G., Liapina, L. A., Syshina, N. P.: "Restriction of epinephrine-heparin and fibrinogen-heparin complex formation under stress conditions in the blood of animals maintained on an atherogenic diet." *Kardiologija* **11** No. 10: 58-65 (1971) (Russian).
J20,546/71

Somogyi, A., Kovacs, K.: "Effect of stress on the adrenocorticolytic and carcinogenic action of *7,12-dimethylbenz(a)anthracene*." *Z. Krebsforsch.* **75**: 288-295 (1971).
G70,482/71

Meltzer, H. Y.: "Muscle toxicity produced by phencyclidine and restraint stress." *Res. Commun. Chem. Pathol. Pharmacol.* **3**: 369-382 (1972).
H52,159/72

In rats stressed by restraint, the toxicity of *phenyclidine* (a potent psychotomimetic agent) is greatly enhanced.

Stern, W. C., Hartmann, E. L.: "Reduced amphetamine lethality following chronic stress." *Psychopharmacologia* (Berlin) **23**: 167-170 (1972).
G88,947/72

"Rats stressed for up to four days by desynchronized sleep deprivation or repeated immersions in cold water showed adrenal gland hypertrophy and thymus gland atrophy. These chronically stressed rats survived markedly longer following a high dose of *amphetamine* than non-stressed rats."

Baskin, F., Masiarz, F. R., Agranoff, B. W.: "Effect of various stresses on the incorporation of [³H]orotic acid into goldfish brain RNA." *Brain Res.* (Amst.) **39**: 151-162 (1972).
J20,141/72

Fraser, C. G.: "Surgical stress and *polyuronide* excretion." *Lancet* May 26, 1973, pp. 1197-1198.
H70,992/73

Contrary to earlier claims, the author found no considerable "increase in the urinary excretion of alcian-blue staining cetyl-pyridinium chloride precipitable material" after surgical stress.

Huszti, Z., Sourkes, T. L.: "Uptake and metabolism of *histidine* during stress." *Agents Actions* **3**: 179-180 (1973).
J21,671/73

Funkhouser, D., Goldstein, L.: "Urea response to pure osmotic stress in the aquatic toad *Xenopus laevis*." *Am. J. Physiol.* **224**: 524-529 (1973).
H67,004/73

Kudriashov, B. A., Bazazian, G. G., Liapina, L. A., Sytina, N. P.: "Restriction of complex formation of *heparin* in the blood of aged animals under stress conditions against the background of natural diet." *Kardiologija* **13** No. 11: 118-120 (1973) (Russian).
J23,976/73

Nagler, A. L., Levenson, S. M.: "The nature of the toxic material in the blood of rats subjected to irreversible hemorrhagic shock." *Circ. Shock* **1**: 251-264 (1974).
J19,533/74

In rats exposed to hemorrhagic shock, there appeared a passively transferable *lethal factor* in the plasma that caused death when transfused into animals in mild, reversible shock.

Colmano, G.: "Corticosterone, glucose, ascorbic acid, ceruloplasmin, oxidation-reduction, protein and stress" (abstracted). *Fed. Proc.* **33**: 1447 (1974).
H89,789/74

Brief abstract stating that in various species the *ceruloplasmin* content of the blood decreases during exposure to various stressors. [No details are given (H.S.).]

Chattopadhyay, S., Uniyal, M.: "The interaction of stress and corticosteroid on the hypothalamus as reflected by GABA content." *5th Asia and Oceania Congr. Endocr.*, p. 48. Chandigarh, India, 1974.
H82,064/74

In rats "the negative feedback influence of the circulating corticosteroid and the administration of triamcinolone induced a low GABA concentration in the hypothalamus, whereas the exposure to stress (kind not mentioned) led to a higher GABA concentration than that in the control.... The interaction of stress-induced excitation and negative feedback inhibition owing to increased concentration of corticosteroid may involve GABA in the integrative processes of the hypothalamus."

Huszti, Z., Sourkes, T. L.: "Uptake and metabolism of histidine during stress." *Can. J. Biochem.* **52**: 782-788 (1974).
J17,068/74

Observations with labeled *histidine* in rats

"suggest that the increased histidine decarboxylase activity of stomach that develops under the stress of restraint is associated with a compensatory decrease in the rate of histidine uptake from the blood into the tissues."

Tomashevsky, P., Tannenbaum, M.: "Seromucoid and albumin syntheses after uninephrectomy and partial hepatectomy in the rat." *Proc. Soc. Exp. Biol. Med.* **146**: 921-925 (1974). H89,030/74

The literature and personal observations on rats suggest that stress increases the synthesis of the *seromucoid* fraction of plasma proteins.

Huxtable, R., Bressler, R.: "Taurine concentrations in congestive heart failure." *Science* **184**: 1187-1188 (1974). H86,743/74

The *taurine* concentration in the left ventricle of patients who died of chronic congestive heart failure was about twice the normal level. "Stress-induced hypertension in rats also led to an increase in taurine concentration in the heart, whereas that in skeletal muscle and brain showed no significant alteration when compared to unstressed animals. Spontaneously hypertensive rats of the Wistar-derived Okamoto strain, showed a similar elevation in cardiac taurine compared to age-matched control Wistar rats." The stressors used were noise, light and vibration.

MORPHOLOGIC CHANGES (including macroscopic, light and electron microscopic changes)

[Changes in somatic growth have been discussed under Chemical Changes in the section on Body Weight]

Hypothalamo-Hypophyseal System

The comparatively few papers that deal with morphologic changes induced by stress in the CNS, particularly the hypothalamus, will be discussed under Theories, in connection with other observations on the role of the hypothalamo-hypophyseal system in the mediation of stress reactions.

Singularly few observations deal specifically with structural changes elicited by stress in the hypophysis, although this gland undoubtedly occupies a central role in the regulation of hormonal defense mechanisms in the G.A.S. Our earlier studies in the rat showing that, during the alarm reaction, nuclear pyknoses appear in some circumscribed regions of the anterior lobe, while other parts may remain normal. After chronic treatment with various types of stressors, an increase in the number of basophils was frequently observed. Many of these were found to assume a "signet ring cell" appearance, not unlike that of "castration cells." This change may have been related to the gonadal atrophy that is induced by chronic exposure to stressors.

In the intermediate lobe, the epithelial cells tend to degenerate during the alarm reaction, and the borderline between the middle and posterior lobe may become indistinct. Occasionally, one has the impression that debris of degenerated middle lobe cells, and perhaps even anterior lobe basophils, invade the posterior lobe. In the latter, vacuolization of the pituicytes with the development of "foam cells" is not uncommon.

Hypertrophy and hyperplasia of the basophils have also been observed by other investigators in rats exposed to stressors, but in all these experiments it was very difficult to separate specific from stress-induced lesions. In any event, no particularly significant

contribution has been made to this topic since the publication of my last series of stress monographs.

Hypothalamus

(See also our earlier stress monographs, p. xiii, and cf. Nervous Mechanisms under Theories)

Fantini, F., Fabiani, F., Cagnoni, M.: "Morpho-functional changes in the hypothalamic nuclei following various stimuli. I. Morphological changes observed in the supraoptic, paraventricular and tuberal nuclei following water overload and cold stress in the white rat." *Rass. Neurol. Veg.* **14**: 397-409 (1959). J24,329/59

Fantini, F., Fabiani, F., Cagnoni, M.: "II. Effect of simultaneous exposure to cold stress and water overload on the morphology of the hypothalamic nuclei in the white rat." *Rass. Neurol. Veg.* **14**: 410-416 (1959).

J24,330/59

Fantini, F., Fabiani, F., Cagnoni, M.: "V. Morphological changes observed in the nuclei of the tuber following cold stress and following treatment with thyroxin and methylthiouracil." *Rass. Neurol. Veg.* **14**: 496-500 (1960). J24,331/60

Kivalo, E., Rinne, U. K.: "The relation between the hypothalamic neurosecretion and the corticotrophin release in experimental conditions." *Acta Endocrinol. (Kbh.)* **34**: 8-18 (1960). J23,117/60

Rodeck, H., Braukmann, R.: "Neurosektion—Stress—Adaptation. I. Mitteilung. Die Wirkung von Schmerz auf das neurosekretorische System" (Neurosecretion—stress—adaptation. I. The effect of pain on the neurosecretory system). *Z. Gesamte Exp. Med.* **141**: 33-44 (1966). F68,675/66

In rats, the stress produced by formalin injections led to depletion of neurosecretory granules in both the neurohypophysis and, to a lesser extent, in certain hypothalamic nuclei.

Krisch, B.: "Different populations of granules and their distribution in the hypothalamo-neurohypophysial tract of the rat under various experimental conditions. I. Neurohypophysis, nucleus supraopticus and nucleus paraventricularis." *Cell Tissue Res.* **151**: 117-140 (1974). J16,399/74

Hypophysis (Anterior, Middle, and Posterior Lobes)

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

First detailed description of the three stages of the G.A.S. and the concept of "adaptation energy," with an extensive and illustrative characterization of the morphologic lesions produced by stress (especially in the hypophysis, adrenals, thymicolumphatic apparatus, pancreas and gastrointestinal tract), and its effect upon inflammation (anaphylactoid edema).

Dhom, G., Scherer, H. P.: "Stress-Reaktionen am Hypophysenvorderlappen der Ratte" (Stress affecting the anterior lobe of the hypophysis in rats). *Virchows Arch. [Pathol. Anat.]* **336**: 368-382 (1963). D63,599/63

Morphologic studies on the anterior lobe changes indicative of TTH and ACTH secretion that occur in rats exposed to the stressor effect of swimming.

Polenov, A. L., Balonov, L. I.: "Morphological analysis of changes in the neurosecretory elements of the neurohypophysis of albino rats in pain stimulation and aminazin action." *Probl. Endokrinol.* **9** No. 5: 40-46 (1963) (Russian). E27,398/63

Akmaiev, I. G., Donath, T.: "The role of sympathetic innervation of the hypophysis in the transport of neurosecretory substances into the blood circulation." *Probl. Endokrinol.* **12** No. 6: 90-94 (1966) (Russian).

F74,162/66

Fluorescence studies on the neurohypophysis of the rat to determine NEP and dopamine levels within terminal sympathetic nerve fibers. "In acute stress the noradrenalin and the dopamine content seems to be increased in the terminal sympathetic nerve fibers. Catecholamine content in the sympathetic nerve fiber terminals of the pars posterior of the neurohypophysis and its increase in acute stress are discussed in connection with the transport of the neurosecretion hormonally-active substances into the blood circulation."

Rodeck, H., Braukmann, R.: "Neurosekretion—Stress—Adaptation. I. Mitteilung. Die Wirkung von Schmerz auf das neurosekretorische System" (Neurosecretion—stress—adaptation. I. The effect of pain on the neurosecretory system). *Z. Gesamte Exp. Med.* **141**: 33–44 (1966). F68,675/66

In rats, the stress produced by formalin injections led to depletion of neurosecretory granules in both the neurohypophysis and to a lesser extent in certain hypothalamic nuclei.

Braukmann, R., Rodeck, H.: "Neurosekretion—Stress—Adaptation. II. Mitteilung. Die Wirkung von körperlicher Anstrengung und Kälte auf das neurosekretorische System" (Neurosecretion—stress—adaptation. II. The effect of physical exertion and cold on the neurosecretory system). *Z. Gesamte Exp. Med.* **141**: 45–54 (1966). F68,676/66

Swimming and exposure to cold cause a diminution of neurosecretory material in the posterior lobe, but after a few days of adaptation this change disappears.

Soler-Vinolo, J., Lopez-Soler, J., Robles-Ceres, R.: "Influencia del 'Dipiridamol' sobre las transformaciones morfológico-estructurales de la adenohipófisis en glándulas denervadas y sin denervar, de animales sometidos a 'stress'" (The influence of 'Dipyridamol' on the morphologic-structural transformations of the denervated and nondenervated adenohypophysis of animals under 'stress'). *Rev. Clin. Esp.* **105**: 372–380 (1967). J22,104/67

Burlet, C.: "Variations des activités phosphatasiques acides du système hypothalamo-neurohypophysaire du lérot dans différentes conditions expérimentales" (Acid phosphatase activity in the hypothalamic-neurohypophyseal system of the lerot [garden door-

mouse] under various conditions). *C.R. Soc. Biol. (Paris)* **163**: 486–488 (1969).

H15,751/69

In the lerot (*Eliomys quercinus L.*), stress (sound, ether) enhances the acid phosphatase activity in the ME and neurohypophysis with a simultaneous increase in vasopressin discharge.

Baba, I.: "L'aspect histologique de l'adenohypophyse chez les porcelets hypotrépiques" (The histology of the adenohypophysis in stressed piglets). *Zentralbl. Veterinaermed. [A]* **17**: 413–421 (1970). H45,310/70

Lehrer, H. Z.: "Angiographic visualization of the posterior pituitary and clinical stress." *Radiology* **94**: 7–18 (1970). H43,723/70

In man, the posterior pituitary "may occasionally be visualized on the lateral view of carotid arteriograms, generally under conditions of clinical stress." Otherwise, it usually appears only as a homogeneous stain.

Valls, G. B.: "Citología adenohipofíssaria en el stress de hambre y sed" (Adenohypophysis cytology in starvation and thirst stress). *An. Anat.* **20**: 409–418 (1971). G95,749/71

In guinea pigs, rats and cats, exposure to the stressor effects of starvation and thirst causes cytologic changes in the adenohypophysis which vary according to the species. In cats the entire gland is sometimes replete with vesicles.

Mikulaj, L., Mitro, A.: "Histologic changes in the adenohypophysis of rats in the course of adaptation to a repeated stress." *Bratisl. Lek. Listy* **58**: 282–288 (1972) (Slovak). J20,221/72

Wegiel, J., Waniewski, E.: "The ultrastructure of the rat adenohypophysis in stress." *Folia Histochem. Cytochem. (Krakow)* **11**: 301–302 (1973). J21,580/73

Adrenals

Loss of lipids from the adrenal cortex and a loss of chromaffin material from the medulla were among the first morphologic changes noted in animals and man exposed to what we would now call "stressors." Such observations were published even before the stress syndrome as such had been recognized, and the alterations were generally ascribed to the specific effects of whatever agents induced them. After chronic exposure to stressors, the initial loss of cortical lipids usually gives way to replenishment of the

secretory granules in the stage of resistance, at which time their amount may even exceed the initial value; but eventually, during the stage of exhaustion, a secondary loss of lipids ensues. These light microscopic changes (usually detected by special stains, such as Sudan red or osmic acid) have also been confirmed by EM. They are generally associated with a corresponding loss of stainable cholesterol and ascorbic acid granules. According to some investigators, it is possible to demonstrate parallel variations of adrenal KS by special histochemical techniques.

These morphologic indicators of increased secretory activity are associated with hyperplasia and mitotic divisions of the adrenocortical cells, especially in the fasciculata.

In the event of exposure to various severe stressors—especially extensive burns and certain bacterial infections—the adrenocortical changes may be accompanied by more or less widespread necrosis, and even bleeding. However, some of these changes, particularly those induced by bacterial toxins, may be modified by the specific actions of the stressors, for example, by the special vasotoxic effects that cause adrenal hemorrhages (as in the Waterhouse-Friderichsen syndrome).

In the case of chronic exposure to stressors, adrenal adenomas or at least adenoma-like enlargements of capsular accessory adrenals are noted in various species, including man. In spontaneously hypertensive rats, such nodule formation is especially common.

EM studies on squirrel monkeys revealed depletion and disorientation of membranes, both of the overdeveloped SER and mitochondria, with a loss of ribosomes, lysosomes, and, to some degree, intracellular lipids.

The infiltration of the adrenals by hemopoietic elements in tumor-bearing rats as well as in those injected with necrotic tissue material is undoubtedly not merely a manifestation of stress, but presumably a specific response to certain toxic materials liberated from dying tissues.

The frequently-encountered statement that during the stage of exhaustion, the collapse of resistance is secondary to a breakdown of adrenal tissue is far from being proven by experimental observations. Although chronic stress may cause degenerative changes or even necroses in the adrenal glands, these are rarely of sufficient intensity not to be amply compensated for by the characteristic hypertrophy and hyperplasia.

The changes in the adrenal medulla are much less polymorphic and mainly limited to evidence of an EP discharge.

In birds, the cortical and medullary cells are intermixed, but there is some evidence that certain regions of the avian interrenal (cortical) tissue may correspond to the zones of the mammalian adrenal cortex. Hypophysectomy causes only a slight decrease in the weight of the pigeon adrenal, mainly as a result of interrenal cell atrophy near the center of the gland.

Stress elicits hypertrophy and hyperplasia of both interrenal and chromaffin tissue, even in hypophysectomized pigeons. These and other observations suggest that the interrenal (cortical) cells in birds are much less dependent upon the pituitary than in mammals.

Occasionally, entire cortical cells have been found within the sinusoids of the adrenals, a phenomenon interpreted as holocrine secretion. This has been noted in the rat, and particularly in the giraffe; it may be enhanced by stress.

Stress-induced adrenal changes have been described in virtually every animal species and after exposure to all types of stressor agents. However, for these, the reader is referred to the abstract section.

Adrenals

(See also our earlier stress monographs, p. xiii)

Babes, V., Jonesco, V.: "Études sur la diminution de la graisse surrenale dans des états pathologiques" (Studies of adrenal lipid decrease in pathologic states.) *C.R. Soc. Biol. (Paris)* **65**: 267-269 (1908).

46,790/08

In rabbits, both diminution and redistribution of adrenal lipids were observed after inanition, various infectious diseases, or repeated injections of EP. Similar changes were noted in humans following death from myocarditis, tuberculosis, certain types of nephritis, enteritis, cholecystitis and pancreatitis. The significance of these changes was not analyzed.

Greenwald, H. M., Eliasberg, H.: "The pathogenesis of death from burns." *Am. J. Med. Sci.* **171**: 682-696 (1926).

B26,710/26

In man and rabbits, extensive burns cause an initial state of shock with hyperglycemia, followed by hypoglycemia and adrenal changes. This process is interpreted as initial stimulation followed by exhaustion.

McEuen, C. S., Selye, H.: "Histologic changes in the adrenals of tumor-bearing rats." *Am. J. Med. Sci.* **189**: 423-424 (1935).

36,705/35

In rats bearing large necrotizing Walker tumors, the adrenals were enlarged and contained many lymphocytic and leukocytic infiltrations. Since similar islands are occasionally seen after various infections, they cannot be regarded as specific for tumors.

Hilgenfeldt, O.: "Die Behandlung und die pathogenetischen Grundlagen der Verbrennungen" (The pathogenesis and treatment of burns). *Ergeb. Chir. Orthop.* **29**: 102-210 (1936).

38,008/36

Review, especially of the old literature, and personal observations on the histologic changes induced by severe surface burns in man. They may be due to shock or to the resorption of protein decomposition products and bacteria from the damaged areas. "It may be assumed that after several weeks exhaustion of the adrenals may become equivalent to their total elimination."

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937).

38,798/37

First detailed description of the three stages of the G.A.S. and the concept of

"adaptation energy," with an extensive and illustrative characterization of the morphologic lesions produced by stress (especially in the hypophysis, adrenals, thymicolympathic apparatus, pancreas and gastrointestinal tract), and its effect upon inflammation (anaphylactoid edema).

Dosne, C., Dalton, A. J.: "Changes in the lipid content of the adrenal gland of the rat under conditions of activity and rest." *Anat. Rec.* **80**: 211-217 (1941).

81,198/41

In rats, various stressors (cold, formaldehyde) cause an initial hypertrophy and lipid loss from the adrenal cortex during the alarm reaction. This is followed by lipid storage during the resistance stage, and a second period of lipid loss during the stage of exhaustion of the G.A.S.

Dohan, F. C.: "Effect of low atmospheric pressure on the adrenals, thymus and testes of rats." *Proc. Soc. Exp. Biol. Med.* **49**: 404-408 (1942).

A37,744/42

"Rats exposed to low atmospheric pressure for more than 2 days exhibited a significant increase in adrenal weight and a significant decrease in the weight of the thymus and testes. This pattern is similar to that found following other forms of stress." These observations are in consonance with the "pituitary shift" theory.

Tonutti, E.: "Die Umbauvorgänge in den Transformationsfeldern der Nebennierenrinde als Grundlage der Beurteilung der Nebennierenrindenarbeit" (The structural reorganization of the transformation fields in the adrenal cortex as the basis of determination of its activity). *Z. Mikrosk. Anat. Forsch.* **52**: 32-86 (1942).

A63,786/42

Very detailed histologic studies on the manifestations of adrenocortical activity, based on ascorbic acid content and structural reorganizations.

Swingle, W. W., Remington, J. W.: "The role of the adrenal cortex in physiological processes." *Physiol. Rev.* **24**: 89-127 (1944).

85,089/44

Review on the functions of the adrenal cortex, with special reference to its role in resistance to stress during the G.A.S. (531 refs.).

Ludewig, S., Chanutin, A.: "The adrenal cholesterol and ascorbic acid contents after injury." *Endocrinology* **41**: 135-143 (1947).

B2,706/47

In rats, pentobarbital anesthesia and ther-

mal injury, as well as nitrogen and sulphur mustards, cause adrenal enlargement, usually with an initial decrease followed by an increase in adrenal ascorbic acid and cholesterol.

Nichols, J.: "Quantitative histochemical changes in the adrenal following exposure to anoxia." *J. Aviat. Med.* **19**: 171-178 (1948).

B26,390/48

In rats, anoxia depletes the adrenal cholesterol esters before the free cholesterol. The other lipid fractions disappear even more slowly. Conversely, cholesterol esters recover last upon interruption of anoxia. The changes are ascribed to the G.A.S. (29 refs.).

Dugal, L. P., Thérien, M.: "The influence of ascorbic acid on the adrenal weight during exposure to cold." *Endocrinology* **44**: 420-426 (1949).

B36,429/49

In guinea pigs as in rats, exposure to cold elicits all the manifestations of the alarm reaction, including ascorbic acid depletion. Treatment with ascorbic acid inhibits adrenal enlargement and raises resistance to cold.

Selye, H., Stone, H.: *On the Experimental Morphology of the Adrenal Cortex*, p. 105. Springfield, Ill.: Charles C Thomas, 1950.

B30,224/50

Brief monograph on the structure and interpretation of various adrenal changes with special reference to those induced by stress.

Mandl, A. M., Zuckerman, S.: "The reaction of the ovaries and adrenal glands of female rats to ovarian and muscle homografts." *J. Endocrinol.* **7**: 344-348 (1951).

B63,009/51

In rats, homografts of ovarian or muscle tissue caused adrenal and ovarian enlargement. The adrenals (but not the ovaries) were also hypertrophied following Avertin anesthesia. The possibility is considered that these reactions may be manifestations of stress.

Rabinovici, N.: "The effect of stress upon the ketosteroid and non-carbonyl lipid content of the adrenal cortex of the rat." *Endocrinology* **49**: 579-588 (1951).

B64,021/51

In rats, various stressors (cold, x-rays, starvation) and ACTH caused depletion of histochemically demonstrable adrenal KS.

Bullough, W. S.: "Stress and epidermal mitotic activity. I. The effects of the adrenal hormones." *J. Endocrinol.* **8**: 265-274 (1952).

B72,094/52

In rats the stress of overcrowding causes a more pronounced increase in the size of the adrenal medulla than of the cortex. Simultaneously, the epidermal mitotic rate decreases by 60 percent. "It is suggested that the antimitotic effects of stress may be due to a high rate of secretion of either or both of these adrenal hormones" (corticoids and catecholamines). All these reactions are regarded as manifestations of the G.A.S.

Woods, J. W.: "Differences in adrenal response to adverse conditions in wild and domesticated Norway rats." *Fed. Proc.* **12**: 159 (1953).

B78,653/53

Wild and domesticated Norway rats were exposed to various stressors (cold, noise, fighting). "The results show that the wild rat endures the conditions of these experiments without a decrease in the amount of assayable ascorbic acid or stainable lipid in his adrenal cortex while results with the white rat are in agreement with the numerous reports of ascorbic acid and lipid depletion following similar stimulation." Also, the adrenals of the wild rat are less sensitive than those of domesticated rats to traumatization of the intestines, hemorrhage, ether anesthesia, unilateral adrenalectomy or even ACTH administration, as indicated by ascorbic acid depletion.

Bahn, R. C., Glick, D.: "Studies in histochemistry: effects of stress conditions, ACTH, cortisone and desoxycorticosterone on the quantitative histological distribution of ascorbic acid in adrenal glands of the rat and monkey." *Endocrinology* **54**: 672-684 (1954).

B94,671/54

In monkeys (*M. rhesus*, *M. cynomolgus*) and in rats, various stressors (cold, struggling, ether anesthesia, hypoxia, and hyperthermia) cause a decrease in the ascorbic acid content of the outer fasciculata and reticularis zones of the adrenal cortex. Intrapерitoneal ACTH produced the same result.

Heroux, O., Hart, J. S.: "Comparison of four indices of adrenal activity in rats acclimated to 30°, 15°, 1°C." *Am. J. Physiol.* **178**: 445-448 (1954).

B98,996/54

Gonzalo-Sanz, L. M.: "Resistencia inespecífica del organismo y lesiones corticosuprarenales" (Nonspecific systemic resistance [alarm situation] and adrenocortical lesions). *Rev. Esp. Fisiol.* **12**: 33-41 (1956).

C19,333/56

Macchitella, E., Crucitti, F.: "Modificazioni surrenaliche in corso di ustioni speri-

mentali. Azione dello stress sull'attività mitotica e sul comportamento degli acidi nucleinici" (Adrenal modifications during experimental burns. Effect of stress on mitosis and nucleic acids). *Chir. Patol. Sper.* **4**: 655-673 (1956). C41,613/56

Symington, T., Davidson, J. N.: "The effect of exogenous ACTH and conditions of stress on the chemical composition of the human adrenal gland." *Scott. Med. J.* **1**: 15-31 (1956). C12,943/56

Sackler, A. M., Weltman, A. S., Bradshaw, M., Jurtshuk, P. Jr.: "Endocrine changes due to auditory stress." *Acta Endocrinol.* (Kbh.) **31**: 405-418 (1959). C71,159/59

In rats, repeated exposure to strong auditory stimulation causes adrenal enlargement, ovarian atrophy and diminution in the weight of the uterus and liver. Food consumption is also markedly reduced.

Jurtshuk, P. Jr., Weltman, A. S., Sackler, A. M.: "Biochemical responses of rats to auditory stress." *Science* **129**: 1424-1425 (1959). C68,703/59

In rats, prolonged, intense auditory stimulation reduced the glutathione level of the blood, and simultaneously caused an increase in the weight, ascorbic acid and cholesterol content of the adrenals.

Kerckhove, D. van de: "Variation de la teneur en acide désoxyribonucléique dans les cellules de la granulosa chez le rat lors du stress par le froid" (Variation in the desoxyribonucleic acid content of the granulosa cells of rats during cold-induced stress). *Ann. Endocrinol.* (Paris) **20**: 893-896 (1959). C85,242/59

Hill, M., Dvořák, K., Pospíšil, M.: "Stress activation of adrenal glomerulosa." *Nature* **183**: 1819 (1959). C73,699/59

In rats, stress induced by formalin causes neutrophilic leukocytosis, lymphopenia, eosinopenia and simultaneous activation of the zona glomerulosa in the adrenals.

Árvay, A., Balázs, L., Jakubecz, S., Takács, I.: "Die Wirkung belastender Nervenreize auf die Struktur und Funktion der Nebennierenrinde" (The effect of nerve irritation on the structure and function of the adrenal glands). *Endokrinologie* **39**: 15-35 (1960). C88,352/60

Lorthioir, J.: "Étude expérimentale et traitement des brûlés" (Experimental study

and treatment of burns). *Acta Chir. Belg.* **60**: 1-88 (1961). D11,420/61

Monograph on the treatment of burns, with special sections on adrenal lesions in severely burned patients (187 refs.).

Roels, H., Lagasse, A.: "Influence of cold stress on the dry weight of the cell nuclei of the adrenal medulla of the white rat." *Exp. Cell. Res.* **23**: 408-409 (1961). D90,357/61

Miller, R. A.: "The role of corticotrophin and of stress in the biphasic changes in fascicular nucleolar size in the rat adrenal." *Acta Endocrinol.* (Kbh.) **40**: 364-374 (1962). E99,481/62

Ohno, T.: "The effects of stress and ACTH-stimulus on the X-zone of the mouse adrenals with and without hypophysectomy." *Tohoku J. Exp. Med.* **77**: 195-203 (1962). D31,888/62

Schwarz, W., Merker, H.-J., Suchowsky, G.: "Elektronenmikroskopische Untersuchungen über die Wirkungen von ACTH und Stress auf die Nebennierenrinde der Ratte" (Electron microscopic studies on the effects of ACTH and stress on the adrenal cortex in rats). *Virchows Arch. [Pathol. Anat.]* **335**: 165-179 (1962). D34,734/62

Deane, H. W.: "The anatomy, chemistry and physiology of adrenocortical tissue." In: Eichler, O. and Farah, A., *Handbuch der Experimentellen Pharmakologie*, Vol. XIV, Part 1, pp. 1-185. Berlin: Julius Springer, 1962. D53,082/62

Extensive chapter on the anatomy, chemistry and physiology of the adrenal cortex, with detailed discussions on the effect of stress (several hundred refs.).

Symington, T.: "Morphology and secretory cytology of the human adrenal cortex." *Br. Med. Bull.* **18**: 117-120 (1962). D23,887/62

Review of the literature and personal observations on the histologic changes produced by stress in the adrenal of man.

Brenner, R. M.: "Radioautographic studies with tritiated thymidine of cell migration in the mouse adrenal after a carbon tetrachloride stress." *Am. J. Anat.* **112**: 81-86 (1963). D56,443/63

In mice stressed by subcutaneous carbon tetrachloride, ^3H -thymidine was given to study its incorporation into DNA-synthesizing cells by stripping film autoradiography.

"Labeled cells were initially distributed at the periphery of the cortex scattered between the glomerulosa and the upper fasciculata, but within four to six weeks heavily labeled cells were found deep within the cortex indicating that centripetal migration had occurred. The upper fasciculata was judged to be a region of maximum cell turnover from which cells had migrated centripetally, but migration of cells from the glomerulosa seemed to be minimal."

Jonek, J., Konecki, J.: "Über die histochemische Lokalisation einiger Enzyme in Rattennebennieren nach intraperitonealer Implantation autogener Organe" (On the histochemical localization of enzymes in the rat adrenal gland following intraperitoneal implantation of autogenous organs). *Z. Mikrosk. Anat. Forsch.* **70**: 536-547 (1963).
G14,659/63

Detailed description of the histochemical changes that occur in rat adrenals after intraperitoneal implantation of autogenous organs. Such alterations are considered to be characteristic of the G.A.S., since they correspond to those produced by other stressors.

Wolman, M.: "Lipides" (Lipids). In: Graumann, W. and Neumann, K., *Handbuch der Histochemie*, Vol. V, Part 2, p. 750. Stuttgart: G. Fischer Verlag, 1964.
E4,270/64

A chapter on lipids in which a special section is devoted to histochemical changes in adrenocortical lipids during stress. An extensive source of the relevant literature.

Pauly, J. E.: "An interpretation of the structural variations seen in the human adrenal cortex in health and disease." *Bull. Tulane Med. Fac.* **24**: 251-264 (1965).
G29,012/65

The adrenals of forty-nine persons who died accidentally were compared with those of 243 patients who succumbed to a variety of systemic diseases. The changes found only in the sick persons are described in detail. They are allegedly "produced either (1) directly by the stress of the systemic disease, (2) by modifications of the gland itself which allows it to increase its efficiency in combatting the stress or (3) by conditions transient between normal and more abnormal degenerative states. These possibilities are discussed in light of the General Adaptation Syndrome" (32 refs.).

Vecsei, P., Csalay, L.: "Vergleichende Untersuchungen über die Corticosteroidbildung

und das morphologische Verhalten der Nebennieren bei chronischen Reizen ausgesetzten Tieren" (Comparative study of corticosteroid formation and the morphologic behavior of the adrenal glands in animals exposed to chronic stress). *Z. Vitamin, Hormon. Fermentforsch.* **14**: 57-65 (1965).

F39,102/65

In rats, the enlargement of the adrenals does not necessarily parallel corticosterone production under the influence of various stressors.

Gabbiani, G., Selye, H., Tuchweber, B.: "Adrenal localization of a thrombohemorrhagic phenomenon." *Endocrinology* **77**: 177-182 (1965).
G19,450/65

In rats pretreated with ACTH, glucocorticoids or restraint, a single intravenous injection of thorium dextrin (an RES-blocking agent) produces thrombohemorrhagic necrosis of the adrenals and liver resembling the Schwartzman-Sanarelli phenomenon.

Murgaš, K., Jonec, V.: "Distribution of ascorbic acid in the adrenal cortex of rats under cold stress." *Biológia* (Bratislava) **20**: 862-866 (1965) (Slovak).
J24,288/65

Ameli, M., Mora, E.: "Effetti della stimolazione acustica prolungata sulle ghiandole surrenali del ratto" (Effects of prolonged acoustic stimulation on the adrenal glands of the rat). *Clin. Otorinolaringol.* **18**: 211-252 (1966).
J24,290/66

Detailed discussion of the histologic changes produced in the adrenals of rats by the stress of acoustic overstimulation.

Pirozynski, T., Bratiano, A., Sneer, A., Odan, O., Paulian, E.: "La morphologie et l'histochimie de la surrénales chez les cobayes femelles en gestation ayant subi le stress non-spécifique (électroconvulsion) et spécifique (ACTH)" (The morphology and histochemistry of the adrenal gland in pregnant female guinea pigs exposed to nonspecific [electroconvulsion] and specific [ACTH] stress). *Ann. Endocrinol.* (Paris) **27**: 429-438 (1966).
F74,373/66

Voigt, J.: "Adrenal lesions in medico-legal autopsies." *J. Forensic Med.* **13**: 3-15 (1966).
G42,472/66

Snapper, A. G., Schoenfeld, W. N., Locke, B.: "Adrenal and thymus weight loss in the food-deprived rat produced by random ratio punishment schedules." *J. Comp. Physiol. Psychol.* **62**: 65-70 (1966).
G44,900/66

Kvetňanský, R., Mitro, A., Mikulaj, L., Hocman, G.: "Catecholamines of the adrenal medulla and the morphologic changes of the adrenal medulla in the course of adaptation to repeated immobilization stress." *Bratisl. Lek. Listy* **46**: 35-41 (1966) (Slovak).

F72,514/66

Khamidov, D. K., Voitkevich, A. A., Zufarov, K. A., Ovchinnikova, G. A.: *The Adrenal Gland (Experimental-Morphologic Investigation)*, p. 358. Tashkent: Fan, 1966 (Russian).

E7,238/66

Monograph on the normal and pathologic histology of the adrenal with sections on its response to stressors. Special attention is given to the Russian literature (several hundred refs.).

Miller, R. A.: "Regional responses of interrenal tissue and of chromaffin tissue to hypophysectomy and stress in pigeons." *Acta Endocrinol. (Kbh.)* **55**: 108-118 (1967).

F79,962/67

In pigeons the cortical and medullary cells of the adrenals are intermixed, and hence three distinct cortical zones, such as are seen in mammals, cannot be distinguished. Yet there is some evidence that certain regions of the avian interrenal tissue may be homologous with the mammalian cortical zones. Hypophysectomy causes only a slight decrease in the weight of the pigeon adrenal, and this is due mainly to atrophy of interrenal (cortical) cells near the center of the gland. Stress (repeated injections of formalin on a low sodium diet) elicits hypertrophy and hyperplasia of both interrenal and chromaffin tissue, even in hypophysectomized pigeons.

Leites, F. L., Semashko, M. I., Zakharova, N. S.: "The dynamics of morphological changes of the adrenal cortex after anti-pertussis vaccination." *Biull. Èksp. Biol. Med.* **66** No. 10: 115-119 (1968) (Russian).

J22,840/68

Arai, S., Suzuki, T., Nokubi, K., et al.: "Histochemical changes in the kidneys and suprarenal glands of rats subjected to stress." *J. Tokyo Med. Coll.* **26**: 239-244 (1968).

J24,400/68

Panarettto, B. A., Ferguson, K. A.: "Comparison of the effects of several stressing agents on the adrenal glands of normal and hypophysectomized sheep." *Aust. J. Agric. Res.* **20**: 115-124 (1969).

J24,295/69

Adrenocortical hemorrhages are seen in intact, but not in hypophysectomized and

ACTH-maintained sheep, following treatment with epinephrine, endotoxin or metyrapone.

Sildjajeva, R., Rozhold, O., Havlíček, V.: "Changes in the adrenal cortex of rabbits in emotional stress." *Activ. Nerv. Sup. (Praha)* **11**: 58-60 (1969).

J23,083/69

Symington, T.: "Part I. The adrenal cortex." In: Symington, T., *Functional Pathology of the Human Adrenal Gland*, pp. 1-216. Edinburgh and London: E & S Livingstone, 1969.

E9,166/69

Monograph on the functional morphology of the human adrenal with a special section on its reaction to stressors. Numerous excellent EM photographs (several hundred refs.).

Berchtold, J. P.: "Contribution à l'étude ultrastructurale des cellules interrénales de Salamandra salamandra L. (Amphibien Urodèle). II. Action de l'ACTH endogène" (A contribution to the ultrastructural study of the interrenal cells of Salamandra salamandra L. [Urodele Amphibian]. II. The effects of endogenous ACTH). *Z. Zellforsch.* **110**: 517-539 (1970) (about 50 refs.).

G79,811/70

Panarettto, B. A., Vickery, M. R.: "The rates of plasma cortisol entry and clearance in sheep before and during their exposure to a cold, wet environment." *J. Endocrinol.* **47**: 273-285 (1970).

H28,932/70

In sheep exposed to cold, "decreased cortisol clearance rates did not appear to contribute to the great increases in plasma concentration until rectal temperature was about 34°." Curiously, the adrenal cortex and liver of the sheep were heavily infiltrated with fat after severe hypothermia.

Trofimova, G. A., Kirillov, O. I.: "Mitotic activity and volumes of nuclei in zona fasciculata of the adrenal cortex under repeated irritation of rats with electric current." *Tsitologija* **13** No. 1: 112-114 (1971) (Russian).

J23,888/71

Penney, D. P., Brown, G. M.: "The fine structural morphology of adrenal cortices of normal and stressed squirrel monkeys." *J. Morphol.* **143**: 447-466 (1971).

G85,767/71

In squirrel monkeys, EM observations show a close correlation between hyperdevelopment of the agranular reticulum and increased plasma cortisol levels during the stress of chair restraint. There is also "depletion and disorientation of membranes both of the agranular endoplasmic reticulum and

mitochondria and a loss of ribosomes, lysosomes and, to some degree, intracellular lipid."

Rhodin, J. A. G.: "The ultrastructure of the adrenal cortex of the rat under normal and experimental conditions." *J. Ultrastruct. Res.* **34**: 23-71 (1971). G82,359/71

EM changes in the adrenal cortex of the rat following inhibition by dexamethasone or stimulation by ACTH. These studies give certain indications concerning the interpretation of stress-induced alterations (127 refs.).

Rantsios, A.: "Some observations on the histology of the adrenal zona glomerulosa in Pietrain pigs." *Vet. Rec.* **90**: 369-370 (1972). J20,516/72

Nvota, J., Lamošová, D., Fáberová, A.: "Critical periods in the development of chicks." *Physiol. Bohemoslov.* **22**: 337-343 (1973). J21,555/73

The stress of restraint during a critical period of about three to four weeks after hatching produced a maximal decrease in thyroid activity in adulthood and a significant drop in the BMR of the chick. "The critical phase for regulation of the function of the pituitary-adrenal and pituitary-gonad axis was found to be the period between the 15th and 21st day after hatching. Exposure to stress in this phase caused a significantly greater reaction of the adrenals to stress situations in the adult hens and significantly stimulated sexual maturation (egg-laying)."

Sugihara, H., Kawai, K., Tsuchiyama, H.: "Pathology of intracortical nodules in rat adrenal glands, especially on their fine-structure." *Acta Pathol. Jap.* **23**: 253-260 (1973). J7,946/73

In rats exposed to the stressor effect of a cold or hot environment, numerous intracortical adenomas appear in the adrenals. Their EM structure is described. In spontaneously hypertensive rats, such nodule formation is particularly frequent.

Lunderquist, A., Voegeli, E.: "Angiographic findings in the adrenals during stress." *Am. J. Roentgenol.* **119**: 560-563 (1973). J8,173/73

Angiographic studies during stress secondary to hemorrhage or trauma showed a marked accumulation of contrast medium in the human adrenal after injection into the celiac artery. In three patients, there was also adrenal hemorrhage.

Koerker, R. L., Hahn, W. E., Schneider,

F. H.: "Electron translucent vesicles in adrenal medulla following catecholamine depletion." *Eur. J. Pharmacol.* **28**: 350-359 (1974). H93,911/74

In rabbits, insulin-induced hypoglycemia produces a typical stress reaction with characteristic changes in the adrenal medulla. From EM observations, "it is concluded that the translucent vesicles arise from dense core chromaffin vesicles and decrease in number as the catecholamine stores are replenished."

Weyrauch, D.: "Über das Vorkommen von Parenchymzellteilen im Sinusoidsystem, im subendothelialen und interstitiellen Raum der Nebennierenrinde der Masaigiraffe (Giraffa camelopardalis tippelskirchii)" (The occurrence of parenchymal cell fractions in sinusoids and in the subendothelial and interstitial space of the adrenal cortex in Masai giraffes [Giraffa camelopardalis tippelskirchii]). *Anat. Anz.* **135**: 267-276 (1974). J13,520/74

EM studies on Masai giraffes showed that certain adrenocortical cells can be found free within the sinusoids. Such a holocrine type of secretion may be enhanced by exposure to stress, although this has not yet been proven.

Faussone-Pellegrini, M. S.: "Ultrastruttura dello spazio pericapillare della corticosurrene di ratti esposti alle basse temperature" (Ultrastructure of the adrenal cortex pericapillary space in rats exposed to low temperature). *Boll. Soc. Ital. Biol. Sper.* **50**: 250-252 (1974). J22,854/74

Clark, O. H., Hall, A. D., Schambelan, M.: "Clinical manifestations of adrenal hemorrhage." *Am. J. Surg.* **128**: 219-224 (1974). J15,481/74

Al-Lami, F., Farman, N.: "Ultrastructural and histochemical study of the adrenal medulla in normal and cold-stressed Syrian hamsters." *Anat. Rec.* **181**: 113-129 (1975). J19,965/75

Ray, P. K., Choudhury, S. R.: "Response of solitary adrenal gland to surgical stress." *Histochem. J.* **7**: 127-137 (1975). J24,030/75

Histochemical observations of various enzymes showed that trauma produces essentially the same response in intact and unilaterally adrenalectomized rats. However, after this operation, the enzymatic responses in the remaining gland are significantly delayed by removal of the contralateral gland. "In experiments using ACTH, the overall pat-

tern of esterase activity shows little deviation from that observed in untreated cases in both groups of animals. The findings indicate that in unilaterally adrenalectomized animals, superadded operative stimuli fail to evoke the early response characteristic of the normal adrenal glands. Such latency points to the

vulnerability of their existing defence mechanisms. The remarkable similarity of adrenal response with or without exogenous ACTH in these animals suggests that the reason for a delayed response is rooted in the target organ itself, and is not due to an altered plasma ACTH level."

Thyroid

The effect of stress upon the thyroid is difficult to interpret because it depends largely upon the species examined and even upon different genetic predispositions within the same species. In rats, localized frostbite caused a loss of colloid from the thyroid concurrent with typical G.A.S. changes in the adrenals and other organs; furthermore, a variety of stressors decreased the uptake of radioiodine as indicated by radioautographic studies in this species. Hence, it was concluded that stress decreases TTH secretion.

However, it has been claimed that, during stress, radioiodine uptake by the thyroid does not give a specific indication of thyroid activity, since stress and cortisone increase the renal clearance of iodine. On the other hand, a drop in radioiodine is evident even after adrenalectomy, which further strengthens the view that stress does, in fact, usually diminish TTH secretion.

It has been claimed that transection of the pituitary stalk reduces the effect of nervous and emotional stressors upon the thyroid and adrenal cortex, without noticeably affecting that of surgical trauma or of large doses of EP. These findings were considered to support the concept that neurogenic and systemic stressors act upon the pituitary through distinct mechanisms.

The problem is further complicated by the observation that, in general, stressors decrease the thyroxin-binding capacity of blood proteins. In man, stress may either raise or diminish PBI, depending upon conditioning factors which have not yet been clarified.

In certain strains of wild rabbits, fear can cause "stress thyrotoxicosis" with histologic signs of thyroid hyperactivity, a fact to which we shall return in the section on Diseases of Adaptation.

According to the concept of a "shift in pituitary hormone secretion" during stress, it might be expected that increased ACTH production is associated with a diminution in the production of TTH, but in fact this is not always the case; hence, at this time, it is not yet possible to formulate any general laws concerning this problem. However, recent radioimmunoassays performed by our group suggest that, in the rat, acute stress causes an increase in ACTH concurrently with a decrease in the STH, LTH and LH concentration of the blood.

Thyroid

(See also our earlier stress monographs, p. xiii)

Herrington, L. P., Nelbach, J. H.: "Relation of gland weights to growth and aging processes in rats exposed to certain environ-

mental conditions." *Endocrinology* 30: 375-386 (1942). A37,641/42

Rats exposed to heat, noise, air blasts, vibration and other stressors exhibited a variety of organ changes similar to those caused by feeding excessive amounts of thyroid extract. "These results should be considered in

relation to Selye's work on the alarm reaction. Our experiments did not involve the extremes of stimulation characteristic of Selye's work, but some relationship is evident. In both the thyroid group and disturbed group the adrenal weights are greater and testicular weights are less, which agrees with Selye's findings. The reactions specific for the thyroid group involve an increase in heart and pituitary weights similar to that seen in the animals of the 65° and 95° temperature group. The disturbed group differ from the common pattern chiefly in the markedly reduced pituitary weight, and a less conspicuous reduction in prostatic weight. The important differences between the thyroid group and the disturbed group are probably associated with the use of thyroid feeding in one group."

Zenow, Z. I.: "Über Veränderungen im endokrinen System bei experimenteller örtlicher Erfrierung" (Changes in the endocrine system caused by experimental localized frostbite). *Virchows Arch. [Pathol. Anat.]* **312**: 486-500 (1944). B28,100/44

In rats, localized frostbite from cooling the tails causes typical G.A.S. changes, with an initial depletion and subsequent increase in adrenocortical lipids, discharge of medullary EP, and loss of colloid from the thyroid.

Bogoroch, R., Timiras, P.: "The response of the thyroid gland of the rat to severe stress." *Endocrinology* **49**: 548-556 (1951). B59,195/51

In rats, various stressors (formalin, spinal cord transection, muscular exercise) depressed the uptake of ^{131}I by the thyroid, as indicated by radioautographic studies. "It was suggested that stress caused a decrease or suppression of thyrotrophic stimulation."

Hetzl, B. S., Haba, D. S., de la, Hinkle, L. E.: "Life stress and thyroid function in human subjects." *J. Clin. Endocrinol. Metab.* **12**: 941 (1952). B71,949/52

In man, various stressful situations may cause sharp rises or falls in PBI.

Kracht, J., Kracht, U.: "Zur Histopathologie und Therapie der Schreckthyreotoxikose des Wildkaninchens" (The histopathology and therapy of fright thyrotoxicosis in wild rabbits). *Virchows Arch. [Pathol. Anat.]* **321**: 238-274 (1952). B68,863/52

In some strains of wild rabbits, fear induced by a pursuing dog or man causes "stress thyrotoxicosis" with histologic signs of thyroid hyperactivity and exophthalmos.

Wase, A. W., Repplinger, E.: "The effect of thermal burns on the thyroid activity of the rat." *Endocrinology* **53**: 451-454 (1953).

B87,006/53

Review of earlier literature showing that under certain circumstances stressors may produce either hyper- or hypothyroidism. Skin burns reduce the radioiodine uptake of the rat's thyroid during the first four hours.

Kracht, J.: "Fright-thyrotoxicosis in the wild rabbit, a model of thyrotrophic alarm-reaction." *Acta Endocrinol. (Kbh.)* **15**: 355-367 (1954).

B93,815/54

In certain species of wild rabbits frightened by man or dog, an atypical G.A.S. develops. "According to Selye's General Adaptation Syndrome, 3 phases are to be distinguished: alarm reaction, stage of resistance and stage of exhaustion. The adrenal cortex of the wild rabbit is unaffected by this special type of stress. During an alarm reaction the increase of thyrotrophic hormone implies an ACTH-stop, which can only be acutely interrupted by additional stressors such as histamine, adrenaline, formalin and ACTH or continued specific or nonspecific infections."

Harris, G. W.: "The reciprocal relationship between the thyroid and adrenocortical responses to stress." In: Wolstenholme, G. E. W. and Cameron, M. P., *Ciba Foundation Colloquia on Endocrinology*, Vol. VIII, pp. 531-550. London: J and A Churchill, 1955.

C3,662/55

Review of the literature indicating that a variety of stressors (typhoid vaccine, trauma, fasting, cold, heat, formalin, spinal cord transection, anoxia, starvation, tourniquet shock) decrease the uptake of radioiodine by the rat thyroid although they simultaneously increase ACTH secretion. However, radioiodine uptake by the thyroid during stress does not give a specific indication of thyroid activity, since stress and cortisone enhance the renal clearance of iodine and thus may lead to an apparent decrease in thyroid uptake because less radioiodine is available. Animals in which the adrenals are denervated or removed (while they are maintained on a constant cortisone regime) also show a similar response, and hence it is assumed that "the inhibition of thyroid activity seen after exposure to stress is due to a decreased secretion of pituitary thyrotrophic hormone."

Macchitella, E., Confortini, P.: "Studio sulle ustioni. III. Sulle modificazioni istologiche della tiroide in corso di ustione. (Ricerca sperimentale)" (Histologic modifi-

cations of thyroid in burns [experimental study]). *Chir. Patol. Sper.* **3**: 936-950 (1955). C10,798/55

Macchitella, E., Confortini, P.: "IV. Sulla attivazione della perossidas tiroidea. (Ricerca sperimentale)" (Activation of thyroid peroxidase in burns [experimental study]). *Chir. Patol. Sper.* **3**: 951-959 (1955).

C10,799/55

Sterescu, N., Kobesianu, S., Stancu, A.: "Features of thyroid gland inhibition during physical stress studies on rats and guinea pigs with the aid of radioactive iodine (I-131) and radiophosphorus (P32)." *Rev. Sci. Med.* (Buc.) **5**: 235-239 (1960) (Roumanian).

J24,628/60

Solano, M. de A.: "Influencia del electrochoque sobre la glandula tiroideas del cobayo" (The influence of electroshock on the thyroid gland of the guinea pig). *Arch. Esp. Morfol.* **18**: 3-31 (1963). J25,174/63

Fediay, Z., Clay, M. M.: "Acid mucopolysaccharide content of dermal connective tissue of normal and stressed rats." *Nature* **202**: 907-908 (1964). F12,108/64

The stress of exposure to cold in combination with restriction of movement in small cages decreased thyroid weight in the rat.

Amat, P., Cruz, F.: "Tiroides y stress. I. Cambios morfoquintéticos de la glándula tiroidea en el stress agudo y continuado" (Thyroid and stress. Morphokinetic changes in the thyroid gland after acute and protracted stress). *An. Anat.* **15**: 189-203 (1966). G72,605/66

Jurczak, M. E.: "Studies on the effect of vibration on thyroid gland function." *Acta Physiol. Pol.* **21**: 671-675 (1970) (Polish). H35,696/70

Voth, H. M., Holzman, P. S., Katz, J. B., Wallerstein, R. S.: "Thyroid 'hot spots': their relationship to life stress." *Psychosom. Med.* **32**: 561-568 (1970). G80,361/70

Burman, L. M.: "Effect of stress on histochemical changes in the thyroid gland." *Fiziol. Zh.* **18**: 332-338 (1972) (Ukrainian). J19,873/72

In rats, histochemical changes indicative of thyroid hyperactivity were noticed during the first hours after a burn, and lasted for several days.

Reklewska, B., Tomaszevska, L., Kaciuba-Uścińska, H., Kożłowski, S.: "Changes in the thyroid and adrenal glands during prolonged immobilization of rats." *Bull. Acad. Pol. Sci. [Biol.]* **20**: 685-689 (1972). H80,415/72

Nvota, J., Lamošová, D., Fáberová, A.: "Critical periods in the development of chicks." *Physiol. Bohemoslov.* **22**: 337-343 (1973). J21,555/73

The stress of restraint during a critical period of about three to four weeks after hatching produced a maximal decrease in thyroid activity in adulthood and a significant drop in the BMR of the chick. The critical phase for regulation of the function of the pituitary-adrenal and pituitary-gonad axis was found to be the period between the 15th and 21st day after hatching. Exposure to stress in this phase caused a significantly greater reaction of the adrenals to stress situations in the adult hens and significantly stimulated sexual maturation (egg-laying)."

Vazquez, R.: "The thyroid gland morphology of cats subjected to hunger and thirst." *Acta Anat. (Basel)* **89**: 70-79 (1974). J16,287/74

Histologic and histochemical examination suggests hyperactivity of the thyroid in cats subjected to ten to twenty-one days of fasting. The literature on thyroid changes during stress is surveyed.

Woeber, K. A., Ingbar, S. H.: "Interactions of thyroid hormones with binding proteins." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. III, pp. 187-196. Washington, D.C.: American Physiological Society, 1974. E10,592/74

An extensive review of the literature suggests that acute or chronic illness and surgical stress are commonly though not invariably associated with a pronounced decrease in the thyroxine-binding capacity of prealbumin, and sometimes with a moderate diminution of thyroxine-binding globulin.

Sex Organs (including Pregnancy and Lactation)

The effect of stress upon the functions of sex organs is arbitrarily discussed here under Morphology in order not to duplicate many facts referring to the functional con-

sequences of structural changes. Likewise included in this section are effects upon pregnancy and lactation, but stillbirth and malformations in the embryo will be discussed under Age in Chapter II.

Chronic stress causes gonadal atrophy and a diminution of sexual activity in males and females of most species so far examined. It also induces menstrual disturbances in women and impotence in men. It retards the onset of puberty, diminishes fertility, and may interfere with the maintenance of gestation or lead to malformations in the embryos.

During lactation, stress diminishes milk secretion; on the other hand, it has been claimed that "the stress of parturition has a significant role in the post-partum initiation of lactogenesis." In rats, the blockade of ovulation produced by pentobarbital can often be reversed by the stressor effect of cardiac puncture, which allegedly causes an LH discharge. A few additional observations also suggest that under certain conditions at least acute stressors can elicit a sudden release of gonadotropic hormones from the pituitary. However, the vast majority of findings support the view that—in consonance with the "pituitary-shift" theory—the increased secretion of ACTH, which is indispensable for the maintenance of life during prolonged emergencies, interferes with the continuous simultaneous production of other pituitary hormones, including gonadotropins.

Sex Organs (including Pregnancy and Lactation)

(See also our earlier stress monographs, p. xiii)

Selye, H.: "The effect of adaptation to various damaging agents on the female sex organs in the rat." *Endocrinology* 25: 615-624 (1939). A18,343/39

In the rat, ovarian atrophy and almost permanent anestrus are produced by various stressors (excessive muscular exercise, inadequate diets, toxic doses of different drugs). Ovarian atrophy during the G.A.S. may be just as severe as that elicited by hypophysectomy and associated with "wheel cell" formation. "It appears that in cases of emergency, the pituitary tends to produce more adrenotropic and less gonadotropic hormone than under normal conditions. The reason for this is probably that, under such conditions, an abundant supply of the life-maintaining principle of the adrenal cortex is a more imminent necessity than the preservation of normal sex function."

Dohan, F. C.: "Effect of low atmospheric pressure on the adrenals, thymus and testes of rats." *Proc. Soc. Exp. Biol. Med.* 49: 404-408 (1942). A37,744/42

"Rats exposed to low atmospheric pressure for more than 2 days exhibited a significant increase in adrenal weight and a significant

decrease in the weight of the thymus and testes. This pattern is similar to that found following other forms of stress." These observations are in consonance with the "pituitary-shift" theory.

Walton, A., Uruski, W.: "The effects of low atmospheric pressure on the fertility of male rabbits." *J. Exp. Biol.* 23: 71-75 (1946). B40,070/46

Gantt, W. H.: "Disturbances in sexual functions during periods of stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 1030-1050. Baltimore: Williams & Wilkins, 1950.

B51,958/50

Discussion of sexual arousal as a stressor agent and conversely as a functional variable readily influenced by stress.

Sager, O., Badenschi, G., Cotăescu, E. Roth, R. R.: "Acțiunea electroșocului asupra glandelor cu secreție internă" (Effects of electroshock on endocrine gland secretion). *Bull. Sci. Acad. R.P.R. Roumanie, Sci. Méd.* 2: 651-659 (1950) (Roumanian).

G99,776/50

In man, electroshocks produce ACTH secretion, eosinopenia and lymphopenia, reaching a maximum within about four hours. Repeated electroshocks may also cause menstrual disturbances in women and impotence

in men. All these effects are ascribed to the G.A.S.

Mandl, A. M., Zuckerman, S.: "The reaction of the ovaries and adrenal glands of female rats to ovarian and muscle homografts." *J. Endocrinol.* 7: 344-348 (1951).

B63,009/51

In rats, homografts of ovarian or muscle tissue caused adrenal and ovarian enlargement. The adrenals (but not the ovaries) were also hypertrophied following Avertin anesthesia. The possibility is considered that these reactions may be manifestations of stress.

Mandl, A. M., Zuckerman, S.: "Factors influencing the onset of puberty in albino rats." *J. Endocrinol.* 8: 357-364 (1952).

B75,210/52

In rats, exposure to cold accelerates the vaginal opening (a sign of puberty), whereas rough handling and a high-protein diet have no such effect. Possibly, certain types of "nonspecific 'stress'" may bring about a raised output of gonadotrophin as well as of ACTH, and thus secondarily stimulate ovarian activity."

Djurišić, S.: "General adaptation syndrome and functional ovarian disorders during wartime." *Acta Med. Jugoslav.* 8: 205-228 (1954) (Serbo-Croatian). B99,192/54

Chisci, R.: "Importanza del timo nella sindrome di adattamento. Nota III. Gli effetti dello stress e della somministrazione di ACTH sull'apparato genitale femminile delle ratte normali e stimizzate" (Importance of thymus in adaptation syndrome; effects of stress and of adrenocorticotrophic hormone on female genitals of normal and stimulated rats). *Folia Endocrinol.* (Roma) 8: 525-543 (1955). C8,681/55

In rats, "typical manifestations of the 'alarm reaction' by the cold stress (such as anestrus ovulations, corticoids-estrogens antagonism, fatty infiltration of the liver etc.) are clearly augmented and prolonged by thymectomy so that the adaptation process becomes delayed."

Bickers, W.: "Uterine contraction patterns. Effects of psychic stimuli on the myometrium." *Fertil. Steril.* 7: 268-275 (1956).

J25,121/56

"The clinical opinion long held that the emotions affect uterine physiology and play an important role in infertility has been

shown to have a valid basis in demonstrable physiologic changes occurring in the human uterus under the impact of fear, pain, and disappointment."

Joël, C. A., Lancet, M.: "The question of a psychogenic factor in some cases of primary amenorrhea." *J. Clin. Endocrinol. Metab.* 16: 909-911 (1956). C19,340/56

"Psychogenic stress" may cause amenorrhea in women.

Arvay, A., Nagy, T., Kovács-Nagy, S.: "Die Wirkung der auf die Sinnesorgane ausgeübten extrem starken Reize auf die Funktion und Morphologie des Ovars" (Functional and morphologic changes of the ovary caused by very strong stimulation of the sense organs). *Z. Geburtshilfe Gynaekol.* 147: 371-388 (1956). C31,632/56

In rats, exposure to intense sound, light or electric stimulation eventually produces degenerative changes in the ovary which may be associated with continuous estrus or diestrus.

Christian, J. J.: "A review of the endocrine responses in rats and mice to increasing population size including delayed effects on offspring." *Naval Med. Res. Inst.* August 6, 1957, pp. 443-462. C53,409/57

Rats and mice living under crowded conditions show many manifestations of stress, including a decrease in fertility which may act as a regulator of population density to maintain an optimal level. Crowding can also cause lasting changes in the offspring of surviving females, probably due to lactational deficiencies.

Sackler, A. M., Weltman, A. S., Bradshaw, M., Jurtschuk, P. Jr.: "Endocrine changes due to auditory stress." *Acta Endocrinol.* (Kbh.) 31: 405-418 (1959).

C71,159/59

Repeated exposure of rats to strong auditory stimulation causes adrenal enlargement, ovarian atrophy and diminution in the weight of the uterus and liver. Food consumption is also markedly reduced.

Soiva, K., Grönroos, M., Rinne, U. K., Näätänen, E.: "The effect of psychic and painful stimuli on the reproductive organs of the female rat." *Acta Obstet. Gynecol. Scand.* 38 Supp. 4: 22 (1959). C96,937/59

Grönroos, M., Kauppila, O.: "Hormonal-cyclic changes in rats under normal conditions and under stress as revealed by vaginal

smears after Shorr staining." *Acta Endocrinol.* (Kbh.) **32**: 261-271 (1959).

C76,461/59

Observations on rats concerning changes in vaginal estrus during the G.A.S.

Zondek, B., Tamari, I.: "Effect of audiogenic stimulation on genital function and reproduction." *Am. J. Obstet. Gynecol.* **80**: 1041-1048 (1960). D4,871/60

"Exposure to stimulation of the auditory organs in mature rats stimulates the anterior pituitary gonadotropic function, manifested by prolonged or persistent estrus, enlargement of the ovaries, and increase of the corpora lutea in number and size." In rabbits, enlargement of the ovaries and follicle hematomas with corpus luteum formation and sometimes galactorrhea are noted. The stimulating effect of auditory stimuli on female genital function is in contrast to the inhibitory action on fertility. The stressor effect of sound can also interrupt pregnancy.

Fitko, R.: "Contemporary view of cystic ovaries and nymphomania in animals." *Med. Weteryn.* **16**: 407-415 (1960) (Polish).

D1,235/60

Cystic ovaries and nymphomania may occur in various domestic animals as a consequence of stress.

Abramson, J. H., Singh, A. R., Mbambo, V.: "Antenatal stress and the baby's development." *Arch. Dis. Child.* **36**: 42-49 (1961). D4,534/61

"A prospective study of Indian expectant mothers in Durban revealed a relationship between emotional stress during pregnancy and a low level of motor development in the infant."

Chaudhury, R. R., Chaudhury, M. R., Lu, F. C.: "Stress-induced block of milk ejection." *Br. J. Pharmacol.* **17**: 305-309 (1961).

D61,414/61

The stress-induced block of milk ejection in guinea pigs can be largely inhibited by tranquilizers.

Vandekerckhove, D.: "Dosage de l'acide désoxyribonucléique et karyométrie au niveau du corps jaune de la lapine pseudogravide. II. L'influence de l'agression opératoire" (Determination of desoxyribonucleic acid and karyometry in the corpus luteum of the pseudopregnant rabbit. II. The influence of operative stress). *Ann. Endocrinol.* (Paris) **23**: 605-607 (1962). D41,344/62

In pseudopregnant rabbits, traumatic stress

decreased the DNA content of corpus luteum cells.

Eleftheriou, B. E., Bronson, F. H., Zarrow, M. X.: "Interaction of olfactory and other environmental stimuli on implantation in the deer mouse." *Science* **137**: 764 (1962).

D30,851/62

In recently inseminated deer mice, various changes in the physical environment can inhibit implantation. [It remains to be shown whether this is a nonspecific stress effect (H.S.).]

Weir, M. W., DeFries, J. C.: "Blocking of pregnancy in mice as a function of stress." *Psychol. Rep.* **13**: 365-366 (1963).

E39,863/63

"Stressful situations during the early stages of pregnancy, including handling, resulted in marked reduction in the number of litters obtained from two highly inbred strains of mice."

Bruce, H. M.: "A comparison of olfactory stimulation and nutritional stress as pregnancy-blocking agents in mice." *J. Reprod. Fertil.* **6**: 221-227 (1963). G1,344/63

In mice, olfactory stimulation and "nutritional stress" act as distinct pregnancy-blocking agents.

Meites, J., Nicoll, C. S., Talwalker, P. K.: "The central nervous system and the secretion and release of prolactin." *Adv. Neuroendocrinol.* **238-277** (1963). G17,019/63

Review on the role of the CNS in the secretion and release of LTH. Certain stressful stimuli can induce mammary growth or lactation in women. The mechanism of this response is not understood.

Schmidt, A. L. C., Christiaans, A. P. L.: "An oestrogenic effect as a component of the stress syndrome." *Acta Endocrinol.* (Kbh.) **46**: 421-439 (1964). F14,822/64

Stress induced by swimming increased the number of cornified cells in the vaginal smears of ovariectomized but not of adrenalectomized rats. Hypophysectomy usually failed to prevent this effect. The authors conclude that "stress induces a release of oestrogens or oestrogenic substances from the adrenal cortex. The most important pathway seems to follow the sympathetic nervous system. As a hypothesis the pathway is suggested to proceed from the hypothalamus via the sympathetic tissue to the adrenal."

Dickson, A. D.: "Delay of implantation in

super-ovulated mice subjected to crowded conditions." *Nature* **201**: 839-840 (1964).
F9,766/64

Ouellette, R., Perrault, H. J., Dugal, L. P.: "Effet du froid sur le testicule endocrinien: chronologie des événements" (Effects of cold on the endocrine testis: chronology of events). *Rev. Can. Biol.* **24**: 7-21 (1965).

F42,194/65

In male rats, "a time study of the response of the sexual accessories reveals the succession of events as distinct phases related to the duration of the stress and reminiscent of the three stages of the General Adaptation Syndrome."

Hahn, E. W., Hays, R. L.: "Modification of the incidence of mating in rats by stimulation with a short air blast." *Psychol. Rep.* **16**: 862-864 (1965).

J23,030/65

Cizkova, J.: "Prenatal endocrine influences on the foetus and their relation to late behaviour." *Clin. Dev. Med.* No. 19: 10-13 (1965).

G66,783/65

A statistical study on a small sample of mongoloid children in Prague suggests that emotional stress during pregnancy predisposes the embryo to this disease.

Copelman, L. S.: "Etudes et recherches sur les facteurs endocriniens et psychologiques dans la pathogénie et le traitement de la stérilité" (Studies and research on endocrine and psychologic factors in the pathogenesis and treatment of sterility). *Thérapie* **20**: 459-465 (1965).

G30,661/65

In both male and female concentration camp survivors, libido and fertility are often diminished. Sperm formation tends to be abnormal, and amenorrhea is common as a consequence of stress, as was shown in the original experiments on the G.A.S.

Roth, L. L., Rosenblatt, J. S.: "Mammary glands of pregnant rats: development stimulated by licking." *Science* **151**: 1403-1404 (1966).

F63,219/66

In pregnant rats which were prevented by neck collars from licking their ventral surface, the mammary glands developed deficiently. "Neither the burden nor the stress effect of the collar is an alternative explanation. A considerable proportion of mammary development during pregnancy is thus caused by the female's own licking."

Sackler, A. M., Weltman, A. S.: "Effects of vibration on the endocrine system of male

and female rats." *Aerosp. Med.* **37**: 158-166 (1966).
G36,884/66

Comparatively low-gravity vibration in a reciprocating Kahn shaker for thirty minutes daily caused more pronounced stress effects (adrenal enlargement, thymicolumphatic or gonadal atrophy, loss of body weight and so on) in male than in female rats (40 refs.).

Skinner, J. D., Louw, G. N.: "Heat stress and spermatogenesis in Bos indicus and Bos taurus cattle." *J. Appl. Physiol.* **21**: 1784-1790 (1966).

G42,859/66

Even short-term exposure of bulls to "heat stress" can adversely affect spermatogenesis and fertility. [Since heat is known to have a specific damaging influence upon the testes, it remains to be shown that this is a non-specific stress effect (H.S.).]

Marini, M. de, Ameli, M.: "Osservazioni istologiche ed istochimiche sul ciclo vaginale del ratto maturo nel corso di esperienze di stimolazione acustica prolungata" (Histologic and histochemical aspects of the vaginal cycle of the mature rat during experiments with prolonged acoustic stimulation). *Clin. Otorinolaringol.* **18**: 380-402 (1966).

J24,401/66

Detailed discussion on the effects of acoustic stress upon the sex organs of the rat (21 refs.).

Ameli, M., Marini, M. de: "Caratteristiche morfologiche ed istochimiche dell'endometrio di ratto a seguito di stimolazione acustica prolungata" (Morphologic and histochemical characteristics of the rat endometrium after prolonged acoustic stimulation). *Clin. Otorinolaringol.* **18**: 354-379 (1966).

J24,444/66

Welter, J. F., Boone, M. A., Barnett, B. D.: "The effects of temperature stress on subsequent egg production of the fowl." *Poultry Sci.* **46**: 646-650 (1967).

J23,502/67

"Pullets, up to 20 weeks of age, can be cooped and hauled without significantly affecting subsequent egg production and other related economic factors during an eight month laying period."

Gilbert, F. F., Bailey, E. D.: "The effect of visual isolation on reproduction in the female ranch mink." *J. Mammal.* **48**: 113-118 (1967).

J11,146/67

Isolation of female ranch minks from other members of the species inhibits sexual development and fertility.

Matsumoto, S., Igaracsi, M., Tohma, K.:

"Endocrinological studies on environmental and psychiatric menstrual disorders." *Endocrinol. Jap.* **14**: 320-326 (1967). F94,454/67

Hormone studies "suggest that the mechanism of the amenorrhea due to acute environmental change or psychiatric disorders is consistent with the shift theory of pituitary function proposed by Selye."

Noel, V.: *Syndrome de Transmission* (Syndrome of transmission), p. 36. Port-au-Prince, Haiti: Imprimerie Theodore, 1967.

G46,108/67

The term "syndrome of transmission" is suggested for the development of anomalies in embryos whose mothers were exposed to stressors during gestation.

Osofsky, H. J., Fisher, S.: "Psychological correlates of the development of amenorrhea in a stress situation." *Psychosom. Med.* **29**: 15-23 (1967).

J23,149/67

Sandler, B.: "Emotional stress and infertility." *J. Psychosom. Res.* **12**: 51-59 (1968).

J22,399/68

"The term 'stress' is here taken to mean 'the internal or resisting force brought into being in the human organism by interaction with the environment.'... There is much evidence of the causal relationship between stress and infertility in the common observation that a 'cure' of the disorder, after years of sterility, has followed very diverse events which could have had no bodily effect on the patient. For example, a patient telephones for an appointment and conception occurs before the consultation; or conception occurs after a semen analysis, even before the results are known; after a simple vaginal examination; after general reassurance; after putting a name down for adoption."

Huston, T. M., Subhas, T.: "The influence of environmental temperature upon adrenal activity of bursectomized chicks." *Poultry Sci.* **47**: 1760-1763 (1968).

J23,073/68

The testes of young cockerels kept at 30°C are larger than those of controls housed at 8°C.

Matsumoto, S., Igarashi, M., Nagaoka, Y.: "Environmental anovulatory cycles." *Int. J. Fertil.* **13**: 15-23 (1968).

G60,304/68

Psychic trauma may produce anovulatory cycles in women.

Schuster, D. H., Schuster, L.: "Study of stress and sex ratio in humans." *Proc. 77th Ann. Conv. APA*, pp. 335-336 (1969).

G69,737/69

"Our theory can be phrased physiologically, the male parent when under stress inhibits the motility or viability of male sperm. Conversely, the female parent when under stress inhibits the motility or viability of female sperm prior to fertilization."

Palti, Z.: "Psychogenic male infertility." *Psychosom. Med.* **31**: 326-330 (1969).

J22,423/69

In men, infertility is frequently due to prolonged emotional stress. It usually results from "impotence, sham ejaculation, retrograde ejaculation and oligospermia."

Gilbert, F. F., Bailey, E. D.: "Visual isolation and stress in female ranch mink particularly during the reproductive season." *Can. J. Zool.* **47**: 209-212 (1969).

J20,525/69

"Visual isolation is apparently more stressful to female mink during the anoestrous period but reduces stress during oestrus and pregnancy. The increased adrenal steroid output of control mink as part of the stress syndrome during the critical reproductive period might be responsible for increased *in utero* losses. But increased adrenocortical output associated with the stress of *long term* visual isolation might result in insufficient gonadal stimulation resulting in fewer pregnancies."

James, W. H.: "The effect of maternal psychological stress on the foetus." *Br. J. Psychiatry* **115**: 811-825 (1969).

G67,988/69

"There is good evidence that severe emotional stress and strong sensory stimuli cause embryonic resorption and stillbirth in some mammals." The risk of stillbirth or death within the first month is above normal in illegitimate infants and in those whose father is absent through death, divorce, desertion and so on. There is no firm evidence that either anencephaly or mongolism is caused by maternal psychogenic stress.

Harrison, R. J., Boice, R. C., Brownell, R. L. Jr.: "Reproduction in wild and captive dolphins." *Nature* **222**: 1143-1147 (1969).

H13,797/69

Among various types of dolphins, ulceration of the forestomach occurred during captivity, while the number of pregnancies decreased considerably.

Singh, K. B., Rao, P. S.: "Studies on the polycystic ovaries of rats under continuous auditory stress." *Am. J. Obstet. Gynecol.* **108**: 557-564 (1970).

G78,701/70

In rats, continuous auditory stress can elicit polycystic ovaries with inhibition of corpus luteum formation, and thereby interfere with reproduction.

Billinson, M. R.: "Prematurity and low birth weight litters: a mechanism elicited by thermal stress." *Am. J. Obstet. Gynecol.* **108**: 970-974 (1970). H45,391/70

In rats, "thermal stress" increases 5-HT excretion, which may be accompanied by premature delivery or low birth weight of the litters.

Machida, T.: "Luteinization of ovarian transplants in gonadectomized male and female rats under stressful conditions and its relation to sexual differentiation of the hypothalamus." *Endocrinol. Jap.* **17**: 189-193 (1970). H31,731/70

Sevy, S.: "Acute emotional stress and sodium in breast milk." *Am. J. Dis. Child.* **122**: 459 (1971). J20,192/71

Champlin, A. K.: "Suppression of oestrus in grouped mice: the effects of various densities and the possible nature of the stimulus." *J. Reprod. Fertil.* **27**: 233-241 (1971). H47,870/71

Singh, K. B.: "Effects of sound on the female reproductive system." *Am. J. Obstet. Gynecol.* **112**: 981-991 (1972).

G89,061/72

Review on the effect of prolonged and intense sound upon the female reproductive system of various mammals. In accordance with the "hypophyseal-shift" theory, this stressor tends to diminish fertility through decreased gonadotropin production, which results in ovarian atrophy. Pregnancy may also be disturbed.

Wagnon, K. A., Rollins, W. C., Cupps, P. T., Carroll, F. D.: "Effects of stress factors on the estrous cycles of beef heifers." *J. Anim. Sci.* **34**: 1003-1010 (1972). J20,504/72

Russell, G. F. M.: "Psychological and nutritional factors in disturbances of menstrual function and ovulation." *Postgrad. Med. J.* **48**: 10-13 (1972). G86,651/72

Amenorrhea can occur in women upon exposure to a variety of psychologic or nutritional stressors.

Stauber, M.: "Männliche Fertilitätsstörungen durch beruflichen Stress" (Professional stress may cause male fertility disturbances). *Med. Monatsschr.* **27**: 108-110 (1973).

H69,981/73

Review of the literature with personal observations showing that the stress involved in professional life, particularly in industry, may lead to impotence or a decrease in fertility.

Ramírez, V. D.: "Endocrinology of puberty." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. II, Part 1, pp. 1-28. Washington, D.C.: American Physiological Society, 1973. E10,356/73

In a handbook article on the endocrinology of puberty, literature is cited to show that a variety of stressors can delay the onset of puberty.

Fries, H., Nillius, S. J.: "Psychological factors, psychiatric illness and amenorrhoea after oral contraceptive treatment." *Acta Psychiatr. Scand.* **49**: 653-668 (1973).

J10,395/73

"Stressful life events in connection with the onset of amenorrhoea were experienced by 36% of the women (41% if travels abroad were included) and significantly correlated to low solidity and high neuroticism scores."

Stott, G. H., Wiersma, F.: "Climatic thermal stress, a cause of hormonal depression and low fertility in bovine." *Int. J. Biometeorol.* **17**: 115-122 (1973). H93,300/73

Preston, F. S., Bateman, S. C., Short, R. V., Wilkinson, R. T.: "Effects of flying and of time changes on menstrual cycle length and on performance in airline stewardesses." *Aerosp. Med.* **44**: 438-443 (1973) (21 refs.).

J14,835/73

Peyser, M. R., Ayalon, D., Harell, A., Toaff, R., Cordova, T.: "Stress induced delay of ovulation." *Obstet. Gynecol.* **42**: 667-671 (1973) (11 refs.).

J7,709/73

Nvota, J., Lamošová, D., Fáberová, A.: "Critical periods in the development of chicks." *Physiol. Bohemoslov.* **22**: 337-343 (1973).

J21,555/73

The stress of restraint during a critical period of about three to four weeks after hatching produced a maximal decrease in thyroid activity in adulthood and a significant drop in the BMR of the chick. "The critical phase for regulation of the function of the pituitary-adrenal and pituitary-gonad axis was found to be the period between the 15th and 21st day after hatching. Exposure to stress in this phase caused a significantly greater reaction of the adrenals to stress

situations in the adult hens and significantly stimulated sexual maturation (egg-laying)."

D'Souza, F., Martin, R. D.: "Maternal behaviour and the effects of stress in tree shrews." *Nature* **251**: 309-311 (1974).

J23,295/74

In tree shrews, the noise of a fire bell accelerates the suckling rhythm but decreases the quantity of milk given over a forty-eight-hour period. More severe stress causes cannibalism.

Nestor, K. E., Brown, K. I., Renner, P. A.: "Effect of genetic changes in egg production, growth rate, semen yield and response to cold stress on early mortality of turkey poultts." *Poultry Sci.* **53**: 204-210 (1974).

J21,594/74

Rodgers, C. H., Schwartz, N. B., Nequin, L. G.: "Interaction between the ovarian and adrenocortical regulating systems: occurrence of ovulation." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 241-252. Tokyo: Igaku Shoin, 1974.

E10,872/74

Rosen, E. F., Petty, L. C.: "Food deprivation effects on some estrogen-sensitive responses in female rats." *Physiol. Behav.* **12**: 767-770 (1974).

J12,899/74

Observations in man during famines, as well as experiments on the folliculoid sensitivity of rats and other animals during stress suggest that "food deprivation may interfere with sexual activity by altering the female's behavior more than the male's. Thus, any control over reproduction which may occur in a famine area may be due to changes in the female's behavior, which provide fewer or lower intensity stimuli to the male.... This is part of the response to stress discussed by Selye."

Yonetani, S., Jojima, M., Suzuki, Y.: "Blockade of ovulation in rats by forced immobilization for surgical treatment." *Endocrinol. Jap.* **21**: 61-68 (1974).

H86,186/74

Stress-induced blockade of ovulation may be due to inhibition of LRF. "The blockade of ovulation by the forced immobilization with a surgical operation can be prevented by the simultaneous application of ether anesthesia."

Barfield, M. A., Lisk, R. D.: "Relative contributions of ovarian and adrenal progesterone to the timing of heat in the 4-day

cyclic rat." *Endocrinology* **94**: 571-575 (1974).

H86,297/74

In the rat, ovariectomy during proestrus induces a brief period of heat which may be dependent upon adrenal progesterone discharged as a result of surgical stress. Dexamethasone prevents this brief heat. Literature on stress-induced gonadotropin discharge is briefly summarized.

Neville, W. E. Jr., Neathery, M. W.: "Effect of temperature under field conditions on the reproductive performance of ewes." *J. Reprod. Fertil.* **36**: 423-426 (1974).

H80,745/74

In sheep, "heat stress" diminishes fertility. [Other stressors have not been used as controls to determine the nonspecificity of this result (H.S.).]

Proudfit, C. M., Schwartz, N. B.: "Reversal of pentobarbital blockade of ovulation after cardiac puncture." *Endocrinology* **94**: 526-531 (1974).

H86,290/74

In rats, the blockade of ovulation produced by pentobarbital can often be reversed by cardiac puncture. This is ascribed to an LH discharge resulting from the stressor effect of the intervention.

Bugard, P.: *Stress, Fatigue et Dépression. (L'homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue and depression. Man and the aggression of daily life), Vol. 1, p. 294, Vol. 2, p. 302. Paris: Doin Edit., 1974.

E10,487/74

Monograph with a brief section on sexual problems.

Wexler, B. C.: "Effect of an oral contraceptive drug on non-arteriosclerotic, male and female virgin rats vs. arteriosclerotic, male and female breeder rats." *Angiology* **25**: 197-227 (1974).

H83,788/74

Review on the stressor effect of repeated pregnancies upon female breeder rats (66 refs.).

Ramaley, J. A.: "Correlation between fertility and the serum corticosterone rhythm in mice." *Fed. Proc.* **33**: 282 (1974).

H84,020/74

Fries, H., Nillius, S. J., Pettersson, F.: "Epidemiology of secondary amenorrhea. II. A retrospective evaluation of etiology with special regard to psychogenic factors and weight loss." *Am. J. Obstet. Gynecol.* **118**: 473-479 (1974).

J15,323/74

Various emotional stressors can cause secondary amenorrhea in women (14 refs.).

Porter, J. C.: "Hormonal regulation of breast development and activity." *J. Invest. Dermatol.* **63**: 85-92 (1974). H89,237/74

Review on the effect of hormones and stressors upon lactogenesis. "The possibility that the stress of parturition has a significant role in the postpartum initiation of lactogenesis is provocative" (77 refs.).

Paris, A. L., Ramaley, J. A.: "Adrenogonadal relations and fertility: the effects of repeated stress upon the adrenal rhythm." *Neuroendocrinology* **15**: 126-136 (1974).

H91,877/74

In female mice housed near males to maintain a normal estrous cycle, restraint reversed the daily plasma corticosterone rhythm, with peaks during the midpoint of the light interval rather than shortly after the onset of darkness. Old females showing no regular estrus exhibited no twenty-four-hour corticosterone rhythm before stress. After restraint had been discontinued, the mice

developed a daily rhythm. It was concluded that the presence of an adrenal rhythm is associated with fertility, its absence with infertility.

Inoue, S., Nagasaki, H., Iriki, M.: "Total sleep deprivation and weight increases of the reproductive organs in male rats." *Endocrinol. Jap.* **21**: 283-286 (1974).

H92,991/74

In rats, long-term sleep deprivation in a cage in which they were continuously forced to move in order to avoid electric shocks caused hypertrophy of the adrenals, testes, ventral prostate and seminal vesicles. "It is supposed that either the sleep deprivation per se or stressful conditions accompanied with the treatment caused a hypersecretion of hypophyseal and testicular hormones." [It is unusual for chronic stress to cause hypertrophy of the sex organs, and these observations appear to be incompatible with the "pituitary-shift" theory (H.S.).]

Pancreas

Acute involution of the excretory pancreatic tissue was observed in the first experiments on the alarm reaction in rats. It was noted then, and has often been confirmed since, that the pancreatic acini immediately surrounding the Langerhans islets make the latter readily discernible by the naked eye as white spots in the atrophic grayish and transparent parenchyma. The formation of these "halos" of undamaged exocrine tissue has still not been explained. The so-called "postoperative pancreatitis" is also a related phenomenon.

More recently it was found that systemic stressors such as restraint can also cause degranulation of the β -cells in the islets themselves. This change is allegedly also characteristic of stress.

Pancreas

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

First detailed description of the three stages of the G.A.S. and the concept of "adaptation energy," with an extensive and illustrative characterization of the morphologic lesions produced by stress (especially in the hypophysis, adrenals, thymicolymphatic apparatus, pancreas and gastrointestinal tract), and its effect upon inflammation (anaphylactoid edema).

Théret, C.: "La neuro-sécrétion des complexes neuro-insulaires du pancréas. Ses

vibrations sous l'action de stress expérimentaux" (The neurosecretion of the neuroinsular complexes of the pancreas. Its variations under the effects of experimental stress). *Ann. Endocrinol. (Paris)* **22**: 312-322 (1961).

D8,823/61

The vegetative neurons associated with Langerhans' islands of various species are the seat of a neurosecretion of nucleolar origin which increases in intensity during stress produced by any kind of agent. [Excellent color photographs (H.S.).]

Caputo, G.: "Rilievi istologici sul pancreas endocrino in cavie sottoposte a shock chimico da metrazolo" (Histologic findings in the endocrine pancreas of guinea pigs ex-

posed to chemical shock with metrazol).
Boll. Soc. Ital. Biol. Sper. **39**: 1624-1626
 (1963).

G10,525/63

Barkalaya, A. I.: "Nature of reaction of the insular apparatus of the pancreas in chronic stress." *Probl. Endokrinol.* **14** No. 6: 71-74 (1968) (Russian). H6,534/68

Observations on the rat suggest that, "in the mechanism of reaction of the islands of Langerhans to stress, a definite role is played by activated secretion of the hormones of hypophyseal-adrenocortical system and their hyperglycemic effect."

Moritz, V., Baumann, R., Hecht, K., Poppe, M., Treptow, K.: "Relationen zwischen neurotisch induzierter Blutdruckdysregulation und Granulagehalt der Pankreas- β -Zellen bei der Albinoratte" (Relation between neurosis-induced blood pressure dysfunction and granule content in the pancreatic β -cells of the albino rat). *Acta Biol. Med. Ger.* **30**: 231-240 (1973). J7,756/73

Under certain circumstances, repeated restraint can cause degranulation of the pancreatic β -cells in the rat. This change is ascribed to stress.

Pineal Gland

The few available data on morphologic changes in the pineal gland during stress will be discussed in the chapter on Theories together with other evidence of pineal participation in the G.A.S.

Thymicolumphatic and Hematopoietic Organs

Thymus involution after severe burns was noted in the nineteenth century, and "accidental thymus involution" in children suffering from various diseases and intoxications was likewise described much before the alarm reaction. However, it was not until the formulation of the G.A.S. concept that thymicolumphatic involution was recognized as part of the nonspecific reaction to any stressor of sufficient intensity.

Histologically, the response of the thymus to stressors is characterized primarily by a disintegration of the thymocytes, with an "inversion of the thymus pattern," in that the majority of the remaining thymocytes migrate from the cortex into the medulla. The epithelioid elements in the medulla of the thymus tend to proliferate during stress, and cystic Hassall's corpuscles are frequently noted.

In the lymph nodes, the first cells to undergo degeneration are the relatively immature lymphocytes in the germinal centers. Similar changes are produced by ACTH and glucocorticoids; hence, the thymicolumphatic alterations characteristic of stress presumably are mediated through the discharge of the latter hormones. This view is further substantiated by the inhibitory effect exerted by adrenalectomy upon stress-induced thymicolumphatic involution.

The lymphatic elements in the spleen, intestine, and Bursa of Fabricius of birds respond essentially in the same manner as do those of the thymus and lymph nodes.

The possible immunologic significance of thymus involution produced by stress in adults has not yet been ascertained, but it would certainly deserve attention.

Finally, it is worth mentioning that although the stress-induced thymicolumphatic involution is undoubtedly mediated through the secretion of corticoids, the actions of the latter can be conditioned by other factors. Even in adrenalectomized animals maintained on a standard dose of glucocorticoids which in itself causes little or no thymus involution, subsequent exposure to stressors results in a pronounced atrophy of this organ.

The hemopoietic tissue usually undergoes transient hyperplasia during stress but its lymphatic elements participate in the generalized atrophy and involution of the thymicolumphatic organs in general. The granulocytes of the bone marrow tend to be discharged during stress, which may be partly responsible for the characteristic polynuclear glucocytosis after exposure to stressors.

Thymicolumphatic and Hematopoietic Organs

(See also our earlier stress monographs, p. xiii)

Bardeen, C. R.: "A study of the visceral changes in extensive superficial burns." *J. Exp. Med.* **2**: 501-514 (1897).

B19,954/1897

Autopsies on several patients who died from severe skin burns revealed gastric or duodenal ulcers and thymicolumphatic atrophy as well as hepatic and renal changes. Patients who died during the first few hours showed predominantly edematous lymphatic organs. "These lesions of the lymphatic tissue furnish most important additional evidence of a toxæmia after superficial burns."

Hammar, J. A.: "Beiträge zur Konstitutionsanatomie, VI." (Studies on constitutional anatomy, VI). *Z. Angew. Anat. Konstit. Lehre* **4**: 1-107 (1918). 50,856/18

Meticulous histologic studies on the human thymus, with special sections on the so-called "accidental involution" elicited by various dietary deficiencies, bacterial infections, snake venoms and other damaging agents. This is probably the first systematic monograph on the subject.

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

First detailed description of the three stages of the G.A.S. and the concept of "adaptation energy," with an extensive and illustrative characterization of the morphologic lesions produced by stress (especially in the hypophysis, adrenals, thymicolumphatic apparatus, pancreas and gastrointestinal tract), and its effect upon inflammation (anaphylactoid edema).

Dohan, F. C.: "Effect of low atmospheric pressure on the adrenals, thymus and testes of rats." *Proc. Soc. Exp. Biol. Med.* **49**: 404-408 (1942). A37,744/42

"Rats exposed to low atmospheric pressure for more than 2 days exhibited a significant increase in adrenal weight and a significant decrease in the weight of the thymus and

testes. This pattern is similar to that found following other forms of stress." These observations are in consonance with the "pituitary-shift" theory.

Dougherty, T. F., White, A.: "An evaluation of alterations produced in lymphoid tissue by pituitary-adrenal cortical secretion." *J. Lab. Clin. Med.* **32**: 584-605 (1947) (93 refs.). B18,513/47

Baker, B. L., Ingle, D. J., Li, C. H.: "The histology of the lymphoid organs of rats treated with adrenocorticotropin." *Am. J. Anat.* **88**: 313-349 (1951). B63,170/51

Extensive light microscopic studies on the effect of ACTH upon the thymicolumphatic tissues of the rat. "The cytological changes which appeared in the thymus were similar to those reported to be elicited by stress" (about 45 refs.).

Klein, H.: "Zur pathologischen Anatomie der Alarmreaktion nach Kerngiften" (The pathology of the alarm reaction after nuclear toxins). *Virchows Arch. [Pathol. Anat.]* **320**: 93-137 (1951). B69,206/51

Comparative studies of the morphologic changes in the liver, thymicolumphatic apparatus (including the spleen) and duodenum of the mouse and rat after an alarm reaction is produced by ethyl ether, colchicine, urethane or hydroquinone. Special attention is given to derangements in mitoses, particularly nuclear pyknosis (191 refs.).

Dougherty, T. F.: "Effect of hormones on lymphatic tissue." *Physiol. Rev.* **32**: 379-401 (1952). B75,769/52

Extensive review on the effect of stress, and of hormones produced during stress, upon thymicolumphatic tissue and blood count, including the development of "stress lymphocytes."

Clarke, J. R.: "The effect of fighting on the adrenals, thymus and spleen of the vole (*Microtus agrestis*)."*J. Endocrinol.* **9**: 114-126 (1953). B77,639/53

Voles kept in a cage viciously attack any strangers of the same species introduced

among them. The fighting results in adrenal enlargement and thymic atrophy characteristic of the alarm reaction, but instead of the usual splenic atrophy there is enlargement, perhaps because of secondary infection.

Schelin, U., Hesselsjö, R., Paulsen, F., Mellgren, J.: "Plasma cell production promoted by pituitary somatotropic hormone in the adaptation syndrome." *Acta Pathol. Microbiol. Scand.* **35**: 503-511 (1954).
C9,504/54

Garren, H. W., Shaffner, C. S.: "How the period of exposure to different stress stimuli affects the endocrine and lymphatic gland weights of young chickens." *Poultry Sci.* **35**: 266-272 (1956).
C43,626/56

Vlăsin, Z., Filkuka, J.: "Beeinflussung der Stressantwort des Thymus und der Hibernationsdrüse der Ratte durch Veränderung der Reaktionslage des Nervensystems" (Modification of stress response of thymus and hibernating gland of rat by change in reactive state of nervous system). *Naunyn Schmiedebergs Arch. Pharmakol.* **227**: 414-426 (1956).
J25,025/56

In rats, the thymolysis and the degranulation of the hibernating gland elicited by formalin-induced stress is prevented by adrenalectomy.

Comsa, J.: *Physiologie et Physiopathologie du Thymus* (Physiology and pathophysiology of the thymus), p. 150. Paris: Doin Edit., 1959.
C89,310/59

Monograph on the physiopathology of the thymus, with special reference to the effects of stress (542 refs.).

Newcomer, W. S., Connally, J. D.: "The bursa of Fabricius as an indicator of chronic stress in immature chickens." *Endocrinology* **67**: 264-266 (1960).
J23,125/60

Mellgren, J., Lundin, P. M.: "Proliferative reaction of lymphoid tissues in stress and to pituitary hormones." *Milit. Med.* **125**: 248-252 (1960).
C86,705/60

Description of conditions under which stress may cause an irregular enlargement of lymphoid tissues with an accumulation of pyroninophil cells possibly related to increased STH secretion and conducive to changes in immune reaction.

Gourwitch, G., Klimentova, A., Kocorine, I.: "La réaction plasmocytaire dans le syndrome général de l'adaptation" (The plasmocytic reaction in the general adaptation

syndrome). *Rev. Can. Biol.* **20**: 805-811 (1961).
J22,947/61

Bartolini, G., Berti, P.: "Istopatologia del timo di 'Mus ratus albinus' nel benzolismo cronico sperimentale" (Thymus histopathology in "Mus ratus albinus" after chronic experimental benzolism). *Arch. Vecchi Anat. Patol.* **63**: 777-786 (1964).
G32,118/64

Chronic benzol intoxication produces a typical G.A.S. with conspicuous thymus involution in the rat.

Miller, J. F. A. P., Dukor, P.: *Die Biologie des Thymus nach dem heutigen Stande der Forschung* (The present status of thymus biology), p. 98. Basel and New York: S. Karger, 1964.
E4,014/64

Monograph on the present status of thymus physiology, in which only cursory reference is made to the thymus involution induced by stress. Its possible significance in the immunologic responses of adults is difficult to appraise (several hundred refs.).

Chatten, J.: "The thymus in systemic disease." *Am. J. Med. Sci.* **248**: 715-727 (1964).
G22,047/64

Survey of the literature on stress-induced thymus involution in children (154 refs.).

Fleming, W. R., Pasley, J. N.: "Effect of cold shock, disease, and mammalian corticoids on the spleen of Lepomis machrochirus." *Proc. Soc. Exp. Biol. Med.* **120**: 196-199 (1965).
F53,560/65

In the blue-gill fish, cortisol causes splenic hypertrophy. DOC and various stressors induce atrophy with pigment deposition in the spleen.

Vaškù, J., Urbánek, E., Doležel, S.: "Über den abweichenden Verlauf der Alarmreaktion im lymphoepithelialen und lymphoreticularen Gewebe unter dem Einfluss von K-Mg-Aspartat" (Irregular evolution of the alarm reaction in lymphoepithelial and lymphoreticular tissues under the influence of K-Mg-aspartate). *Arzneim. Forsch.* **16**: 559-565 (1966).
F65,898/66

In rats, the development of the alarm reaction can be modified by K-Mg-aspartate.

Snapper, A. G., Schoenfeld, W. N., Locke, B.: "Adrenal and thymus weight loss in the food-deprived rat produced by random ratio punishment schedules." *J. Comp. Physiol. Psychol.* **62**: 65-70 (1966).
G44,900/66

Kendler, J., Harry, E. G.: "Systemic Escherichia coli infection as a physiological

stress in chickens." *Res. Vet. Sci.* **8**: 212-218 (1967). J23,505/67

In chickens, *coli* septicemia caused a characteristic stress syndrome with involution of the spleen and bursa, associated with increased bursal β -glucuronidase.

Goldstein, G., MacKay, I. R.: "The thymus in systemic lupus erythematosus: a quantitative histopathological analysis and comparison with stress involution." *Br. Med. J.* May 20, 1967, pp. 475-478. F81,223/67

In man, stress involution reduced the thymus cortex and caused the appearance of epithelial cell aggregates in the medulla with cystic Hassall's corpuscles. In lupus erythematosus, there was complete cortical atrophy due to lymphocyte depletion and disorganization of the medulla, which was largely occupied by epithelial cell aggregates and cystic Hassall's bodies. The number of plasma cells increased and germinal centers were present in two cases. "Our interpretation is that the thymus in systemic lupus erythematosus is a target organ. There is histological evidence of extreme stress involution and of an autoimmune reaction which could augment changes usually associated with stress involution."

Huston, T. M., Subhas, T.: "The influence of environmental temperature upon adrenal activity of bursectomized chicks." *Poultry Sci.* **47**: 1760-1763 (1968). J23,073/68

Although earlier experiments had shown that severe stress causes involution of the bursa in chicks, moderate cold has no such effect. In bursectomized chicks, adrenal ascorbic acid content diminishes, particularly after exposure to stress.

Zimin, I. I.: "Changes in hematopoiesis in rats under stress." *Biull. Éksp. Biol. Med.* **68**: No. 7: 19-22 (1969) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **68**: 715-717 (1969). J24,918/69

"In rats under stress [repeated electroshocks] a decrease in the number of cells in the lymphoid organs was accompanied by an increase in the number of lymphocytes in the bone marrow. The total number of cells in the thymus and spleen rose after an initial decrease. The number of lymphocytes in the bone marrow fell, after an initial increase, to its original level, and this was accompanied by activation of granulocytopoiesis. More prolonged exposure to stress led to a decrease in the total number of myelokaryocytes, re-

peated involution of the thymus, and lymphocytopenia."

Lucas, D. R., Peakman, E. M.: "Ultrastructural changes in lymphocytes in lymphnodes, spleen and thymus after sublethal and supralethal doses of x-rays." *J. Pathol.* **99**: 163-169 (1969). G72,305/69

The EM changes induced by ionizing irradiation in various lymphatic organs are described and well illustrated.

Pora, E. A., Toma, V.: "L'involution normale et accidentelle du thymus" (Normal and accidental thymus involution). *Ann. Endocrinol.* (Paris) **30**: 519-531 (1969). G72,660/69

Speculations concerning the adaptive value of stress-induced thymus involution.

Iusfina, E. Z., Iakovleva, A. N.: "Some structural and biochemical changes in the organs of thymico-lymphatic system in stress." *Patol. Fiziol. Éksp. Ter.* **13** Nos. 3-4: 23-26 (1969) (Russian). J22,294/69

Gorizontov, P. D.: "Role of the hypophyso-corticoadrenal system in the pathogenesis of stress conditions (Changes in the hematopoietic organs)." *Vestn. Akad. Med. Nauk SSSR* **24**: 23-34 (1969) (Russian).

J22,893/69

Zimin, I. I., Ermolaeva, N. V.: "Cellular depletion of the thymus and of the spleen of rats in stress-reaction." *Probl. Endocrinol.* **16** No. 1: 96-101 (1970) (Russian).

J22,357/70

Review of the stress syndrome with special emphasis upon the thymic and splenic involution produced by electroshock in rats.

Gorizontov, P. D., Belousova, O. I., Zimin, I. I.: "Role of the adrenal glands in hematopoietic organ changes in the beginning period of the stress reaction." *Patol. Fiziol. Éksp. Ter.* **14** Nos. 3-4: 38-44 (1970) (Russian).

J21,367/70

In rats, adrenalectomy failed to prevent the elevation of lymphocyte counts in bone marrow and the liberation of mature lymphocytes into the blood following exposure to stressors (e. g. electroshock). However, it depressed the activation of myelopoiesis normally seen during stress. "The authors claim that migration of lymphocytes into the bone marrow and mobilization of granulocyte reserves of the bone marrow bear the character of an emergency reaction, primarily conditioned by altered tone of the sympa-

thetic nervous system, whereas activation of myelopoiesis depends upon the action of corticosteroids."

Oksanen, A.: "Multilocular fat in thymuses of rats and mice associated with thymus involution: a light- and electronmicroscope and histochemical study." *J. Pathol.* **105**: 223-226 (1971). G89,299/71

Various stressors (formaldehyde, starvation, forced exercise) cause the appearance of both brown multilocular and common white monolocular fat in the involuting thymuses of the mouse and rat. The associated enzyme histochemical and EM changes are also described.

Gelfand, D. W., Goldman, A. S., Law, E. J., MacMillan, B. G., Larson, D., Abston, S., Schreiber, J. T.: "Thymic hyperplasia in children recovering from thermal burns." *J. Trauma* **12**: 813-817 (1972). G94,744/72

In children recovering from burns, the thymus is often enlarged.

Henning, W., Möllmann, H., Kindler, J., Reisch, J., Alfes, H.: "Einfluss von synthetischen Glucocorticoiden und von Metopiron auf ketosteroidhaltige Zellen des postnatalen Kaninchenthymus" (The influence of synthetic glucocorticoids and of metopryrone on the ketosteroid-containing cells of the postnatal rabbit thymus). *Z. Zellforsch. Mikrosk. Anat.* **143**: 37-44 (1973).

J7,271/73

In rabbits, administration of glucocorticoids beginning immediately after birth causes a marked increase in NAHD-positive KS granules (Camber reaction). Metopryrone elicits an opposite response. These cells, which are regarded as eosinophils, apparently transform circulating glucocorticoids into KS, a process associated with thymus lesions characteristic of the alarm reaction.

Seifter, E., Rettura, G., Zisblatt, M., Levenson, S. M., Levine, N., Davidson, A., Seifter, J.: "Enhancement of tumor development in physically-stressed mice inoculated with an oncogenic virus." *Experientia* **29**: 1379-1382 (1973). H80,975/73

In rats, restraint by a partial body-cast produced the typical manifestations of systemic stress and at the same time increased susceptibility to the tumorigenic action of murine sarcoma virus. In the restrained animals, "there appeared to be a smaller number of small lymphocytes due to stress and a proliferation of epithelioid elements.

Hassal bodies were also involved in agreement with earlier findings of Selye. If stress or cortisone treatment result in impaired function of these structures, then the endocrine function of the thymus gland as well as its role in providing circulating cells would be disturbed." In any event, the response of the thymus during stress is assumed to increase susceptibility to the virus through interference with immune reactions.

Gorizontov, P. D.: "Regularities of the nonspecific reaction of haemopoietic organs to the action of extreme stimulators (stressors)." *Arkh. Patol.* **35** No. 8: 1-11 (1973).

J7,647/73

Studies on the bone marrow, spleen and thymus of various species, particularly the rat, after exposure to diverse stressors (electroshock, restraint, hemorrhage, x-rays, cold, drugs and so on). Moderate stress produces transient hyperplasia of the myeloid tissue.

Zimin, I. I.: "Increase of emigration of cells from the thymus of rats at the initial period of stress-reaction." *Izv. Akad. Nauk SSSR [Biol.]* **4**: 517-524 (1973) (Russian).

J25,193/73

Gorizontov, P. D.: "Stress and the reaction of the hematopoietic organs (the question of the role of pathological physiology in the development of theoretical medicine)." *Patol. Fiziol. Éksp. Ter.* **10** No. 2: 3-6 (1974) (Russian).

J24,152/74

Dourov, N.: "Study of the cytoplasmic lipids in thymic involution." *Pathol. Eur.* **9**: 43-57 (1974).

J19,465/74

"A large number of lipid and small paraldehyde-fuchsinophilic granules are found in the reticular cells of the thymus cortex after the involution following a single injection of hydrocortisone. However, after regeneration nearly all these granules disappear. The ultrastructure of the reticular cells indicates their mesenchymal nature. They contain granular, vesicular and lamellar inclusions showing acid phosphatase activity. In the human species, 'inverted thymuses' contain a considerable amount of lipids in reticular cells that have phagocytized debris of thymocytes destroyed during involution. These cells contain also small paraldehyde fuchsinophil granules. In the atrophic thymuses, in infants, these are coarse, acid-resistant and auto-fluorescent. Their ultrastructure is similar to that observed in rats."

Blood Cells, Blood Volume

In most species, the alarm reaction is characterized by pronounced eosinopenia, lymphopenia and polymorphonuclear leukocytosis. These hematologic changes usually parallel the involution of the thymicolumphatic apparatus.

The lymphocytopenia characteristic of corticoid excess during stress probably results from a decreased outpouring of lymphocytes from the thymus and lymph nodes. ACTH diminishes the lymphocyte count in the thoracic duct within fifteen to thirty minutes.

ACTH and glucocorticoids produce essentially similar changes in blood count, which —like the corresponding changes elicited by stressors—are inhibited by adrenalectomy. In fact, eosinopenia and lymphopenia are used as standard indicators of glucocorticoid secretion, even in patients treated with ACTH or exposed to stressors. Curiously, hypophysectomy only partially blocks the eosinopenia induced by stress, although it does not prevent that elicited by ACTH.

As might be expected, destruction of the hypothalamic areas responsible for ACTH secretion prevents stress-induced eosinopenia.

A variety of stressors produce "*stress polycythemia*" manifested by a normal erythrocyte mass but a high hematocrit reading, secondary to contracted plasma volume. It is often associated with hypertension.

Allegedly, various stressors producing a typical G.A.S. cause plasma cell proliferation, ascribed to increased secretion of STH.

In pregnant women, aggregation of circulating neutrophils into clumps has been described as a "leukoergic phenomenon."

Several authors speak of "*stress reticulocytes*," which may be a source of erythropoietic bilirubin formation. Allegedly, in adrenalectomized mice, stressors produce a paradox lymphocytosis which cannot be prevented by splenectomy and hence is not merely the result of evacuating the splenic reservoir. A special type of "*stress lymphocyte*" has also been described, it being characterized by a large, purely basophilic cytoplasm. However, these findings, published about twenty years ago, have not been subjected to more detailed investigation in recent years.

Blood Cells, Blood Volume

(See also our earlier stress monographs, p. xiii)

Harlow, C. M., Selye, H.: "The blood picture in the alarm reaction." *Proc. Soc. Exp. Biol. Med.* **36**: 141-144 (1937).

A8,400/37

In mice and rats the alarm reaction produced by EP, formalin, cold, forced muscular exercise or traumatic shock is associated with polymorphonuclear leukocytosis and pronounced lymphopenia. These alterations are not specific and roughly parallel the involution of the thymicolumphatic apparatus. [This was the first publication on changes in the peripheral blood count caused by stress (H.S.).]

Dalton, A. J., Selye, H.: "The blood picture during the alarm reaction." *Folia Haematol.* (Leipz.) **62**: 397-407 (1939).

A31,950/39

"It appears that the so-called non-specific leukocytosis, preceded by a decrease and followed by an increase in eosinophils, is a constant feature of the alarm reaction." This view is based on personal observations on formalin-induced stress in the rat and on a survey of the literature on the hematologic effects of various agents whose stressor activity has since been recognized.

Selye, H., Dosne, C., Bassett, L., Whitaker, J.: "On the therapeutic value of adrenal cortical hormones in traumatic shock

and allied conditions." *Can. Med. Assoc. J.* **43**: 1-8 (1940). A32,768/40

During the shock phase of the alarm reaction produced by heavy formaldehyde dosage in the rat, there is hypochloremia, hypoglycemia and hemoconcentration, all of which can be at least partially inhibited by a crude cortical extract (cortin). This is even more obvious in surgical shock produced by partial hepatectomy, but here a specific effect of hepatic insufficiency could not be excluded.

Dougherty, T. F., White, A.: "Influence of hormones on lymphoid tissue structure and function. The role of the pituitary adrenotropic hormone in the regulation of the lymphocytes and other cellular elements of the blood." *Endocrinology* **35**: 1-14 (1944). A94,353/44

In mice, rats and rabbits, single injections of ACTH produce absolute lymphopenia and an increase in polymorphonuclear leukocytes. These changes are prevented by adrenalectomy and resemble those of the alarm reaction in which probably "non-specific factors cause some of their effects on lymphoid tissue through the pituitary adrenal cortex relationship, although large doses of toxic agents may have a direct action on lymphoid cells."

Elmadjian, F., Pincus, G.: "The adrenal cortex and the lymphocytopenia of stress." *Endocrinology* **37**: 47-49 (1945).

B366/45

In mice, both restraint and exposure to cold produce a typical stress lymphocytopenia.

Reinhardt, W. O., Li, C. H.: "Depression of lymphocyte content of thoracic duct lymph by adrenocorticotropic hormone." *Science* **101**: 360-361 (1945). 85,615/45

In intact but not in adrenalectomized rats, intraperitoneal or subcutaneous ACTH caused a rapid decrease of lymphocytes in the thoracic duct lymph within fifteen to thirty minutes. No such effect was obtained by pure STH or LTH. The lymphocytopenia characteristic of corticoid excess (such as occurred during stress) probably results from a reduced outpouring of lymphocytes from the thymus and lymph nodes.

Pincus, G., Elmadjian, F.: "The lymphocyte response to heat stress in normal and psychotic subjects." *J. Clin. Endocrinol.* **6**: 295-300 (1946). B1,243/46

Normal men exposed to 40.5-44.0°C at 85 to 95 percent relative humidity exhibited

marked "stress lymphocytopenia," attributed to increased corticoid secretion. "With the short-time stress employed here it is entirely likely that we are dealing with the first stage of the adaptation syndrome which involves adrenocortical hypersecretion as the result of the pituitary stimulation." By contrast, twenty out of twenty-one psychotic (mostly schizophrenic) subjects exhibited a rise in blood lymphocytes after heat exposure.

Long, C. N. H.: "Recent studies on the function of the adrenal cortex." *Bull. N.Y. Acad. Med.* **23**: 260-282 (1947).

B35,087/47

Review of the literature and personal observations concerning the lymphopenia and the "anamnestic reaction" produced by stressors and corticoids.

Pincus, G.: "Studies of the role of the adrenal cortex in the stress of human subjects." *Rec. Prog. Horm. Res.* **1**: 123-145 (1947). 98,426/47

Excellent review on the biochemical changes characteristic of the G.A.S. in man, with special reference to 17-KS excretion and blood count under the influence of circadian variations, the stresses of daily life, operating a Hoagland-Werthessen pursuit meter, flying and exposure to heat. The response of schizophrenics is abnormal in many respects, and the question is raised whether adrenal malfunction may play a pathogenic role in mental disease (20 refs.).

Gellhorn, E., Frank, S.: "Sensitivity of the lymphopenic reaction to adrenalin." *Proc. Soc. Exp. Biol. Med.* **69**: 426-429 (1948).

B28,597/48

In intact but not in adrenalectomized rats, intraperitoneal EP causes neutrophilia and lymphopenia.

Hills, A. G., Forsham, P. H., Finch, C. A.: "Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotropic hormone (ACTH) in man." *Blood* **3**: 755-768 (1948). B33,083/48

In man, ACTH causes pronounced lymphopenia and eosinopenia with a moderate polymorphonuclear leukocytosis. The comparable blood count changes associated with the alarm reaction are ascribed to endogenous ACTH secretion.

Hungerford, G. F.: "Effect of epinephrine in decreasing number of circulating mononuclear leucocytes in the rat." *Proc. Soc. Exp. Biol. Med.* **70**: 356-358 (1949).

B31,654/49

EP decreases the number of circulating mononuclear leukocytes in intact and adrenomedullated rats, but does not do so after complete adrenalectomy, and only slightly after hypophysectomy.

Speirs, R. S., Meyer, R. K.: "The effects of stress, adrenal and adrenocorticotropic hormones on the circulating eosinophils of mice." *Endocrinology* **45**: 403-429 (1949).

E56,284/49

Detailed description of the determination of blood eosinophils in mice and rats as an indicator of stress. Adrenalectomy prevented the response to both rough handling and EP injections, but did not do so after treatment with adrenocortical extract. Hypophysectomy did not prevent the response to ACTH, but curiously it only partially blocked eosinopenia after stress.

Pincus, G.: "Adrenal cortex function in stress." *Ann. N.Y. Acad. Sci.* **50**: 635-645 (1949).

B37,780/49

General review on changes in adrenocortical function during stress and psychiatric illness. Special emphasis is placed upon blood sugar, blood lymphocytes, corticoids and 17-KS.

Love, W. D.: "Failure of adrenalectomy immediately following stress to prevent eosinopenia in rats." *Proc. Soc. Exp. Biol. Med.* **75**: 639-641 (1950).

B54,242/50

In rats, adrenalectomy ten minutes after EP injection does not prevent stress-eosinopenia. Apparently, ACTH and corticoid discharge occurs almost immediately following application of the stressor.

Taylor, R. H., Gross, M., Ruby, I. J.: "Nonconvulsive electrostimulation and the pituitary-adrenocortical system." *J. Nerv. Ment. Dis.* **114**: 377-383 (1951).

J8,693/51

Both convulsive and nonconvulsive electrostimulation produce marked eosinopenia even in schizophrenic patients, although earlier investigators claimed that they usually failed to show such a response. Pentothal anesthesia did not prevent this eosinopenia which was therefore not attributed to stress but to a direct action of electric current on the hypothalamus. The literature on the effect of electroshock upon blood eosinophils is reviewed (17 refs.).

Bacchus, H.: "Leukocyte response to stress in normal and adrenalectomized rats

pretreated with ascorbic acid." *Proc. Soc. Exp. Biol. Med.* **77**: 167-169 (1951).

B59,311/51

In rats, stress caused by sham adrenalectomy induces eosinopenia with polymorphonuclear leukocytosis developing within three hours. Pretreatment with ascorbic acid or adrenalectomy prevents and may even reverse the eosinopenia.

Kuhl, W. J. Jr., Ralli, E. P.: "Effect of acute stress upon blood constituents, white cells, and urine constituents in normal individuals." *Proc. Assoc. for the Study of Internal Secretions—33rd. Meeting*, p. 51. Atlantic City, N.J., 1951. Also in: *J. Clin. Endocrinol. Metab.* **11**: 776 (1951).

B58,505/51

Normal men immersed in cold water (9.5°C) for eight minutes showed: "1—A decrease in temperature (immediate, 1 and 2 hours); 2—An increase in systolic and diastolic blood pressure (immediate) and a decrease (2 hours); 3—A decrease in heart rate (1, 2 and 4 hours); 4—An increase in neutrophiles (immediate); 5—A decrease in lymphocytes (2 hours); 6—A decrease in eosinophiles (2 hours); 7—A decrease in serum chloride (immediate); 8—An increase in total proteins (immediate and 4 hours); 9—A decrease in serum water (immediate); 10—An increase in total cholesterol (4 hours); 11—An increase in the urine uric acid/creatinine ratio (2 and 4 hours)." All of these changes were significant and ascribed to stress, but no one indicator gave uniformly positive results.

Faurbye, A., Vestergaard, P., Kobbernagel, F., Nielsen, A.: "Adrenal cortical function in chronic schizophrenia (Stress, adrenaline-test, ACTH-test)." *Acta Endocrinol. (Kbh.)* **8**: 215-246 (1951).

B63,996/51

In man, EP treatment and the production of fever by injections of killed *B. faecalis alcaligenes* are regarded as adequate "stress tests" as indicated by the increase in uric acid and potassium excretion as well as by the hematologic changes that result.

Fisher, B., Fisher, E. R.: "Observations on the eosinophil count in man. A proposed test of adrenal cortical function." *Am. J. Med. Sci.* **221**: 121-132 (1951).

B63,230/51

Dougherty, T. F., Kumagai, L. F.: "Influence of stress stimuli on lymphatic tissue of adrenalectomized mice." *Endocrinology* **48**: 691-699 (1951).

B60,246/51

Mice stressed two hours after adrenalectomy developed a significant lymphocytosis lasting several hours, which is the reverse of the response seen in intact animals. After adrenalectomy, the lymphatic organs of mice in sublethal anaphylaxis were actually enlarged. The stress lymphocytosis was not prevented by splenectomy, and hence could not be ascribed to an evacuation of the splenic reservoir. The findings "are compatible with the concept that the stimulus of stress not only augments pituitary adrenocortical secretion which inhibits lymphatic tissue growth, but also augments, directly or indirectly, lymphatic tissue growth promoting influences unrelated to adrenocortical secretion."

Dougherty, T. F.: "Effect of hormones on lymphatic tissue." *Physiol. Rev.* **32**: 379-401 (1952). B75,769/52

Extensive review on the effect of stress, and of hormones produced during stress, upon thymicolympathic tissue and blood count, including the development of "stress lymphocytes."

Dougherty, T. F., Frank, J. A.: "Relative adrenocortical insufficiency determined by morphological alterations in lymphocytes." *Am. J. Physiol.* **171**: 721 (1952).

B77,237/52

Stressors produce lymphopenia in intact mice, whereas they cause lymphocytosis after adrenalectomy owing to the excessive development of hyaline lymphocytes. The latter can be prevented by cortisol.

Dreyfuss, F., Feldman, S.: "Eosinopenia induced by emotional stress." *Acta Med. Scand.* **144**: 107-113 (1952). B82,162/52

Eosinopenia occurred in medical students just before examinations, and sometimes persisted even later. The same phenomenon was noted in women during the anxiousness prior to diagnostic curettage, and this was "ascribed to the considerable emotional stress undergone in the two situations."

Bacchus, H., Altszuler, N.: "Eosinophil response to stress in ascorbic acid pretreated mice." *Endocrinology* **51**: 1-4 (1952).

B74,531/52

In mice, ascorbic acid pretreatment prevents the eosinopenia caused by EP but not that elicited by ACTH. "These observations were interpreted as indicating that the vitamin operated in this mechanism by depressing the release of pituitary corticotrophic hormone."

Kuhl, W. J. Jr., Wilson, H., Ralli, E. P.: "Measurements of adrenal cortical activity in young men subjected to acute stress." *J. Clin. Endocrinol. Metab.* **12**: 393-406 (1952). B69,085/52

Normal men immersed in cold water for eight minutes exhibited significant eosinopenia, lymphopenia and hypochloremia, with increased ascorbic acid and uric acid excretion. Serum sodium, potassium, blood sugar and ascorbic acid were not significantly altered.

Ellestad, M. H., Reed, J.: "Circulating eosinophils in cardiovascular stress." *Ann. Intern. Med.* **36**: 551-561 (1952).

J22,938/52

Lawrence, J. H., Berlin, N. I.: "Relative polycythemia—the polycythemia of stress." *Yale J. Biol. Med.* **24**: 498-505 (1952).

B74,019/52

Patients under intense psychogenic stress may develop polycythemia.

Wake, R. F., Graham, B. F., McGrath, S. D.: "A study of the eosinophil response to exercise in man." *J. Aviat. Med.* **24** Supp., Sect. 2: 127-130 (1953). J23,815/53

In healthy young men, physical exercise—like other stressors—causes eosinopenia.

Frank, J. A., Dougherty, T. F.: "Evaluation of susceptibility to stress stimuli determined by stress lymphocytes" (abstracted). *Fed. Proc.* **12**: 45 (1953). B78,552/53

Louch, C., Meyer, R. K., Emlen, J. T.: "Effect of stress on diurnal fluctuations in eosinophils of the laboratory mouse." *Proc. Soc. Exp. Biol. Med.* **82**: 668-671 (1953).

B82,222/53

In mice, there are pronounced circadian variations in eosinophil counts, showing peaks during the day and drops during the night, presumably owing to the characteristic nocturnal activity of this species. Exposure to cold decreased the eosinophil count but did not eliminate the circadian fluctuations. Presumably, nocturnal activity in these experiments acted as a secondary stress superimposed upon the sustained stress of exposure to cold. "The adrenal gland of the mouse exposed to cold is capable of responding further to the daily stress of nocturnal activity."

Thorn, G. W., Jenkins, D., Laidlaw, J. C.: "The adrenal response to stress in man." *Rec. Prog. Horm. Res.* **8**: 171-215 (1953).

B73,567/53

Extensive review lecture on clinical indices of adrenal responses to stress in man, and the role of the G.A.S. in the pathogenesis of diseases of adaptation. Special emphasis is placed upon reactivity to infusions of ACTH, corticoids and EP, as well as upon the diagnostic value of blood eosinophils and 17-KS excretion, as indicators of adrenocortical participation in stress responses (47 refs.).

Persky, H.: "Response to a life stress: evaluation of some biochemical indices." *J. Appl. Physiol.* **6**: 369-374 (1953).

J11,917/53

Pilots under training were subjected to various stressors (parachute jumps, physical exercise and so on) which caused a significant diminution in blood eosinophil and glutathione levels but did not affect the synthesis of hippuric acid from administered sodium benzoate. "These findings are taken to indicate that airborne training focal stresses are of intermediate severity on a scale whose poles are fear of failure and fear of bodily injury."

Thorn, G. W.: "The eosinophil, ACTH, epinephrin and stress." *Am. J. Med.* **14**: 139-140 (1953).

B88,002/53

Brief résumé on the value of eosinopenia in the assessment of stress and ACTH or glucocorticoid discharge in man under various conditions.

Dougherty, T. F., Frank, J. A.: "The quantitative and qualitative responses of blood lymphocytes to stress stimuli." *J. Lab. Clin. Med.* **42**: 530-537 (1953).

B92,713/53

In addition to the normal lymphocytes, the mouse has "stress lymphocytes" with a large, poorly basophilic cytoplasm. The lymphopenia induced by stress in intact mice is due to a decrease in the number of normal lymphocytes, whereas the stress lymphocyte count remains unchanged or even rises. Apparently, they are resistant to the lytic effect of glucocorticoids. "The production of stress lymphocytes is due to nonadrenocortically mediated effects of stressors which bring factors into play which increase the number of lymphocytes and induce specific cytologic changes."

Porter, R. W.: "I. Nervous system—Hormone interrelationships. The central nervous system and stress-induced eosinopenia." *Rec. Prog. Horm. Res.* **10**: 1-18 (1954).

B98,592/54

In rhesus monkeys the nervous regulation

of the pituitary-adrenocortical response to stress was demonstrated by the following observations: 1) Increased electrical activity was noted in the posterior hypothalamus on application of certain acute stress stimuli. 2) The integrity of the hypothalamus was essential for the production of stress-induced eosinopenia. 3) Electrical excitation of this region evoked a marked eosinopenia. It was concluded that although many regions of the brain can modify the eosinopenic response to an acute stress stimulus, the hypothalamus alone is essential for its manifestation."

Cowie, A. T., Ganong, W. F., Hume, D. M.: "The eosinopenic response to graded doses of hydrocortisone in the adrenalectomized dog with and without surgical trauma." *Endocrinology* **55**: 745-750 (1954).

C264/54

The eosinopenic effect of low doses of cortisol is increased by surgical trauma, even in adrenalectomized dogs. "These and other data throw doubt on the hypothesis that increased corticoid utilization is responsible for the pituitary release of ACTH in response to operative trauma."

Lundin, P. M., Schelin, U., Pellegrini, G., Mellgren, J.: "Plasma cell production in the adaptation syndrome." *Acta Pathol. Microbiol. Scand.* **35**: 339-356 (1954).

C9,986/54

In rats, various types of stressors eliciting a typical G.A.S. cause plasma cell proliferation, which has been ascribed to increased production of STH.

Dumm, M. E., Ralli, E. P.: "A critical analysis of the eosinophil response in rats to ACTH and cortisone." *Endocrinology* **54**: 71-80 (1954).

B88,876/54

In rats the eosinopenic effect of ACTH and cortisone can be modified by the pantothenate content of the diet. When eosinopenia is used as an indicator of stress, the influence of such conditioning factors must not be disregarded.

Stullken, D. E., Hiestand, W. A.: "Hematological changes influenced by short and long exposure to cold." *Proc. Soc. Exp. Biol. Med.* **86**: 253-255 (1954).

B95,324/54

In mice, brief or prolonged exposure to cold produced no significant change in blood hemoglobin or red cell count, but in the acute state raised the blood sugar level. These findings are discussed in relation to the G.A.S.

Alexander, F., Ash, R. W.: "The effect of emotion and hormones on the concentration

of glucose and eosinophils in horse blood." *J. Physiol.* **130**: 703-710 (1955).

C51,993/55

Neither handling, repeated venipuncture nor EP in doses large enough to produce hyperglycemia elicited eosinopenia in ponies. On the other hand, insulin hypoglycemia, histamine and ACTH in adequate doses did exert this effect.

Hoagland, H., Bergen, J. R., Bloch, E., Elmadjian, F., Gibree, N. R.: "Adrenal stress responses in normal men." *J. Appl. Physiol.* **8**: 149-154 (1955). C12,916/55

Manipulation of the Hoagland-Werthessen pursuit meter was used as a stress test. Young men (sixteen to twenty years) "appear to call very little on adrenal cortical mechanisms to meet stresses which enhance adrenocortical responses of older men. Eosinopenia correlates better with the urinary excretion" of EP than with that of 17-KS. Both are regarded as indicators of adrenocortical activity.

Hamilton, L. H., Lowenthal, J.: "Effect of heparin pretreatment on stress-induced leukocyte changes in the rat." *Endocrinology* **58**: 546-549 (1956). J25,028/56

Kerr, A. C.: "The effect of mental stress on the eosinophil leucocyte count in man." *Q. J. Exp. Physiol.* **41**: 18-24 (1956).

C35,686/56

Eosinopenia was observed in students during examinations in dental surgery. Controls performing similar operations in daily practice showed no such changes in blood counts.

MacFarlane, R. G.: "The reactions of the blood to injury." In: Florey, H., *General Pathology*, pp. 162-179. Philadelphia: W B Saunders, 1958. C67,909/58

Review on the effect of stressors upon blood in various species. The most characteristic type of response is an increase in neutrophils with a diminution of lymphocytes and particularly of eosinophils.

Southwick, C. H.: "Eosinophil response of C57BR mice to behavioral disturbance." *Ecology* **40**: 156-157 (1959). J11,123/59

When isolated male mice were brought together in groups of four or put into strange cages, pronounced eosinopenia resulted as a consequence of stress.

Hill, M., Dvořák, K., Pospíšil, M.: "Stress activation of adrenal glomerulosa." *Nature* **183**: 1819 (1959). C73,699/59

In rats, stress induced by formalin causes

neutrophilic leukocytosis, lymphopenia, eosinopenia and simultaneous activation of the zona glomerulosa in the adrenals.

Moyer, K. E., Bunnell, B. N.: "Relationship between emotional elimination, startle response, and blood count after stress." *J. Genet. Psychol.* **97**: 237-243 (1960).

J23,573/60

Ship, I. I., White, C. L.: "Physiologic response to dental stress." *Oral Surg.* **13**: 368-376 (1960).

J23,326/60

Eosinopenia occurred during various dental interventions.

McDonald, R. D., Yagi, K.: "A note on eosinopenia as an index of psychological stress." *Psychosom. Med.* **22**: 149-150 (1960).

C84,340/60

In subjects made to believe that they accidentally caused serious injury to a companion through misuse of explosives, attempts to repair an inoperative telephone switchboard in order to call for medical assistance led to pronounced eosinopenia. Controls asked to repair the same switchboard merely as a psychomotor test showed no such change. Hence, eosinopenia appears to be a reliable index of psychogenic stress.

Gollender, M., Law, O. T., Isaacson, R. L.: "Changes in the circulating eosinophil level associated with learned fear: conditioned eosinopenia." *J. Comp. Physiol. Psychol.* **53**: 520-523 (1960).

G50,316/60

In rats, intermittent electroshock causes eosinopenia. After conditioning, this reaction can be elicited by mere anticipation of shock.

Hall, C. E., Nash, J. B., Hall, O.: "Erythrocyte survival in normal and stressed rats." *Tex. Rep. Biol. Med.* **19**: 769-773 (1961).

D99,575/61

Forssberg, A., Tribukait, B., Vikterlöf, K.-J.: "Early blood leucocyte changes in mice and guinea pigs following X-irradiation and stress caused by operative manipulations." *Acta Physiol. Scand.* **52**: 1-7 (1961).

D7,253/61

Hazelwood, R. L., Wilson, W. O.: "Comparison of hematological alterations induced in the pigeon and rat by fasting and heat stress." *Comp. Biochem. Physiol.* **7**: 211-219 (1962).

J23,447/62

Gindin, A. P., Ogienko, N. M., Ushakova, A. V.: "Ribonucleic acid in the lymphocytes during adrenal lymphocytosis. (Data relating to the mechanisms of the general adaptation

syndrome)." *Biull. Éksp. Biol. Med.* **54** No. 9: 62-64 (1962) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **54**: 998-1000 (1962).

J25,032/62

In horses in which stress was produced by EP injections, "the number of RNA-saturated lymphocytes doubled in 4 minutes and increased 2.5-fold in 2 hours, 3-fold in 24 hours, but in 48 hours it dropped almost to the normal level. Adrenal lymphocytosis occurred mainly at the expense of RNA-rich lymphocytes."

Rigano, A.: "Osservazioni e ricerche sulla leucoergia gravidica" (Observations and research on the leukoergic phenomenon of pregnancy). *Monit. Ostet. Ginecol.* **33**: 34-46 (1962).

D24,465/62

The "leukoergic phenomenon" occurs in women during pregnancy and is allegedly characteristic of the G.A.S. It consists of aggregation of circulating neutrophils into clumps.

Jovy, D., Brüner, H., Klein, K. E., Wegman, H. M.: "Adaptive responses of adrenal cortex to some environmental stressors, exercise and acceleration." In: Martini, L. and Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, Vol. 2, pp. 545-553. New York and London: Academic Press, 1965.

E5,499/65

Plasma corticoid and eosinophil determinations in healthy young men exposed to several stressors encountered during space flights (hypoxia, cold, heat, acceleration, muscular work). The results of exposure to these stressors alone or in various combinations are taken as an expression of individual sensitivity towards stress, and offer a criterion of practical importance.

Zlody, R. L.: "Changes in three blood components as a result of a stress situation." *Psychosomatics* **7**: 14-18 (1966).

F61,990/66

In male graduate students a stressful examination causes a shift of the blood acid-base level to the alkaline direction, an increase in red-cell count and leukocytosis (21 refs.).

Mendels, J.: "Stress polycythemia." *Am. J. Psychiatry* **123**: 1570-1572 (1967) (12 refs.).

G47,203/67

Burton, R. R., Sluka, S. J., Besch, E. L., Smith, A. H.: "Hematological criteria of chronic acceleration stress and adaptation." *Aerosp. Med.* **38**: 1240-1243 (1967).

G63,027/67

Card, R. T., Valberg, L. S.: "Characteristics of shortened survival of stress erythrocytes in the rabbit." *Am. J. Physiol.* **213**: 566-572 (1967).

F88,152/67

Dasgupta, S. R., Mukherjee, B. P.: "Effect of chlordiazepoxide on eosinopenia of stress in rabbits." *Nature* **213**: 199-200 (1967).

F75,231/67

Sasaki, J.: "Effects of tooth extraction on the eosinophile count." *Shikwa Gaku* **67**: 1463-1473 (1967).

J24,724/67

Anderlik, P., Bános, S., Szeri, H.: "Stress reaction of mice treated with antilymphocyte serum." *Acta Microbiol. Acad. Sci. Hung.* **15**: 327-330 (1968).

G66,896/68

"Stress-induced lymphopenic reaction decreased or failed to occur in mice treated previously with antilymphocyte serum."

Sasa, S., Takaku, F., Chiba, S., et al.: "Pathology of pseudopolycythemia (stress erythrocytosis)." *Naika* **21**: 153-158 (1968).

J24,618/68

Prabhu, S., Sharma, V. N.: "Study of thermal stress induced haematological changes and their modification by chlorpromazine in rats." *Indian J. Med. Res.* **56**: 742-753 (1968).

G61,228/68

Golikov, P. P., Popova, A. M.: "Corticosterone secretion and some indices of stress reaction." *Patol. Fiziol. Éksp. Ter.* **13** No. 1: 71-72 (1969) (Russian).

J22,379/69

In rats, neither the corticosterone and ascorbic acid content of the adrenals nor the blood eosinopenia is an accurate indicator of the intensity of stress caused by restraint, but both do give approximations of it.

Jensen, M. M.: "Changes in leukocyte counts associated with various stressors." *J. Reticuloendothel. Soc.* **6**: 457-465 (1969).

G71,085/69

In mice exposed to various stressors (avoidance-learning, confinement, high-intensity sound), a stress leukopenia developed which could be prevented by adrenalectomy.

Zimin, I. I.: "On the mechanism of lymphopenia in stress." *Patol. Fiziol. Éksp. Ter.* **13** Nos. 5-6: 36-39 (1969) (Russian).

J22,297/69

Observations in rats suggest that "lymphopenia in electrostimulation may result from intensified migration of cells from the blood circulation not compensated by their supply."

Benitone, J., Kling, A.: "Polycythemia of stress in psychiatric hospital populations." *J. Psychosom. Res.* **14**: 105-108 (1970).

G74,356/70

"The significantly higher incidence of polycythemia of stress in the psychiatric patient population is felt to confirm the hypothesis that individuals known to suffer chronic emotional stress have a significant tendency to manifest this physiologically by an elevation of the hematocrit and hemoglobin."

Rothman, I. K., Zanjani, E. D., Gordon, A. S., Silber, R.: "Nucleoside deaminase: an enzymatic marker for stress erythropoiesis in the mouse." *J. Clin. Invest.* **49**: 2051-2067 (1970).

H31,285/70

Hypoxia, hemorrhage, and phenylhydrazine were used as stressors. "The persistence of high levels of nucleoside deaminase for the full life span of a generation of erythrocytes formed during stress, viewed in contrast to the virtual absence of the enzyme from normal erythrocytes of all ages, represents an enzymatic difference between the normal red blood cell and the cell produced under conditions of accelerated erythropoiesis" (87 refs.).

Robinson, S. H., Tsong, M.: "Hemolysis of 'stress' reticulocytes: a source of erythropoietic bilirubin formation." *J. Clin. Invest.* **49**: 1025-1034 (1970).

H24,148/70

Lewi, S., Vibert, J.-F., Quillot, J.-M.: "La pseudo-polyglobulie. Observations personnelles et revue de la littérature" (Pseudo-polycythemia. Personal observations and literature review). *Rev. Méd. Psychosom.* **12**: 41-53 (1970).

J21,829/70

"Pseudo-polycythaemia is defined as a reduction of the plasma volume, the red cell volume remaining within the normal range." It is often induced by stressors.

Anderlik, P., Báños, Z., Szeri, I., Koltay, M., Virág, I.: "Response to stressors of mice undergoing graft-versus-host reaction." *Experientia* **26**: 94-95 (1970).

H21,168/70

In mice, intravenous injection of homologous splenic cells causes lymphopenia with body weight loss. Following such treatment, these animals no longer respond to a second stressor with further lymphopenia.

Vácha, J., Kačer, O.: "Attempt at quantitative analysis of interindividual variability in stress response of leucocyte levels in mice

from the viewpoint of control theory." *Bioophysik* **6**: 280-289 (1970).

J21,423/70

James, V. H. T., Horner, M. W., Moss, M. S., Rippon, A. E.: "Adrenocortical function in the horse." *J. Endocrinol.* **48**: 319-335 (1970).

H32,502/70

In the horse, surgical trauma or hypoglycemia increases plasma cortisol levels, whereas exercise is much less effective in this respect. The cortisol variations are not necessarily associated with changes in the eosinophil count. "It is concluded that the mechanisms of control of adrenocortical function in the horse are not dissimilar to those described for other mammalian species."

Pickford, G. E., Srivastava, A. K., Slicher, A. M., Pang, P. K. T.: "The stress response in the abundance of circulating leucocytes in the killifish, Fundulus heteroclitus. I. The cold-shock sequence and the effects of hypophysectomy." *J. Exp. Zool.* **177**: 89-96 (1971).

G83,471/71

In the killifish, brief immersion in very cold water causes peculiar waves of leukopenia followed by leukocytosis, a phenomenon ascribed to stress. Hypophysectomy inhibits the leukocytic phase.

Pickford, G. E., Srivastava, A. K., Slicher, A. M., Pang, P. K. T.: "The stress response in the abundance of circulating leucocytes in the killifish, Fundulus heteroclitus. II. The role of catecholamines." *J. Exp. Zool.* **177**: 97-108 (1971).

G83,472/71

Pickford, G. E., Srivastava, A. K., Slicher, A. M., Pang, P. K. T.: "III. The role of the adrenal cortex and a concluding discussion of the leucocyte-stress syndrome." *J. Exp. Zool.* **177**: 109-117 (1971).

G83,473/71

The singular leukocytic response of killifish is ascribed to stress. On the basis of some experiments, "a tentative interpretation of the cold-shock sequence is proposed on the assumption that catecholamines (presumably epinephrine) are leucopenic and that cortisol is leucocytic."

Hauss, W. H., Schmitt, G., Müller, U. S., Tillmann, P.: "Über die gleichförmige Reaktion des hämopoetischen Systems auf heterogene Reize" (Homogeneous reaction of the hematopoietic system to heterogeneous stimuli). *Med. Welt* **22**: 627-631 (1971).

H39,958/71

Gorizontov, P. D., Fedotova, M. I.: "Hematologic changes in rats following the multi-

fold action of a weak stimulus (the problem of stress)." *Patol. Fiziol. Éksp. Ter.* **15** Nos. 7-8: 35-38 (1971) (Russian).

J21,256/71

In contrast to strong electric stimuli, "a weak stimulus produced no leukocytosis, increase in the number of lymphoid cells in the bone marrow, or activation of myelopoiesis during the stage of mobilization, and no transitory marrow hypertrophy at the stage of resistance."

Weber, H.: "A quantitative study of eosinopenia and other stress indices." *J. Sports Med.* (Torino) **11**: 12-23 (1971) (37 refs.).

J21,823/71

Boyne, R., Fell, B. F.: "Observations on the alkaline phosphatase content of the neutrophil granulocytes of some laboratory and farm animals, with particular reference to the effects of intensive management and reproduction." *Res. Vet. Sci.* **13**: 347-355 (1972).

J19,597/72

Alkaline phosphatase activity in circulating polymorphonuclears was raised "under relatively mild conditions of stress in cattle, pigs and rats. Marked increases occurred in association with pregnancy in pigs, sheep and rabbits." The effect is presumably caused by enhanced corticoid secretion.

Yousef, M. K. el., Bakewell, W. E. Jr.: "The Gaisböck syndrome." *J.A.M.A.* **220**: 864 (1972). H55,016/72

The "Gaisböck syndrome" has been called a "stress polycythemia," as it often occurs in connection with psychic stress, particularly anxiety. It is associated with a number of biochemical and functional alterations characteristic of stress.

Wessels, F., Losse, H.: "Untersuchungen des Natriumtransports und -gehaltes der Erythrozyten unter Stresseinwirkung" (Studies on the sodium transport and content of erythrocytes under the effects of stress). *Med. Welt* **23**: 1394-1395 (1972).

H60,857/72

Müller, U. S., Schmitt, G., Hauss, W. H.: "Über Veränderungen des ^3H -Thymidinmarkierungsindex mononukleärer Rundzellen im Blut der Ratte nach verschiedenen Reizeinwirkungen" (Changes in the ^3H -thymidine labeling index of mononuclear round cells in the blood of rats after varied stimulation). *Med. Welt* **23**: 1396-1397 (1972).

H60,858/72

Kolczak, T., Bobek, S., Styczynski, H.:

"Effect of short-term stress on red cell and plasma volumes in the rabbit." *Bull. Acad. Pol. Sci. [Biol.]* **20**: 581-586 (1972).

H79,761/72

Rabbits were exposed to the stresses of: (1) being held by hind legs, head down, (2) immersion in ice-cold water, (3) vibration and (4) cold. "Each of the stress factors caused an increase in hematocrit value, and RBC, decrease in the plasma volume and no changes in the red cell volume. It was suggested that under short-term stress conditions a fluctuation of fluid between vascular bed and extravascular space occurs."

Berenbaum, M. C., Fluck, P. A., Hurst, N. P.: "Depression of lymphocyte responses after surgical trauma." *Br. J. Exp. Pathol.* **54**: 597-607 (1973). H82,462/73

In patients undergoing surgery, blood lymphocyte responses to phytohemagglutinin, pokeweed, mitogen and tuberculin fell in proportion to the severity, but not the length, of the operation. These changes could not be due to cortisol liberation, since the latter hormone itself does not duplicate them.

Makarov, I. A.: "Mechanisms of eosinopenia after stress," p. 15. Thesis, University of Gorkii, 1973 (Russian). J19,081/73

Smith, J. F. B., Lucie, N. P.: "Alcohol—a cause of stress erythrocytosis?" *Lancet* March 24, 1973, pp. 637-638. H67,158/73

In man, high ethanol intake causes "stress erythrocytosis" due to a reduced plasma volume.

Gońba, S., Gońba, M., Wilczok, T.: "The effect of trauma, in the form of intraperitoneal injections or puncture of the orbital venous plexus, on peripheral white blood cell count in rats." *Acta Physiol. Pol.* **25**: 339-345 (1974). J23,507/74

Emery, A. C. Jr., Whitcomb, W. H., Frohlich, E. D.: "Stress' polycythemia and hypertension." *J.A.M.A.* **229**: 159-162 (1974). H87,420/74

"'Stress' polycythemia is a term that refers to a disorder manifested by a normal red blood cell mass, but a high hematocrit reading secondary to a contracted plasma volume. The latter has been ascribed to a wide variety of stressful factors including emotional stress, chronic anxiety, alcoholism, and a variation of the normal state. Hypertension (perhaps too long associated with 'stress') has been closely associated with 'stress' polycythemia" (30 refs.).

Ahmed, A., Herman, C. M., Knudsen, R. C., Sode, J., Strong, D. M., Sell, K. W.: "Effect of exogenous and endogenous glucocorticosteroids on the in vitro stimulation of lymphocytes from sedated and awake-restrained healthy baboons." *J. Surg. Res.* **16**: 172-182 (1974). J12,487/74

In baboons, the stress of squeeze-cage manipulation and restraint decreases the relative and total blood lymphocyte counts. There is an associated suppression of methyl-³H-thymidine incorporation by unstimulated, as well as by T-cell mitogen- and B-cell mitogen-stimulated lymphocytes. Subsequent injection of methylprednisolone further inhibits this incorporation; however, exogenous corticoids affect the thymus-derived T-cells more than the bursa of Fabricius equivalent B-cells. The T-cells seem to be directly concerned with cell-mediated immunity and the B-cells with the production of humoral antibodies. Hence, the immunosuppressive effect of stress and glucocorticoids is probably one of the characteristic consequences of the thymicolymphatic involution and lymphopenia that have been recognized as a typical

stress effect since the first formulation of the G.A.S. concept.

Jacey, M. J., Tappan, D. V., Ritzler, K. R.: "Hematologic responses to severe decompression stress." *Aerospace Med.* **45**: 417-421 (1974) (26 refs.). J11,927/74

Leise, E. M., LeSane, F., Gray, I.: "Lymphocyte and polymorphonuclear enzymes in stress. III. Variations resulted from multiple bleedings and source of New Zealand white rabbits." *Biochem. Med.* **9**: 193-205 (1974). J11,684/74

Leise, E. M., LeSane, F., Gray, I.: "IV. Changes associated with an acute bacterial infection with *Diplococcus pneumoniae*." *Biochem. Med.* **9**: 206-213 (1974). J11,685/74

Leise, E. M., LeSane, F., Chambers, R. W., Gray, I.: "Lymphocyte and polymorphonuclear enzymes in stress. V. Changes associated with a viral infection: herpes simplex." *Biochem. Med.* **9**: 214-224 (1974). J11,686/74

Cardiovascular System

The intense effects that stress may exert upon the cardiovascular system are among the earliest manifestations of the emergency reaction in preparation for fight or flight, various forms of surgical and toxic shock and so on. Flushing of the face or pallor, and in predisposed individuals after chronic exposure, a great variety of cardiovascular diseases, are likewise indubitably related to the actions of stressors. These latter phenomena will be discussed at length in the section on Diseases of Adaptation.

Among the less frequently discussed cardiovascular manifestations of stress, let us merely mention that cardiac glycogen tends to be depleted and focal necroses may occur in rats exposed to acute stress situations. The associated functional changes (variations in the ECG, blood pressure and so on) will be dealt with later in the section on Functional Changes.

Cardiovascular System

(See also our earlier stress monographs, p. xiii)

Raab, W., Chaplin, J. P., Bajusz, E.: "Myocardial necroses produced in domesticated rats and in wild rats by sensory and emotional stresses." *Proc. Soc. Exp. Biol. Med.* **116**: 665-669 (1964). F17,034/64

"Wild rats exposed after periods of isolation to frightening noises (tape recording of hissing cat and squealing rat) displayed myo-

cardial necroses in nearly 70% of the experiments."

Sharma, V. N., Barar, F. S. K.: "Restraint stress as it influences the myocardium of rat." *Indian J. Med. Res.* **54**: 1102-1107 (1966). F77,431/66

In rats, "restraint stress" produces depletion of glycogen from the myocardium with round cell infiltration, edema, focal necrosis and fragmentation of fibers.

Geber, W. F., Anderson, T. A.: "Cardiac hypertrophy due to chronic audiogenic stress in the rat, *Rattus norvegicus albinus*, and rabbit, *Lepus cuniculus*." *Comp. Biochem. Physiol.* **21**: 273-277 (1967). F83,292/67

Geber, W. F., Anderson, T. A.: "Ethanol inhibition of audiogenic stress induced cardiac hypertrophy." *Experientia* **23**: 734-736 (1967). F88,482/67

Raab, W., Bajusz, E., Kimura, H., Herrlich, H. C.: "Isolation-stress, myocardial electrolytes and epinephrine cardiotoxicity in rats." *Proc. Soc. Exp. Biol. Med.* **127**: 142-147 (1968). F96,287/68

Tomanek, R. J., Banister, E. W.: "Myocardial ultrastructure after acute exercise stress with special reference to transverse tubules and intercalated discs." *Cardiovasc. Res.* **6**: 671-679 (1972). G98,110/72

Corley, K. C., Shiel, F. O., Mauck, H. P., Greenhoot, J.: "Electrocardiographic and cardiac morphological changes associated with environmental stress in squirrel monkeys." *Psychosom. Med.* **35**: 361-364 (1973). J19,680/73

Hauss, W. H.: "Tissue alterations due to experimental arteriosclerosis." In: Vogel, H. G., *Connective Tissue and Ageing* (Int. Congr. Ser. No. 264), pp. 23-33. Amsterdam: Excerpta Medica, 1973. J14,882/73

In rats, the emotional stress produced by restraint elicits typical mesenchymal reactions in the blood vessel walls with increased ³⁵S-sulfate and ³H-thymidine incorporation. Essentially similar changes occur after exposure to other stressors, and these are considered to be the first step in the arteriosclerotic process characteristic of aging. "The deformation of the structure of the arterial wall participates essentially in the development of lipidosis, fibrinosis, and cell necroses. Aggregation of thrombocytes and thrombosis in the arterial wall results from the frequent reduplication of intima cells."

Bani-Sacchi, T.: "Il miocardio del ratto esposto a bassa temperatura. Ricerche al microscopio elettronico" (The myocardium of the rat exposed to low temperature. Electron microscopic research). *Boll. Soc. Ital. Biol. Sper.* **50**: 242-245 (1974). J22,853/74

Gastrointestinal System

Acute hemorrhagic erosions of the gastric and intestinal mucosa are among the most characteristic manifestations of the typical "stress triad." They have been described and illustrated in the first publications on the alarm reaction, and will be discussed in greater detail in the section on Experimental Diseases of Adaptation conjointly with the various prophylactic and therapeutic measures developed to deal with them.

These ulcers are usually superficial and tend to heal rapidly following discontinuation of treatment with the stressor. They may be localized in the stomach, duodenum or upper small intestine, depending upon circumstances, particularly the species of experimental animal examined. In the rat, they are limited to the glandular stomach (ventriculus) and rarely if ever occur in the proventriculus.

The pathogenesis of these ulcers is still not very well understood; however, digestive juices undoubtedly play a decisive role in their formation, which depends partly upon glucocorticoids and partly upon autonomic nervous stimuli. In man, ACTH and cortisol increase basal nocturnal gastric hydrochloric acid and pepsin secretion, with a concomitant rise in uropepsin excretion. Similar changes are seen during stress which notoriously increases gastric secretion. Under normal conditions, the stomach requires adrenocortical function for acid-peptic activity, but during stress it is more directly under adrenocortical control, and the two factors play a conditioning, mutually synergistic role in both gastric secretion and in the development of stress ulcers.

Vagotomized rats are largely protected against stress ulcers, whereas hypophysectomy or adrenalectomy has no prophylactic effect. Curiously, both a deficiency and an excess of glucocorticoids enhance gastric ulcer formation during stress.

However, it is very difficult to draw any precise line of demarcation between more or less physiologic and distinctly pathologic responses of the gastrointestinal system to stressors; hence, much pertinent information will be found in the section Experimental Diseases of Adaptation.

In the following abstracts the reader will also find a few additional data concerning functional changes in the gastrointestinal system during stress, for example, in connection with motility and absorbing power. Most of these are associated with morphologic changes, and we did not create a special section dealing with the gastrointestinal tract under Functional Changes.

Gastrointestinal System

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

First detailed description of the three stages of the G.A.S. and the concept of "adaptation energy," with an extensive and illustrative characterization of the morphologic lesions produced by stress (especially in the hypophysis, adrenals, thymicolumphatic apparatus, pancreas and gastrointestinal tract, and its effects upon inflammation (anaphylactoid edema).

Klein, H.: "Zur pathologischen Anatomie der Alarmreaktion nach Kerngiften" (The pathology of the alarm reaction after nuclear toxins). *Virchows Arch. [Pathol. Anat.]* **320**: 93-137 (1951). B69,206/51

Comparative studies of the morphologic changes in the liver, thymicolumphatic apparatus (including the spleen) and duodenum of the mouse and rat after an alarm reaction is produced by ethyl ether, colchicine, urethane, or hydroquinone. Special attention is given to derangements in mitoses, particularly nuclear pyknosis (191 refs.).

Gray, S. J., Ramsey, C., Reifenstein, R. W., Benson, J. A. Jr.: "The significance of hormonal factors in the pathogenesis of peptic ulcer." *Gastroenterology* **25**: 156-172 (1953). B89,103/53

In man, ACTH and cortisone enhance the basal nocturnal gastric hydrochloric acid and pepsin secretion with a concomitant increase in uropepsin excretion. Similar changes are seen during stress, but vagotomy and anticholinergic agents "do not appear to alter the gastric acid, pepsin and urinary uropepsin response to adrenal stimulation or stress. . . . Although the gastric response to stress is undoubtedly mediated through the vagus nerve, there appears to be an additional hormonal

mechanism which is intimately associated with the adrenal gland and the general adaptation syndrome."

Shay, H.: "Stress and gastric secretion." *Gastroenterology* **26**: 316-319 (1954).

J11,408/54

Review of the literature on stress-induced increases in gastric secretion with a theory of the possible underlying mechanism. [Based largely on considerations no longer accepted (H.S.).]

Brown, M. S., Groves, W. G.: "Intestinal propulsion in restrained and unrestrained rats." *Proc. Soc. Exp. Biol. Med.* **121**: 989-992 (1966). F65,801/66

In rats, restraint decreases the speed with which a meal passes through the intestine.

Selye, H.: "Stressbedingte Veränderungen im Gastrointestinaltrakt" (Stress-dependent changes in the gastrointestinal tract). *Ver. Dtsch. Ges. Inn. Med.* **75**: 213-224 (1969).

G60,038/69

Kowalski, R.: "L'effet des émissions radiophoniques sur l'image radiologique du tube digestif chez l'enfant" (The effect of radio-phonic emission on the radiologic appearance of the gut in childhood). *Ann. Radiol.* **12**: 827-833 (1969). J21,830/69

In children listening to the radio, intestinal motility may be greatly altered.

Boles, J., Russell, R. W.: "Relations between the electrogastrogram and gastric ulceration during exposure to stress." *Psychophysiology* **6**: 404-410 (1970).

J21,700/70

Mannino, J. R.: "The in vivo measurement of the short circuit potential in the small intestine: II. The effect of stress on the electrical activity of the jejunum." *J. Am. Osteopath. Assoc.* **70**: 1114-1115 (1971).

J21,809/71

Yau, W. M. W., Nudd, M. F., Gass, G. H.: "Chronic restraint and glycine, phenylalanine and oleic acid absorption." *Comp. Biochem. Physiol. [A]* **39**: 545-547 (1971).

H41,770/71

Carnot, F.: "Etude anatomo-pathologique des lésions digestives survenant au cours des grandes détresses" (Anatomopathologic study of digestive lesions occurring during severe distress). *Ann. Chir.* **26**: C907-C911 (1972).

J20,202/72

Tutton, P. J. M., Helme, R. D.: "Stress induced inhibition of jejunal crypt cell proliferation." *Virchows Arch. [Zellpathol.]* **15**: 23-34 (1973). H81,883/73

Studies on the effect of electroshock upon the jejunal mucosa. "Stress was found to inhibit crypt cell proliferation in intact rats and in both adrenalectomised rats and in rats subjected to beta adrenergic blockage. However, sympathectomy appeared to prevent the inhibition of crypt cell proliferation by stress."

Oral (Teeth, Periodontal) Structures

Numerous investigators have examined the effect of stress upon various oral structures. It has been claimed that minor histologic changes can be observed in the teeth, alveolar bones and periodontal tissues of various rodents exposed to chronic stress, and indeed that even psychogenic stressors can increase the incidence of dental caries in rats. The frequency of fluctuating dental asymmetry and ulcer formation in the oral mucosa is allegedly also increased. However, it would still be difficult to delineate, with any degree of precision, those changes in the oral structures that are truly nonspecific and due to systemic stress.

Of course, the effects of topical stress such as mechanical trauma (grinding of the teeth, dental surgery), and of chemical or bacterial injury, are well established and represent an integral part of everyday dentistry.

Oral (Teeth, Periodontal) Structures

(See also our earlier stress monographs, p. xiii)

Shklar, G., Glickman, I.: "The periodontium and salivary glands in the alarm reaction." *J. Dent. Res.* **32**: 773-778 (1953).

C83,851/53

In rats, typical manifestations of the alarm reaction were produced with formalin. These were not associated with any growth or histologic alterations in the periodontal tissues, but "degenerative changes in the salivary glands were noted."

Zander, H. A., Mühlmann, H. R.: "The effect of stresses on the periodontal structures." *Oral Surg.* **9**: 380-390 (1956).

J13,137/56

Extensive study on the effect of topical and systemic stress upon the teeth and periodontal structures of rhesus monkeys.

Strean, L. P.: "Stress and the adaptation syndrome as related to dental practice." *N.Y. Dent. J.* **24**: 44-45 (1958). D7,325/58

Brief editorial on "the various oral condi-

tions that may be observed in patients under stress."

Fedi, P. F. Jr.: "The effects of stress on the periodontium of the Syrian hamster." *J. Periodontol.* **29**: 292-300 (1958).

J6,489/58

"The alveolar bone and periodontal membrane of the Syrian hamsters are affected by non-specific stress," such as formalin, cold or muscular exercise (36 refs.).

Gupta, O. P., Blechman, H., Stahl, S. S.: "Effects of stress on the periodontal tissues of young adult male rats and hamsters." *J. Periodontol.* **31**: 413-417 (1960).

J12,376/60

In hamsters and rats exposed to chronic stress (noise, light), minor histologic lesions were observed in both the alveolar bones and in periodontal tissue.

Zackin, S. J., Goldhaber, P.: "Experimental production of oral ulcerations in the rat." *Oral Surg.* **13**: 1267-1272 (1960).

J23,159/60

Sutton, P. R. N.: "Mental stress and acute

dental caries." *Nature* 195: 254-256 (1962).
D27,533/62

On the basis of statistical studies in man, it is suggested that "there is an association between mental stress and acute caries."

Hollomand, R.: "Anxiety and the oral cavity in experimental animals." IADR Abstract. *Fortieth General Meet. No.* 227 (1962). J24,339/22

Manhold, J. H. Jr.: "Oral manifestations of psychosomatic disease." *Psychosomatics* 4: 279-282 (1963). E27,148/63

Review and personal observations on the effects of diverse stressors upon the development of dental and periodontal disease in various animal species (21 refs.).

Reyna, L. J., Mascio, A. di, Berezin, N.: "Psychological stress and experimental caries." *Psychosomatics* 8: 138-140 (1967). F85,046/67

In rats, psychogenic stressors (electroshock, sound) can increase the incidence of dental caries.

Forest, D.: "The effects of chronic systemic stress on the initiation and progress of periodontal disease in the Syrian hamster." Thesis, University of Montreal, 1967.

J13,721/67

Master's thesis on the effect of stress upon periodontal tissues in the hamster.

DeWalt, E. M., Haines, A. K.: "The effects of specified stressors on healthy oral mucosa." *Nurs. Res.* 18: 22-27 (1969).

J23,692/69

Wilson, T. R., Whittaker, D. K.: "Stress-induced oral and gastric ulcers in rats." *Br. J. Pharmacol.* 37: 543-544 (1969).

G74,615/69

Wilson, T. R., Whittaker, D. K.: "Ulceration of oral and gastric mucosa produced by stress in rats." *Scand. J. Gastroenterol.* 4: 17-24 (1969). H21,747/69

In rats, restraint causes ulceration of both oral and gastric mucosa.

Manhold, J. H. Jr.: "Relationship of social stress and oral disease." *Psychosomatics* 11: 41-44 (1970). H23,479/70

Review of the literature and personal observations on rats suggesting that crowding interferes with the oxygen utilization of gingival tissue and hence may cause periodontal disease (21 refs.).

Whittaker, D. K., Wilson, T. R.: "The effect of age and strain differences on the incidence of restraint-induced oral and gastric ulcers in three strains of rats." *J. Dent. Res.* 51: 619-625 (1972). J19,863/72

In different strains of rats, the stress of restraint may cause predominantly gastric or oral ulcers. The clinical literature suggesting that ulcerative gingivitis, chronic periodontitis and herpes labialis may also be related to stress in man is reviewed.

Siegel, M. I., Smookler, H. H.: "Fluctuating dental asymmetry and audiogenic stress." *Growth* 37: 35-39 (1973). J8,473/73

Dental asymmetry had previously been ascribed to environmental stress. In this study, pregnant rats were exposed to intermittent audiogenic stress. "The degree of fluctuating asymmetry of mandibular molar width and length was determined for stressed litters and shown to be significantly greater than for controls reared under normal laboratory conditions."

Salivary Glands

Several earlier investigators claimed that the salivary glands participate in the alarm reaction, somewhat as does the pancreas, by the loss of secretion granules and occasional focal necroses. At the same time, there is a decrease in the RNA content and in the granularity of the acini, especially in the submaxillary glands. Such changes occur only under the influence of severe stressors, but a reduction in salivary secretion is evident even during minor psychogenic stress such as examinations.

Allegedly, the pre-parotid Loewenthal gland shows signs of increased activity in rats exposed to stressful acoustic stimulation.

Although several investigators have studied these problems, objective quantitative data are scarce. It is a matter of everyday experience that salivary flow diminishes and

that the oral mucosa becomes dry during various stressful situations of daily life, including public speaking or academic examinations, if these are experienced as demanding and distressful.

Salivary Glands

(See also our earlier stress monographs, p. xiii)

Ehrich, W. E., Seifter, J.: "Role played by the salivary glands in the 'alarm reaction.'" *Arch. Pathol.* **45**: 239-245 (1948).

B31,789/48

"An alarm reaction was produced experimentally in rats, dogs and rabbits with large doses of colchicine, aminopyrine, selenium compounds and other drugs. It was found that the salivary glands participate in this reaction. As in the pancreas, there was marked loss of zymogen granules, and in severe cases there was also focal necrosis."

Frawley, T. F., Thorn, G. W.: "The relation of the salivary sodium-potassium ratio to adrenal cortical activity." In: Mote, J. R., *Proceedings of the Second Clinical ACTH Conference. I. Research*, pp. 115-122. New York, Philadelphia and Toronto: Blakiston, 1951.

B58,733/51

In man, the salivary sodium:potassium ratio is normally about 1:3 but rises to 5:0 in Addison's disease and falls to 0:5 in Cushing's syndrome. DOC treatment produces a 25 percent drop in the ratio. Patients responding adequately to ACTH exhibit decreases of 18 to 68 percent. "The salivary Na/K ratio affords a simple means of following changes in adrenal cortical activity in terms of electrolyte regulation."

Rosenman, H., Charipper, H. A., Stahl, S. S.: "The effects of stress on the submaxillary glands of young adult male rats. Selected histochemical observations." *Arch. Oral Biol.* **2**: 196-202 (1960).

J23,137/60

In rats, "during the alarm reaction, the submaxillary glands showed a decrease in RNA, a decrease in the granularity of the acini, a decrease in interacinar connective tissue and an increase in granularity of the duct cells. The ducts stained more PAS-positive than the acini. A highly insoluble, heat-resistant, diastase-fast, PAS-positive material was present in the duct cells. During the stage of resistance, the duct cells showed a decrease in granules with little acinar change.

No observable difference in alkaline phosphatase activity was noted."

Bogdonoff, M. D., Bogdonoff, M. M., Wolf, S. G. Jr.: "Studies on salivary function in man: variations in secretory rate as part of the individual's adaptive pattern." *J. Psychosom. Res.* **5**: 170-174 (1961).

J23,512/61

Croce, G., Simoncelli, C.: "Esperienze sullo 'stress' sensoriale acustico. Nota III. Le ghiandole sottomascellari di ratto nello 'stress' audiogeno" (Research on sensory acoustic stress. Note III. The submaxillary gland in rats after audiogenic stress). *Valsalva* **40**: 323-328 (1964).

J10,966/64

In contradiction to earlier investigators who used other stressors, the authors were unable to produce any significant changes in the salivary glands of rats exposed to intense sound. [Under the conditions of this experiment, other manifestations indicative of the G.A.S. have likewise not been reported (H.S.).]

Croce, G., Simoncelli, C.: "Esperienze sullo stress sensoriale acustico. Nota IV. Rilievi isotologici e istochimici sulla ghiandola preparotidea di Loewenthal del ratto" (Research on sensory acoustic stress. Note IV. Histologic and histochemical findings in the preparotid Loewenthal gland of the rat). *Clin. Otorinolaringol.* **16**: 251-258 (1964).

J24,287/64

In rats exposed to stressful acoustic stimulation, histologic studies of the preparotid Loewenthal gland revealed signs of increased activity.

Bates, J. F., Adams, D.: "The influence of mental stress on the flow of saliva in man." *Arch. Oral Biol.* **13**: 593-596 (1968).

J22,671/68

Psychogenic stress (examinations) diminishes salivary flow in man.

Groza, P., Zamfir, V., Ionescu, S.: "Salivary secretion in children following operative stress." *Rev. Roum. Physiol.* **6**: 253-258 (1969).

H21,989/69

In children, surgical stress reduces salivary secretion for two days.

Croce, G., Frenguelli, A., Campora, E. de: "Esperienze sullo 'stress' sensoriale acustico. V. Il comportamento del sodio e del potassio nella ghiandola sottomascellare di ratto nello 'stress' audiogeno" (Experiments with acoustic sensory stress. V. Behavior of sodium and potassium in the rat submandibular gland in audiogenic stress). *Boll. Mal. Orecch.* **87**: 300-306 (1969). G74,773/69

The marked changes in salivary potassium and sodium in the submandibular glands of rats exposed to the stressor effect of sound indicate that the salivary glands are important "organs of stress."

Campora, E. de, Frenguelli, A.: "Modificazioni metaboliche nelle ghiandole sottomascellari di ratto nello 'stress' sensoriale acustico. Nota introduttiva" (Metabolic changes in the rat submaxillary gland in acoustic sensory "stress." Introductory note). *Boll. Mal. Orecch.* **88**: 195-200 (1970).

G83,919/70

Groza, P., Zamfir, V., Ionescu, S., Lungu, D.: "Secreția salivară și stress-ul operator" (Salivary secretion and operative stress). *Fiziol. Norm. Patol.* **17**: 313-322 (1971) (Roumanian). J20,495/71

Groza, P., Zamfir, V., Lungu, D.: "Postoperative salivary amylase changes in children"

J20,495/71

dren." *Rev. Roum. Physiol.* **8**: 307-312 (1971). J20,219/71

In children, surgical trauma decreases secretion of saliva and induces an "elevation of the concentration and output of salivary amylase, seemingly by the interference of glucocorticoid hormones."

Igarashi, T.: "Influence of sialoadenectomy and cyanide on the stress loop." *Shikwa Gakuho* **71**: 1356-1370 (1971) (Japanese). J24,561/71

Hafner, R. J.: "Physiological changes with stress in depression and obsessional neurosis." *J. Psychosom. Res.* **18**: 175-179 (1974). J15,135/74

Comparative studies on the salivary flow and potassium:sodium ratio in the saliva of depressed and obsessional subjects.

Hafner, R. J.: "Relationships between personality and autonomic nervous reactions to stress." *J. Psychosom. Res.* **18**: 181-185 (1974). J15,136/74

Salivary secretion and particularly the sodium:potassium ratio correlates well with psychogenic stress in man. In subjects who react defensively, the response is essentially different from that of subjects who react with aggressive attributes (16 refs.).

Lung

Comparatively few reliable observations are available concerning the participation of the lung in stress reactions. There is some evidence that the pulmonary circulation is affected and that stress predisposes to pulmonary edema, disseminated hemorrhages and to the "white lung syndrome."

However, most of the relevant observations have been made on alveolar macrophages, which may undergo degenerative changes during acute stress. It has also been claimed that the mitochondria of the lung may undergo "lamellar" transformation under the influence of stressors but the functional significance of this change is not clear.

Lung

(See also our earlier stress monographs, p. xiii)

Szidon, J. P., Fishman, A. P.: "Participation of pulmonary circulation in the defense reaction." *Am. J. Physiol.* **220**: 364-370 (1971). J20,735/71

Observations on dogs suggest that "engagement of the pulmonary vasomotor nerves in the defense reaction may be relevant to the pattern of adjustment of the pulmonary circulation during exercise and other forms of stress."

Brown, H. S., Turk, L. N., Hopkins,

W. A.: "Management of the white lung syndrome." *Ann. Thorac. Surg.* **13**: 411-419 (1972). J20,020/72

"Similar clinical pulmonary characteristics may develop after severe body stress and can be placed into one category for purposes of definition and treatment. Seventeen patients satisfying the criteria of so-called white lung syndrome were treated in private hospitals in metropolitan Atlanta during a three-year period."

Pattle, R. E., Schock, C., Dirnhuber, P., Creasey, J. M.: "Lamellar transformation of lung mitochondria under conditions of stress." *Nature* **240**: 468-469 (1972).

H68,274/72

Lockard, V. G., Grogan, J. B., Brunson, J. G.: "Alterations in the bactericidal ability of rabbit alveolar macrophages as a result of tumbling stress." *Am. J. Pathol.* **70**: 57-68 (1973). H64,681/73

EM studies suggest that "the degradative phase of the phagocytic process in rabbit alveolar macrophages is altered by subjecting the animals to tumbling stress."

Alexander, S. A., Maples, M. D., McGee,

C., Lockard, V. G., Brunson, J. G.: "Decrease in the degradative ability of alveolar macrophages from stressed guinea pigs as measured by the nitro blue tetrazolium test" (abstracted). *Am. J. Pathol.* **74**: 93a-94a (1974). H82,450/74

In guinea pigs subjected to "rotational stress," the degradative ability of alveolar macrophages decreases, as measured by the nitro blue tetrazolium test.

Metz, G., Classen, H. G., Vogel, W., Mittermayer, C.: "Sympathico-adrenerge Stimulation und Lungenveränderungen" (Sympathico-adrenergic stimulation and pulmonary changes) (abstracted). *Fifth Europ. Congr. Anaesthesiology*, p. 202. Madrid, Spain, 1974. J18,264/74

In rats, the stress of restraint causes edema and disseminated hemorrhages in the lungs which can be prevented by certain α -adrenergic blocking agents and analgesics.

Metz, G., Spiess, B., Classen, H. G., Mittermayer, C., Vogel, W.: "Akuter Stress und Lungenödem" (Acute stress and pulmonary edema). *Arzneim. Forsch.* **24**: 1625-1627 (1974). J18,272/74

Ocular Structures

Even in my earliest experiments on the stress reaction, I noticed that the cornea tends to become cloudy under severe stress in the rat and cat, an observation consequently confirmed in several other species. In the Japanese literature, this is referred to as "Komi's nonspecific corneal reaction." Furthermore, various stressors can produce herpetic keratitis in rabbits and sometimes, allegedly, even chorioretinitis, all of which were considered nonspecific responses associated with the G.A.S.

In young people of both sexes, the stress of muscular exercise on a bicycle ergometer may increase intraocular pressure. The associated biochemical changes in the eye, particularly altered enzyme activities, have also been the subjects of intensive studies, but their participation in spontaneous ophthalmologic diseases of man remains to be clarified.

Ocular Structures

(See also our earlier stress monographs, p. xiii)

Ikeda, I.: "The stress and changes of the cornea." *Folia Ophthalmol. Jap.* **12**: 639-650 (1961). E84,262/61

Stress causes corneal opacity (Komi's non-specific corneal reaction) in the rabbit. Fur-

thermore, "various stressors, such as electro-shock, moist heat, gravity shock, enucleatio bulbi without anesthesia, are found to favour the incidence of experimental herpetic keratitis in rabbits, to shorten its latent period, to make worse its clinical course and to delay its natural healing."

- Ikeda, I.: "Consideration of the therapy of diseases of the outer layer of the cornea, from the viewpoint of the stress theory." *Folia Ophthalmol. Jap.* **13**: 424-427 (1962). *J24,345/62*
- Taketani, T.: "Variations of total vitamin B2 content in the cornea, iris and ciliary body and the blood of rabbits in stress. (A preliminary report)." *Folia Ophthalmol. Jap.* **13**: 489-494 (1962). *J24,376/62*
- Ikeda, I.: "Stress and the eye with special reference to corneal changes." *Ber. Dtsch. Ophthalmol. Ges.* **65**: 401-404 (1964). *J24,344/64*
- Croce, G.: "Lo 'stress' uditivo e le sue riverberazioni extralabirintiche" (Noise stress and its extra-labyrinthine repercussions). *Valsalva* **40**: 381-384 (1964). *J10,965/64*
- No definite changes were noted in the extraorbital lacrimal gland of the rat upon exposure to the stress of noise.
- Umezaki, Y.: "Effects of stress on the healing of the corneal wound in rabbits." *Folia Ophthalmol. Jap.* **17**: 22-25 (1966). *J24,378/66*
- Ikeda, I., Kawaguchi, N., Ueda, Y.: "A histochemical study of rabbit's eye in stress with special reference to succinic dehydrogenase, DPN-diaphorase and TPN-diaphorase of cornea." *Folia Ophthalmol. Jap.* **17**: 26-32 (1966). *J23,777/66*
- Ikeda, I., Kawaguchi, N., Ueda, Y.: "A histochemical study of the rabbit eye in stress with special reference to succinic dehydrogenase, DPN-diaphorase and TPN-diaphorase of the retina." *Folia Ophthalmol. Jap.* **18**: 61-67 (1967). *J24,397/67*
- Shinmyo, T.: "Effects of stress on MAO activity in the brain and the ocular tissues of rabbits." *Folia Ophthalmol. Jap.* **18**: 312-314 (1967). *J24,622/67*
- Sunada, I.: "Effects of stress on sugar content of the aqueous and the cornea of rabbits." *Acta Soc. Ophthalmol. Jap.* **72**: 149-171 (1968). *H28,223/68*
- Mueller, F. O., Magos, L.: "Reversible lenticular opacities induced in rats by emotional stress." *Experientia* **26**: 169-170 (1970). *H21,860/70*
- In rats, acute stress (intense sound) produced reversible subcapsular lenticular opacities.
- Yoshida, S.: "A supplementary study of effects of stress on the incorporation of tritium-labeled thymidine by the corneal epithelium of rabbits. Effects of stress on the incorporation of tritium-labeled thymidine by the corneal epithelium in the corneal wound healing." *Acta Soc. Ophthalmol. Jap.* **75**: 1391-1398 (1971) (Japanese). *J20,493/71*
- Miki, T., Sunada, I., Higaki, T.: "Studies on chorioretinitis induced in rabbits by stress (repeated administration of epinephrine)." *Acta Soc. Ophthalmol. Jap.* **76**: 1037-1045 (1972) (Japanese). *J19,656/72*
- "The nonspecific ocular reaction, based on the General Adaptation Syndrome theory of Selye, was first described by Komi and Ikeda et al. in 1954. It was reported that nonspecific choroidal reaction due to stress is quite similar to central serous retinopathy of the human eye." Further studies along these lines confirmed that, in rabbits, repeated injections of EP can cause chorioretinitis.
- Kypke, W., Höllge, J., Scriba, B.: "Augeninnendruck während und nach körperlicher Belastung. Eine systematische Untersuchung unter reproduzierbaren Arbeitsbedingungen. I. Kreislaufparameter" (Intraocular pressure under physical stress. A methodical investigation under reproducible conditions. I. Circulatory parameters). *Albrecht von Graefes Arch. Klin. Ophthalmol.* **186**: 91-104 (1973). *H92,275/73*
- In young people of both sexes, the stress of muscular exercise on a bicycle ergometer caused a decrease in intraocular pressure. This correlated well with pulse frequency and blood pressure.
- Kypke, W., Höllge, J., Scriba, B.: "Augeninnendruck während und nach körperlicher Belastung. Eine systematische Untersuchung unter reproduzierbaren Arbeitsbedingungen. II. Säuren-Basenhaushalt" (Intraocular pressure under physical stress. A methodical investigation under reproducible conditions. II. Acid-base parameter). *Albrecht von Graefes Arch. Klin. Ophthalmol.* **188**: 43-53 (1973). *J19,560/73*
- In man, a highly significant correlation was found between intraocular pressure and metabolic acidosis during and after stressful exercise on a bicycle ergometer.

Kidney

The effect of stress upon diuresis and the excretion of various metabolites has been dealt with in the section on Chemical Changes, whereas diseases of the kidney in which stress plays a decisive role will be considered under Diseases of Adaptation. Here, we shall only consider a few reports on morphologic changes in the kidney that are not, strictly speaking, disease manifestations.

It has been claimed that such stressors as formaldehyde, cold or forced muscular exercise elicit an immediate enlargement of the kidney, with mitotic proliferation in the proximal convoluted tubules of the rat. Allegedly, these alterations can be prevented by adrenalectomy, and should be considered characteristic of the alarm reaction.

In tree shrews, repeated fighting, or merely continuous fear induced in the loser by the sight of a previously victorious male, causes a gradual loss of renal weight, allegedly suggesting "the great significance which social stress may have in the origin of renal disease—possibly in man as well as in animals."

In healthy young boys, the considerable physical effort of a swimming race led to the appearance of abundant urinary casts and proteinuria.

An overview of the pertinent literature indicates that acute stress may cause some renal enlargement and tubular proliferation, but chronic stress with the associated catabolism undoubtedly diminishes the size of the kidney at least as much as that of other organs. In addition, certain humoral changes, such as increased secretion of mineralocorticoids and renal pressor factors may adversely influence the kidney during stress, especially in combination with high sodium and protein diets. Furthermore, the very severe stress associated with surgical, hemorrhagic or toxic shock can cause acute and severe vascular derangements in the kidney, leading to necrosis.

Kidney

(See also our earlier stress monographs, p. xiii)

Leblond, C. P., Dugal, L. P.: "Manifestations pathologiques produites par le froid au niveau des reins et des extrémités" (Pathologic manifestations produced by cold in the kidneys and extremities). *Rev. Can. Biol.* **2**: 543-546 (1943). A72,918/43

The nephrosis-like changes produced in rats by cold are ascribed to stress.

Constantinides, P.: "An immediate kidney response to acute stress." *Endocrinology* **49**: 512-521 (1951). B64,013/51

In rats, acute stress caused by formalin, cold or forced exercise results in an immediate enlargement of the kidney with mitotic proliferation in the proximal convoluted tubules. These changes are largely prevented by adrenalectomy, and are ascribed to the alarm reaction.

Bello, C. T., Sevy, R. W., Ohler, E. A., Papacostas, C. A., Bucher, R. M.: "Renal

hemodynamic responses to stress in normotensive and hypertensive subjects." *Circulation* **22**: 573-582 (1960). C92,607/60

Comparison of renal and cardiovascular responses in normo- and hypertensive patients.

Anderson, R. S.: "Diuresis due to stress in cattle." *Nature* **192**: 460 (1961).

D14,301/61

Selye, H.: "Stress and renal function in relation to the hyalinizing and calcifying lesions of connective tissue." *J. Urol.* **86**: 687-701 (1961). D5,555/61

Baines, R. D., Geurkink, N. A., Schottstaedt, W. W.: "Renal clearances of insulin and PAH associated with the stress of mental concentration." *Psychosom. Med.* **24**: 584-589 (1962). D46,951/62

During stress caused by enforced mental concentration, normal people showed a decrease in the glomerular filtration rate and renal plasma flow.

Selzer, M. L.: "Stress ulcers and renal disease following electric convulsive therapy." *Psychiatr. Q.* **37**: 509-517 (1963).

J24,548/63

Sarre, H., Gessler, U.: "Zur Pathogenese der Schockniere" (The pathogenesis of shock kidney). *Med. Klin.* **58**: 2125-2130 (1963).

E37,703/63

Review on "shock kidney" with special reference to intrarenal circulatory disturbances, particularly the "Trueta-Shunt," and their significance in human pathology (15 refs.).

Gabbiani, G.: "Sensitization by stress for renal lesions resembling those of generalized Schwartzman phenomenon." *Med. Exp. (Basel)* **11**: 209-216 (1964).

G11,111/64

Perri, R. di, Iorio, G. dello, Cioffi, F., Vacca, L.: "Studio sperimentale sul comportamento del detrusore e dello sfintere vescicale striato durante electroshock" (Experimental study of the behavior of the detrusor muscle and striated vesical sphincter during electroshock). *Boll. Soc. Ital. Biol., Sper.* **42**: 1761-1764 (1966). J22,837/66

Characteristic changes in the musculature of the cat bladder during electroshock.

Schrier, R. W., Henderson, H. S., Tisher, C. C., Tannen, R. L.: "Nephropathy associated with heat stress and exercise." *Ann. Intern. Med.* **67**: 356-376 (1967). G48,992/67

Arai, S., Suzuki, T., Nokubi, K., et al.: "Histochemical changes in the kidneys and suprarenal glands of rats subjected to stress." *J. Tokyo Med. Coll.* **26**: 239-244 (1968). J24,400/68

Pashchenko, V. P.: "Effect of extremal factors on growth of kidney tissue in culture." *Biull. Èksp. Biol. Med.* **70** No. 8: 94-98 (1970) (Russian). Engl. trans.: *Bull. Èksp. Biol. Med.* **70**: 940-943 (1970). J21,610/70

On the basis of experiments in mice, "it is postulated that changes in growth of kidney tissue after exposure of the animals to extremal factors are a manifestation of the general adaptation syndrome."

Hoshizaki, T., McNew, J. J., Sabbot, I., Adey, W. R.: "Micturition patterns of an unrestrained chimpanzee under entrained and free running conditions." *Aerosp. Med.* **43**: 149-154 (1972). J20,222/72

In a male chimpanzee, stress altered the normal circadian pattern of micturition and

urine volume, especially during the stage of resistance of the G.A.S. (22 refs.).

Holst, D. von: "Renal failure as the cause of death in *Tupaia belangeri* exposed to persistent social stress." *J. Comp. Physiol.* **78**: 236-273 (1972). G93,301/72

When two adult male *Tupaias* are introduced, they immediately begin to fight. Subsequently, merely seeing the victor induces stress manifestations in the defeated *Tupaia*. This is associated with a constant decline in body weight, liver glycogen, blood hemoglobin and kidney weight, eventually resulting in fatal uremia. "The evidence from natural populations, when examined along with the findings from tree-shrews, show the great significance which social stress may have in the origin of renal disease—possibly in man as well as in animals."

Mullane, J. F., Wilfong, R. G., Phelps, T. O., Fischer, R. P.: "Metabolic acidosis, stress and gastric lesions in the rat." *Arch. Surg.* **107**: 456-459 (1973). J5,966/73

In rats, the acidosis induced by restraint and ingestion of ammonium chloride was compared with that in patients with renal failure. "These studies suggest that metabolic acidosis may account in part for gastric lesions associated with renal failure."

Fernández, A. E., Miatello, V. R., Zanetti, N. L., Olego, O., Carballo, J.: "Manifestaciones renales consecutivas al esfuerzo físico" (Renal effects of physical effort). *Prensa Méd. Argent.* **60**: 1006-1008 (1973). H81,565/73

Among perfectly healthy boys thirteen to fifteen years of age in whom careful examination showed no renal anomalies, the considerable physical effort of a swimming race led to the appearance of abundant urinary casts and proteinuria. "These urinary patterns are similar to those found in severe glomerulopathies."

Knochel, J. P., Dotin, L. N., Hamburger, R. J.: "Heat stress, exercise and muscle injury: effects on urate metabolism and renal function." *Ann. Intern. Med.* **81**: 321-328 (1974). J16,296/74

Description of the "heat stress nephropathy" which develops during intense physical training in hot climates.

Fröberg, J., Karlsson, C.-G., Lennquist, S., Levi, L., Mathé, A. A., Theorell, T.: "Renal and adrenal function: a comparison between responses to cold and to psychosocial stres-

sors in human subjects. A pilot study." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 40: 1-27 (1974). J18,098/74

In man, "psychosocial stressors can elicit a renal response which is fully analogous to the response to cold, including increased diuresis accompanied by significant increases in osmolal clearance and excretion of sodium,

chloride, calcium, phosphate and uric acid along with a significant decrease in the tubular reabsorption of sodium and calcium. This seems to indicate that cold-induced diuresis is not a response specific to cold, since the same response can also be elicited by other forms of stimuli, e.g., psychosocial ones."

Liver

The literature on the effect of various stressors upon the liver is so voluminous that the reader will have to depend almost entirely upon the data cited in the abstract section, since only a few of the best-established highlights can be briefly mentioned here.

The weight of the liver—like that of most organs other than the adrenals—is diminished during severe stress as part of the general catabolic response. The commonly mentioned nonspecific changes detectable by the light microscope are: congestion (especially of the sinusoids), centrilobular necrosis and sometimes single-cell necrosis throughout the acini, fatty degeneration, loss of glycogen, the appearance of "plant-like cells," "ballooning" of hepatocytes, and PAS-positive hyaline droplets of the Councilman type, as well as "toxic hepatitis," which presumably is often related to the development of postoperative icterus and perhaps intrahepatic cholestasis.

In addition, some authors have noted an increase in the alkaline phosphatase content of perithelial cells; however, this is histochemically demonstrable only using certain substrates.

Stress-induced lipidosis may be detectable as early as ten minutes after sham operations, both in the cytoplasm of hepatocytes and in Disse's spaces (which are also often distended by edema). Only the hepatocytes contain the lipid bodies, whereas the Kupffer cells and Ito's fat-storing cells do not; this "may indicate a very specific lipid mobilization response on the part of the cells of the hepatic parenchyma."

EM observations suggest mitochondrial fragmentation with swelling of the cristae, as well as an increase in intramitochondrial dense bodies and autophagic vacuoles. The liver obviously plays a central role in the metabolic changes characteristic of stress, and its light microscopic and ultrastructural response has been described after exposure to a great variety of stressors (hypoxia, hemorrhage, temperature variations, particularly heat stroke, acceleration and deceleration, malnutrition and so on); yet virtually no systematic attempt has been made to strictly characterize which of the changes are truly nonspecific, and what the conditioning factors are for the predominance of one or the other type of response.

Liver

(See also our earlier stress monographs, p. xiii)

MacMahon, H. E.: "Electric shock." *Am. J. Pathol.* 5: 333-347 (1929). 27,847/29

In cats, dogs and guinea pigs, repeated sublethal electric shocks produce only congestion in the periphery of the hepatic lobules.

Leblond, C. P., Nguyen-van Thoai, Segal, G.: "Infiltration graisseuse du foie sous l'action des agents nocifs" (Lipid infiltration of the liver under the influence of noxious agents). *C.R. Soc. Biol. (Paris)* 130: 1557-1559 (1939). A18,194/39

Zinck, K. H.: "Gestaltliche Leber-Nieren-schädigungen und Hepato-Renale Insuffizienz

nach Verbrennung. Ein Beitrag zur Frage des Verbrennungskollapses" (Hepatic-renal lesions and insufficiency after burn. The problem of burn shock). *Klin. Wochenschr.* **19**: 78-84 (1940). B33,768/40

In patients with extensive skin burns, centrilobular necroses often accompany the characteristic renal changes.

Müller, E., Rotter, W.: "Ueber histologische Veränderungen beim akuten Höhentod" (Histologic changes in death due to anoxia). *Beitr. Pathol. Anat.* **107**: 156-172 (1942). C45,858/42

In pilots who died as a consequence of acute hypoxia, only minor hepatic changes were noted, such as slight hepatocyte vacuolization and occasional single cell necrosis.

Cleghorn, R. A.: "Studies of shock produced by muscle trauma. II. Pathological changes in various tissues." *Can. J. Res. [E]* **24**: 155-162 (1946). B2,573/46

In dogs, muscle trauma conducive to severe shock produces various organ changes, including congestion of the liver with centrilobular hepatocyte degeneration.

Gillman, J., Gillman, T.: "Anoxia and the liver with special reference to shock and chronic malnutrition." *S. Afr. J. Med. Sci.* **13**: 11-43 (1948). B43,992/48

Microscopic examination of the livers of 275 patients who died rapidly from asphyxia, hemorrhage, carbon monoxide or prussic acid poisoning frequently showed fat- and glycogen-free vacuoles in their hepatocytes. A sharp distinction is made between cells having discrete multiple vacuoles (vacuolated cells) and those containing few, but large, rectangular- or trapezoidal-shaped vacuoles (plant-like cells). Both types tend to occur in clusters. Plant-like cells are also found in the livers of pellagrins and of protein-deficient rats or dogs. They often terminate in necrosis (65 refs., 22 microphotographs).

Moon, V. H.: "The pathology of secondary shock." *Am. J. Pathol.* **24**: 235-273 (1948).

B19,951/48

Review on the pathology of secondary shock, especially in man. "Hepatic degeneration and necrosis were regular features, but their degree and distribution were inconstant. Degeneration tended to be diffuse and the degree varied from granular cytoplasm and vesicular nuclei to necrosis. Absence of nuclei, pyknosis, and disintegrating cells were the criteria for necrosis. Frequently this involved only scattered groups of cells; when

the groups were larger, focal necrosis was seen. Occasionally, as after burns, heat stroke, or death from low atmospheric pressure, extensive necrosis involved the centers of the lobules and resembled that produced by poisons" (57 refs.).

Altmann, H. W.: "Über Leberveränderungen bei allgemeinem Sauerstoffmangel nach Unterdruckexperimenten an Katzen" (Hepatic changes induced by general hypoxia and decompression experiments in cats). *Frankfurt. Z. Pathol.* **60**: 376-494 (1949).

A49,602/49

Extensive review on structural changes in the liver following exposure to decreased oxygen pressure, especially in cats. The most characteristic lesions are vacuoles and hyaline droplets, with occasional single-cell necroses in the hepatocytes and serous inflammation during the acute stage. After chronic hypoxia, centrilobular necrosis becomes very widespread and may lead to cirrhosis, or it may heal without leaving any scars (numerous refs.).

Leduc, J., Guillemin, R.: "Le syndrome général de l'adaptation. Etude comparée de l'involution des différents organes au cours de la réaction d'alarme" (The general adaptation syndrome. A comparative study of the involution of various organs during the alarm reaction). *Arch. Int. Physiol.* **56**: 207-218 (1949).

B27,410/49

In rats exposed to different stressors (cold, fasting), various organs, particularly the liver, thymus and spleen, undergo considerable involution.

Gore, I., Isaacson, N. H.: "The pathology of hyperpyrexia. Observations at autopsy in 17 cases of fever therapy." *Am. J. Pathol.* **25**: 1029-1059 (1949).

B41,903/49

In seventeen cases of fatal therapeutic hyperpyrexia, jaundice with hemorrhages and necroses in various organs, particularly the liver, were characteristic. A review of the literature suggests that fever due to causes other than therapeutic pyrogens can elicit similar organ lesions (83 refs.).

Desmarais, A.: "Contribution à l'étude du choc" (Contribution to the study of shock). *Laval Méd.* **14**: 346-379; 443-476 (1949).

B49,433/49

Review on the effect of stress upon various organs, particularly the liver, with special reference to the G.A.S. (149 refs.).

Skelton, F. R.: "Some specific and non-specific effects of thiamine deficiency in the

rat." *Proc. Soc. Exp. Biol. Med.* **73**: 516-519 (1950). B41,300/50

In rats, thiamine deficiency, as well as partial starvation, produces a typical stress response with adrenocortical hypertrophy, thymus involution and organ manifestations of the alarm reaction. Simultaneously, various parenchymal organs, including the liver, undergo considerable involution.

Herlant, M., Timiras, P. S.: "Alkaline phosphatases in various tissues of the rat during the alarm-reaction." *Endocrinology* **46**: 243-252 (1950). B41,763/50

In rats, exposure to various stressors, such as formalin, cold or severe hypoxia, causes an increase in alkaline phosphatase (using glycerophosphate and fructose diphosphate as substrates) in the liver, lung, spleen, lymph nodes and thymus. No such increase was observed in these organs with yeast nucleic acid substrate. In the liver, the enzyme is located principally in the perithelial cells of the vessels and the bile ducts. Some reaction also occurs in the nuclei and particularly in the nucleoli of the hepatocytes, but not in the cytoplasm. Preliminary studies revealed no significant change in the acid phosphatase content of the organs that could be ascribed to stress.

Ellenberg, M., Osserman, K. E.: "The role of shock in the production of central liver cell necrosis." *Am. J. Med.* **11**: 170-178 (1951). B64,361/51

In patients, "central liver cell necrosis, as defined by (1) congestion, (2) eosinophilic staining, (3) nuclear changes, (4) cellular infiltration and (5) architectural disruption, all centrilobular in location, is definitely related to shock" (29 refs.).

Klein, H.: "Zur pathologischen Anatomie der Alarmreaktion nach Kerngiften" (The pathology of the alarm reaction after nuclear toxins). *Virchows Arch. [Pathol. Anat.]* **320**: 93-137 (1951). B69,206/51

Comparative studies of morphologic changes in the liver, thymicolumphatic apparatus (including the spleen), and duodenum of the mouse and rat after an alarm reaction is produced by ethyl ether, colchicine, urethane or hydroquinone. Special attention is given to derangements in mitoses, particularly nuclear pyknosis (191 refs.).

Xavier, A. A., Corrêa, J. C.: "Alterações patológicas consequentes a estados emocionais experimentais (comunicação preliminar)" (Pathologic changes following experimental

emotional states. [Preliminary communication]). *Brasil-Méd.* **65**: 373-374 (1951) (Portuguese). B94,758/51

In rabbits, strong emotional excitement (anxiety, terror, rage, pain, hunger, sleeplessness) produces structural alterations in various organs, including "degenerative changes in the liver" with "deposition of mineral substances" [Report in anecdotal style; no quantitative data (H.S.).]

Moysen, F.: *Etude des Modifications Morphologiques et Fonctionnelles du Foie dans les Etats Posttraumatiques* (A study of the morphologic and functional changes of the liver in post traumatic states), p. 62. Bruxelles: Les Editions Acta Medica Belgica, 1952. B68,706/52

Monograph on the changes in the liver during "posttraumatic states," particularly in relation to the G.A.S. (numerous refs.).

Milin, R., Janjatović, M.: "A contribution to the study of syndromes in the so-called 'southern wind disease' (zajuživanje) in sheep." *Veterinaria* (Sarajevo) **5**: 401-431 (1952) (Serbo-Croatian). B72,751/52

In sheep suffering from "southern-wind-disease" due to sudden migration of a herd from high mountains to the lowlands, the ensuing moderate hepatic lesions are ascribed to stress.

Stenram, U.: "Basophilic rods in the liver cell cytoplasm of rat." *Acta Anat.* (Basel) **18**: 360-377 (1953). A68,449/53

In rat hepatocytes, basophilic, palisade-like arranged rods appear following thyroid administration. They show no sex, age or diurnal variations, and develop also after acute bleeding, starvation, EP or NEP treatment. These rods contain RNA and presumably indicate increased cellular activity.

Wilson, M. E., Stowell, R. E.: "Cytological changes following roentgen irradiation of the liver in mice." *J. Natl. Cancer Inst.* **13**: 1123-1137 (1953). G98,462/53

Comparison of cytologic changes produced by x-irradiation and other stressors in the mouse.

Bottiglioni, E., Sturani, P. L.: "Stress da formaldeide e tubercolosi sperimentale. Nota III. Sulle localizzazioni metastatiche nei filtri ematici" (Formalin stress and experimental tuberculosis. Note III. On metastatic localizations in the hematic filters). *Arch. Patol. Clin. Med.* **32**: 220-227 (1955). C11,775/55

In guinea pigs, formalin- or tuberculosis-induced stress produces only minor changes in the liver. [The data do not lend themselves to statistical evaluation (H.S.).]

Manzini, C.: "La degenerazione vacuolare plasmatica delle cellule epatiche come segno istologico probabile nella sindrome di adattamento di Selye" (Vacuoloplasmatic degeneration of liver cells as a probable histologic sign of Selye's adaptation syndrome). *Bull. Sci. Med.* **127**: 289-297 (1955). C10,644/55

Selye, H.: "Stress and the liver." *Il Fegato* **1**: 333-340 (1955). C7,849/55

Review of the literature and personal observations on the participation of the liver in the G.A.S., including the effect of stress hormones upon the liver, the role of the liver in the metabolism of these hormones, and changes in nonspecific resistance induced by hepatic interventions.

Cole, J. W., Leuchtenberger, C.: "Cellular changes during surgical stress. 1. Morphologic alterations in hepatic cells." *Surg. Gynecol. Obstet.* **102**: 702-704 (1956).

C18,418/56

In dogs exposed to various traumatic stressors, condensation of hepatocyte nuclear chromatin and increased nuclear-associated chromatin were noted.

Popper, H., Schaffner, F.: *Liver: Structure and Function*, p. 776. New York, Toronto and London: McGraw-Hill, Blakiston Division, 1957. E9,234/57

Review on toxic hepatic injury in man and experimental animals, including sections on liver lesions produced by immune reactions, arsphenamine, methyltestosterone, chlorpromazine and thyrotoxicosis. Nonspecific stress is probably the principal factor in the production of postoperative toxic hepatitis and hepatic lesions following anoxia, loss of blood and other systemic insults (numerous refs.).

Baxter, C. R., Teschan, P. E.: "Atypical heat stroke, with hypernatremia, acute renal failure, and fulminating potassium intoxication." *Arch. Intern. Med.* **101**: 1040-1050 (1958). C54,584/58

In patients who died from heat stroke, renal damage and hemorrhages in various organs were particularly obvious. In the liver, there was centrilobular necrosis. The literature on the pathology of heat stroke in man is reviewed (25 refs.).

Herman, R. H., Sullivan, B. H. Jr.: "Heat-stroke and jaundice." *Am. J. Med.* **27**: 154-166 (1959). C70,269/59

Review and personal observations on heat stroke with jaundice and histologic liver lesions in man (54 refs.).

Sackler, A. M., Weltman, A. S., Bradshaw, M., Jurtshuk, P. Jr.: "Endocrine changes due to auditory stress." *Acta Endocrinol. (Kh.)* **31**: 405-418 (1959).

C71,159/59

In rats, repeated exposure to strong auditory stimulation causes adrenal enlargement, ovarian atrophy and diminution in the weight of the uterus and liver. Food consumption is also markedly reduced.

Bassi, M., Bernelli-Zazzera, A., Cassi, E.: "Electron microscopy of rat liver cells in hypoxia." *J. Pathol. Bacteriol.* **79**: 179-183 (1960). G95,537/60

In mice kept under hypoxic conditions, the principal EM changes in the liver were "the presence in the cytoplasm of smooth, round vesicles, varying in size and electron-density. These vesicles do not seem to be related to mitochondria, which have generally a normal appearance, a conclusion that accords with the results of biochemical assays carried out on homogenates of hypoxic livers. Catalase, uricase and succinic-dehydrogenase-activities, which are bound to cytoplasmic particles of different size, are not altered in homogenates of vacuolated liver cells."

Arturson, G.: "Pathophysiological aspects of the burn syndrome with special reference to liver injury and alterations of capillary permeability." *Acta Chir. Scand. [Supp.]* **274**: 1-135 (1961). D15,482/61

Monograph on the burn syndrome as it appears in the rat, dog and man, with special reference to hepatic changes (dilatation of sinusoids, vacuolization of hepatocytes with ballooning of their nuclei and eventually necrosis) (approx. 300 refs.).

Hirose, S., Hirayama, C., Ikemi, Y.: "The influence of emotional stress on the liver blood flow." *Kyushu J. Med. Sci.* **12**: 319-323 (1961). D56,369/61

Pohl, W.: "Die Substruktur der Leberzelle unter hormonalen und toxischen Reizen" (Hormonal and toxic stimuli affecting the subcellular structure of the hepatocyte). *Z. Gesamte Inn. Med.* **17**: 199-203 (1962).

D31,127/62

In rats treated with EP, cortisone, thy-

roxine, insulin or carbon tetrachloride, the EM changes in the hepatocytes are essentially the same. There is swelling of mitochondria, fragmentation, and shortening of their cristae, which eventually become more or less homogeneous, irrespective of the agent used. [The stereotyped nature of the response suggests that it is the consequence of stress as such (H.S.).]

Scharf, J. H., Borysenko, M., Ehrenbrand, F.: "Aktivierung des Nebennierenrindenorgans durch Kochsalzlösungen im Zusammenhang mit der Morphokinese von Adenohypophyse, Schilddrüse und Leber bei der Ratte" (Sodium chloride solutions activating the adrenal cortex and affecting the morphokinesis of the adenohypophysis, thyroid and liver in rats). *Z. Mikrosk. Anat. Forsch.* **68**: 176-213 (1962).

D32,197/62

In rats, large amounts of hypertonic sodium chloride given orally elicit various organ changes characteristic of stress. Liver cells show pronounced shrinkage of the cytoplasm and nucleus, with a significant diminution of glycogen shortly after an initial increase, allegedly symptomatic of a toxic influence. Earlier literature is reviewed (about 130 refs.).

Brown, J. M. M.: "Biochemical lesions in the pathogenesis of geeldikkop (Tribulosis ovis) and enzootic icterus in sheep in South Africa." *Ann. N.Y. Acad. Sci.* **104**: 504-538 (1963).

D58,732/63

In sheep, the enzootic icterus produced by icterogenin and other pentacyclic triterpene acids is greatly aggravated by stressors such as long-distance traveling by road or rail, inoculation with vaccines, intercurrent diseases and so on.

Vido, I., Tomík, F.: "Morphologische Veränderungen der Leber und ihre biochemischen Begleiterscheinungen im Serum während wiederholter unspezifischer Eingriffe bei Versuchstieren" (Morphologic changes in liver and biochemical alterations in serum during repeated nonspecific interventions in experimental animals). *Acta Hepato-Splenol. (Stuttg.)* **10**: 176-181 (1963).

E21,325/63

In dogs, various interventions considered as nonspecific stimuli (repeated anesthesia, liver biopsy, hemorrhage, administration of olive oil) produce hepatic steatosis.

Lalli, G., Paolucci, G.: "Comportamento di alcune attività enzimatiche valutate in funzione del danno anatomo-patologico nel ratto sottoposto a decelerazioni di notevole

entità e di breve durata. Nota II" (Behavior of various serum enzymes in the rat in relation to the anatomo-pathologic lesions produced by deceleration of great intensity and short duration. Note II). *Riv. Med. Aero-naut. Spaz.* **26**: 410-426 (1963).

E31,375/63

In rats exposed to deceleration of great intensity and short duration, there develop hepatic lesions and serum enzyme changes.

Scharf, J. H., Saffari, E.: "Histologische, histotopochemische und sequentialanalytische Untersuchungen über die Frage des unterschiedlichen Aktivierungsgrades von Endocrinum und Leber nach Operation, Muskelhomoiotransplantation und Plastoff-implantation beim Meerschweinchen" (Histologic, histochemical and sequential analytic studies on the problem of a different degree of activation of the endocrines and liver following surgery, musculo-homoiotransplantation and implantation of plastic material in guinea pigs). *Z. Mikrosk. Anat. Forsch.* **71**: 32-84 (1964).

D19,998/64

Shoemaker, W. C., Szanto, P. B., Fitch, L. B.: "Hepatic physiologic and morphologic alterations in hemorrhagic shock." *Surg. Gynecol. Obstet.* **118**: 828-836 (1964).

F6,735/64

In dogs and rats, extensive in vivo studies on the microcirculation of the liver revealed the time sequence of the changes elicited by hemorrhagic shock. "Evidence is presented suggesting that 'acute hepatic sinusoidal congestion' may be the pathophysiological entity underlying the shocked state in both experimental hemorrhagic shock and clinical hypotensive shock from hemorrhage, trauma, and other forms of acute stress."

Minick, O. T., Kent, G., Orfei, E., Volini, F. I.: "Non-membrane enclosed intramitochondrial dense bodies." *Exp. Mol. Pathol.* **4**: 311-319 (1965).

G94,952/65

In rats, ethionine intoxication causes the appearance of nonmembrane enclosed intramitochondrial dense bodies in hepatocytes. Hypoxia elicits a considerable increase in the number of these dense bodies, which "are considered to be responses to severe though non-specific cellular injuries. They appear to be derived, at least in part, from altered groups of cristae."

Trotter, N. L.: "Electron-opaque, lipid-containing bodies in mouse liver at early intervals after partial hepatectomy and sham

operation." *J. Cell Biol.* **25**: 41-52 (1965).
G97,137/65

In mice, "as early as 10 minutes after both sham operation and partial hepatectomy, lipid-containing bodies have been observed not only in the cytoplasm of hepatic parenchymal cells, but also in the spaces of Disse. . . . The fact that only hepatic parenchymal cells contain the lipid bodies, whereas von Kupffer, endothelial lining, and Ito's fat-storing cells do not, may indicate a specific lipid mobilization response on the part of the cells of the hepatic parenchyma."

Minio, F., Gardiol, D.: "Hépatopathie périopératoire. Etude histologique, histoquímica, ultrastructural et expérimental" (Surgical hepatopathy. A histologic, histochemical, ultrastructural and experimental study). *Ann. Anat. Pathol. (Paris)* **10**: 301-316 (1965).
G92,562/65

In patients and dogs, various abdominal operations produce ultrastructural changes, especially in the vascular pole of hepatocytes and Disse's spaces, which might partly be due to anesthesia, and could explain post-operative icterus.

Webb, T. E., Blobel, G., Potter, V. R.: "Polyribosomes in rat tissues. III. The response of the polyribosome pattern of rat liver to physiologic stress." *Cancer Res.* **26**: 253-257 (1966).
F62,094/66

In rats, the polyribosome pattern of the liver undergoes similar changes following fasting, partial hepatectomy, dinitrophenol or carbon tetrachloride, presumably "in response to physiologic stress."

Petera, V., Špinka, J., Jiroušek, F., Vojáček, V., Maňhal, J., Hoenig, K.: "Acute intrahepatic cholestasis following stress." *Čas. Lék. Česk.* **105**: 464-465 (1966) (Czech).
G64,201/66

In patients, various surgical operations can produce intrahepatic cholestasis which is interpreted as a consequence of stress.

Glinsmann, W. H., Ericsson, J. L. E.: "Observations on the subcellular organization of hepatic parenchymal cells. II. Evolution of reversible alterations induced by hypoxia." *Lab. Invest.* **15**: 762-777 (1966).
G95,943/66

EM studies on the reversible alterations induced by hypoxia in the hepatocytes of rats (49 refs.).

Peters, J. M., Boyd, E. M.: "Resistance to pentobarbital in rats fed a cachexigenic diet."

Toxicol. Appl. Pharmacol. **8**: 464-471 (1966).
J1,581/66

The body weight of rats kept on a biotin-deficient rancid-fat diet decreased in proportion to the increase of hepatic weight. Simultaneously, these animals showed typical manifestations of the stress reaction and an enhanced resistance to pentobarbital. It remains to be seen whether the latter was due to hepatic enlargement or to some other stress effect.

Lambusta, A.: "Atrofia giallo-acuta del fegato e stress psico-emotivi" (Acute yellow atrophy of the liver and psycho-emotional stress). *Minerva Med. Leg.* **86**: 182-183 (1966).
J24,553/66

Kingsley, D. P. E.: "Hepatic damage following profound hypothermia and extra-corporeal circulation in man." *Thorax* **21**: 91-98 (1966).
J2,183/66

In patients who underwent cardiac surgery under profound hypothermia and circulatory arrest, evidence of hepatic damage was obtained from several enzyme changes and in a few cases centrilobular necrosis was noted postmortem.

Dietze, A.: "Leberschädigung und Tod nach Überstehen extremer Lebensverhältnisse" (Investigation of the cause of death and of liver damage in persons surviving extreme living conditions). *Acta Hepato-Splenol. (Stuttg.)* **14**: 105-109 (1967).
F95,153/67

Autopsies on more than three hundred former POWs who had lived under extremely stressful conditions. In 15 percent the immediate cause of death was liver disease; in an additional 8 percent, there was liver disease associated with other fatal lesions. These percentages are considerably higher than in ordinary autopsies, but this study does not reveal the relative role of stress, captivity and malnutrition in causing the hepatic damage.

Kerr, J. F. R.: "Lysosome changes in acute liver injury due to heliotrine." *J. Pathol. Bacteriol.* **93**: 167-174 (1967).
G91,076/67

In rats, sublethal doses of heliotrine induced a great variability in the size and distribution of hepatocyte lysosomes. Large, spherical lysosomes were especially numerous in the most severely damaged cells. They contained both acid phosphatase and esterase. In coagulative necrosis, there was diffuse staining of the paracanalicular cytoplasm

in hydrolase preparations. Similar lysosome changes were previously observed in ischemia and probably "represent standard reactions to injury, irrespective of its cause."

Šimek, J., Erbenová, Z., Deml, F., Dvořáčková, I.: "Liver regeneration after partial hepatectomy in rats exposed before the operation to the stress stimulus." *Experientia* **24**: 1166-1167 (1968).

H13,837/68

In partially hepatectomized rats, exposure to various stressors or treatment with ACTH enhances DNA synthesis in the liver remnant as well as hepatic regeneration and triglyceride storage.

Schattenfroh, C., Stracke, U., Eger, W.: "Änderung der Leberfunktion durch Tourniquet, Mesenterialgefäßligatur und Immobilisation im Tierexperiment" (Change in liver function due to tourniquet, mesenteric vessel ligation and immobilization in animal experiments). *Brun's Beitr. Klin. Chir.* **216**: 560-568 (1968).

J22,743/68

In rats, stress induced by traumatic injuries offers immediate protection against the hepatic necrosis normally produced by allyl alcohol.

Tsukada, K., Moriyama, T., Doi, O., Lieberman, I.: "Ribosomal change in liver after partial hepatectomy and acute stress." *J. Biol. Chem.* **243**: 1152-1159 (1968).

G56,019/68

Laurentaci, G., Monosi, V.: "Sull'azione protettiva del butil-sympatol nello shock da laccio del coniglio" (The protective effect of butyl-sympatol on tourniquet shock in the rabbit). *Osped. Ital. Chir.* **18**: 25-39 (1968).

F98,700/68

In rabbits, severe stress produced by tourniquet shock is associated with centrilobular hepatic necrosis of moderate intensity.

Klatskin, G.: "Introduction: mechanisms of toxic and drug induced hepatic injury." In: Fink, B. R., *Toxicity of Anesthetics (Proc. Res. Symp., Seattle, 1967)*, pp. 159-175. Baltimore: Williams & Wilkins, 1968.

G93,609/68

Brief description of hepatic lesions produced by halothane anesthesia or hemorrhagic shock in man.

Morgenstern, L.: "Postoperative jaundice." In: Schiff, L., *Diseases of the Liver*, pp. 1036-1050. Philadelphia and Toronto: J B Lippincott, 3rd ed., 1969.

E9,960/69

Review on postoperative jaundice in man (150 refs.).

Cook, G. C.: "Hepatic changes associated with shock." *Int. Anesthesiol. Clin.* **7**: 883-894 (1969).

G98,418/69

Review on hepatic changes associated with postoperative shock in man (26 refs.).

Ionescu, A., Chiotan, N., Paulian, V.: "Intravital and post-mortem study of liver structure changes in the burned." *Panminerva Med.* **11**: 47-50 (1969).

G98,803/69

Detailed description of histologic changes in the liver of severely burned patients.

Müller, R., Korb, G., Gedigk, P.: "Über zentrale Nekrosen in der Leber nach einem Schock" (Central liver necrosis after shock). *Verh. Dtsch. Ges. Pathol.* **54**: 511-513 (1970).

G96,741/70

In man the hepatic changes after shock (particularly surgical trauma) are essentially similar to those previously described in animals, and consist mainly of single-cell, reticular and zonal central necroses. The literature is reviewed.

Mori-Chavez, P., Upton, A. C., Salazar, M., Conklin, J. W.: "Influence of altitude on late effects of radiation in RF/Un mice: observations on survival time, blood changes, body weight, and incidence of neoplasms." *Cancer Res.* **30**: 913-928 (1970).

H27,012/70

In mice exposed to total body x-irradiation and reduced oxygen tension, neoplasms occurred in various organs. "The liver occasionally disclosed multiple, pinpoint, umbilicated, necrotic foci on its surface, which microscopically were found to consist of thromboembolic septic abscesses."

Panaretto, B. A., Vickery, M. R.: "The rates of plasma cortisol entry and clearance in sheep before and during their exposure to a cold, wet environment." *J. Endocrinol.* **47**: 273-285 (1970).

H28,932/70

In sheep exposed to cold, "decreased cortisol clearance rates did not appear to contribute to the great increases in plasma concentration until rectal temperature was about 34°." Curiously, the adrenal cortex and liver of the sheep were heavily infiltrated with fat after severe hypothermia.

Paolucci, G.: "Effetti delle decelerazioni ripetute di modesta entità e di brevissima durata in animali da esperimento" (The effects of repeated moderate decelerations of very brief duration on scientific research animals). *Riv. Med. Aeronaut. Spaz.* **33**: 88-99 (1970).

H57,012/70

Repeated moderate decelerations cause no immediate macroscopic change, but after a certain time they lead to hepatic cirrhosis in some species.

Kerr, J. F. R.: "Shrinkage necrosis: a distinct mode of cellular death." *J. Pathol.* **105**: 13-20 (1971). G90,887/71

In rats, ligation of portal vein branches causes massive loss of hepatocytes through "shrinkage necrosis" in the corresponding lobes. There is cellular condensation, followed by prolific budding of compact masses, often referred to as "Councilman bodies." These are ingested by hepatocytes and histiocytes, whereupon they undergo changes similar to coagulative necrosis of whole cells. The eventual degradation of these bodies is brought about by lysosomal enzymes. Shrinkage necrosis is regarded as a distinct type of cell death caused by various noxious stimuli. The literature on the formation of Councilman bodies in man and experimental animals is reviewed (23 refs.).

Adam, S. E. I., Thorpe, E.: "Influence of cold environment on hepatic changes produced by repeated doses of carbon tetrachloride." *J. Pathol.* **106**: 155-163 (1972).

G92,088/72

In mice given a single oral dose of carbon tetrachloride, centrilobular hepatic necrosis developed at room temperature. Exposure to a cold environment caused greater lipid accumulation and marked glycogen depletion in the liver, with increased "ballooning" of midzonal hepatocytes. Repeated administration of carbon tetrachloride at weekly intervals led to greater resistance at room temperature than in the cold. Histochemically, alkaline phosphatase and ATPase activity was greatest in the necrotic cells and the adjacent sinusoids.

Bianchi, L., Ohnacker, H., Beck, K., Zimmerli-Ning, M.: "Liver damage in heat-stroke and its regression. A biopsy study." *Hum. Pathol.* **3**: 237-248 (1972).

G94,903/72

Two patients with heat stroke developed

centrilobular hepatic necrosis, cholestasis and leukocytic cholangiolitis.

Oette, K., Phlippen, R.: "Fettleber durch Stress?" (Fatty liver due to stress?). *Dtsch. Med. Wochenschr.* **98**: 1635-1636 (1973). H75,594/73

Tentative clinical observations suggest but do not prove that repeated exposure to stressors can predispose to fatty degeneration of the liver in man.

Remmeli, W., Loeper, H.: "Zur pathologischen Anatomie des Kreislaufschocks beim Menschen. IV. Pathomorphologie der Schockleber" (The pathology of circulation shock in man. Pathomorphology of the liver). *Klin. Wochenschr.* **51**: 10-24 (1973).

H65,988/73

Review on the pathology of shock-induced hepatic changes in man (66 refs.).

Rotermund, A. J. Jr., Johnson, H. A.: "Temperature-induced alteration of hepatic ultrastructure and function within the goldfish, *Carassius auratus*" (abstracted). *Physiologist* **17**: 389 (1974). H89,987/74

Kalant, H., Khanna, J. M., Seymour, F., Loth, J.: "Acute alcoholic fatty liver. Metabolism or stress." *Biochem. Pharmacol.* **24**: 431-434 (1975). H98,210/75

Comparative studies on the biochemistry of fatty liver formation in rats given ethanol, exposed to a new environment, or stressed by both these agents.

Salas, M., Tuchweber, B.: "Effect of stress on the liver ultrastructure." *Proc. Can. Fed. Biol. Soc.* (In press). J4,286/

In rats, various stressors (restraint, spinal cord transection, heat, cold, forced exercise) and cortisol injections caused a decrease in hepatic weight and rectal temperatures, concurrently with the typical triad of the alarm reaction. The hepatocytes showed EM evidence of RER degranulation, SER proliferation, glycogen depletion, slight lipid accumulation, mitochondrial enlargement and numerous lysosomes. The most striking change was an increase in the number of autophagic vacuoles.

Connective Tissue, Wound Healing, Regeneration and Inflammation

One of the most striking effects of systemic stress is its ability to influence connective tissue, especially in the presence of topical stress causing inflammation or necessitating wound healing and scar formation. In fact, one of the first observations on the

therapeutic effect of glucocorticoids was the demonstration of their antiphlogistic actions in experimental inflammation (topical irritation arthritis test, granuloma pouch test, anaphylactoid inflammation, cotton pellet granulomas, adjuvant polyarthritis), and in typical inflammatory diseases such as rheumatoid arthritis, various forms of dermatitis, conjunctivitis and so on.

Such anti-inflammatory effects are obtained both by endogenous secretion of glucocorticoids during systemic stress and by exogenous administration of these compounds or their artificial synthetic homologues. In very large doses, glucocorticoids also interfere with wound healing and scar formation.

By using the granuloma pouch technique, it could be shown that both cortisone and stress (restraint) exert their maximal antiphlogistic effects during a "*critical period*" on about the third day after local application of an inflammatory irritant.

Under certain conditions, even *calciphylaxis* can be inhibited by glucocorticoids, particularly if tissue calcification occurs under the influence of a mast cell discharge in the course of anaphylactoid inflammation.

Recently, a good deal of work has been published on the "*nonspecific mesenchymal reaction*," which develops during both systemic and topical stress and is characterized by increased incorporation of ^{35}S -sulphate into connective tissue.

Connective Tissue, Wound Healing, Regeneration and Inflammation

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

First description of the anaphylactoid inflammation produced in the rat by parenteral administration of egg white. This response is aggravated by adrenalectomy, and hence presumably some adrenal factor has antiphlogistic effects. The experiment also shows that "in this case an alarm reaction, elicited by another drug, exerted a protective influence" against egg white. Thus we are dealing with a type of cross-resistance.

Selye, H.: "The 'critical period' in the development of inflammation." *Acta Physiol. Lat. Am.* **3**: 188-193 (1953). B85,700/53

In rats with granuloma pouches produced by croton oil, cortisone inhibits exudate formation most markedly during a "critical period" at about the third day of local stress.

Selye, H.: "The part of inflammation in the local adaptation syndrome." *Rev. Can. Biol.* **12**: 155-176 (1953). A97,423/53

Review of the relationship between inflammation and the L.A.S.

Selye, H.: "The first international symposium on the mechanism of inflammation." *Q. Rev. Allergy* **7**: 471-484 (1953).

B88,037/53

Résumé of a colloquium on factors influencing inflammation, particularly hormone release during stress.

Heuser, G.: "Stress und Entzündung" (Stress and inflammation). *Medizinische No.* **1**: 13-17 (1954). B86,556/54

Review on the effect of systemic stress and stress hormones upon inflammation (13 refs.).

Swingle, W. W., Maxwell, R., Ben, M., Fedor, E. J., Baker, C., Eisler, M., Barlow, G.: "Epinephrine and resistance of hypophysectomized and adrenalectomized rats to stressor agents." *Am. J. Physiol.* **177**: 1-6 (1954). B93,484/54

The 24-hour adrenalectomized rat is extremely sensitive to intravenous infusions of globin and dextran, and reacts to both by an anaphylactoid syndrome terminating fatally in 87-93% of the animals. Prophylactic foretreatment with cortisone confers adequate protection. The hypophysectomized rat, despite severe atrophy of the cortex, does not exhibit symptoms when similarly infused. However, when the adrenals are removed from such animals they become sensitized and die within a few minutes after infusion. Medullectomized rats lacking adrenal medullae, but with well regenerated cortices are also quite sensitive and most of them succumb when infused. The data indicate that epinephrine, released from the intact medulla by the stress of infusion, is the agent

responsible for the surprising resistance shown by these hypophysectomized rats. Confirmation was obtained by markedly increasing resistance of adrenalectomized as well as adrenalectomized-hypophysectomized rats to globin by repeated pre- and postinfusion injections of epinephrine. Apparently the amine antagonizes the toxic action upon the peripheral circulation of some agent (possibly histamine) released from tissue cells by globin and dextran infusion, and thus prevents the anaphylactoid response to these two stressor agents."

Selye, H.: "Role of the quotient stressor/tissue in inflammation." *Arch. Int. Pharmacodyn. Ther.* **97**: 379-388 (1954).

B86,264/54

Experiments on rats suggest that "if a given tissue-area is exposed to various dilutions of croton oil, there is, within limits, a proportionality between the strength of the irritant and the intensity of the resulting inflammation (as expressed by exudation and granuloma formation). However, a near-maximal result is obtained, at relatively low concentrations of croton oil and, by further raising the strength of the irritant, the phlogistic response cannot be proportionately augmented. Similarly, if the same amount of croton oil is applied to varying areas of tissue-surface, the phlogistic response rises rapidly, in proportion with the tissue-area affected. Yet, here again, the response does not rise, and may even decline, after the contact-area is raised above a certain optimum. Cortisol, whether administered systemically, or topically, exerts its antiphlogistic actions (as regards exudation and granuloma formation) most effectively, under those conditions which, without the hormone, would have enabled a given amount of irritant to elicit a maximal response. In our experimental arrangement, this was the case, when a connective-tissue compartment was delimited by 25 ml. of air, and irritated by the topical application of 0.5 ml. of an 0.25% solution of croton oil in corn oil."

Chassin, J. L., McDougall, H. A.: "Effect of adrenalectomy on wound healing in normal and in stressed rats." *Proc. Soc. Exp. Biol. Med.* **86**: 446-448 (1954).

B96,585/54

Selye, H.: "'Critical period' for inhibition of inflammation by a primarily neurogenic stress-situation." *Psychosom. Med.* **17**: 124-127 (1955).

B88,520/55

"Inflammation, produced by means of the 'granuloma-pouch' technique, permits the objective volumetric assessment of exudation under strictly standardized conditions. By transient, forcible immobilization, a primarily neurogenic stress-situation can be induced which is highly effective in suppressing this type of inflammation." The literature on the antiphlogistic effect of stress and stress-induced hyperglucocorticoidism is briefly surveyed, and its relationship to psychosomatic diseases of adaptation is emphasized, since forced restraint as used in the present experiments is regarded primarily as a neurogenic stressor.

Selye, H., Jasmin, G.: "Screening of possible therapeutic agents by means of experimental replicas of connective-tissue diseases." *Ann. N.Y. Acad. Sci.* **64**: 481-493 (1956).

C10,860/56

Summary of the laboratory tests recommended for the study of inflammation and drugs which modify its course. For this purpose, the authors recommend the following tests in the rat: a granuloma-pouch test, the topical-irritation arthritis test, the experimental polyarthritis produced by Murphy Rat Lymphosarcoma tissue (presumably because it contains PPLO), the anaphylactoid reaction to mast cell discharges, and the "hyalinosis" with its characteristic cardiovascular inflammatory changes produced by DOC.

Bottiglioni, E., Prodi, G.: "Contributo allo studio dei rapporti esistenti fra il cosiddetto 'stress' e la sostanza fondamentale del connettivo" (Studies on the interrelations between so-called "stress" and the connective ground substance). *Sperimentale* **106**: 121-129 (1956).

C20,154/56

Ink, J.: "Alteraciones del sistema conectivo microarteriovenocapilar en las enfermedades infecciosas. Síndrome infeccioso inespecífico conectivo-microvascular" (Changes in microarteriovenous capillary connective system in infectious diseases. Nonspecific infectious microvascular connective syndrome). *Sem. Méd. (B. Aires)* **109**: 745-870 (1956).

C26,781/56

Extensive review on the behavior of connective tissue during the G.A.S.

Localio, S. A., Chassin, J., MacKay, M.: "The effect of stress, the adrenal and the pituitary on healing." *Am. J. Surg.* **91**: 521-524 (1956).

D75,850/56

Hill, M., Pospíšil, M.: "The patterns of mucopolysaccharide secretion in mast cells in the course of stress." *Acta Histochem.* (Jena) **10**: 109-121 (1960). C99,519/60

In rats, stress produced by formaldehyde causes cyclic swelling and shrinking of mast cells. Adrenalectomy permits only shrinkage and lysis of mast cell granules. "The observed stress changes in mast cells are considered to be two distinct patterns of their mucopolysaccharide secretion elicited by two antagonistic hormone groups, i.e. by glucocorticoids in the case of mast cell swelling, granule release, and vacuole formation, and by mineralocorticoids and/or STH in the case of mast-cell shrinking and granule lysis."

Toivanen, P., Hulkko, S., Näätänen, E.: "Effect of psychic stress and certain hormone factors on the healing of wounds in rats." *Ann. Med. Exp. Fenn.* **38**: 343-349 (1960). D89,254/60

Allegedly, psychogenic stress retards wound healing in male but not in female rats.

Geschickter, C. F., O'Malley, W. E., Rubacky, E. P.: "A hypersensitivity phenomenon produced by stress: the 'negative phase' reaction." *Am. J. Clin. Pathol.* **34**: 1-8 (1960). C88,483/60

Various stressors inhibit the anaphylactoid reaction produced by egg white in the rat, but this may be followed by a "negative phase" of hypersensitivity. "Although the 'negative phase' is similar to Selye's exhaustion stage of the general adaptation syndrome, it differs by being a more acute, frequent, and repetitive occurrence, and of a lesser degree of severity than that observed with exhaustion."

Smith, L. W., Molomut, N., Gottfried, B.: "Effect of subconvulsive audiogenic stress in mice on turpentine induced inflammation." *Proc. Soc. Exp. Biol. Med.* **103**: 370-372 (1960). C81,345/60

Csaba, G., Törö, I., Horváth, C., Ács, Th., Mold, K.: "Thymus and stress." *J. Endocrinol.* **23**: 423-431 (1962).

D17,079/62

Thymectomy slightly exacerbated the course of formalin arthritis and allegedly "cortisone, which prevented or arrested the arthritis in intact rats, produced serious aggravation of the condition in thymectomized animals. The action of the thymus is not apparently hormonal but depends on the presence of thymic tissue. It seems that this

phenomenon is connected with the participation of the thymus in polysaccharide metabolism."

Selye, H.: "Trente années de recherches: le 'stress' et la 'calciphylaxie'" (Thirty years of research: "stress" and "calciphylaxis"). *Rev. Franç.* (Montreal) No. 148: 63-65 (1963). D28,649/63

Gabbiani, G., Ortega, J. M. R.: "Stress et calciphylaxie" (Stress and calciphylaxis). *Pathol. Biol.* **12**: 192-194 (1964).

D55,958/64

Selye, H.: *The Mast Cells*, p. 498. London: Butterworths, 1965. G19,425/65

Extensive monograph on mast cells with several sections on the effect of stress, corticoids and catecholamines upon their development.

Castelli, A., Clay, M. M.: "Effect of cold and restriction of movement on mast cells and metachromasia of rat skin." *Nature* **207**: 89-90 (1965). F44,634/65

Guth, P. H., Hall, P.: "Microcirculatory and mast cell changes in restraint-induced gastric ulcer." *Gastroenterology* **50**: 562-570 (1966). G39,152/66

On the basis of experiments in the rat, a new hypothesis concerning the mechanism of gastric ulcers is formulated: "Stress → gastric mucosal mast cell degranulation with release of vasoactive substances → gastric mucosal vascular engorgement → decreased resistance to acid-pepsin digestion → mucosal ulceration."

Umezaki, Y.: "Effects of stress on the healing of the corneal wound in rabbits." *Folia Ophthalmol. Jap.* **17**: 22-25 (1966). J24,378/66

Selye, H.: "Ischemic necrosis: prevention by stress." *Science* **156**: 1262-1263 (1967). G39,929/67

Complete interruption of the circulation for nine hours by means of a special clip in a skin flap results in necrosis of the ischemic area. Prior treatment with various severe stressors (spinal cord transection, prolonged restraint, quadriplegia due to transection of motor nerves, forced exercise or cold baths), as well as systemic injection of EP, NEP or chlorpromazine, offer virtually complete protection against this form of topical tissue injury.

Funk, G. A., Jensen, M. M.: "Influence of

stress on granuloma formation." *Proc. Soc. Exp. Biol. Med.* **124**: 653-655 (1967).

F77,633/67

"Mice subjected to sound stress or a combination of avoidance-learning stress and sound stress showed a highly significant decrease in their ability to produce foreign body granulomas against subcutaneously-implanted cotton pellets."

Hauss, W. H., Junge-Hülsing, G., Gerlach, U.: *Die unspezifische Mesenchymreaktion. Zur Pathogenese der reaktiven Mesenchymerkrankungen* (The nonspecific mesenchymal reaction. The pathogenesis of reactive mesenchyme diseases), p. 155. Stuttgart: Georg Thieme Verlag, 1968. E166/68

After direct exposure to topical stressors, as well as during systemic stress, there develops a so-called "nonspecific mesenchymal reaction" in connective tissue which is characterized by increased incorporation of ^{35}S -sulfate.

Geschickter, C. F.: "Hypothermic stress in rats challenged with foreign protein." *Cryobiology* **4**: 232-236 (1968).

J21,243/68

It is confirmed that in rats, the anaphylactoid reaction to egg white is suppressed by such stressors as swimming in cold water or injections of EP.

Lindner, D., Dietsch, V.: "Quantitativ-morphologische und zytochemische Untersuchungen der Mastzellen in der Subcutis experimentell belasteter Ratten" (Quantitative morphologic and cytochemical studies on the mast cells in the subcutis of rats exposed to experimental stress). *Z. Mikrosk. Anat. Forsch.* **80**: 589-601 (1969).

H18,454/69

Guth, P. H., Kozbur, X.: "Microcirculatory and mast cell changes in restraint stress. Role of gastric acid." *Am. J. Dig. Dis.* **14**: 113-117 (1969).

G64,510/69

Palmer, B.: "The influence of stress on the survival of experimental skin flaps. A study on rats." *Scand. J. Plast. Reconstr. Surg.* **6**: 110-113 (1972).

G99,625/72

In rats with very long skin flaps which normally undergo partial necrosis, stress (restraint) distinctly diminished skin survival, but this could be inhibited by α -adrenergic blocking agents, presumably because they prevent vasoconstriction. [Since the skin flap, even at the end farthest removed from its attachment to normal skin,

was equivalent to an autotransplant which usually heals without necrosis in the absence of all vascular connections, it is difficult to understand why this was not the case here (H.S.).]

Török, O., Csaba, G.: "Effect of cold stress on mast cell formation in tissue culture." *Z. Mikrosk. Anat. Forsch.* **86**: 465-471 (1972).

J1,559/72

Naik, S. R., Kelkar, M. R., Sheth, U. K.: "Effect of stress on carrageenin inflammation in rats." *Indian J. Med. Res.* **60**: 1316-1322 (1972).

G98,320/72

In intact, unlike in adrenalectomized rats, different stressors inhibit carrageenin-induced inflammation.

Gabbiani, G., Tuchweber, B., Selye, H.: "Experimental ectopic calcification. (Calciphylaxis and calcergy)." In: Zipkin, I., *Biological Mineralization*, pp. 547-586. New York and London: John Wiley & Sons, 1973.

G60,019/73

A chapter which deals specifically with calciphylaxis and calcergy. One section is devoted to the effect of stress and the pituitary-adrenal axis (157 refs.).

Heughan, C., Grislis, G., Hunt, T. K.: "The effect of anemia on wound healing." *Ann. Surg.* **179**: 163-167 (1974).

J10,036/74

Hauss, W. H.: "Klinische Aspekte der mesenchymalen Reaktion und Suppression" (Clinical aspects of the mesenchymal reaction and its suppression). *Arzneim. Forsch.* **24**: 250-259 (1974).

H83,500/74

Detailed light microscopic and EM studies on the "nonspecific mesenchymal reaction" elicited by various stressors.

Romagnoli, P., Cortesini, C.: "Comportamento delle mastzellen del mesenteric in ratti shock-resistenti" (Behavior of mesenteric mast cells in shock-resistant rats). *Boll. Soc. Ital. Biol. Sper.* **50**: 253-255 (1974).

J22,855/74

Szafarczyk, A., Moretti, J. M., Boissin, J., Assenmacher, I.: "Effect of time of administration of an inflammatory agent on plasma corticosterone and haptoglobin levels in the rat." *Endocrinology* **94**: 284-287 (1974).

H80,857/74

Haptoglobin, the plasma glycoprotein, is synthesized in the liver of rats under the influence of corticosterone, and represents a fairly accurate index of the intensity of in-

flammatory reactions. In rats injected with turpentine, the fastest and highest haptoglobin levels occur concurrently with maximum corticosterone hypersecretion after injections at 09:00, while persistently low haptoglobin levels result from phlogogen administration at the time of lowest circadian adrenal reactivity (03:00). "These data are consistent with the concept of an adrenocortical control of haptoglobin biosynthesis."

Chernukh, A. M., Gorizontova, M. P., Alexeyev, O. V.: "The mechanism of participation of the mast cells in regulation of the vascular permeability." *Biochem. Exp. Biol.* **11**: 105-110 (1974). H96,177/74

In rats, restraint causes degranulation of mast cells with liberation of histamine, 5-HT

and heparin. These substances may have a role in the mechanism of vascular reactions during stress.

Billewicz-Stankiewicz, J., Krępińska-Urbaniak, A.: "The effect of vibration and noise on development of inflammatory reaction in rats." *Acta Physiol. Pol.* **25**: 235-240 (1974). J23,160/74

Cohen, I.: "Stress and wound healing," p. 112. Thesis, City University of New York, 1975. E10,838/75

Doctoral dissertation on the effect of stressors (noise, heat, cold) upon wound healing in the mouse. The effect depends largely upon whether the stressor is applied before or after the wound.

Skin

In the rat, epidermal mitotic activity diminishes during stress, perhaps owing to the antimitotic effect of corticoids.

In tree shrews, the hairs on the tail normally lie flat, but they become erect and bushy at the slightest stimulation, and thus act as a readily appraisable indicator of increased sympathetic activity—for example, during stress.

Skin

(See also our earlier stress monographs, p. xiii)

Bullough, W. S.: "Stress and epidermal mitotic activity. I. The effects of the adrenal hormones." *J. Endocrinol.* **8**: 265-274 (1952). B72,094/52

In rats the stress of overcrowding causes a more pronounced increase in the size of the adrenal medulla than of the cortex. The epidermal mitotic rate simultaneously decreases by sixty percent. "It is suggested that the antimitotic effects of stress may be due to a high rate of secretion of either or both of these adrenal hormones" (corticoids and catecholamines). All these reactions are regarded as manifestations of the G.A.S.

Bullough, W. S.: "Stress and epidermal mitotic activity. II. The effects of the sex hormones." *J. Endocrinol.* **8**: 365-376 (1952). B75,211/52

In mice, glucocorticoids inhibit epidermal mitotic activity, although this action may be influenced by sex hormones. The possibility that this effect of the glucocorticoids may

become apparent during stress is mentioned but not discussed in detail.

Katzberg, A. A.: "Epidermal cells and environmental stress." *Anat. Rec.* **136**: 339 (1958). J11,442/58

In man a variety of stressors (temperature variations, light, dessication, mechanical friction, microorganisms) affect both fetal and adult epidermal cells in a nonspecific manner so that "they respond with an attempt at accommodation by an alteration of the cytomorphological pattern and a decrease in their life span." [The brief abstract does not lend itself to evaluation (H.S.).]

Bullough, W. S., Laurence, E. B.: "Stress and adrenaline in relation to the diurnal cycle of epidermal mitotic activity in adult male mice." *Proc. R. Soc. Lond. Biol.* **154**: 540-556 (1961). E90,812/61

Kreyberg, L., Evensen, A., Iversen, O. H.: "Influence of stress on the diurnal rhythm in the mitotic activity in the epidermis of hairless mice." *Acta Pathol. Microbiol. Scand.* **64**: 176-184 (1965). G31,802/65

In hairless mice, epidermal mitotic counts show regular circadian variations due to the

duration, not the rate, of mitoses. This is true even after the circadian rhythmicity has been markedly changed by "acoustic stress."

Holst, D. von: "Sozialer Stress bei Tupaias (*Tupaia belangeri*). Die Aktivierung des sympathischen Nervensystems und ihre Beziehung zu hormonal ausgelösten ethologischen und physiologischen Veränderungen" (Social stress in *Tupaia* [*Tupaia belangeri*]. Activation of the sympathetic nervous system and its relation to hormonal stimulated etho-

logic and physiologic changes). *Z. Vergl. Physiol.* **63**: 1-58 (1969). G90,282/69

In the tree shrew the hairs on the tail normally lie flat, but become erect and bushy at the slightest stimulation. Thus, they act as a readily appraisable indicator of sympathetic activity. This response is elicited especially by other members of the species through sexual excitation or aggression. On the basis of studies on the mechanism of this reaction, "an attempt to interpret the results according to Selye's 'general adaptation syndrome' is made" (several hundred refs.).

Reticuloendothelial System (RES)

It is practically impossible to deal separately with the functional and morphologic aspects of RES activity, and hence these will be considered together here.

One of the earliest observations concerning the behavior of the RES was that following intravenous injection of India ink in rats exposed to various stressors, phagocytosis of the carbon particles was increased in the lung, kidneys, adrenals, bone marrow and hibernating gland. "In the spleen which undergoes marked atrophy during the alarm reaction, there was a slight decrease in the India ink phagocytosis." It was concluded that the RES participates actively in the G.A.S. Possibly, the apparently increased ink deposition during the alarm reaction reported in these earliest experiments might have been due to the use of preparations not sufficiently stabilized to prevent precipitation of the carbon particles, and their agglutination in capillaries may have been enhanced by stress. This could have been responsible for the increased ink deposition in various organs.

The phagocytic activity of the RES is considerably diminished after major abdominal surgery in dogs; allegedly this defect can be prevented by passive opsonin administration. Preliminary findings suggest that a depletion of opsonic protein, and the hypothalamic-adrenocortical axis are involved in this response.

In both children and rats a plasma "humoral recognition factor" essential for optimal phagocytosis is depleted after burns, which may partly explain the increased susceptibility to infection.

Following pretreatment with stressors, ACTH or glucocorticoids, intravenous thorium dextrin produces thrombohemorrhagic necroses in the adrenals and liver of the rat, reminiscent of the Shwartzman-Sanarelli phenomenon.

Reticuloendothelial System (RES)

(See also our earlier stress monographs, p. xiii)

Timiras, P. S., Selye, H.: "On the participation of the reticulo-endothelial system in the alarm reaction." *Science* **110**: 560-561 (1949). B36,271/49

Following intravenous injection of India ink in rats stressed by cold, spinal cord transection or forced exercise, the lungs,

kidneys, adrenals, bone marrow and "hibernating gland" exhibited increased ink deposition. "In the spleen, which undergoes marked atrophy during the alarm reaction, there was a slight decrease in the India ink phagocytosis." The experiment suggests an active participation of the RES "in the defense of the organism during the alarm reaction."

Zweifach, B. W., Benacerraf, B., Thomas,

L.: "The relationship between the vascular manifestations of shock produced by endotoxin, trauma, and hemorrhage. II. The possible role of the reticulo-endothelial system in resistance to each type of shock." *J. Exp. Med.* **106**: 403-414 (1957) (24 refs.).
G22,062/57

Zweifach, B. W., Benacerraf, B.: "Effect of hemorrhagic shock on the phagocytic function of Kupffer cells." *Circ. Res.* **6**: 83-87 (1958). E55,634/58

In rats, hemorrhagic shocks greatly decrease the phagocytic ability (colloidal carbon) of the Kupffer cells. "Histologic evidence suggests two possibilities: a localized impairment of Kupffer cell activity in the area about the central veins of the lobule, or an abnormal circulation through preferential pathways restricted to the periphery of the liver lobule."

Chiovato, I.: "Stress e poteri immunitari. Comportamento del potere fagocitario nello shock da eviscerazione" (Stress and immunologic capacity. Behavior of the phagocytic capacity in the shock of evisceration). *Rass. Med. Sper.* **9**: 70-73 (1962).

J23,139/62

D'Amico, G., Cambria, S.: "'Stress' ed attività fagocitaria del sistema reticoloendoteliale" (Stress and phagocytic activity of the reticuloendothelial system). *G. It. Chir.* **19**: 501-516 (1963). G15,973/63

In rabbits exposed to various stressors (partial evisceration, crushing of posterior limbs, burns), the phagocytic activity of the RES was always diminished.

Fujihara, J.: "Studies on the influence of stressors on reticuloendothelial function and experimental Salmonella infection." *J. Yonago Med. Assoc.* **14**: 389-407 (1963).

J24,336/63

Bauer, H., Horowitz, R. E., Watkins, K. C., Popper, H.: "Immunologic competence and phagocytosis in germfree animals with and without stress." *J.A.M.A.* **187**: 715-718 (1964). F2,297/64

Zweifach, B. W.: "Relation of the reticuloendothelial system to natural and acquired resistance in shock." *Int. Anesthesiol. Clin.* **2**: 271-286 (1964). J23,544/64

Gabbiani, G., Selye, H., Tuchweber, B.: "Adrenal localization of a thrombohemor-

rhagic phenomenon." *Endocrinology* **77**: 177-182 (1965). G19,450/65

In rats pretreated with ACTH, glucocorticoids or restraint, a single intravenous injection of thorium dextrin (an RES-blocking agent) produces thrombohemorrhagic necrosis of the adrenals and liver resembling the Schwartzman-Sanarelli phenomenon.

Ter-Markarian, N. G.: "Participation of adrenal glands and adrenocorticotrophic hormone of the hypophysis in changes of the phagocytic activity of blood leukocytes of rats in the action of a strong sound stimulus." *Probl. Endokrinol. Gormonoter.* **12** No. 5: 81-84 (1966). F72,472/66

In rats, convulsive attacks induced by a strong sound ("bell epilepsy") increased phagocytosis by leukocytes. The same sound in the absence of convulsions caused an opposite result. The effects of adrenalectomy and ACTH upon this phenomenon are discussed. [The published results are difficult to evaluate (H.S.).]

Saba, T. M., Luzio, N. R. di: "Surgical stress and reticuloendothelial function." *Surgery* **65**: 802-807 (1969).

G66,086/69

Saba, T. M.: "Mechanism mediating reticuloendothelial system depression after surgery." *Proc. Soc. Exp. Biol. Med.* **133**: 1132-1136 (1970). J21,499/70

In rats, the stressor effect of surgical interventions significantly depressed RES activity. "These findings support the concept that the increased host susceptibility to disease after surgery may be mediated in part by an alteration of the opsonic system and reticuloendothelial function."

Chernikov, I. T.: "Effect of nociceptive stimulation on phagocytic activity of the leukocytes in postnatal ontogenesis." *Biull. Èksp. Biol. Med.* **71** No. 1: 18-20 (1971) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **71**: 17-18 (1971). J21,616/71

Mullaney, J. F., Wilfong, R. G., LaForce, F. M., Huber, G. L.: "Effect of acute stress on pulmonary host defenses." *Clin. Res.* **20**: 580 (1972). H54,070/72

Scovill, W. A., Saba, T. M.: "Humoral recognition deficiency in the etiology of reticuloendothelial depression induced by surgery." *Ann. Surg.* **178**: 59-64 (1973). J4,221/73

The phagocytic activity of the RES is greatly depressed in dogs during and after major abdominal surgery. This depression

can be prevented by passive opsonin administration. "The potential depletion of opsonic protein by the entrance of damaged tissue or denatured protein in the circulation or the consumption of opsonin at the site of tissue injury may trigger this state of 'hypo-opsonemia.' In addition, preliminary findings suggest a role for the pituitary-adrenal axis in this response."

Grogan, J. B., Lockard, V.: "Acute alterations in the bactericidal capacity of rabbit alveolar macrophages following stress." *J. Trauma* **13**: 877-883 (1973).

J7,190/73

Lockard, V. G., Grogan, J. B., Brunson, J. G.: "Alterations in the bactericidal ability of rabbit alveolar macrophages as a result of tumbling stress." *Am. J. Pathol.* **70**: 57-68 (1973). H64,681/73

EM studies suggest that "the degradative phase of the phagocytic process in rabbit alveolar macrophages is altered by subjecting the animals to tumbling stress."

Kaplan, J. E., Saba, T. M.: "Humoral opsonic deficiency in the etiology of hepatic reticuloendothelial failure following shock." *Physiologist* **17**: 257 (1974). H89,915/74

Loegering, D. J., Saba, T. M.: "Systemic hypoopsonemia and reticuloendothelial failure during hemorrhagic hypotension in dogs." *Physiologist* **17**: 275 (1974). H89,922/74

Goldman, A. S., Rudloff, H. B., McNamee, R., Loose, L. D., Luzio, N. R. di: "Deficiency of plasma humoral recognition factor activity following burn injury." *J. Reticuloendothel. Soc.* **15**: 193-198 (1974). J12,833/74

"Plasma humoral recognition factor activity, which is essential for optimal phagocytosis, is significantly depleted in severely burned children, both in the presence or absence of bacteremia, as well as in burned rats." This may explain the increased susceptibility to infection following thermal injury (30 refs.).

Won, W. D., Ross, H. C.: "Catecholamine and phagocytic responses in infected mice exposed to hyperbaric helium-oxygen atmospheres." *Aviat. Space Environ. Med.* **46**: 191-193 (1975). J22,139/75

In mice in which stress was elicited by exposure to a helium-oxygen atmosphere, "hyperbaricity induced an acute depression in phagocytic activity and a marked elevation in the circulating levels of epinephrine, norepinephrine and dopamine."

Tumors

[Cf. Tumors under Diseases of Adaptation and Stressors and Conditioning Agents]

The development of neoplastic tissue can also be influenced by stress. Thus, in mice, stressors capable of causing thymic lymphatic involution produce similar regressive changes in malignant lymphoid tissue, although to a much lesser extent.

In leukemic strains of mice, fighting among males allegedly tends to delay the development of the disease, presumably through increased production of glucocorticoids. However, these claims are contradicted by other investigators. In any event, not all types of neoplastic tissue react the same way; indeed, according to certain studies, stress enhances the development of metastases in tumor-bearing experimental animals.

Tumors

(See also our earlier stress monographs, p. xiii)

Bass, A. D., Feigelson, M.: "Response of normal and malignant lymphoid tissue to non-specific tissue damage." *Proc. Soc. Exp. Biol. Med.* **69**: 339-341 (1948).

B28,259/48

In mice, "ethyl alcohol is an alarming stimulus.... Fasting begun 30 hours after the initial stimulus gives an additional 'lympholytic' effect. It has been shown that stimuli which are known to produce an alarm reaction with resulting atrophy of the normal thymus and normal spleen produce a similar type of reaction in tissue composed of malignant lymphocytes."

Lemonde, P.: "Influence of fighting on leukemia in mice." *Proc. Soc. Exp. Biol. Med.* **102**: 292-295 (1959). C77,947/59

In leukemic strains of mice, fighting among males tends to delay the development of the disease, probably through the stress-induced discharge of ACTH and corticosterone.

Marsh, J. T., Miller, B. E., Lamson, B. G.: "Effect of repeated brief stress on growth of Ehrlich carcinoma in the mouse." *J. Natl. Cancer Inst.* **22**: 961-977 (1959).

C69,305/59

"Exposure to shuttlebox or confinement stress tends to inhibit the growth of Ehrlich tumors in mice."

Slawikowski, G. J. M.: "Tumor development in adrenalectomized rats given inoculations of aged tumor cells after surgical stress." *Cancer Res.* **20**: 316-320 (1960).

C84,855/60

In rats, surgical stress tends to increase susceptibility to Walker tumor transplant growth.

Griffiths, J. D., Hoppe, E.: "Effect of metabolic 'stress' on development of tumor following inoculation of Walker carcinosarcoma cells." *Proc. Soc. Exp. Biol. Med.* **104**: 467-469 (1960).

C89,551/60

Such stressors as starvation or dehydration did not increase the susceptibility of rats to Walker tumor implants in acute experiments. However, "if starvation is continued for 7 days there is increase in percentage 'takes' of the tumor as compared to incidence in normal healthy animals."

Renaud, S.: "Effect of stress on toxicity and tumor growth inhibition of neomycin." *Antibiot. Chemother.* **10**: 109-113 (1960).

C70,026/60

Various stressors failed to influence significantly the growth of Walker sarcomas in rats.

Dufour, D., Rochette, A.: "Etude de l'influence des acides nucléiques du thymus sur la réponse non-spécifique à l'agression" (Study of the influence of thymic nucleic acids on the nonspecific response to stress). *Ann. Endocrinol. (Paris)* **22**: 9-13 (1961).

D3,652/61

In rats, "thymic nucleic acid extract has been able to diminish in a significative manner the unspecific effects of tumor graft, inhibiting particularly the catabolism and preventing adrenal hypertrophy and thymus

atrophy. On the other hand, this action is specific of the stress-cancer while, in the rat exposed to cold, thymic DNA are unable to exert such a protection."

Gottfried, B., Molomut, N.: "The influence of surgical trauma on the growth of tumor. An experimental evaluation." *J. Int. Coll. Surg.* **36** Sect. 1: 596-602 (1961).

J23,558/61

"Repeated surgical trauma had the effect of stimulating tumor growth in both a transplanted mammary adenocarcinoma and a chemically induced neoplasm" in mice.

Minster, J. J.: "Decreased resistance to tumor cells after stress, followed by increased resistance." *Proc. Soc. Exp. Biol. Med.* **113**: 377-379 (1963). D68,996/63

Molomut, N., Lazere, F., Smith, L. W.: "Effects of audiogenic stress upon methylcholanthrene-induced carcinogenesis in mice." *Cancer Res.* **23**: 1097-1101 (1963).

E26,094/63

Griepentrog, F.: "Spontane Hypophysentumoren als häufiger Befund bei weissen Laboratoriumsratten" (Spontaneous hypophyseal tumors as a frequent finding in white laboratory rats). *Beitr. Pathol. Anat.* **130**: 40-50 (1964). F18,218/64

Lutherer, L. O., Wunder, C. C., Moretti, W. J., Dodge, C. H.: "Implanted tumour growth in mice exposed to continuous centrifugation." *Nature* **201**: 303-304 (1964).

F9,114/64

Gottfried, B., Molomut, N.: "Effects of surgical trauma and other environmental stressors on tumor growth and wound healing." *Acta Un. Int. Cancr.* **20**: 1617-1620 (1964).

J23,645/64

In mice, "repeated surgical trauma had the effect of stimulating tumor growth in both a transplanted mammary adenocarcinoma, and a chemically induced neoplasm.... The effects of other environmental stressors, namely, audiogenic stress, and electric shock stress are discussed, and their differences from those found with the surgical trauma are pointed out."

Matthes, T.: "Experimental contribution to the question of emotional stress reactions on the growth of tumors in animals." *Acta Un. Int. Cancr.* **20**: 1608-1610 (1964).

J23,726/64

In rats, mice and chickens, the growth of tumors produced by carcinogens is inhibited

by emotional stress. Such "tumour inhibitions on an emotional basis surely do not constitute regressions of autonomous tumour cells, but a non-specific effect of adrenal cortex hormones which influence the stroma and the blood supply in an antiphlogistic respect."

Buinauskas, P., Brown, E. R., Cole, W. H.: "Inhibiting and enhancing effect of various chemical agents on rat's resistance to inoculated Walker 256 tumor cells." *J. Surg. Res.* **5**: 538-546 (1965). J23,158/65

Otis, L. S., Scholler, J.: "Effects of stress during infancy on tumor development and tumor growth." *Psychol. Rep.* **20**: 167-173 (1967). J12,075/67

Mice exposed to daily electric shocks received tumor implants or carcinogenic substances. The results "failed to support the reports of other investigators that stress applied to the infant or young adult organism alters its susceptibility to develop cancer."

Kaliss, N., Fuller, J. L.: "Incidence of lymphatic leukemia and methylcholanthrene-induced cancer in laboratory mice subjected to stress." *J. Natl. Cancer Inst.* **41**: 967-983 (1968). G62,089/68

Various stressors (crowding, sound, electroshock) failed to exert any significant influence upon the appearance of the neoplasms mentioned in the title.

Jensen, M. M.: "The influence of stress on murine leukemia virus infection." *Proc. Soc. Exp. Biol. Med.* **127**: 610-614 (1968). F96,630/68

Newberry, B. H., Frankie, G., Beatty, P. A., Maloney, B. D., Gilchrist, J. C.: "Shock stress and DMBA-induced mammary tumors." *Psychosom. Med.* **34**: 295-303 (1972). G93,557/72

In rats, the incidence of mammary tumors induced by 7,12-dimethylbenz(α)anthracene tends to be diminished by stressors, but the results are not striking (27 refs.).

Cole, W. H.: "The mechanisms of spread of cancer." *Surg. Gynec. Obstet.* **137**: 853-871 (1973). H77,359/73

Review of the literature indicating that various stressors enhance tumor metastasis in experimental animals (125 refs.).

Pradhan, S. N., Ray, P.: "Effects of stress on growth of transplanted and 7,12-dimethylbenz[α]anthracene-induced tumors and their modification by psychotropic drugs." *J. Natl. Cancer Inst.* **53**: 1241-1245 (1974). J24,475/74

Various stressors (restraint, sound, electroshock) increased the growth of transplanted or induced tumors in rats concomitantly with an increase in adrenal and a decrease in splenic weight. Chlorpromazine abolished this protective action.

Other Morphologic Changes

The literature on other morphologic changes is too scanty to warrant separate discussion. However, we might briefly mention that some investigations, listed in the abstract section, indicate that stress may affect the nucleus pulposus in the *intervertebral discs*, the *external lacrimal glands* of the rat, various elements of the *nervous system*, the "hibernating gland," *brown adipose tissue* and *skeleton*.

Other Morphologic Changes

(See also our earlier stress monographs, p. xiii)

Chitty, D., Chitty, H., Leslie, P. H., Scott, J. C.: "Changes in the relative size of the nucleus in the intervertebral discs of stressed Orkney voles (*Microtus orcadensis*)."*J. Pathol. Bacteriol.* **72**: 459-469 (1956).

C32,079/56

In Orkney voles, stress was produced by provoking fighting, chasing and superficial wounding. "The more severely wounded ani-

mals, in comparison with their litter-mate controls, had higher liver, spleen, adrenal and bodyweights, a smaller thymus and a relatively larger cross-sectional area of *nucleus pulposus*." It had previously been suggested that stress may cause disc lesions in man.

Vlăšin, Z., Filkuka, J.: "Beeinflussung der Stressantwort des Thymus und der Hibernationsdrüse der Ratte durch Veränderung der Reaktionslage des Nervensystems" (Modification of stress response of thymus and hibernating gland of rat by change in

reactive state of nervous system). *Naunyn Schmiedebergs Arch. Pharmacol.* **227**: 414-426 (1956). J25,025/56

In rats, the thymolysis and the degranulation of the *hibernating gland* elicited by formalin-induced stress is prevented by adrenalectomy.

Croce, G.: "Lo 'stress' uditorio e le sue riverberazioni extralabirintiche" (Noise stress and its extra-labyrinthine repercussions). *Valsalva* **40**: 381-384 (1964).

J10,965/64

No definite changes were noted in the *extra-orbital lacrimal gland* of the rat upon exposure to the stress of noise.

Ichiki, H., Usui, K.: "Studies on the bone disorder of rats caused by heavy exercise. I. Etiology." *Jap. J. Vet. Sci.* **28**: 45-56 (1966).

J24,915/66

In rats, prolonged forced swimming caused typical G.A.S. manifestations accompanied by a decrease in the nitrogen content of the *bones*, as well as osteoporosis, similar to the changes produced by glucocorticoids.

Gabrielescu, E.: "The lability of lysosomes during the response of neurons to stress." *Histochem. J.* **2**: 123-130 (1970).

G75,574/70

In guinea pigs and rats, histochemical studies on neurolyssosomes (acid phosphatase test) in certain regions of the *brain* showed increased lability after stress induced by physical efforts, acceleration, hyperthermia and emotional arousal.

Dropp, J. J., Sodetz, F. J.: "Autoradio-

graphic study of neurons and *neuroglia* in autonomic ganglia of behaviorally stressed rats." *Brain Res.* **33**: 419-430 (1971).

J20,190/71

Linck, G., Petrovic, A.: "Does brown adipose tissue of the European hamster (*Cricetus cricetus*) store and synthesize corticosteroids? The isolation of a corticosteroid-like compound." *Arch. Sci. Physiol.* **26**: 85-100 (1972).

J11,335/72

Brief survey of the literature suggesting that the brown adipose tissue or "*hibernating gland*" of the rat, which reacts to cold like the adrenal by releasing lipid granules, contains a "survival principle." The hibernating gland cells of the hamster produce a corticoid-like principle in vitro. [It remains to be seen whether this plays any role in resistance to stress (H.S.).]

Hunter, C., Clegg, E. J.: "Changes in skeletal proportions of the rat in response to hypoxic stress." *J. Anat.* **114**: 201-219 (1973).

J2,542/73

Bennett, T. E., Farwell, R. W., Anthony, A.: "Spiral *ganglion* RNA changes in rats exposed to acute noise stress" (abstracted). *Physiologist* **17**: 179 (1974). H89,871/74

Skála, J. P., Hahn, P.: "Changes in interscapular *brown adipose tissue* of the rat during perinatal and early postnatal development and after cold acclimation. VI. Effect of hormones and ambient temperature." *Int. J. Biochem.* **5**: 95-106 (1974) (28 refs.).

J13,050/74

FUNCTIONAL CHANGES

The effects of stress upon the sex organs (including pregnancy and lactation), gastrointestinal system, salivary glands, lung, kidney, liver and various other organs are arbitrarily discussed under Morphologic Changes in order not to duplicate many findings that refer to both structural and functional changes.

Resistance

Many observations on the triphasic variations of resistance during chronic exposure to stress have demonstrated the characteristic decrease in resistance during the alarm reaction, the increase in the stage of resistance and the final decline during the stage of exhaustion. These have been discussed in the General Outline, whereas the phe-

nomena of cross-resistance and cross-sensitization have received adequate attention in the section on the effects of exposure to Multiple Stressors; hence, here it will suffice to give a few key references.

Resistance

(See also our earlier stress monographs, p. xiii, and cf. the section on Multiple Stressors)

Renaud, S.: "The toxicity of kanamycin and bacitracin as influenced by stress and sodium chloride." *Toxicol. Appl. Pharmacol.* **2**: 708-714 (1960). C85,849/60

In rats, the myocardial lesions produced by kanamycin and bacitracin resulted in particularly severe nephrocalcinosis, such as had previously been caused with neomycin plus stress. However, cardiac lesions were not obtained after treatment with neomycin plus stress.

Geschickter, C. F., O'Malley, W. E., Rubacky, E. P.: "A hypersensitivity phenomenon produced by stress: the 'negative phase' reaction." *Am. J. Clin. Pathol.* **34**: 1-8 (1960). C88,483/60

Various stressors inhibit the anaphylactoid reaction produced by egg white in the rat, but this may be followed by a "negative phase" of hypersensitivity. "Although the 'negative phase' is similar to Selye's exhaustion stage of the general adaptation syndrome, it differs by being a more acute, frequent, and repetitive occurrence, and of a lesser degree of severity than that observed with exhaustion."

Marino, A.: "Physical stress and emetine cardiotoxicity." *Experientia* **17**: 116-117 (1961). D4,522/61

In guinea pigs, the stress of forced swimming increases the cardiotoxicity of emetine.

Marino, A.: "Psychological stress and emetine cardiotoxicity." *Experientia* **17**: 117-119 (1961). D6,102/61

Leikola, A.: "Influence of stress on alcohol intoxication in rats." *Q. J. Stud. Alcohol* **23**: 369-375 (1962). D38,054/62

Rats stressed by swimming exhibited an accelerated clearance of orally-administered ethanol. Upon intraperitoneal treatment, they showed the same alcohol concentrations in blood as unstressed animals. "The stressed rats, however, were less intoxicated than the unstressed animals with corresponding blood

alcohol levels." Possibly, adrenal hormones released during stress may be responsible for this increased tolerance.

Marino, A., Parise, A., Galdi, R.: "Stress psicologico e cardiotossicità strofantinica" (Psychologic stress and strophanthin cardio-toxicity). *Arch. It. Sci. Farmacol.* **13**: 208-209 (1963). G19,379/63

In guinea pigs, the cardiotoxicity of strophanthin is enhanced by exposure to various stressors.

Rupe, B. D., Bousquet, W. F., Miya, T. S.: "Stress modification of drug response." *Science* **141**: 1186-1187 (1963).

E26,910/63

In rats, tourniquet stress decreases the toxicity of various drugs that can be metabolized by hepatic enzymes. "The effect of stress on drug response is not noted with barbital, a compound which is not metabolized; this effect is inhibited by treatment of the animal with a drug metabolism inhibitor such as SKF 525-A." Similar actions are obtained with ACTH or corticosterone. "Compounds which can stimulate adrenocorticotrophic hormone secretion or act directly on the adrenals to produce corticosteroids should thus be able to stimulate their own metabolism or that of other drugs."

Bajusz, E., Jasmin, G., Mongeau, A.: "Dissociation by forced muscular exercise of the cardiotoxic from the myotoxic actions of plasmocid." *Rev. Can. Biol.* **23**: 29-36 (1964). F9,053/64

Forced muscular exercise, restraint, fasting or cold environmental temperatures counteract the cardiotoxic effects of plasmocid on the one hand, and enhance its myotoxic properties on the other, so that the skeletal muscle becomes affected.

Marino, A.: "Influence of psychological stress on the specific cardiotoxicity of drugs." *Nature* **203**: 1289-1290 (1964).

F21,708/64

In guinea pigs, "psychological stress was able to potentiate the specific cardiotoxicity of emetine, strophanthin, pitressin and hypertensine. Research in progress is showing similar results with thyroxin and adrenaline. Moreover, we found promazine, a psycho-

tropic drug, and 'Persantin,' a coronary vasodilator, especially when combined, to exert a highly significant protection against the experimental cardiopathy [produced] by psychological stress and pitressin. Such a protection was also shown by mebutamate, a centrally acting drug with hypotensive and tranquillizer effects, against the cardiopathy induced by psychological stress and strophanthin or hypertensine."

Selye, H., Tuchweber, B., Gabbiani, G.: "Protection by restraint against parathyroid hormone intoxication." *Acta Endocrinol. (Kbh.)* **45** Supp. 90: 203-209 (1964).

E24,101/64

In rats, restraint offers complete protection against the osteitis fibrosa and soft tissue calcification normally produced by large doses of parathyroid extract.

Stahnke, H. L.: "Stress and the toxicity of venoms." *Science* **150**: 1456-1457 (1965).

F57,253/65

Resistance to scorpion or rattlesnake venom is diminished by previous exposure to various stressors.

Lal, H., Chessick, R. D.: "Lethal effects of aggregation and electric shock in mice treated with cocaine." *Nature* **208**: 295-296 (1965).

F54,339/65

Lee, N. H., Hospador, M. A., Manthei, R. W.: "Influence of age and dietary stress on hexobarbital activity in mice." *Proc. Soc. Exp. Biol. Med.* **125**: 153-156 (1967).

F80,166/67

On an 8 percent casein diet, mice can still synthesize drug-metabolizing enzymes despite rapid growth. However, hexobarbital sleeping time is prolonged, perhaps because of a less active TPNH generating system.

Schattenfroh, C., Stracke, U., Eger, W.: "Änderung der Leberfunktion durch Tourniquet, Mesenterialgefäßligatur und Immobilisation im Tierexperiment" (Change in liver function due to tourniquet, mesenteric vessel

ligation and immobilization in animal experiments). *Brunns Beitr. Klin. Chir.* **216**: 560-568 (1968).

J22,743/68

In rats, stress induced by traumatic injuries offers immediate protection against the hepatic necrosis normally produced by allyl alcohol.

Goldberg, M. E., Salama, A. I.: "Amphetamine toxicity and brain monoamines in three models of stress." *Toxicol. Appl. Pharmacol.* **14**: 447-456 (1969).

G66,997/69

In the mouse and rat, a significant rise in the level of brainstem 5-HT was caused by trauma or electroshock but not by cold. "This increase was obtained in animals subjected to stress alone, or those given the highest possible nonlethal dose of amphetamine. These same doses did not augment the catecholamine-releasing properties of amphetamine in drum- or electric shock-stressed animals. It does not appear that stress potentiates the effects of amphetamine, as no evidence of excitation was obtained in stressed animals given amphetamine. It is postulated that amphetamine enhances the effects of stress."

Ermolov, V. I.: "Effects of disturbance of the normal course of pregnancy in dogs on development of natural immunity in the progeny." *Biull. Èksp. Biol. Med.* **71** No. 3: 64-66 (1971) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **71** No. 3: 285-287 (1971).

J21,617/71

In dogs exposed to stressors during pregnancy, "the immunologic properties of the blood of the fetuses and newborn puppies were appreciably weakened. The phagocytic response was depressed most sharply, and this was accompanied by a decrease in the digestive power of the leukocytes. Weakening of the immunobiological properties led to the appearance of inflammation in the lungs and intestine by the action of the automicr flora and was responsible for death of a large proportion of the newly born animals."

Nervous System

Generalities. Among the functional disturbances characteristic of stress, neuropsychologic changes play a very important role, especially in man, because of his highly developed and sensitive CNS. It is particularly difficult to present the enormous amount

of relevant literature in an orderly fashion because of the many overlaps between the central nervous alterations produced by stress, such as various forms of performance, learning, emotional changes, cravings for food and drugs (including alcohol), accident proneness and so on. Hence, the available data had to be more or less arbitrarily subdivided according to the most pertinent topics.

It is sometimes difficult to differentiate between simple impairments of neuropsychologic functions and psychologic defense mechanisms, such as narcissism, submission to a higher power (God, fate, a leader or doctors), masochistic attempts at self-punishment, or a type of deeper depersonalization. The establishment of a feeling of unreality also helps to protect against frightening psychogenic stress.

Additional pertinent information may be found in the subsequent section on Stress Tests (many of which are based upon mental reactions), as well as in the chapter on Theories (which will deal with the morphologic and neurohumoral alterations induced in the nervous system by stress).

Nervous System

(See also our earlier stress monographs, p. xiii)

Generalities. Russell, R. W.: "Behaviour under stress." *Int. J. Psychoanal.* **34** Supp.: 1-12 (1953). D87,619/53

A lecture before the British Psycho-Analytical Society summarizing the G.A.S., with special emphasis upon behavioral changes induced by stress.

Menninger, K. A.: "Psychological aspects of the organism under stress." *Gen. Systems* **2**: 142-172 (1954). C3,535/54

Detailed review of the literature on common psychologic causes of stress, with special reference to the homeostatic regulatory function and devices of the ego under major stress, in relation to the G.A.S. (99 refs.).

Schaffer, H. R.: "Behavior under stress: a neurophysiological hypothesis." *Psychol. Rev.* **61**: 323-333 (1954). D77,848/54

On the basis of an analysis of pertinent publications, the "hypothesis is here advanced that under stress a shift in emphasis occurs from cortical to subcortical centers, and that consequently behavior under stress must be seen primarily in relation to subcortical processes. This hypothesis is supported by the similarity of general activity under stress to that of decorticate animals" (37 refs.).

Fox, H. M., Gifford, S., Murawski, B. J., Rizzo, N. D., Kudarauskas, E. N.: "Some methods of observing humans under stress." *Psychiatr. Res. Rep. APA* **7**: 14-26 (1957). J11,149/57

Review on the G.A.S. with special reference to behavioral changes in man. Among the leading psychologic defenses against stress are various forms of narcissism, submission (to a higher power such as God, "fate" or doctors) and activity. On the other hand, some patients respond with masochistic attempts at self-punishment or a hysterical kind of depersonalization and unreality to protect themselves against frightening fantasies about impending operations or other sources of psychogenic stress.

Coleman, J. C.: *Personality Dynamics and Effective Behavior*, p. 566. Chicago: Scott, Foresman, 1956. C92,253/30

A monograph on human behavior with several sections on the psychologic effects of stress and the stressor actions of anxiety. An annotated bibliography deals with such problems as the stress of college life, marriage and the family, and aging.

Mandler, G., Mandler, J., Kremen, I., Sholiton, R. D.: "The response to threat: relations among verbal and physiological indices." *Psychol. Monogr.* **75** (1961). J13,071/61

Nikolov, N. A.: "The effect of the stress reaction on higher nervous activity." *Biull. Èksp. Biol. Med.* **54** No. 10: 63-66 (1962) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **54**: 1121-1123 (1962). J25,031/62

In dogs in which stress was produced by formalin injection into a paw, nervous responses were studied during the various phases of the G.A.S. "The excitatory process in the brain cortex suffers more than in subcortical nervous formations. This is explained

by the greater resistance of the latter to strong stimuli formed during the phylogensis."

Ruff, G. E.: "Psychological and psychophysiological indices of stress." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 33-59. Glencoe, Ill.: Free Press, 1963. E10,425/63

Brief review on psychologic indices of stress, with special reference to performance.

Ostow, M.: "Stress and psychic function." *Forest Hosp. Lect. Ser. on Stress and Adaptation* (Des Plaines, Ill.) 4 (1965).

J11,874/65

Jacobson, H. A., Handler, L.: "Extroversion-introversion and the effects of stress on the Draw-A-Person Test." *J. Consult. Psychol.* 31: 433 (1967). J22,776/67

Levi, L.: "Sympatho-adrenomedullary and related biochemical reactions during experimentally induced emotional stress." In: Michael, R. P., *Endocrinology and Human Behaviour*, pp. 200-219. London, New York and Toronto: Oxford University Press, 1968. G64,344/68

Wied, D. de: "Effects of peptide hormones on behavior." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 97-140. New York, London and Toronto: Oxford University Press, 1969.

E10,614/69

Review of the effects exerted by ACTH, vasopressin and MTH upon behavior.

Montagu, A.: *The Direction of Human Development*, 2nd ed., p. 406. New York: Hawthorn Books, 1970. E10,932/70

Monograph on various factors influencing human behavior and development with several sections concerning the effect of stress and stress hormones.

Lazarus, R. S., Averill, J. R., Opton, E. M. Jr.: "Towards a cognitive theory of emotion." In: Levi, L., *Society, Stress and Disease. I. The Psychosocial Environment and Psychosomatic Diseases*, pp. 190-205. London, New York and Toronto: Oxford University Press, 1971. E9,312/71

Cooper, C. L.: "Coping with life stress after sensitivity training." *Psychol. Rep.* 31: 602 (1972). J19,722/72

Willett, E. A., Heilbronn, M.: "Repression-sensitization and discrepancy between

self-report and official report of illness." *J. Psychol.* 81: 161-166 (1972). J19,862/72

"The Repression-Sensitization (R-S) scale has been used to differentiate between two major defensive styles. Studies relating the R-S scale to measures of adjustment suggest that repressors are better adjusted than sensitizers."

Levi, L., Kagan, A.: "A synopsis of ecology and psychiatry: some theoretical psychosomatic considerations, review of some studies and discussion of preventive aspects." *Proc. 5th World Congr. of Psychiatry*, Mexico, D. F., 1971. Int. Congr. Ser. No. 274, pp. 369-379 (1973). J16,708/73

Lindvall, T., Radford, E. P.: "Measurement of annoyance due to exposure to environmental factors." *Environ. Res.* 6: 1-36 (1973). J15,317/73

Review on various environmental factors, especially sound, pollution, crowding and stressful interpersonal relations, as objective indicators of somatic stress (about 150 refs.).

Broverman, D. M., Klaiber, E. L., Vogel, W., Kobayashi, Y.: "Short-term versus long-term effects of adrenal hormones on behaviors." *Psychol. Bull.* 81: 672-694 (1974). J16,920/74

Review with special emphasis on comparative effects of long- and short-term stress upon behavior in general (about 300 refs.).

Cronholm, B.: "Ethology, psychiatry and psychosomatic medicine. A review with particular regard to basic research by the 1973 Nobel Prize laureates: Karl von Frisch, Konrad Lorenz and Nikolas Tinbergen." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 39: 1-34 (1974). J19,033/74

Brief monograph emphasizing the relationship between stress and behavior.

Horowitz, M.: "Stress response syndromes. Character style and dynamic psychotherapy." *Arch. Gen. Psychiatry* 31: 768-781 (1974) (45 refs.). J19,758/74

Wied, D. de: "Pituitary-adrenal system hormones and behavior." In: Schmitt, F. O. and Worden, F. G., *The Neurosciences. Third Study Program*, pp. 653-666. Cambridge, Mass. and London: MIT Press, 1974. J17,220/74

Glassman, E.: "Macromolecules and behavior: a commentary." In: Schmitt, F. O.

and Worden, F. G., *The Neurosciences. Third Study Program*, pp. 667-677. Cambridge, Mass. and London: MIT Press, 1974.

J17,221/74

Dunn, A., Entingh, D., Entingh, T., Gispen, W. H., Machlus, B., Perumal, R., Rees, H. D., Brogan, L.: "Biochemical correlates of brief behavioral experiences." In: Schmitt, F. O. and Worden, F. G., *The Neurosciences. Third Study Program*, pp. 679-

684. Cambridge, Mass. and London: MIT Press, 1974.

J17,222/74

Silva, G. da: "La situation d'être malade. Essai d'une théorie de la psychothérapie" (The situation of being sick. A tentative theory of psychotherapy). *Un. Méd. Can.* **103**: 1920-1926 (1974).

H96,158/74

Psychoanalytic study of the possibly beneficial mental effects of the "syndrome of just being sick" (21 refs.).

Performance. Perhaps the least well-defined neuropsychiatric parameter of stress is "performance in general," since this is an all-inclusive concept which depends upon and influences virtually all activities.

However, one generalization appears to be justifiable, namely, that a certain degree of stress is necessary to provide the alertness required by all kinds of performance, whereas fatigue and the exhaustion produced by intense or continued severe stress result in a decline in the ability to perform any task.

Research in this field has been especially handicapped by the difficulty of making any generalizations on the basis of objective tests which measure performance in general. However, on the basis of more or less subjective indicators, a good deal of information has been accumulated in relation to the effect of stress upon individual skills, social attainment and recently, on the multiple duties of astronauts working under conditions of acceleration, deceleration and a weightless environment.

Performance (See also Stress Tests). Bills, A. G.: *The Psychology of Efficiency. A Discussion of the Hygiene of Mental Work*, p. 361. New York and London: Harper & Brothers, 1943.

E10,657/43

Monograph on the psychologic factors involved in efficient performance and fatigue, which presents many data useful in the interpretation of stress effects but does not analyze their somatic basis (only key refs.).

Pomeroy, D. S.: "Ameliorative effects of 'counseling' upon maze performance following induced stress" (abstracted). *Am. Psychol.* **5**: 327 (1950).

D76,308/50

Fraser, D. C.: "Stress conditions in skilled performance." *Q. Bull. Br. Psychol. Soc.* **2**: 31 (1951).

D27,636/51

There is a clearcut relationship between the degree of variously-induced stress and the deterioration in a subject's performance. In fact, "the deterioration in a subject's performance under stress can provide a sound index of his overall efficiency."

Dykman, R. A., Gantt, W. H.: "A comparative study of cardiac conditioned responses and motor conditioned responses in

controlled 'stress' situations" (abstracted). *Am. Psychol.* **6**: 263-264 (1951).

J12,710/51

Lybrand, W.: "The effects of psychological stress on reasoning performance." *Indicators of Behavior Decrement*. Technical Report No. 8, College Park, Md.: University of Maryland, 1953.

J16,131/53

Phillips, L., Cowitz, B.: "Social attainment and reactions to stress." *J. Pers.* **22**: 270-283 (1953).

J10,409/53

The relationship between psychologic and physiologic responses to stress and performance in everyday life was investigated by means of the Worcester scale of social attainment, the use of which is described in detail.

Feffer, M., Phillips, L.: "Social attainment and performance under stress." *J. Pers.* **22**: 284-297 (1953).

J10,414/53

Pronko, N. H., Leith, W. R.: "Behavior under stress: a study of its disintegration." *Psychol. Rep.* **2**: 205-222 (1956).

B28,732/56

Review of the literature and personal observations on the effects of psychogenic

stress, particularly anxiety, on perception and performance in various tests, some of which are described in detail (29 refs.).

Farber, I. E., Spence, K. W.: "Effects of anxiety, and task variables on reaction time." *J. Pers.* **25**: 1-18 (1956). B29,418/56

In man, variations in the amount of anxiety did not consistently affect reaction time to visual stimuli (41 refs.).

Peterson, P. L., Wright, R. S., Sleight, R. B.: *Performance as a Function of Time: An Annotated Bibliography*. Arlington, Va.: Century Res. Corp., 1959. J16,130/59

Rao, K. U., Russell, R. W.: "Effects of stress on goal setting behavior." *J. Abnorm. Soc. Psychol.* **61**: 380-388 (1960).

J23,622/60

Review of motivation as influenced by stress.

Sperber, Z.: "Test anxiety and performance under stress." *J. Consult. Psychol.* **25**: 226-233 (1961).

J23,536/61

Ruff, G. E.: "Psychological and psychophysiological indices of stress." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 33-59. Glencoe, Ill.: Free Press, 1963.

E10,425/63

Brief review on the effect of psychologic indices of stress, with special reference to performance.

Siegel, A. I., Wolf, J. J.: "Computer simulation of man-machine systems." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 61-86. Glencoe, Ill.: Free Press, 1963.

E10,426/63

Design for a computer model to estimate stress-induced changes in performance, particularly in relation to space flights.

Chambers, R. M.: "Operator performance in acceleration environments." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 193-319. Glencoe, Ill.: Free Press, 1963.

E10,430/63

Brief review on performance in acceleration environments, with special reference to space flights.

Handler, E.: "Temperature effects on operator performance." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environ-*

ments and Human Behavior, pp. 321-352. Glencoe, Ill.: Free Press, 1963.

E10,431/63

Review on the effect of high and low temperatures on performance, with special reference to aerospace medicine.

Loftus, J. P. Jr., Hammer, L. R.: "Weightlessness." In: Burns, N. M., Chambers, R. M. et al., *Unusual Environments and Human Behavior*, pp. 353-377. Glencoe, Ill.: Free Press, 1963.

E10,432/63

Review of the literature on space travel suggests that man can function effectively in a weightless environment.

Berkun, M. M.: "Performance decrement under psychological stress." *Hum. Factors* **6**: 21-30 (1964).

J18,097/64

Studies using the SSS, as well as corticoid excretion, eosinopenia and so on, to estimate performance under stress situations simulating those encountered in warfare.

Thiesen, J. W., Forgas, R. H., Spaner, F. E.: "An objective method of assessing a stress syndrome related to achievement motivation." *Percept. Mot. Skills* **19**: 183-197 (1964).

G35,813/64

A multifactorial battery of stress tests indicate that the sustained heart-rate response, as utilized in this procedure, is a sensitive and convenient measure of stress associated with achievement motivation. It is suggested that the test battery and methodology described may be useful in research concerning striving-induced stress and its role in psychosomatic disorders."

Thiesen, J. W., Brown, K. D., Forgas, R. H., Evans, S. M., Williams, G. M., Taylor, J.: "Further data on a stress syndrome related to achievement motivation: relationships with age and basal serum cholesterol level." *Percept. Mot. Skills* **20**: 1277-1292 (1965).

G35,812/65

Verification of a multifactorial stress test based on heart rate acceleration. "While a tendency toward higher over-all heart rates with increased age was observed, the principal specific finding was a positive association of basal serum cholesterol level with post-stress heart rate, independent of age. Individuals with higher serum cholesterol levels showed less complete recovery following stress and higher initial heart rates, but they did not necessarily show a stronger immediate response to the stressors."

Torrance, E. P.: *Constructive Behavior: Stress, Personality and Mental Health*, p. 432. Belmont, Cal.: Wadsworth, 1965.

E10,436/65

Monograph on the psychologic implications of the G.A.S., with reference to performance and the development of a healthy personality. There are chapters examining constructive responses to stress, personality resources which help develop such responses, how groups cope with stress, and individual resources and strategies useful in coping with stress (350 refs.).

Ruff, G. E., Korchin, S. J.: "Adaptive stress behavior." In: Appley, M. H. and Trumbull, R., *Psychological Stress. Issues in Research*, pp. 297-323. New York: Appleton-Century-Crofts, 1967. E10,417/67

Studies on Mercury astronauts showed "the effectiveness of adaptive responses based on past experience and professional competence. Given a group of men with repeated success in accomplishment of hazardous duties, followed by training which led to highly organized, efficient patterns of behavior, evidence of disruptive stress behavior was minimal."

Haythorn, W. W., Altman, I.: "Personalit factors in isolated environments." In: Appley, M. H. and Trumbull, R., *Psychological Stress. Issues in Research*, pp. 363-399. New York: Appleton-Century-Crofts, 1967.

E10,418/67

Guidelines for the analysis of performance in task-oriented, isolated groups, with special reference to space travel.

Wilkinson, R.: "Some factors influencing the effect of environmental stressors upon performance." *Psychol. Bull.* **72**: 260-272 (1969). J8,026/69

Review of the literature on the effect of various stressors (particularly heat, sleep deprivation, noise, hypoxia and vibration) upon human performance, as indicated by a number of tests.

Jacobs, P. D., Kirk, R. E.: "Effects of 'task-related stress' on human performance on a two-component monitoring task." *Percept. Mot. Skills* **29**: 815-823 (1969).

J18,093/69

Martens, R., Landers, D. M.: "Motor performance under stress: a test of the inverted-U hypothesis." *J. Pers. Soc. Psychol.* **16**: 29-37 (1970). J12,679/70

High school boys were exposed to various

intensities of anxiety by the threat of punishment with electroshock if they performed standard motor tasks poorly. Heart rate, palmar sweat and questionnaire responses served as indicators of stress, and the Children's Manifest Anxiety Scale was used to appraise anxiety. "Results supported the inverted-U hypothesis for the stress factor and the anxiety factor separately." The inverted-U hypothesis states that increases in arousal are associated with improvements in the quality of performance up to a certain point, after which additional increases in arousal impair performance.

Bergström, B.: "Tracking performance under threat-induced stress." *Scand. J. Psychol.* **11**: 109-114 (1970). J20,638/70

Thornton, J. W., Jacobs, P. D.: "Analysis of task difficulty under varying conditions of induced stress." *Percept. Mot. Skills* **31**: 343-348 (1970). J19,076/70

Houston, B. K., Hodges, W. F.: "Situational denial and performance under stress." *J. Pers. Soc. Psychol.* **16**: 726-730 (1970). J21,190/70

Broadbent, D. E.: *Decision and Stress*, p. 522. New York and London: Academic Press, 1971. E10,531/71

Monograph on decision making in relation to stress with a chapter on "the arousal theory of stress." Comparatively little reference is made to the hypothalamus-pituitary-adrenal system (about 100 refs.).

Bergström, B., Arnberg, P.: "The effect of threat- and task-oriented attitude upon performance under stress." *Scand. J. Psychol.* **12**: 14-20 (1971). J20,639/71

Renner, J., Renner, V.: "Effects of stress on group versus individual problem solving." *Psychol. Rep.* **30**: 487-491 (1972). J20,570/72

Morris, L. W., Perez, T. L.: "Effects of test-interruption on emotional arousal and performance." *Psychol. Rep.* **31**: 559-564 (1972). J19,721/72

Prather, D. C., Berry, G. A., Jones, G. L.: "The training of a perceptual skill by either rewarding or aversive feedback compared on efficiency, transfer, and stress." *J. Appl. Psychol.* **56**: 514-516 (1972). J19,600/72

Leith, G.: "The relationships between intelligence, personality and creativity under

two conditions of stress." *Br. J. Educ. Psychol.* 42: 240-247 (1972). J19,602/72

Observations on nine- to thirteen-year-old children "indicate that the number and originality of responses are greater in the stressful condition and that there is a disordinal interaction of both extroversion and anxiety with stress."

Azer, N. Z., McNall, P. E., Leung, H. C.: "Effects of heat stress on performance." *Ergonomics* 15: 681-691 (1972).

H79,383/72

In man, "heat stress" (95° F at 75 percent relative humidity) causes deterioration in performance (tracking task) and an increase in reaction time to peripheral stimuli. [In the absence of control experiments with other stressors, it remains to be seen whether this is due to a specific effect of heat or to stress (H.S.).]

Hecht, K., Treptow, K., Poppei, M.: "Der Einfluss von chronisch applizierten Stressmustern auf die Informationsverarbeitung des ZNS in Entscheidungsprozessen" (The influence of chronically applied stress patterns on the processing of information in the

CNS with regard to decisions). *Ergeb. Exp. Med.* 8: 338-342 (1972). H79,376/72

Studies on the limits of stress endurance with regard to the function of information processing by the human CNS.

Welford, A. T.: "Stress and performance." *Ergonomics* 16: 567-580 (1973).

J8,260/73

Theoretical considerations on the effect of stress upon performance. "A model is proposed which ties together three previously existing models current in this field: the Inverted-U Hypothesis, Signal Detection Theory, and the Yerkes-Dodson Law."

Houston, B. K.: "Viability of coping strategies, denial, and response to stress." *J. Pers.* 41: 50-58 (1973).

J19,607/73

Shearer, E., Fulkerson, F. E.: "The effects of physical and psychological stress on the performance of high- and low-anxious Ss on a difficult verbal discrimination task." *Bull. Psychonomic Soc.* 1: 255-256 (1973).

H91,958/73

Studies using the TMAS to examine performance in verbal discriminating tasks.

Learning, Cognition and Memory. The effect of stress upon learning and memory has been examined in both experimental animals and in man; yet here again few generalizations can be made.

In rats, hypophysectomy interferes with the acquisition of avoidance responses, and this defect can allegedly be corrected by ACTH.

In man, any severe stress impairs learning ability, but at least according to one study, when subjects are exposed to stress while under the influence of nitrous oxide, the effect of stress on subsequent learning is abolished.

Undoubtedly, stress—particularly that of psychogenic origin—tends to impair memory in a manner very similar to that of aging. An oft-quoted example of this effect is the case of a high executive who consulted a psychoanalyst because of the gradual deterioration of his memory, which he ascribed to "management stress," and who, when asked for an illustration, replied "of what?"

Learning, Cognition and Memory. Keenan, J. W., Deese, J., Lazarus, R. S.: "Anxiety-reduction and stress in verbal learning" (abstracted). *Am. Psychol.* 7: 277-278 (1952). J13,016/52

Lazarus, R. S., Deese, J., Hamilton, R.: "Anxiety and stress in learning: the role of intraserial duplication." *J. Exp. Psychol.* 47: 111-114 (1954). J13,308/54

Applezweig, M. H., Baudry, F. D.: "The pituitary-adrenocortical system in avoidance

learning." *Psychol. Rep.* 1: 417-420 (1955). D78,108/55

In rats, hypophysectomy "did interfere with the acquisition of avoidance responses, and sham-restoration of the system by exogenous administration of ACTH appeared to improve conditioning somewhat."

Russell, R. W., Steinberg, H.: "Effects of nitrous oxide on reactions to 'stress.'" *Q. J. Exp. Psychol.* 7: 67-73 (1955).

D81,503/55

"The present investigation using insoluble and soluble problems has demonstrated that both nitrous oxide and exposure to stress impair learning; but that, when subjects are exposed to stress while under the influence of the drug, the effects of the stress on subsequent learning are abolished."

MacCalman, D. R.: "Stress in childhood." *Med. J. Aust.* **1**: 353-357 (1956).

J25,024/56

Review of the G.A.S. in relation to stress in children, especially in relation to maternal deprivation during the first years of life. "Learning in general is inhibited under stress."

Barcroft, H., Brod, J., Heil, Z., Hirsjärvi, E. A., Kitchin, A. H.: "The mechanism of the vasodilation in the forearm muscle during stress (mental arithmetic)." *Clin. Sci.* **19**: 577-586 (1960).

D2,280/60

Singer, H. A.: "The management of stress." *Adv. Management* **25**: 11-13 (1960).

J14,314/60

Stress predisposes to various diseases and reduces efficiency by causing mental blocks. One "executive" claimed that he kept forgetting things after he said them. When the analyst asked him for an illustration he replied: 'Of what?'

Zaidi, S. M. H.: "Reactions to stress as a function of the level of intelligence." *Genet. Psychol. Monogr.* **62**: 41-104 (1960).

J23,535/60

An extensive review of the literature and personal observations led to the conclusion that "there is no evidence for a significant or systematic relation between the level of intelligence and reactions to stress. There is only partial evidence for the prediction that the effect of stress on subsequent learning increases directly with the level of intelligence. There also is only slight evidence that stress interfered with the transfer of training from one learning task to another. However, there is a significant difference between poststress learning when exposure to stress is preceded by learning and when it is not. The latter shows relatively greater effect of exposure to the insoluble task on subsequent learning of the subjects" (80 refs.).

Chorover, S. L., Schiller, P. H.: "Reexamination of prolonged retrograde amnesia in one-trial learning." *J. Comp. Physiol. Psychol.* **61**: 34-41 (1966).

J22,883/66

Electroconvulsive shock may cause prolonged retrograde amnesia.

Ross, B. M., Chambers, R. M.: "Effects of transverse G-stress on running memory." *Percept. Mot. Skills* **24**: 423-435 (1967).

J23,604/67

Chapouthier, G., Legrain, D., Spitz, S.: "'Stress' de la mère gravide et capacités d'apprentissage des jeunes souris" ("Stress" of the pregnant mother and learning capacity of young mice). *C.R. Acad. Sci. (Paris)* **269**: 504-506 (1969).

J21,283/69

Wyon, D. P.: "Studies of children under imposed noise and heat stress." *Ergonomics* **13**: 598-612 (1970).

J19,068/70

Marteniuk, R. G., Wenger, H. A.: "Facilitation of pursuit rotor learning by induced stress." *Percept. Mot. Skills* **31**: 471-477 (1970).

J19,077/70

Duncan, N. C., Grossen, N. E., Hunt, E. B.: "Apparent memory differences in inbred mice produced by differential reaction to stress." *J. Comp. Physiol. Psychol.* **74**: 383-389 (1971).

G82,094/71

Burmistrova, N. N.: "Current problems of the education of children with somatic diseases under hospital conditions." *Pediatria* **61** No. 10: 61-65 (1972) (Russian).

J20,501/72

Houston, B. K.: "Viability of coping strategies, denial, and response to stress." *J. Pers.* **41**: 50-58 (1973).

J19,607/73

Becker, S. S., Horowitz, M. J. Campbell, L.: "Cognitive responses to stress: effects of changes in demand and sex." *J. Abnorm. Psychol.* **82**: 519-522 (1973).

J15,757/73

Observations on men watching stress-provoking films "support the hypotheses that intrusive and repetitive thinking are general cognitive responses to stress and that such changes in conscious experience can be quantified in the experimental laboratory."

Marton, F. I., Fransson, A., Jonsson, B., Klenell, A.-C., Roos, B.: "Differential effects of stress-inducing instructions on anxiety, learning and performance." *Scand. J. Psychol.* **14**: 213-219 (1973).

J21,827/73

Neufeld, R. W. J.: "Effect of cognitive appraisal on d' and response bias to experimental stress." *J. Pers. Soc. Psychol.* **31**: 735-743 (1975).

J23,534/75

Emotions (Aggression, Frustration, Fear). Among the emotional disturbances induced by stress, the most common appear to be aggressiveness, a sense of frustration, and fear, particularly loose anxiety, a condition in which the patient is afraid without knowing precisely of what.

Frustration as a consequence of stress is mainly due to a loss of goal orientation and the feeling that nothing is worthwhile—which may gradually progress to severe depression. Aggressiveness may result in the development of special hates (especially among different racial, religious or political groups) or in general irritability and intolerance.

In male mice, isolation causes aggressiveness, which allegedly is reduced by adrenalectomy or ACTH but enhanced by glucocorticoids.

In any event, it is well to realize that severe emotional disturbances during stress are due to changes in the metabolism of certain neurohormonal factors whose elucidation may offer clues to pharmacotherapy when counseling fails.

In man, continuous infusions of EP produce moderate anxiety and its acknowledged somatic manifestations. It is hardly necessary to mention the well-known emotional changes induced by excessive treatment with glucocorticoids.

Emotions (Aggression, Frustration, Fear). Maier, N. R. F.: *Frustration: The Study of Behavior Without a Goal*. New York: McGraw-Hill, 1949. J13,881/49

General discussion of frustration as a manifestation of the stress caused by loss of goal orientation.

Scott, J. P.: *Aggression*, p. 149. Chicago: University of Chicago Press, 1958.

C60,444/58

Popularized description of the factors regulating aggressive behavior, with only cursory reference to the G.A.S.

Hawkins, D. R., Monroe, J. T., Sandifer, M. G., Vernon, C. R.: "Psychological and physiological responses to continuous epinephrine infusion. An approach to the study of the affect, anxiety." *Psychiatr. Res. Rep. APA* 12: 40-52 (1960). J11,148/60

In man, continuous intravenous infusions of EP produced a moderate anxiety reaction in addition to the well-known somatic effects (sweating, tachycardia, hypertension, skin pallor).

Gunderson, E. K. E.: "Emotional symptoms in extremely isolated groups." *Arch. Gen. Psychiatry* 9: 362-368 (1963).

J4,088/63

Observations on scientists and Navy men exposed to prolonged isolation at scientific stations in Antarctica revealed that the most

consistent changes were sleep disturbances, depression and irritability (9 refs.).

Rule, B. G.: "Anti-Semitism, stress, and judgments of strangers." *J. Pers. Soc. Psychol.* 3: 132-134 (1966). D98,287/66

Data indicated that extremely high and extremely low prejudiced individuals react differently under stress than moderately prejudiced individuals. High and low scorers on the Anti-Semitism scale tended to report greater personality differences between two strangers and were more negative in their evaluations of strangers than moderately prejudiced subjects."

Brain, P. F., Nowell, N. W., Wouters, A.: "Some relationships between adrenal function and the effectiveness of a period of isolation in inducing intermale aggression in albino mice." *Physiol. Behav.* 6: 27-29 (1971).

J10,867/71

In male mice, isolation causes aggressiveness (fighting) which is reduced by adrenalectomy or ACTH injection but enhanced by dexamethasone (17 refs.).

Thor, D. H., Ghiselli, W. B., Ward, T. B.: "Infantile handling and sex differences in shock-elicited aggressive responding of hooded rats." *Dev. Psychobiol.* 7: 273-279 (1974).

J12,750/74

Handling during infancy caused only minor changes in the aggressive response of male and female rats exposed to electric footshock in adulthood.

Appetite (including Cravings for Drugs and Alcohol). One of the earliest observations that led to the formulation of the stress concept was the finding that disease of any kind, hemorrhage, surgical trauma or even severe emotional arousal causes a loss of appetite. On the other hand, it has been equally well established that minor psychogenic stress (interpersonal difficulties, the need to abandon smoking and so on) frequently induces an increase in appetite and consequently an excessive gain in body weight. Also, it is common knowledge that certain individuals may be "driven to drink" or become subject to various toxicomanias as a result of stressful life situations or constant pain, but it remains to be seen whether these are truly nonspecific stress effects which could develop upon exposure to any stressor. In any event, the intensity and direction (increase or decrease) of changes in appetite and special cravings are highly subject to individual conditioning factors and represent typical examples of pluricausal responses to stress.

Appetite (including cravings for drugs and alcohol). Thomas, C. B., Ross, D. C.: "Observations on some possible precursors of essential hypertension and coronary artery disease. VIII. Relationship of cholesterol level to certain habit patterns under stress." *Bull. Johns Hopkins Hosp.* **113**: 225-238 (1963). E29,405/63

Among medical students, "subjects in the lower cholesterol group more often reported loss of appetite, exhaustion, nausea and anxiety when under [psychogenic] stress; in addition, urge to be alone, tremulousness and depression were more frequent than expected, although these items only approached significance. The only item with a significant positive relationship to higher cholesterol levels was the urge to eat" (35 refs.).

Krumbacher, K., Meyer, J. E.: "Das Appetitverhalten des Gesunden unter emotionalem Stress" (The appetite behavior of healthy people under emotional stress). *Z. Psychosom. Med. Psychoanal.* **9**: 89-94 (1963). E24,287/63

Paré, W. P.: "Stress and consummatory behavior in the albino rat." *Psychol. Rep.* **16**: 399-405 (1965). J22,032/65

Spence, D. P., Gordon, C. M., Rabkin, J.: "Effects of rejection on psychogenic hunger." *Psychosom. Med.* **28**: 27-33 (1966). J23,040/66

Imms, F. J.: "The effects of stress on the growth rate and food and water intake of rats." *J. Endocrinol.* **37**: 1-8 (1967). F76,001/67

McClymont, G. L.: "Selectivity and intake in the grazing ruminant." In: Code, C. F., *Handbook of Physiology. Section 6. Alimen-*

tary Canal, pp. 129-137. Washington, D.C.: American Physiological Society, 1967.

E7,301/67

Effect of various stressors on the eating habits of ruminants, particularly cattle and sheep (64 refs.).

March, H.: "Untersuchungen zum hyperphagen Reaktionstypus" (The hyperphagic reaction type). *Z. Psychosom. Med. Psychoanal.* **15**: 272-276 (1969). J21,323/69

Stress increases appetite under certain conditions and decreases it under others (19 refs.).

Boone, M. A., Hughes, B. L.: "Wind velocity as it affects body temperature, water consumption and feed consumption during heat stress of roosters." *Poultry Sci.* **50**: 1535-1537 (1971). J20,545/71

Pudel, V.: "Experimentelle Untersuchungen über das menschliche Appetitverhalten unter Stress" (Studies on appetite changes in men under stress). *Z. Psychosom. Med. Psychoanal.* **17**: 347-355 (1971). G87,356/71

Anecdotal description of the effects of various stressors upon appetite. The reason why certain stressors can increase or decrease appetite remains unknown.

Pudel, V., Meyer, J.-E.: "Die Fettsucht als Störung des Appetitverhaltens. I. Experimentelle Untersuchungen der Appetit- und Sättigungsregulation" (Obesity caused by changes in appetite. I. Experiments on the regulation of appetite and satiation). *Dtsch. Med. Wochenschr.* **99**: 618-628 (1974). H86,345/74

Review of the literature and numerous personal observations indicating that, depen-

ding upon conditions, stress can produce either a loss or an increase of appetite in different people (22 refs.).

Meyer, J.-E., Pudel, V.: "Die Fettsucht als Störung des Appetitverhaltens. II. Psychosoziale und psychodynamische Aspekte

der Fettsucht" (Obesity caused by changes in appetite. II. Psychosocial and psychodynamic aspects of obesity). *Dtsch. Med. Wochenschr.* **99**: 648-651 (1974).

H86,347/74

Observations on stress-induced hyperphagia in man (17 refs.).

Accident Proneness. There can be little doubt that stress predisposes to accidents in that it interferes with the ability to concentrate and perform various tasks. Several review articles have been devoted to this extremely important problem which affects safety, especially in industry, driving, flying, and other potentially dangerous occupations. Naturally, here again, individual conditioning factors determine the likelihood of a person becoming accident prone during stress.

Accident Proneness. McLean, A. A.: "Accident proneness. A clinical approach to injury-liability." *Ind. Med. Surg.* **24**: 122-126 (1955).

J25,161/55

Hirschfeld, A. H., Behan, R. C.: "The accident process. III. Disability: acceptable and unacceptable." *J.A.M.A.* **197**: 85-89 (1966).

F67,942/66

Stress and especially depression are often associated with accident proneness.

Brenner, B., Selzer, M. L.: "Risk of causing a fatal accident associated with alcoholism, psychopathology, and stress: further analysis of previous data." *Behav. Sci.* **14**: 490-495 (1969).

J22,571/69

EEG. Depending upon conditions, the EEG changes produced by stress may differ, but in general they are characterized by a decrease in the amplitude of "specific activities."

In normal people, the stress of decision-making has a readily detectable effect upon the EEG. Pertinent studies suggest that sensory signals reach the frontal cortex by a process of "idiodromic projection" to establish a "dispersive convergence." However, the arousal level as indicated by EEG records is not determined solely by any one factor, but represents the combination of several stimuli of varying degrees of specificity.

EEG (See also EEG under Stress Tests). Ulett, G. A., Gleser, G.: "The effect of experimental stress upon the photically activated EEG." *Science* **115**: 678-682 (1952).

B70,782/52

Sem-Jacobsen, C. W.: "Electroencephalographic study of pilot stresses in flight." *Aerosp. Med.* **30**: 797-801 (1959).

C77,977/59

Fukuda, T., Funasaka, O.: "Factor analysis of the slow waves induced by electroconvulsive shock. Further studies of electroencephalographic findings under various experimental conditions in adult albino rats." *Bull. Osaka Med. Sch.* **7**: 130-140 (1961).

J24,996/61

Dési, I., Csalay, L., Gát, T., Nikolits, I., Hajtman, B.: "EEG in experimental neuro-

genic hypertension (evaluation with Fourier analysis)." *Activ. Nerv. Sup. (Praha)* **7**: 19-24 (1965).

J23,488/65

In rats, hypertension was produced by combined sound, light and electric stimulation, and the associated EEG changes were registered.

Servít, Z., Machek, J., Strejčková, A., Fischer, J.: "Comparative pathophysiology of the paroxysmal EEG. Laminar analysis of the electrogenesis of spike and wave activity in the frog telencephalon." *Physiol. Bohemoslov.* **15**: 327-336 (1966).

J22,664/66

Studies on frogs stressed by electroshock led the authors to the conclusion that "the electrographic spike of the spike and wave complex is generated by successive depolarisation of the paleopallial cortex from the sur-

face into the depth (type I) or from the depth towards the surface (type II). The first type apparently arises by propagation of the paroxysm along afferent pathways from other brain structures, the second type by paroxysmal discharge of the granular layer of the pallium effected directly by the electrical stimulus. The slow wave of the complex is accompanied by protracted negativity in the molecular (dendritic) layer."

Leeuwen, W. S. van, Kamp, A., Kok, M. L., Dequartel, F., Tielen, A.: "EEG of unrestrained animals under stressful conditions." *Electroencephalog. Clin. Neurophysiol.* Supp. 25: 212-225 (1967). G59,749/67

Detailed description of the EEG changes in unrestrained dogs exposed to various stressors. "General stress—active or passive—is accompanied by a general decrease of the amplitude of the 'specific activities.'"

Walter, W. G.: "Electrical signs of association, expectancy and decision in the human brain." *Electroencephalogr. Clin. Neurophysiol.* Supp. 25: 258-262 (1967).

J23,883/67

EEG studies in normal people suggest that "sensory signals reach frontal cortex by a process of 'idiodromic projection' to establish a 'dispersive convergence.'"

Sano, K., Miyake, H., Mayanagi, Y.: "Steady potentials in various stress conditions in man." *Electroencephalogr. Clin. Neurophysiol.* Supp. 25: 264-275 (1967).

G59,750/67

Mercier, J., Assouline, G., Fondarai, J.: "Modifications électrocorticographiques observées chez le rat albinos soumis à la contrainte" (Electrocorticographic modifications observed in albino rats exposed to restraint). *C.R. Soc. Biol. (Paris)* 161: 1639-1641 (1967). F95,016/67

Stille, G., Sayers, A.: "Motor convulsions and EEG during maximal electroshock in the rat." *Int. J. Neuropharmacol.* 6: 169-174 (1967). J22,699/67

Malyshenko, N. M.: "Bioelectrical activity in rat's brain after injection of thyroidine and 6-methylthiouracile under stress and adrenalectomy." *Fiziol. Zh. SSSR* 54: 176-181 (1968) (Russian). J25,005/68

Malyshenko, N. M.: "Changes of the cerebral bioelectrical activity of intact and adrenalectomized rats following administration of hydrocortisone, DOCA and in stress reaction." *Probl. Endokrinol.* 14 No. 1: 62-68 (1968) (Russian). F96,018/68

Beyer, C., Sawyer, C. H.: "Hypothalamic unit activity related to control of the pituitary gland." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 255-287. New York, London and Toronto: Oxford University Press, 1969.

E10,616/69

Gofman, S. S., Freidin, I. V.: "Data of multicanal radioelectroencephalography in man in neuroemotional stress." *Biull. Éksp. Biol. Med.* 70 No. 11: 19-22 (1970) (Russian). J22,792/70

Rogge, K.-E.: "EEG-Veränderungen nach verzögter akustischer Rückmeldung der Lautsprache" (EEG variations following delayed feedback of speech). *Z. Exp. Angew. Psychol.* 19: 641-670 (1972). J22,118/72

Provins, K. A., Glencross, D. J., Cooper, C. J.: "Thermal stress and arousal." *Ergonomics* 16: 623-631 (1973). J8,263/73

Studies on healthy young men kept in a water bath of varying temperature "suggested that the arousal level as indicated by both the subjective and EEG records is not determined solely by either the body temperature or ambient conditions but is a resultant of their combined influences."

Sudakov, K. V.: "Emotional stress and its manifestation in dynamic of electroencephalographical and somatovegetative reactions." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 49-53. Baku, USSR, 1974. (Russian, with extensive English summary). J17,536/74

Varia. The importance of *genetic* factors in the development of neuropsychologic disturbances during stress has been amply illustrated. We have seen that certain strains of wild rabbits develop a "stress thyrotoxicosis" when threatened by a dog or man. Similarly, audiogenic convulsions ascribed to the stressor effect of intense sound develop only in genetically hypersensitive individuals, for example, in certain strains of mice and rats. As we shall see in the section on Diseases of Adaptation, even epileptic convulsions may be precipitated by stress in predisposed people.

Women who do not readily adapt to *odors* (measured by an olfactometer) have the greatest incidence of stressful life events.

ACTH raises the *muscle action potential* after stimulation of the gastrocnemius in the rat, while hypophysectomy has an opposite effect.

In his Nobel lecture on *Ethology and Stress Diseases*, Tinbergen reported data in support of the concept that *autism* in children is usually the result of environmental stress.

Varia (See also Diseases of Adaptation).
 Kracht, J., Kracht, U.: "Zur Histopathologie und Therapie der Schreckthyreotoxikose des Wildkaninchens" (The histopathology and therapy of fright thyrotoxicosis in wild rabbits). *Virchows Arch. [Pathol. Anat.]* **321**: 238-274 (1952). B68,863/52

In some strains of wild rabbits, fear induced by a pursuing dog or man causes "*stress thyrotoxicosis*" with histologic signs of thyroid hyperactivity and exophthalmos.

Bevan, W.: "Sound-precipitated convulsions: 1947 to 1954." *Psychol. Bull.* **52**: 473-504 (1955). D78,855/55

Review of genetic and stress factors causing *audiogenic convulsions*. It is deplored that "despite general preference for a physiological model, nothing has been done to assay systematically physiological differences among susceptible and nonsusceptible animals. Although electroshock convulsions have been discussed within the framework of Selye's adaptation syndrome hypothesis, and although audiogenic seizures have been regarded as a stress phenomenon by both physiologically and psychologically biased investigators, no vigorous attempt to exploit Selye's logic has been made for the latter phenomenon" (145 refs.).

Hart, F. M., King, J. A.: "Distress vocalizations of young in two subspecies of *Peromyscus maniculatus*." *J. Mammal.* **47**: 287-293 (1966). J25,104/66

Hecker, M. H. L., Stevens, K. N., Bismarck, G. von, Williams, C. E.: "Manifestations of task-induced stress in the acoustic speech signal." *J. Acoust. Soc. Am.* **44**: 993-1001 (1968). J25,047/68

Schneider, R. A., Costiloe, J. P.: "Limitation of olfactory adaptation in subjects under stress" (abstracted). *Fed. Proc.* **28**: 829 (1969). H10,717/69

In women who kept a diary of their daily life events, *olfactory thresholds* were measured repeatedly with a recording olfacto-

meter. "Those subjects who did not adapt or rarely adapted to the odor had the greatest incidence of stress recorded in their diary on the test days."

Horowitz, M. J., Becker, S. S., Moskowitz, M., Rashid, K.: "Intrusive thinking in psychiatric patients after stress." *Psychol. Rep.* **31**: 235-238 (1972). J20,571/72

After viewing stressful films, both psychiatric patients and normal individuals had increased *intrusive and repetitive thoughts*.

Horowitz, M. J., Becker, S. S.: "Cognitive response to stress: experimental studies of a 'compulsion to repeat trauma.'" In: Holt, R. R. and Peterfreund, E., *Psychoanalysis and Contemporary Science*, Vol. 1, pp. 258-305. New York: Macmillan, 1972.

G89,099/72

Observations strongly supporting "the hypothesis of a tendency toward *intrusive repetitive thought* after mild or moderate, as well as major, stresses in persons without psychiatric illness."

Reeves, R. B. Jr.: "What happens to the patient's religion?" *Delaware Med. J.* **45**: 40-43 (1973). J19,880/73

A pastor describes his experience in the change of the *religious feelings* of patients in hospitals. "We are dismayed by our own humanity, unable to accept our creatureliness as proper to our being, unable to love ourselves. This, of all the stresses a patient may suffer, can be the most disturbing."

Warburton, D. M.: "Modern biochemical concepts of anxiety. Implications for psychopharmacological treatment." *Int. Pharmacopsychiatry* **9**: 189-205 (1974).

J21,388/74

In man, "corticosteroids produce agitation and enhance *anxiety*. It is proposed that anxiety results from the neurochemical changes induced by corticosteroids. Evidence was presented to show that the critical changes for anxiety are due to modifications in serotonin pathways in the tegmental region of the midbrain."

Schmidt, R. T.: "Personality and fainting." *J. Psychosom. Res.* 19: 21-25 (1975).

J22,160/75

Vasodepressor *fainting* often occurs in response to stressful situations in predisposed individuals. It may be precipitated by "a situation, which elicits little emotional response from most people, [but which] can be extremely unpleasant for the fainter. The

injury threatened may be minimal, but the related psychic stress is great. Chronic fainters learn to anticipate fainting and avoid precipitating stresses." This differs from hysterical fainting, in which pulse and blood pressure remain normal. "A vasodepressor reaction leads to collapse of the circulatory system, which sometimes resembles shock and has been known to result in death."

LIST OF STRESS TESTS

For convenience, the most commonly used stress tests are listed here with their abbreviations:

AAR Adjusted Averaged Evoked Response Questionnaire.

APQ Autonomic Perception Questionnaire.

BPI Berkeley Psychological Inventory.

BUPI Boston University Personality Inventory.

CFF Critical Flicker Fusion.

CMACL Composite Mood Adjective Check List.

CMI Cornell Medical Index.

CST Controlled Stress Test.

EPI Eysenck Personality Inventory.

FPJP Frequency of Perceived Job Pressure.

GSR Galvanic skin resistance (or response, or reflex).

HOS Health Opinion Survey.

HSTT Harrower Stress Tolerance Test.

IES Impulse Expression Scale.

IPAT Anxiety Scale Institute for Personality and Ability Testing Anxiety Scale.

JAS Jenkins Activity Survey.

LCI Life Change Inventory.

LCU Life Change Unit.

LEI Life Events Inventory.

MARS Manifest Affect Rating Scale.

MAS See **TMAS**.

MMPI Minnesota Multiphasic Personality Inventory.

MPI Maudsley Personality Inventory.

RLCQ Recent Life Change Questionnaire.

RMM Running Matching Memory Test.

SEI Subjective Experience Inventory.

SHG Sustained handgrip.

SIRS Seriousness of Illness Rating Scale.

SPL Skin potential level. Cf. also **GSR**.

SPQ Somatic Perception Questionnaire.

SPRS Suicide Potential Rating Scale.

S-R Inventory Stimulus-Response Inventory.

SRE Schedule of Recent Experience.

SRRQ Social Readjustment Rating Questionnaire.

SRRS Social Readjustment Rating Scale.

SSFIPD Social Stress and Functionability Inventory for Psychotic Disorders.

SSS Subjective Stress Scale.

STAI State-Trait Anxiety Inventory.

SVS Stress Value Scale.

TAQ Test Anxiety Questionnaire.

TMAS Taylor Manifest Anxiety Scale.

TPT Halstead Tactual Performance Test. An assessment of 3-trial learning as well as a test of tactual efficiency.

TRI Total Response Index.

WCST Wisconsin Card Sorting Test.

WSSA Worcester Scale of Social Attainment.

Stress Tests

Generalities. One of the greatest difficulties encountered in research is the measurement of stress intensity by accurate objective indices. The reason for this difficulty is that every agent also has specific effects which may selectively affect and alter the response of one or the other target used as an indicator of nonspecific stress.

It is virtually impossible to categorize the diverse Stress Tests because they often overlap; yet we had to arrange them in some order that would permit cognate procedures to be surveyed conjointly. Hence, we shall arbitrarily distinguish the following classes: chemical parameters, hematologic parameters, muscular function, EEG, questionnaires, "stress interviews," exposure to media (especially stressful film or television shows), flicker fusion frequency, culture stress tests, Rorschach test, problem solving, temperature variations, cutaneous conductance and sweating, multifactorial stress tests and adrenocortical function tests (pyrogens, EP, metyrapone). Finally, we shall list a few special instruments designed for the measurement of stress.

Stress Tests

(See also our earlier stress monographs, p. xiii, and *cf.* Blood Cells, Skin, and other Characteristic Manifestations of Stress, including EEG)

Generalities. Miller, J. G.: "The development of experimental stress-sensitive tests for predicting performance in military tasks." *PRB Technic. Res. Rep.* 1079, p. 63. Washington, D.C.: Psychol. Res. Assoc., 1953.

B90,654/53

A detailed report on various "stress tests," with special reference to their applicability in appraising candidates for paratroop training. Among the tests mentioned are: Tachistoscopic Presentation of Broken Circles, Wisconsin Concept Formation test, Level of

Aspiration test, CFF, Digit Symbol and Digit Span subtests from the Wechsler-Belle-
vue Intelligence Scale, tapping, leg-swinging,
word fluency and number subtests from the
SRA Primary Mental Abilities test, ergo-
graph, Myokinetic test, Luria technique,
pneumograph, Sentence Completion test,
Cancellation of C's, Auditory Flutter, trem-
bleometer and the Taylor Anxiety Scale
from the MMPI. "The four most promising
measures were: the CFF (dim intensity);
the trembleometer, Cancellation of C's; and
the Primary Mental Abilities Word Fluency
test." Some comments are made on the test
value of viewing bloody battle movies and
simulated dangerous situations, hearing abu-
sive or derogatory remarks, reliving stressful
combat experiences under sodium amyral,
diving in a submarine training tower, partici-

pating in an infiltration course or simulated battle, jumping from a tower used for training paratroopers and throwing live hand-grenades.

Bridges, P. K.: "Practical aspects of the use of some psychological tests of anxiety in a situation of stress." *Br. J. Psychiatry.* **123**: 587-596 (1973). J8,356/73

In students undergoing the stress of academic oral examinations, respiration rate, heart rate, blood pressure, plasma corticoids, 17-KGS and urine flow were the "physiologic variables" correlated with various psychologic tests, namely: the TMAS, the MMPI, the EPI, the IPAT Anxiety Scale and the S-R Inventory. "The psychological instruments used showed close relationships together, but there were few associations between the overall psychological test results and the physiological responses. The linear analogue scale is

a useful measure of situational anxiety. The other tests used purported to be measures of trait anxiety and should therefore have been relatively stable, but most were found to increase significantly when completed by subjects during states of anxiety."

Silverman, J., Rappaport, M., Hopkins, H. K., Ellman, G., Hubbard, R., Belleza, T., Baldwin, T., Griffin, R., Kling, R.: "Stress, stimulus, intensity control, and the structural integration technique." *Confin. Psychiatr.* **16**: 201-219 (1973). J11,971/73

Review and personal observations on EEG, eye movement and various biochemical tests as indicators of stress.

Pryor, T. A., Ridges, J. D.: "A computer program for stress test data processing." *Comput. Biomed. Res.* **7**: 360-368 (1974). J16,017/74

Chemical Parameters. The various chemical determinations and bioassays of hormones and other compounds characteristic of stress have been discussed in detail under Chemical Changes. Let us merely repeat here that the most common chemical indicators are the plasma and/or urine levels of ACTH, glucocorticoids and catecholamines. In addition, the FFA and cholesterol content of blood rises regularly, and this is frequently used as an objective basis for the assessment of stress situations in experimental animals as well as in man.

Most other chemical indicators, though fairly constant, are less reliable, since they merely show increases or decreases, depending upon conditioning factors which are difficult to control or even identify. Thus, for example, the blood sugar, STH, LTH, insulin, glucagon and vasopressin content may be shown as either an increase or decrease, depending upon the intensity and duration of the stress as well as the body's reactivity. Hence, they are not reliable indicators of stress, although they are definitely subject to modification by it.

Capillary blood oxygen saturation and oxygen uptake by tissues have also been used for the quantification of stress, but they are too dependent upon the specific characteristics of the stressor to be employed except under certain conditions when all other modifying circumstances can be standardized.

Chemical Parameters. Rohdenburg, G. L., Manheims, P. J.: "A clinical laboratory procedure for the study of the General Adaptation Syndrome." *J. Clin. Endocrinol. Metab.* **12**: 1031-1039 (1952). B72,657/52

A turbidity test "applicable to blood and urine, which renders it possible to evaluate the General Adaptation Syndrome of Selye, is reported. A series of cases is presented illustrating the clinical application of the procedure."

Tayeau, F., Neuzil, E., Nivet, R., Grouillé,

J.: "Le phénomène d'obstacle de Donaggio. Recherches physiopathologiques sur l'apparition de la mucoprotéine urinaire" (Obstacle phenomenon of Donaggio; physiopathologic studies on appearance of urinary mucoprotein during alarm reaction). *J. Physiol. (Paris)* **46**: 536-537 (1954). B96,231/54

The so-called obstacle phenomenon of Donaggio is due to an increased excretion of mucoprotein metabolites in the urine and is characteristic of the alarm reaction.

Lovett-Doust, J. W., Schneider, R. A.:

"Studies on the physiology of awareness: an oximetrically monitored controlled stress test." *Can. J. Psychol.* **9**: 67-78 (1955).

C6,045/55

The CST attempts to quantify the emotional aspect of awareness by determining capillary blood-oxygen saturation, which is allegedly related to emotional change in normal subjects but not in psychotics.

Marconi, R., Cravero, D.: "Il test del Tween 80. Un indice della reattività organica al trauma operatorio" (The tween 80 test. An index of organic reactivity to surgical trauma). *Minerva Chir.* **15**: 774-778 (1960). J24,042/60

Some metabolite causing turbidity in human blood when mixed with tween 80 is considered to be indicative of stress.

Back, K. W., Bogdonoff, M. D.: "Plasma lipid responses to leadership, conformity, and deviation." In: Leiderman, P. H. and Shapiro, D., *Psychobiological Approaches to Social Behavior*, pp. 24-42. Stanford, Cal.: Stanford University Press, 1964.

J11,130/64

Detailed review of plasma FFA as an objective indicator of stress in man, particularly in social relations. Plasma FFA are very sensitive to changes in autonomic nervous activity, and are especially useful in assessing situational demands and group interactions.

Fessel, W. J.: "Dextran turbidity: acute distress-phase reaction." *Nature* **205**: 771-773 (1965). F32,709/65

Among patients treated for various types of psychogenic stress, heavy turbidity in the plasma occurs after additional dextran ther-

apy. This response can also be induced experimentally by exposing the subjects to stressful mental experiences. "The presence of so much fibrinogen in the precipitate suggests the possibility that the increased levels of dextran turbidity in mental disease and emotional stress result from activation of various serum enzyme systems which cause changes in the internal structure of blood proteins. Plasmin, which affects the fibrinogen molecule, is activated by various agents including emotional stress, physical stress, adrenal steroids, adrenaline, acetylcholine and histamine, and some evidence suggests that plasmin may be under reflex control. Other serum enzymes are also activated by stress, which is known to influence a variety of blood proteins" (20 refs.).

Auchincloss, J. H. Jr., Gilbert, R.: "Estimation of maximum oxygen uptake with a brief progressive stress test." *J. Appl. Physiol.* **34**: 525-526 (1973). H79,368/73

An exercise test in which measurements of oxygen uptake aided in evaluation of cardiac patients is referred to as a "stress test," although there is no proof or even probability of any relationship between the specific effect of muscular work upon oxygen utilization and the nonspecific response to stress as commonly defined.

Combs, D. T., Martin, C. M.: "Evaluation of isoproterenol as a method of stress testing." *Am. Heart J.* **87**: 711-715 (1974). H86,844/74

Description of the advantages of the ECG responses to isoproterenol for the evaluation of myocardial efficiency, as compared to coronary arteriography or the treadmill test.

Hematologic Parameters. Among the hematologic changes characteristic of stress, eosinopenia, lymphopenia, polymorphonuclear leukocytosis and the appearance of "stress lymphocytes" have been described in the section on Morphologic Changes. Of all these, eosinopenia proved to be the most reliable, especially in clinical medicine.

Hematologic Parameters. Laragh, J. H., Almy, T. P.: "Changes in circulating eosinophils in man following epinephrine, insulin, and surgical operations." *Proc. Soc. Exp. Biol. Med.* **69**: 499-501 (1948).

B31,814/48

Surgical trauma and injections of EP or insulin caused eosinopenia in man.

Hills, A. G., Forsham, P. H., Finch, C. A.: "Changes in circulating leukocytes induced

by the administration of pituitary adrenocorticotropic hormone (ACTH) in man." *Blood* **3**: 755-768 (1948). B33,083/48

In man, ACTH causes pronounced lymphopenia and eosinopenia with a moderate polymorphonuclear leukocytosis. The comparable blood count changes of the alarm reaction are ascribed to endogenous ACTH secretion.

Thorn, G. W., Forsham, P. H., Prunty, F. T. G., Hills, A. G.: "A test for adrenal

cortical insufficiency." *J.A.M.A.* **137**: 1005-1009 (1948). D98,669/48

Eosinopenia and a rise in uric acid excretion consistently follow ACTH injection in man, and may be used as a test of adrenocortical activity.

Recant, L., Hume, D. M., Forsham, P. H., Thorn, G. W.: "Studies on the effect of epinephrine on the pituitary-adrenocortical system." *J. Clin. Endocrinol.* **10**: 187-229 (1950). B47,003/50

"A simple clinical test for the evaluation of pituitary-adrenocortical integrity is presented, based on the four-hour fall in circulating eosinophils following the subcutaneous injection of 0.3 mg. of epinephrine or the intravenous administration of 0.2 mg. in 200 cc. of saline over a one-hour period. A fall exceeding 50 per cent excludes both adrenocortical and pituitary ACTH deficiency."

Fisher, B., Fisher, E. R.: "Observations on the eosinophil count in man. A proposed test

of adrenal cortical function." *Am. J. Med. Sci.* **221**: 121-132 (1951). B63,230/51

Renold, A. E., Quigley, T. B., Kennard, H. E., Thorn, G. W.: "Reaction of the adrenal cortex to physical and emotional stress in college oarsmen." *N. Engl. J. Med.* **244**: 754-757 (1951). B65,108/51

Observations on the Harvard-Yale boat race crews showed a marked eosinopenia, interpreted as a sign of stress-induced corticoid secretion. However, muscular effort was not the only stressor, since the coxswain also responded with pronounced eosinopenia although he was almost exclusively under emotional stress.

Wheeler, W. M., Little, K., Dorcus, R. M., Clemens, T. L., Sternberg, T. H., Zimmerman, M. C.: "The effects of psychological stress as measured by a decrease in the number of circulating eosinophiles." *J. Clin. Exp. Hypnos.* **2**: 130-135 (1954). J22,382/54

In patients, eosinopenia is produced by actual and by hypnotically-suggested anxiety.

Muscular Function. Stress tests based on muscular function are of two kinds: those that measure muscular tone and those that determine resistance to muscular exercise. In general, stressors increase muscular tension and hence the EMG, particularly in psychoneurotic and psychotic patients. Pain, often localized to the neck and shoulder muscles, is also characteristic of stress but hardly suitable for use as an objective quantitative indicator. The same can be said of hyperkinesia (the urge to walk up and down, contraction of the jaw muscles or table drumming with the fingers). Besides, these changes are usually elicited only by emotional stressors and are not truly non-specific.

Exercise (for example, on a bicycle ergometer or treadmill as well as "step-stress tests") with measurements of cardiovascular function (ECG, blood pressure, pulse rate, provocation of anginal attacks) is often referred to as a "stress test" although it is virtually a specific means of determining the functional capacity of the heart and vessels.

Muscular Function (See also Muscular System). Pinneo, L. R.: "The effects of induced muscle tension during tracking on level of activation and on performance." *J. Exp. Psychol.* **62**: 523-531 (1961).

D84,799/61

Call, R. W., Clyman, B., Kaserman, D. R.: "Practical use of stress testing in industry." *J. Occup. Med.* **10**: 649-659 (1968).

J10,261/68

A radiotelemetry exercise test was applied to industrial management personnel to appraise their stress resistance by detecting unsuspected coronary artery disease (33 refs.).

Cureton, T. K.: "The relative value of stress indicators, related to prediction of strenuous athletic (treadmill) performance: a review." *Am. Correct. Ther. J.* **23**: 59-62 (1969). J23,436/69

Borg, G.: "Perceived exertion as an indicator of somatic stress." *Scand. J. Rehab. Med.* **2**: 92-98 (1970). J20,213/70

Description of a new "work test" and "walktest" for the measurement of physical fitness.

Knowlton, R. G., Sutton, A. I.: "The predictive significance of ballistocardiographic

dynamics to determine submaximal exercise stress." *Am. Correct. Ther.* **25**: 84-88 (1971). J20,534/71

Aronow, W. S., Papageorge's, N. P., Ueyama, R. R., Cassidy, J.: "Maximal treadmill stress test correlated with postexercise phonocardiogram in normal subjects." *Circulation* **43**: 884-888 (1971). J20,539/71

Snyder, C. R.: "Amount of body movement as an indicant of task-irrelevant test anxious responses." *J. Psychol.* **80**: 147-150 (1972). J20,336/72

In general, task-irrelevant movements are characteristic of stress, but in one particular "classroom-type learning situation" this was not so. A possible reason for this finding may be that the nature of the task-irrelevant response occurs principally at the internal cognitive level rather than at the overt physical level."

Hoyt, W. H. Jr., Bonbrisco, D. E., Brown, D. R., Roby, S. H., Yacavone, D. W., Harvard, T. J., Bowers, R. K., Mooney, W. P., McWilliams, G. J.: "A comparison of treadmill, bicycle ergometer, and step stress tests based on oxygen consumption at submaximal and maximal stress." *J. Am. Osteopath. Assoc.* **72**: 789-793 (1973). H81,622/73

Aronow, W. S.: "Thirty-month follow-up of maximal treadmill stress test and double Master's test in normal subjects." *Circulation* **47**: 287-290 (1973). H81,628/73

Buderer, M. C., Rummel, J. A., Sawin, C. F., Mauldin, D. G.: "Use of the single-breath method of estimating cardiac output during exercise-stress testing." *Aerosp. Med.* **44**: 756-760 (1973). J18,276/73

Rios, J. C., Hurwitz, L. E.: "Electrocardiographic responses to atrial pacing and multistage treadmill exercise testing. Correlation with coronary arteriography." *Am. J. Cardiol.* **34**: 661-666 (1974). H94,391/74

Schweitzer, P., Jelinek, V. M., Herman, M. V., Gorlin, R.: "Comparison of the two-step and maximal exercise tests in patients with coronary artery disease." *Am. J. Cardiol.* **33**: 797-800 (1974). H86,257/74

Strand, F. L., Stoboy, H., Cayer, A.: "A possible direct action of ACTH on nerve and muscle." *Neuroendocrinology* **13**: 1-20 (1974). H81,371/74

ACTH may have a direct effect upon peripheral nerves. Endogenous ACTH (in-

duced in rats by exposure to cold) as well as administration of exogenous ACTH raised the muscle action potential after stimulation of the gastrocnemius. Hypophysectomy had an opposite effect.

Kelley, K.: "Validity of sub-maximal treadmill stress test in predicting the presence of significant coronary artery disease." *Clin. Res.* **22**: 145A (1974). H84,753/74

Martin, C. E., Shaver, J. A., Leon, D. F., Thompson, M. E., Reddy, P. S., Leonard, J. J.: "Autonomic mechanisms in hemodynamic responses to isometric exercise." *J. Clin. Invest.* **54**: 104-115 (1974).

H87,404/74

Analysis of the SHG as a "cardiac stress test" (51 refs.).

Bruce, R. A.: "Methods of exercise testing." *Am. J. Cardiol.* **33**: 715-720 (1974). H86,245/74

Rosing, D. R., Reichek, N., Perloff, J. K.: "The exercise test as a diagnostic and therapeutic aid." *Am. Heart J.* **87**: 584-596 (1974). H86,092/74

Bartel, A. G., Behar, V. S., Peter, R. H., Orgain, E. S., Kong, Y.: "Graded exercise stress tests in angiographically-documented coronary artery disease." *Circulation* **49**: 348-356 (1974). J10,767/74

Call, R. W., Clyman, B., Kaserman, D. R., Eckardt, D.: "Five year prospective study: use of submaximal stress testing." *J. Occup. Med.* **16**: 9-13 (1974). J9,773/74

Testing industrial personnel by ECG changes during exercise on an ascending treadmill is highly recommended because CHD, "the major health concern to industry, may be undetectable in large numbers of people through routine clinical evaluation. Within an industrial setting the prompt diagnosis of such individuals is crucial not only for safe employability, but also for the institution of vigorous preventive measures" (17 refs.).

Ellestad, M. H., Wan, M. K. C.: "Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing." *Circulation* **51**: 363-369 (1975). J22,240/75

Among twenty-seven hundred subjects exposed to severe treadmill tests, in those who reacted with characteristic ST-segment depression, subsequent coronary infarcts were much more common than in others.

EEG. Several investigators have described EEG changes, especially blockade of the alpha rhythm, with various stressors in animals and man, but none of these can be regarded as truly nonspecific. At best, the EEG may serve as an indicator of arousal during psychogenic stress.

EEG (See also EEG under Nervous System). Roth, M., Osselton, J. W., Givens, J. G.: "Some common features of the EEG changes associated with severe metabolic and other stress and their bearing on the problem of homeostasis." *Electroencephalogr. Clin. Neurophysiol.* Supp. 25: 276-281 (1967). G59,751/67

The EEG changes produced in man by various stressors have many features in common and may reflect nervous activity important for homeostasis.

Lairy, G. C.: "L'EEG comme moyen d'investigation des modalités individuelles d'adaptation aux situations de stress" (The EEG as a method of investigation of individual adaptation to stress situations). *Electroencephalogr. Clin. Neurophysiol.*, Supp. 25: 282-298 (1967). G59,752/67

Review of the literature and personal observations on the EEG features especially characteristic of those suffering from psychogenic stress. "The paroxysmal discharges encountered in situations of psychological stress could be interpreted as a sign of impaired adaptation: homeostatic mechanisms are released, which tend to re-establish equilibrium and cause a discharge of energy which relieves anxiety in cases in which the discharge cannot be effectuated through somato-motor or vegetative pathways. The prognostic value depends on the degree of impaired control

and the possibilities of recovering equilibrium."

Baekeland, F., Koulack, D., Lasky, R.: "Effects of a stressful presleep experience on electroencephalograph-recorded sleep." *Psychophysiology* 4: 436-443 (1968).

J22,711/68

Löw, M. D., Swift, S. J.: "The contingent negative variation and the 'resting' D.C. potential of the human brain: effects of situational anxiety." *Neuropsychologia* 9: 203-208 (1971).

J20,328/71

Anokhin, A. P. K., Shumilina, A. I., Mamedov, A. M.: "Statistical characteristics of tension-rhythm parameters in the EEG of cerebral cortex and subcortical structures during painful stress." *Dokl. Akad. Nauk. SSSR* 209 No. 1: 249-252 (1973) (Russian). Engl. transl.: *Proc. Acad. Sci. U.S.S.R., Biol. Sci.* 208 No. 1: 156-158 (1973).

J19,679/73

Silverman, J., Rappaport, M., Hopkins, H. K., Ellman, G., Hubbard, R., Belleza, T., Baldwin, T., Griffin, R., Kling, R.: "Stress, stimulus, intensity control, and the structural integration technique." *Confin. Psychiatr.* 16: 201-219 (1973).

J11,971/73

Review and personal observations on EEG, eye movement and various biochemical tests as indicators of stress.

ECG. The ECG is considerably altered by both emotional and physical stress conditions. Several instruments have been devised to determine ECG changes, often in combination with other indices such as blood pressure variations, by telemetry while patients are exercising on a treadmill. For the interpretation of various stress-induced ECG changes, the reader is referred to the original publications in the corresponding abstract section.

ECG responses to isoproterenol have been recommended for the evaluation of myocardial efficiency in preference to arteriography or the treadmill test; however, the claims behind this recommendation require confirmation.

ECG (See also under Cardiovascular System, including Blood Pressure, ECG). Weiss, B.: "Electrocardiographic indices of emotional stress." *Am. J. Psychiatry* 113: 348-351 (1956). J25,137/56

Hiss, R. G., Smith, G. B. Jr., Lamb, L. E.:

"Pitfalls in interpreting electrocardiographic changes occurring while monitoring stress procedures." *Aerosp. Med.* 31: 9-18 (1960).

C80,106/60

Sigler, L. H.: "Abnormalities in the electrocardiogram induced by emotional strain.

Possible mechanism and implications." *Am. J. Cardiol.* **8**: 807-814 (1961).

D15,794/61

Ellestad, M. H.: "Telemetry in monitoring stress electrocardiograms." *Biomed. Sci. Instrum.* **3**: 249-256 (1967). J23,433/67

Description of an instrument that records by telemetry a patient's ECG and blood pressure while he is exercising on a treadmill.

Simonson, E.: "Electrocardiographic stress tolerance tests." *Prog. Cardiovasc. Dis.* **13**: 269-292 (1970). J20,487/70

So, C. S., Oversohl, K.: "Die klinische Bedeutung des Kalium-Belastungs-EKG" (The clinical significance of the potassium stress ECG). *Münch. Med. Wochenschr.*

116: 1657-1660 (1974). H95,277/74

Observations in man suggest that "the fasting ECG and potassium stress ECG are good diagnostic aids for the differentiation of repolarization disorders."

Amsterdam, E. A., Hughes, J. L., Maria, A. N. de, Zelis, R., Mason, D. T.: "Indirect assessment of myocardial oxygen consumption in the evaluation of mechanisms and therapy of angina pectoris." *Am. J. Cardiol.* **33**: 737-743 (1974). H86,247/74

Simonov, P. V., Frolov, M. V., Sviridov, E. P.: "Characteristics of the electrocardiogram under physical and emotional stress in man." *Aviat. Space Environ. Med.* **46**: 141-143 (1975). J22,134/75

Questionnaires. Replies to standardized questions are most commonly used to determine a person's subjective appraisal of psychogenic stress elicited by various stimuli and everyday life events. Some of the most popular among these are the: MMPI, WSSA, TMAS, BPI, IES, APQ, SEI, SRE, SRRQ, JAS (which distinguishes coronary-prone or Type A behavior), FPJP (based on certain indices—frustration, pressure, upset, jumpy nerves, tension, stress and strain), CMACL (which evaluates stress in ATCs by their subjective assessment of a standard list of feelings), MPI, EPI, and the Los Angeles Heart Study's SSS.

Currently, perhaps the most frequently used stress questionnaire is Holmes' and Rahe's SRRQ, which enumerates forty-three life events that the subject must rate with regard to the demand they place upon him for readjustment in his life. This, like all other such questionnaires, reflects only psychogenic stress but it has the advantage of including both eustress and distress. Its great disadvantage is that the meaning of a life event listed in the questionnaire—for example, divorce, marriage or a mortgage of less than \$10,000—depends much more on the individual who experiences it than on the event itself. For example, divorce may be pleasant, indifferent, or catastrophic, depending upon the relationship of the spouses, and a mortgage of less than \$10,000 may be a relief to a person who gradually worked it down from \$100,000 or a tragedy to someone who believes he could never collect that much money. It is true that in statistically analyzed large groups of patients, the ratings coincided with the onset of what we may regard as diseases of adaptation or of stress, but this may be partly due to psychologic factors in stress-prone individuals who are most likely to attribute high subjective ratings to virtually any event. If this is correct, the nature of the items selected is of little consequence as long as they are sufficiently common and meaningful in a given social class to serve for the assessment of the emotionality of its members. Nevertheless, a list of this kind has its justification as long as we understand its limitations and do not extend its evaluation to stress resistance beyond that of emotional arousal.

Questionnaires. Haggard, E. A.: "Experimental studies in affective processes: I. Some effects of cognitive structure and active participation on certain autonomic reactions dur-

ing and following experimentally induced stress." *J. Exp. Psychol.* **33**: 257-284 (1943). B33,896/43

Experiments on man using a test consisting

of three time periods. "I, the conditioning or stressful session, during which the S's were asked to give chained associations to each of 42 stimulus words. They were always (and only) shocked between 10 and 12 sec. after the stimulus word *sword*, which recurred five times during the list; II, the therapy session, in which one of three experimental procedures was employed to alleviate the general disturbance and extinguish the specific reactions initiated during the first session; and finally, III, a test period to measure the relative effectiveness of the therapies." A strong electric shock was used as the stressor and GSR as the principal indicator of autonomic activity. "In general, those individuals who knew most about the conditions involved in the situation and who took an active attitude or role in facing this experience consistently showed less disturbance on all measures of autonomic reactivity during the stressful and therapy sessions" (87 refs.).

Hales, W. M., Simon, W.: "Minnesota Multiphasic Personality Inventory patterns before and after insulin shock therapy." *Am. J. Psychiatry* **105**: 254-258 (1948).
B59,134/48

Welsh, G. S.: "An anxiety index and an internalization ratio for the MMPI." *J. Consult. Psychol.* **16**: 65-72 (1952).
B27,525/52

Phillips, L., Cowitz, B.: "Social attainment and reactions to stress." *J. Pers.* **22**: 270-283 (1953).
J10,409/53

* The relationship between psychologic and physiologic responses to stress and performance in everyday life was investigated by means of the Worcester Scale of Social Attainment, the use of which is described in detail.

Taylor, J. A.: "A personality scale of manifest anxiety." *J. Abnorm. Soc. Psychol.* **48**: 285-290 (1953).
B30,512/53

On the basis of the MMPI, a manifest anxiety scale was developed which is suitable for the appraisal of psychogenic stress. [Details of the test procedure must be gathered from the original paper (H.S.).]

Kamin, L. J.: "Relations between discrimination, apparatus stress, and the Taylor scale." *J. Abnorm. Soc. Psychol.* **51**: 595-599 (1955).
J13,197/55

"Data of studies relating the Taylor Scale to eyelid conditioning may be attributable to the mechanical aptitude-Taylor scale relation, or 'apparatus stress.'"

Levi, L.: "A new stress tolerance test with simultaneous study of physiological and psychological variables. A preliminary study." *Acta Endocrinol. (Kbh.)* **37**: 38-44 (1961).
D3,436/61

Vaughan, R. P.: "The effect of stress on the MMPI scales K and D." *J. Clin. Psychol.* **19**: 432 (1963).
J23,459/63

Chansky, N. M.: "Stress, personality and visual closure." *J. Psychol.* **57**: 289-301 (1964).
J23,594/64

A modified Rorschach test with a questionnaire is used to show what personality traits are connected with defects in "visual closure," the ability to fill gaps in incomplete patterns during stress.

Berkun, M. M.: "Performance decrement under psychological stress." *Hum. Factors* **6**: 21-30 (1964).
J18,097/64

Studies using the SSS, corticoid excretion, eosinopenia and so on, to estimate performance under stress situations simulating those encountered in warfare.

Stewart, H.: "The relationship of physical illness to the IPAT 16 Personality Factors Test." *J. Clin. Psychol.* **21**: 264-266 (1965).
J23,269/65

Lazarus, R. S., Tomita, M., Opton, E. Jr., Kodama, M.: "A cross-cultural study of stress-reaction patterns in Japan." *J. Pers. Soc. Psychol.* **4**: 622-633 (1966).
J15,487/66

Comparative studies on the responses of Japanese students and middle-aged adults to stressful motion picture films. "The pattern of mood and the degree and timing of reported distress were similar, and the defensive orientations reduced stress reaction for both subjective and physiological measures. However, the hypothesized interaction between MMPI-scaled personality disposition and defensive orientations was not observed. Unlike Americans, Japanese Ss' skin conductance was almost as high during the benign film as during the stressful film, and their conductance during the stressful film was poorly correlated to the specific stressful scenes."

Antonovsky, A., Kats, R.: "The life crisis history as a tool in epidemiological research." *J. Health Soc. Behav.* **8**: 15-21 (1967).
J23,004/67

Opton, E. M. Jr., Lazarus, R. S.: "Personality determinants of psychophysiological re-

sponse to stress: a theoretical analysis and an experiment." *J. Pers. Soc. Psychol.* **6**: 291-303 (1967).

J8,942/67

An effort to find connections between personality and individual differences in response to stressors. "A 795-item personality inventory revealed 131 discriminating items in an ipsative (intraindividual) design. Ss who responded relatively more strongly to a threatening motion picture film than to threat of electric shock described themselves as lacking in impulse expression, socially inhibited, introverted, submissive, suggestible or obedient, insecure, passive, anxious and not caring about friends. Ss who responded more strongly to threat of shock than to the movie attributed the opposite qualities to themselves. Normative (interindividual) analyses (high response to film compared to low response to film, high response to shock compared to low response to shock) found no more discriminating personality items than would be expected by chance." The questionnaire included five hundred items of the BPI, MMPI, IES, APQ, SEI and other miscellaneous tests.

Casey, R. L., Masuda, M., Holmes, T. H.: "Quantitative study of recall of life events." *J. Psychosom. Res.* **11**: 239-247 (1967).

J13,891/67

Description of the SRE, a self-administered questionnaire based on the total LCU scores of Rahe and Holmes. It indicates what life events are salient to the subject and hence are likely to cause stress.

Masuda, M., Holmes, T. H.: "The Social Readjustment Rating Scale: a cross-cultural study of Japanese and Americans." *J. Psychosom. Res.* **11**: 227-237 (1967).

J13,504/67

Description of the SRRQ designed to quantify the amount of change in life adjustment required by forty-three categories of life events. Some of these are socially desirable, others undesirable, but "each usually evokes or is associated with some adaptive or coping behavior on the part of the involved individual. The emphasis is on change from the existing steady state, and not on psychological meaning, emotion, or social desirability." Similarities and differences between American and Japanese population samples are discussed (22 refs.).

Holmes, T. H., Rahe, R. H.: "The Social Readjustment Rating Scale." *J. Psychosom. Res.* **11**: 213-218 (1967).

J11,293/67

Description of the SRRQ, which serves as

a basis for the SRRS. The questionnaire contains forty-three life events which the subject must rate with regard to the demand for readjustment in his life, regardless of the pleasantness or unpleasantness of the situation. As expected, there were great individual variations in the significance of, and emotions raised by, a given event. In five thousand patients the ratings given to the events that coincided with disease onset were collated in the Social Readjustment Rating Scale (see p. 677).

These and similar investigations suggest a "relationship of what has been called 'life stress,' 'emotional stress,' 'object loss,' etc." The greater the magnitude of life change (or crisis) the greater the probability that it will be associated with disease onset as a consequence of stress involved in meeting demands for readaptation. [Although the questionnaires on which this scale is based very correctly avoided distinguishing between desirability of events (that is, between eustress and distress), application of the mean scores to any individual is handicapped by the fact that the degree of adaptive effort to meet the situation is subject to great variations. These had to be disregarded, since they are impossible to quantify (H.S.).]

Rahe, R. H.: "Life-change measurement as a predictor of illness." *Proc. R. Soc. Med.* **61**: 1124-1126 (1968).

H65,680/68

Brief description of the SRE questionnaire of Rahe and Holmes. "By the completion of this instrument a subject may indicate which of the several life changes listed in the questionnaire have happened to him, and how often, over the past few years. These life changes cover a broad spectrum of social interaction ranging from matters of occupation, residence, community, family and marriage, to matters of religion, personal habits and health. Previous studies have indicated that the more these separate life changes accumulate in a subject's life over a year's time the greater becomes the likelihood that he will experience a major illness within the following year."

Rahe, R. H.: "Multi-cultural correlations of life change scaling: America, Japan, Denmark, and Sweden." *J. Psychosom. Res.* **13**: 191-195 (1969).

J13,505/69

Social stress among inhabitants of various countries was compared using the SRRQ. "Despite many cross-cultural differences, similarities between twentieth century cultures are far more pronounced" (15 refs.).

SOCIAL READJUSTMENT RATING SCALE

Rank	Life event	Mean value
1	Death of spouse	100
2	Divorce	73
3	Marital separation	65
4	Jail term	63
5	Death of close family member	63
6	Personal injury or illness	53
7	Marriage	50
8	Fired at work	47
9	Marital reconciliation	45
10	Retirement	45
11	Change in health of family member	44
12	Pregnancy	40
13	Sex difficulties	39
14	Gain of new family member	39
15	Business readjustment	39
16	Change in financial state	38
17	Death of close friend	37
18	Change to different line of work	36
19	Change in number of arguments with spouse	35
20	Mortgage over \$10,000	31
21	Foreclosure of mortgage or loan	30
22	Change in responsibilities at work	29
23	Son or daughter leaving home	29
24	Trouble with in-laws	29
25	Outstanding personal achievement	28
26	Wife begin or stop work	26
27	Begin or end school	26
28	Change in living conditions	25
29	Revision of personal habits	24
30	Trouble with boss	23
31	Change in work hours or conditions	20
32	Change in residence	20
33	Change in schools	20
34	Change in recreation	19
35	Change in church activities	19
36	Change in social activities	18
37	Mortgage or loan less than \$10,000	17
38	Change in sleeping habits	16
39	Change in number of family get-togethers	15
40	Change in eating habits	15
41	Vacation	13
42	Christmas	12
43	Minor violations of the law	11

Reproduced, by permission, from T. H. Holmes and R. H. Rahe, *J. Psychosom. Res.* 11: 216 (1967).

Zyzanski, S. J., Jenkins, C. D.: "Basic dimensions within the coronary-prone behavior pattern." *J. Chron. Dis.* 22: 781-795 (1970).

J8,980/70

The self-administered JAS identifies men with a coronary-prone behavior pattern (Type A) with about 70 percent accuracy.

Actually, this behavior pattern is composed of at least three independent behavioral syndromes: (1) Hard-Driving Temperament, (2) Job Involvement, (3) Speed and Impatience. "A system was constructed for deriving factor scores for individuals on these dimensions, and these scores were demon-

strated to be reliable across forms of the test and stable over time. The 3 scores were uncorrelated with each other."

Rahe, R. H., Mahan, J. L. Jr., Arthur, R. J.: "Prediction of near-future health change from subjects' preceding life changes." *J. Psychosom. Res.* **14**: 401-406 (1970).
J14,839/70

On the basis of the LCU questionnaire, it was possible to predict subsequent illness frequency among U.S. naval personnel on three combat cruises, thus confirming many earlier retrospective studies which documented the association between a subject's life stress and illness rate. "The finding, then, that the life change and subsequent illness hypothesis held up in the prospective test is perhaps more impressive when it is realized these experiments dealt with a very restricted portion of the spectrum of stress and disease" (23 refs.).

Harmon, D. K., Masuda, M., Holmes, T. H.: "The Social Readjustment Rating Scale: a cross-cultural study of Western Europeans and Americans." *J. Psychosom. Res.* **14**: 391-400 (1970).
J13,507/70

The SRRQ is described in detail. In French translation, it was administered to French, Belgian and Swiss subjects of widely different cultural backgrounds, and in comparison with the scores of Americans, "a high correlation of relative rank ordering of readjustment required by life events was observed ($r_s = 0.89$), but differences in cultures and living conditions were reflected in the SRRS obtained."

Scholz, O. B.: "Zur Diagnostik des Ermüdungs-, Monotonie- und Sättigungserlebnisses- Vorläufige Mitteilung über die Konstruktion eines Fragebogens" (Diagnosis of fatigue, monotony and satiation experiences. Preliminary report on the construction of a questionnaire). *Z. Psychol.* **178**: 203-225 (1970).
J24,487/70

Berkhout, J., Walter, D. O., Adey, W. R.: "Autonomic responses during a replicable interrogation." *J. Appl. Psychol.* **54**: 316-325 (1970).
J20,823/70

McKendry, J. M., Hurst, P. M.: "Adaptation to speed stress in an immediate memory task." *Hum. Factors* **13**: 543-552 (1971).
J20,327/71

In a "speed stress test," the subjects were faced with comparatively simple questionnaires to which responses had to be given at

different rates of speed. "Whenever the minimal response time was surpassed, both performance accuracy and the amount of information transmitted per minute fell to a degree that was disproportionately greater than increases in input speed relative to the minimal response time."

Berkman, P. L.: "Life stress and psychological well-being: a replication of Langner's analysis in the Midtown Manhattan study." *J. Health Soc. Behav.* **12**: 35-45 (1971).
J20,538/71

Replies to an eight-item Index of Psychological Well-Being in Alameda County, California, indicated that a close association exists between stress factors in daily life and mental health as rated by psychiatrists.

Paykel, E. S., Prusoff, B. A., Uhlenhuth, E. H.: "Scaling of life events." *Arch. Gen. Psychiatry* **25**: 340-347 (1971).
J20,187/71

Description of a questionnaire containing sixty-one life events which can be rated as subjective indicators of stress, irrespective of whether they act as eustress or distress.

Spilken, A. Z., Jacobs, M. A.: "Prediction of illness behavior from measures of life crisis, manifest distress and maladaptive coping." *Psychosom. Med.* **33**: 251-264 (1971).
J21,205/71

In college students, it was found that "premorbid indicators of unresolved life stress accurately predict who will seek care for illness."

Landy, F. J., Stern, R. M.: "Factor analysis of a somatic perception questionnaire." *J. Psychosom. Res.* **15**: 179-181 (1971).
J21,204/71

Discussion of the SPQ and its use in measuring stress among college students.

Rubin, R. T., Gunderson, E. K. E., Arthur, R. J.: "Life stress and illness patterns in the U.S. Navy. V. Prior life change and illness onset in a battleship's crew." *J. Psychosom. Res.* **15**: 89-94 (1971).
G82,945/71

The SRE questionnaire is used to assess recent life changes in personal, family, social, religious, residential, community, economic, occupational and health experience. This test has been modified by including appropriate questions for use on military populations.

Wyler, A. R., Masuda, M., Holmes, T. H.: "Magnitude of life events and seriousness of illness." *Psychosom. Med.* **33**: 115-122 (1971).
J11,297/71

The SRE, the SRSS and the SIRS are briefly discussed and the pertinent literature quoted. Mainly on the basis of the SRE, "a significant positive relationship of life events to illness magnitude was found."

Takakuwa, E.: "Maintaining concentration (TAF) as a measure of mental stress." *Ergonomics* 14: 145-157 (1971). J17,215/71

Discussion of a technique for measuring the ability to maintain concentration as an indicator of stress. For reasons not explained in this article, the author refers to it as the "TAF test."

Smith, R. C., Melton, C. E., McKenzie, J. M.: *Affect Adjective Check List Assessment of Mood Variations in Air Traffic Controllers*, p. 8. Washington, D.C.: Department of Transportation, Federal Aviation Administration, 1971. G86,726/71

Description of the CMACL, which evaluates stress in ATCs by their subjective assessment of eighty adjectives (including aggression, anxiety, concentration, depression, distrust, dizziness, fatigue and so on). Night shifts prove to be especially fatiguing.

Thurlow, H. J.: "Illness in relation to life situation and sick-role tendency." *J. Psychosom. Res.* 15: 73-88 (1971). J14,015/71

Life stress, determined by the SRE of Rahe and Holmes in 165 industrial employees, showed a definite correlation with "sick-role tendency." However, "the most effective predictor of the number of future illness episodes was the number of past illness episodes and the most effective predictor of future absenteeism was past absenteeism" (23 refs.).

Holmes, T. H., Masuda, M.: "Psychosomatic syndrome: when mothers-in-law or other disasters visit, a person can develop a bad, bad cold. Or worse." *Psychol. Today* April, 1972, pp. 71-72, 106. J13,886/72

Semipopular description of the close relationship between life events (as determined by the questionnaire of Rahe and Holmes) and various maladies, including peptic ulcers, tuberculosis, psychic breakdown, heart disease, nasal infections and even common cold.

Buck, V. E.: *Working Under Pressure*, p. 252. London: Staples Press, 1972.

E10,629/72

Description of the FPJP questionnaire, which is based on seven key indices: frustration, pressure, upset, jumpy-nervousness, tension, stress and strain.

Neufeld, R. W. J., Davidson, P. O.: "Scaling of the Subjective Stress Scale with a sample of university undergraduates." *Psychol. Rep.* 31: 821-822 (1972).

J13,318/72

Hare, E. H., Payne, H., Laurence, K. M., Rawnsley, K.: "Effect of severe stress on the Maudsley Personality Inventory score in normal subjects." *Br. J. Soc. Clin. Psychol.* 11: 353-358 (1972). G97,218/72

In mothers of spina bifida children, the MPI score is considerably influenced by the stress of grief.

Smith, R. C.: "A study of the state-trait anxiety inventory and the assessment of stress under simulated conditions." *Federal Aviation Administration*, Aviation Med. pamphlet, pp. 1-5. Washington, D.C., 1972. G96,466/72

The STAI "produces scores indicating the individual's current level of anxiety, i.e., A-State, and how prone the individual is to experience anxiety, i.e., A-Trait. It is easily administered and scored and, since it contains only 40 items which are to be rated on four-point scales, it takes only a few minutes for the respondent to complete." Its possible use in the study of aviation stress is examined. "It appears that the STAI can be used for measuring the anxiety of air traffic controllers, or workers in other high-demand occupations, with considerable confidence that the validity of findings will not be reduced by the unsuspected effects of biasing response sets."

Paykel, E. S., Uhlenhuth, E. H.: "Rating the magnitude of life stress." *Can. Psychiatr. Assoc. J.* 17 Supp. 2: SS93-SS100 (1972).

J13,508/72

A questionnaire inquiring to what extent sixty-one life events (ranging from death of child or spouse to trivial or desirable experiences) produced substantially similar reactions in different socio-demographic groups. [Very similar to the SRSS of Rahe and Holmes (H.S.).]

Leighton, D. C.: "Measuring stress levels in school children as a program-monitoring device." *Am. J. Public Health* 62: 799-800 (1972). G91,217/72

A simple and rapid program-monitoring test has been developed which lends itself to computer analysis. It consists of twenty psychologic screening questions followed by eight questions about the child's situation

and feelings. Girls and blacks have disproportionately high stress scores.

Heisel, J. S.: "Life changes as etiologic factors in juvenile rheumatoid arthritis." *J. Psychosom. Res.* **16**: 411-420 (1972).

J19,671/72

Children who develop juvenile rheumatoid arthritis or Still's disease "tend to have recently experienced a cluster of changes in their world, higher in amount and intensity than the average child." Several life change questionnaires have been worked out for different age groups.

Nelson, P., Mensh, I. N., Hecht, E., Schwartz, A. N.: "Variables in the reporting of recent life changes." *J. Psychosom. Res.* **16**: 465-471 (1972).

J19,674/72

Mendels, J., Weinstein, N.: "The Schedule of Recent Experiences. A reliability study." *Psychosom. Med.* **34**: 527-531 (1972).

J19,668/72

Morris, L. W., Perez, T. L.: "Effects of test-interruption on emotional arousal and performance." *Psychol. Rep.* **31**: 559-564 (1972).

J19,721/72

Myers, J. K., Lindenthal, J. J., Pepper, M. P., Ostrander, D. R.: "Life events and mental status: a longitudinal study." *J. Health Soc. Behav.* **13**: 398-406 (1972).

J19,658/72

Using a special questionnaire to appraise psychiatric derangements (insomnia, irritability, tension, etc.), the authors "found a substantial and positive relationship between changes in life events and changes in psychological impairment over a two-year period."

Aponte, J. F., Miller, F. T.: "Stress-related social events and psychological impairment." *J. Clin. Psychol.* **28**: 455-458 (1972).

J19,676/72

Rahe, R. H., Biersner, R. J., Ryman, D. H., Arthur, R. J.: "Psychosocial predictors of illness behavior and failure in stressful training." *J. Health Soc. Behav.* **13**: 393-397 (1972).

J19,655/72

"A new unit scoring method was used to delineate recent life-change events from the Schedule of Recent Experience (SRE) questionnaire which correlated significantly with U.S. Navy Underwater Demolition Team (UDT) trainees' dispensary visits."

McDonald, B. W., Pugh, W. M., Gundersen, E. K. E., Rahe, R. H.: "Reliability of life change cluster scores." *Br. J. Soc. Clin. Psychol.* **11**: 407-409 (1972).

J19,547/72

Ziv, A., Israeli, R.: "Effects of bombardment on the manifest anxiety level of children living in kibbutzim." *J. Consult. Clin. Psychol.* **40**: 287-291 (1973).

J20,147/73

A Hebrew version of the Children's Manifest Anxiety Scale was administered to children in frequently-shelled kibbutzim and to those in others where life was peaceful. Contrary to expectations, there was no great difference in the anxiety level of the two groups.

Estes, R.: "Determinants of differential stress levels among university students." *J. Amer. Coll. Health Assoc.* **21**: 470-476 (1973).

J19,897/73

"The Index of Emotional Stress (IES) successfully discriminated between users and nonusers of a large public university mental health clinic."

Ramprasad, G.: "Evaluation of stress in non-manual work: an empirical investigation." *Indian J. Med. Res.* **61**: 1714-1721 (1973).

J12,450/73

Description of a questionnaire designed to test stress and work satisfaction among the personnel of research and teaching institutions.

Smith, R. C., Melton, C. E. Jr.: "Susceptibility to anxiety and shift difficulty as determinants of state anxiety in air traffic controllers." *Federal Aviation Administration, Aviation Med. pamphlet*, pp. 1-3. Washington, D.C., 1973.

J17,246/73

Anxiety proneness scores as determined by the STAI "were predictive of the general A-state level of controllers, but were not predictive of the degree of anxiety experienced under the stress of difficult shifts."

Holmes, T. H., Masuda, M.: "Life change and illness susceptibility." In: Scott, J. P. and Seney, E., *Separation and Depression*, pp. 161-186. Washington, D.C.: Amer. Assoc. Advancement of Science, 1973.

J10,480/73

Detailed description of the SRSS which is meant to give an objective assessment of an individual's adaptive and coping behavior in dealing with stress, regardless of the desirability of an event.

Cochrane, R., Robertson, A.: "The Life Events Inventory: a measure of the relative severity of psycho-social stressors." *J. Psychosom. Res.* **17**: 135-139 (1973).

J726/73

The LEI of Rahe and Holmes has three distinct advantages over the SRE: "it is more comprehensive; more consistent in the kind of events included, and has weights derived from groups most likely to have experience of the events involved."

Cline, D. W.: "A stress-value scale for officer candidates." *J. Psychosom. Res.* **17**: 15-20 (1973). G98,344/73

An SVS has been established for officer candidates by asking 191 trainees to assign values from 0 to 1000 to twenty-eight items encountered in their daily life (for example, assuming command position, lack of sleep, writing examinations, corrective criticism from superior).

Reeder, L. G., Schrama, P. G. M., Dirken, J. M.: "Stress and cardiovascular health: an international cooperative study. I." *Soc. Sci. Med.* **7**: 573-584 (1973). J15,755/73

The data obtained from questionnaires used in the SSS correlate well with a similar psychosomatic stress scale developed in the Netherlands. An extensive study on postal and telegraph workers indicated that "a relatively low job level was related to a relatively high number of EKG abnormalities. These latter findings may be predictive of future coronary artery disease in this group" (53 refs.).

Rahe, R. H.: "Life change and subsequent illness reports." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 58-78. Springfield, Ill.: Charles C Thomas, 1974.

E10,682/74

Detailed discussion of the SRE questionnaire in relation to subsequent illness (28 refs.).

Nelson, P. D.: "Comment." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 79-89. Springfield, Ill.: Charles C Thomas, 1974. E10,683/74

Comments on the SRE questionnaire.

Ander, S., Lindstrom, B., Tibblin, G.: "Life changes in random samples of middle-aged men." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 121-

124. Springfield, Ill.: Charles C Thomas, 1974. E10,686/74

The SRE questionnaire correlates fairly well with CHD in a retrospective study.

Horowitz, M. J., Schaefer, C., Cooney, P.: "Life event scaling for recency of experience." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 125-133. Springfield, Ill.: Charles C Thomas, 1974.

E10,687/74

Discussion of factors which influence the stress value of life events in the SRE questionnaire, such as age, sex, time elapsed since the event and so on.

Rahe, R. H., Romo, M., Bennett, L., Siltananen, P.: "Recent life changes, myocardial infarction, and abrupt coronary death." *Arch. Intern. Med.* **133**: 221-228 (1974).

J20,915/74

Wershaw, H. J., Reinhart, G.: "Life change and hospitalization. A heretical view." *J. Psychosom. Res.* **18**: 393-401 (1974).

J19,265/74

Markush, R. E., Favero, R. V.: "Epidemiologic assessment of stressful life events, depressed mood, and psychophysiological symptoms. A preliminary report." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 171-190. New York, London and Sydney: John Wiley & Sons, 1974.

E10,789/74

Brown, G. W.: "Meaning, measurement, and stress of life events." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 217-243. New York, London and Sydney: John Wiley & Sons, 1974. E10,792/74

Dohrenwend, B. P.: "Problems in defining and sampling the relevant population of stressful life events." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 275-310. New York, London and Sydney: John Wiley & Sons, 1974. E10,795/74

Smith, R. C.: "Response bias in the state-trait anxiety inventory: detecting the exaggeration of stress." *J. Psychol.* **86**: 241-246 (1974).

J21,593/74

Rahe, R. H., Fløistad, I., Bergan, T., Ringdal, R., Gerhardt, R., Gunderson, E. K. E.,

Arthur, R. J.: "A model for life changes and illness research. Cross-cultural data from the Norwegian Navy." *Arch. Gen. Psychiatry* **31**: 172-177 (1974). J20,849/74

Payne, R. L.: "Recent life changes and the reporting of psychological states." *J. Psychosom. Res.* **19**: 99-103 (1975). J22,163/75

Stress Interviews. The so-called "stress interviews" have become very popular, especially in industry, the army and the air force, to appraise a candidate's suitability for a demanding job. In general, they are based on behavior (poised, resourceful, well-adjusted, nervous) and somatic reactions (blood pressure variations, heart rate, cutaneous conductance, plasma hormone levels) during and after the interview, which is planned to be disturbing or confusing and which demands of the candidate a high degree of self-control. Often, such interviews are coupled with interfering distractive stimuli.

Stress Interviews. Freeman, G. L., Manson, G. E., Katzoff, E. T., Pathman, J. H.: "The stress interview." *J. Abnorm. Soc. Psychol.* **37**: 427-447 (1942). B26,742/42

General description of stress interview techniques in selecting proper candidates for a variety of tasks. "The stress interview is designed to select those individuals, who, when highly aroused internally, are able to maintain such intelligent control over their behavior as to be judged 'poised,' 'master of the situation,' 'resourceful,' and 'well adjusted.' It appears that some individuals manifest these attributes better when under stress than when under non-stress conditions. Another important aspect of the personality structure is the rate of recovery in outward poise and higher-order control of total behavior following removal of the stress situation. Adequate control of self during stress and quick recovery of higher-order adjustments after stress is removed are the qualities sought in candidates selected by the stress-interview technique."

Freeman, G. L.: "Suggestions for a standardized 'stress' test." *J. Gen. Psychol.* **32**: 3-11 (1945). 35,101/45

Any complex discrimination problem coupled with interfering distraction stimuli will arouse emotional stress if the subject considers the outcome important for his future or a threat to his present security. There are several possible ways of constructing stress tests on the basis of ability to manipulate machines or answer questions under difficult conditions, and evaluation of the results may be reinforced by such objective indices as GSR.

Wolf, S., Cardon, P. V. Jr., Shepard, E. M., Wolff, H. G.: *Life Stress and Essential Hypertension. A Study of Circulatory Adjustments in Man*, p. 253. Baltimore: Williams & Wilkins, 1955. E145/55

tional Hypertension. A Study of Circulatory Adjustments in Man, p. 253. Baltimore: Williams & Wilkins, 1955. E145/55

Monograph on the role of stress in the production of essential hypertension in man. Principal emphasis is placed upon stress interviews and a cold pressor test as diagnostic indices. Adrenocortical participation is only briefly considered (158 refs.).

Hetzell, B. S., Schottstaedt, W. W., Grace, W. J., Wolff, H. G.: "Changes in urinary 17-hydroxycorticosteroid excretion during stressful life experiences in man." *J. Clin. Endocrinol. Metab.* **15**: 1057-1068 (1955). C8,424/55

In patients a one-hour discussion of "stressful subjects" caused diuresis with increased excretion of 17-OHCS, nitrogen, sodium and potassium.

Cline, V. B.: "Ability to judge personality assessed with a stress interview and sound-film technique." *J. Abnorm. Soc. Psychol.* **50**: 183-187 (1955). J1,948/55

Analysis of the predictive value of sound movies or stress interviews.

Cohen, S. I., Silverman, A. J., Zuidema, G.: "Physiologic stress response evaluation by focused interviewing." *Arch. Neurol. Psychiatry* **76**: 670-674 (1956). J25,081/56

Persky, H., Hamburg, D. A., Basowitz, H., Grinker, R. R., Sabshin, M., Korchin, S. J., Herz, M., Board, F. A., Heath, H. A.: "Relation of emotional responses and changes in plasma hydrocortisone level after stressful interview." *Arch. Neurol.* **79**: 434-447 (1958). C50,671/58

Miller, L. H., Shmavonian, B. M.: "Repli-

cability of two GSR indices as a function of stress and cognitive activity." *J. Pers. Soc. Psychol.* **2**: 753-756 (1965). J8,698/65

Through the use of GSR as an indicator of

psychogenic stress during stress interviews, "it was concluded that the changes following the interview could not be attributed solely to the interview."

Media. The viewing of films or television shows which cause arousal (pornographic, suspenseful, cruel or fear-inspiring subjects) or relaxation (nature films, mild humor) may be employed to assess a subject's predisposition to psychogenic stress, using objective indicators such as blood catecholamines, glucose, FFA, triglycerides, blood pressure, cutaneous conductance and so on as measures of the stress produced.

Media. Speisman, J. C., Osborn, J., Lazarus, R. S.: "Cluster analyses of skin resistance and heart rate at rest and under stress." *Psychosom. Med.* **23**: 323-343 (1961).

D10,039/61

Handlon, J. H., Wadeson, R. W., Fishman, J. R., Sachar, E. J., Hamburg, D. A., Mason, J. W.: "Psychological factors lowering plasma 17-hydroxycorticosteroid concentration." *Psychosom. Med.* **24**: 535-542 (1962). D46,696/62

Viewing Disney nature-study films actually lowers 17-OHCS levels, whereas arousing films have an opposite effect. The former "may serve to narrow the subjects' attention away from other possibly stressful stimuli of either internal or external origin."

Lazarus, R. S., Speisman, J. C., Mordkoff, A. M., Davison, L. A.: "A laboratory study of psychological stress produced by a motion picture film." *Psychol. Monogr.* **76**: 1-35 (1962). J11,289/62

Detailed description of a technique for measuring stress reactions by having subjects view a "stressor film" on subincision that "vividly presents a sequence of crude operations performed with a piece of flint on the penis and scrotum of several adolescent boys." The psychologic reactions to this experience are then estimated on the basis of answers to a standard questionnaire and are compared with the response to a control film (*Corn Farming in Iowa*) which has no emotionally charged content. Apart from the psychologic effects, the authors also measured GSR and heart rate.

Handlon, J. H.: "Hormonal activity and individual responses to stresses and easements in everyday living." In: Roessler, R. and Greenfield, N. S., *Physiological Correlates of Psychological Disorder*, pp. 157-170. Madison: University of Wisconsin Press, 1962. D55,075/62

The plasma 17-OHCS levels of normal persons are increased during viewing of "arousing" films, whereas "bland" films have an opposite effect.

Wadeson, R. W., Mason, J. W., Hamburg, D. A., Handlon, J. H.: "Plasma and urinary 17-OHCS responses to motion pictures." *Arch. Gen. Psychiatry* **9**: 146-156 (1963).

E22,691/63

"Significant elevations in plasma 17-OHCS levels were observed during a war movie in one group. Marked decreases in plasma 17-OHCS levels occurred rather consistently during the viewing of Disney nature films. Plasma and urinary values did not consistently correlate well, and plasma measurements were regarded as more reliable."

Mordkoff, A. M.: "The relationship between psychological and physiological response to stress." *Psychosom. Med.* **26**: 135-150 (1964). G12,092/64

During viewing of *Subincision*, a "stressor film" depicting the puberty rites of an Australian aboriginal tribe (crude operations performed with a piece of flint on the penis and scrotum of adolescent boys), the ratings of psychologic impact upon the audience were closely related to such physiologic indices of stress as GSR, heart rate and respiration (21 refs.).

Speisman, J. C., Lazarus, R. S., Davison, L., Mordkoff, A. M.: "Experimental analysis of a film used as a threatening stimulus." *J. Consult. Psychol.* **28**: 23-33 (1964).

J23,441/64

Tannenbaum, P. H., Gaer, E. P.: "Mood change as a function of stress of protagonist and degree of identification in a film-viewing situation." *J. Pers. Soc. Psychol.* **2**: 612-616 (1965). J8,271/65

Among subjects viewing films with a happy or unhappy ending, those identifying more with the hero experienced significantly

more stress than those identifying less. The degree of stress was rated only on the basis of answers to a questionnaire.

Lazarus, R. S., Opton, E. M. Jr.: "The study of psychological stress: a summary of theoretical formulations and experimental findings." In: Spielberger, C. D., *Anxiety and Behavior*, pp. 225-262. New York and London: Academic Press, 1966.

J10,620/66

Detailed description of the authors' use of films, occasionally combined with tape recording, in order to produce psychogenic stress. GSR and heart rate proved to be helpful objective indicators of autonomic activity, yet the two were not necessarily parallel. This may be due to differences in endocrine sensitivity.

Goldstein, M. J., Jones, R. B., Clemens, T. L., Flagg, G. W., Alexander, F. G.: "Coping style as a factor in psychophysiological response to a tension-arousing film." *J. Pers. Soc. Psychol.* **1**: 290-302 (1966).

J23,667/66

Lazarus, R. S.: "Some principles of psychological stress and their relation to dentistry." *J. Dent. Res.* **45** Supp. 6: 1620-1626 (1966).

J22,584/66

Clemens, T. L., Selesnick, S. T.: "Psychological method for evaluating medication by repeated exposure to a stressor film." *Dis. Nerv. Syst.* **28**: 98-104 (1967).

J22,641/67

Horowitz, M. J.: "Psychic trauma. Return of images after a stress film." *Arch. Gen. Psychiatry* **20**: 552-559 (1969).

J21,605/69

Kamen, G. B.: "Effects of a stress-producing film on the test performance of adults." *J. Project. Techn.* **33**: 281-285 (1969).

J23,472/69

Starlinger, H., Hawel, W., Rutenfranz, J.: "Untersuchungen zur Frage der Catecholaminausscheidung im Harn als Kriterium für emotionalen Stress unter verschiedenen Umgebungsbedingungen. Vibrationsbelastung, Filmdarbietungen und Prüfungssituation" (Studies on the question of urinary catecholamine excretion as a criterion of emotional stress under various environmental conditions. Vibration load, presentation of motion pictures and examination periods). *Int. Z. Angew. Physiol.* **27**: 1-14 (1969).

G65,048/69

Kaiser, C., Roessler, R.: "Galvanic skin responses to motion pictures." *Percept. Mot. Skills* **30**: 371-374 (1970). H45,603/70

Watkins, R. E., Davidson, P. O.: "Stress reactions of psychiatric patients to a stressor film: an attempt at experimental reduction of threat." *Behav. Res. Ther.* **8**: 175-178 (1970). G79,867/70

Roessler, R., Collins, F.: "Personality correlates of physiological responses to motion pictures." *Psychophysiology* **6**: 732-739 (1970). J21,192/70

Davidson, P. O., Hiebert, S. F.: "Relaxation training, relaxation instruction, and repeated exposure to a stressor film." *J. Abnorm. Psychol.* **78**: 154-159 (1971).

J20,333/71

Horowitz, M. J., Becker, S. S.: "The compulsion to repeat trauma. Experimental study of intrusive thinking after stress." *J. Nerv. Ment. Dis.* **153**: 32-40 (1971).

G85,446/71

Kamen, G. B.: "A second look at the effects of a stress-producing film on adult test performance." *J. Clin. Psychol.* **27**: 465-467 (1971). J20,217/71

Davidson, P. O., Watkins, R. E.: "Represor-sensitizer differences in psychiatric patients on repeated exposures to film induced stress." *Psychol. Rep.* **28**: 159-162 (1971). J22,042/71

Hülemann, K. D., Mayer, H., Stahlheber, R.: "Fernsehen und Herz-Kreislauf-Regulation. Kreislaufuntersuchungen bei Herzinfarktpatienten und Normalpersonen während der Fernsehübertragung von Fussballweltmeisterschaftsspielen" (Television viewing and cardiovascular regulation. Studies on circulation in healthy persons and in patients suffering from myocardial infarction watching live telecasts of World Soccer Championships). *Münch. Med. Wochenschr.* **113**: 1401-1406 (1971). H45,473/71

In six persons watching a World Soccer Championship on television, ECG, blood pressure and plethysmograph tracings showed increased heart rates and diastolic pressure during the game with a decreased magnitude of skin-volume-pulse amplitude. Two subjects with previous myocardial infarction showed arrhythmic episodes during exciting moments. "Live telecasting with its uncertain result is interpreted as an unspecific stimulus on the autonomic nervous system, which may have a stress effect."

Koriat, A., Melkman, R., Averill, J. R., Lazarus, R. S.: "The self-control of emotional reactions to a stressful film." *J. Pers.* **40**: 601-619 (1972). J19,662/72

Geer, J. H., Maisel, E.: "Evaluating the effects of the prediction-control confound." *J. Pers. Soc. Psychol.* **23**: 314-319 (1972). J19,660/72

Horowitz, M. J., Becker, S. S.: "Cognitive response to erotic and stressful films." *Arch. Gen. Psychiatry* **29**: 81-84 (1973). J19,557/73

Maguire, G. P., MacLean, A. W., Aitken, R. C. B.: "Adaptation on repeated exposure to film-induced stress." *Biol. Psychol.* **1**: 43-51 (1973). J20,663/73

Horowitz, M. J., Becker, S. S., Malone, P.: "Stress: different effects on patients and nonpatients." *J. Abnorm. Psychol.* **82**: 547-551 (1973). J21,554/73

Wroblewski, T. E., Markiewicz, L.: "Excretion of catecholamines in urine under conditions of emotional stress (shocking movies)." *Int. Z. Angew. Physiol.* **31**: 327-331 (1973). H94,450/73

Carruthers, M., Taggart, P.: "Vagotonicity of violence: biochemical and cardiac responses to violent films and television programmes." *Br. Med. J.* August 18, 1973, pp. 384-389. H74,499/73

Description of the changes in blood EP, glucose, FFA, triglycerides and STH that occurred in men and women watching films and television programs depicting violence, humor or suspense. "Groups of people taken

to see two particularly violent films showed similar evidence suggesting vagal overactivity, together with increases in plasma free fatty acids and decreases in triglycerides. As these changes occurred even with β -blockade it is suggested that they might be caused by non-sympathetically mediated changes in the levels of hormones, such as growth hormone, producing lipolysis."

Horowitz, M. J.: "Phase oriented treatment of stress response syndromes." *Am. J. Psychother.* **27**: 506-515 (1973). J17,978/73

In concentration camp survivors, psychologic "stress response syndromes" may persist for decades. Their characteristics are classified, and treatment schedules are recommended. Even viewing "stress films" may induce persistent, intrusive and repetitive thoughts in normal subjects (23 refs.).

Ancona, L., Capoleoni, M.: "L'aggressione giustificata e non giustificata attraverso il dosaggio catecolaminico" (Justified and unjustified aggression through dosage of catecholamines). *Totus Homo* **5**: 17-26 (1974). H97,091/74

In man, "stress produced by a stimulus set on film representing a sadistic scene induces diverse biochemical and psychodynamic reactions depending on whether the subject thinks that the stressing action seen by him is justified or not. When the subject watches an action that he judges socially and normally deplorable, the ratio of noradrenaline/adrenaline excreted in the urine varies in favor of the adrenaline and there is a significant increase in the projected aggressiveness."

Flicker Fusion Frequency. This test is based on the ability to distinguish between separate flickers and their fusion with increasing flicker rates. However, well-controlled experiments failed to confirm the validity of this alleged stress indicator.

Flicker Fusion Frequency. Brozek, J., Simonson, E., Taylor, H. L.: *Changes in Flicker Fusion Frequency Under Stress*, p. 5. Randolph Field, Texas: USAF School of Aviation Med. Report No. 3, 1953. B94,564/53

The flicker fusion frequency test is based on the ability to distinguish between separate flickers and fusion with increasing flicker rates. Performance has previously been claimed to be impaired during stress, but in the present experiments work in a laboratory,

illumination, nutritional stressors, physical effort and so on failed to confirm the validity of this alleged indicator.

Kubzansky, P. E.: "Anxiety, stress, and flicker fusion measurements" (abstracted). *Am. Psychol.* **9**: 410-411 (1954). J13,187/54

"There were no effects in the flicker measures attributable to stress."

Landis, C., Clausen, J., Gjesvik, A.: "Effect of varying stimulus conditions on the

flicker-fusion threshold when nitroglycerin or the cold pressor test was employed." *J. Appl. Physiol.* **7**: 513-518 (1955). J25,408/55

Nair, C. S., Malhotra, M. S., Gopinath, P. M.: "Effect of altitude acclimatization and simultaneous acclimatization to altitude

and cold on critical flicker frequency at 11,000 ft. altitude in man." *Aerosp. Med.* **43**: 1097-1100 (1972). H81,634/72

In healthy men, acclimatization to high altitude did not significantly affect critical flicker frequency, whereas "cold stress produced a profound deterioration."

Culture Stress. The index of "culture stress" is based on a comparison of traditions and social habits in a large number of totally dissimilar societies of different races. Protest suicide, defiant homicide, drunken brawling and witchcraft attribution were used as tentative indices of "culture stress." These aspects have repeatedly been discussed in relation to the G.A.S.

Culture Stress. Naroll, R.: "A tentative index of culture-stress." *Int. J. Soc. Psychiatry* **5**: 107-116 (1959). J11,585/59

A tentative index of "culture-stress" in thirty-seven totally dissimilar societies and races, based upon comparison of four symptoms: protest suicide, defiant homicide, drunken brawling and witchcraft attribution. This report reviews the theoretical grounds for supposing each indicator to be a symptom of culture-stress and offers a formal set of definitions, rules and corollaries to delineate each. "The construction of the index is described and its validity and reliability discussed."

Naroll, R.: *Data Quality Control: A New Research Technique. Prolegomena to a Cross-cultural Study of Culture Stress*, p. 198. Glencoe, Ill.: Free Press, 1962.

E10,632/62

A monograph on "culture stress" with reference to the G.A.S. Special attention is given to witchcraft attribution as a symptom of culture stress, and an extensive bibliography on this topic is provided. There is also an "index of culture stress," based upon this phenomenon and such others as drunken brawling, defiant homicide and protest suicide among numerous peoples of different racial and ethnic backgrounds.

Rorschach Test. Although often recommended to appraise actual psychogenic stress or predisposition to it, the Rorschach test was not found to be especially instructive and it lost its popularity.

Rorschach Test. Williams, M.: "An experimental study of intellectual control under stress and associated Rorschach factors." *J. Consult. Psychol.* **11**: 21-29 (1947) (29 refs.). B75,220/47

Eichler, R. M.: "Experimental stress and alleged Rorschach indices of anxiety." *J. Abnorm. Soc. Psychol.* **46**: 344-355 (1951). G65,604/51

Rorschach indices did not prove to be particularly reliable for the detection of stress.

Smith, S., George, C. E.: "Rorschach factors related to experimental stress." *J. Consult. Psychol.* **15**: 190-195 (1951). E41,451/51

Eriksen, C. W., Lazarus, R. S., Strange, J. R.: "Psychological stress and its personality correlates. Part II. The Rorschach test and other personality measures." *J. Pers.* **20**: 277-286 (1952). B29,029/52

A review on various personality tests designed to predict performance under psychogenic stress. "No relationships were found between performance under stress from various personality measures. No relationships were found between performance under stress and any Rorschach variable. Some nonsignificant trends were found on the Guilford-Martin Inventory of Factors (GAMIN) and the Bell Adjustment Inventory indicating that subjects who improve in performance under stress are more ascendant and have greater self-confidence." It is concluded that subjects themselves can usually predict how they would perform under stress, and "with our present techniques, the best way to predict how a man will perform under stress is to ask him."

Carlson, V. R., Lazarus, R. S.: "A repetition of Meyer Williams' study of intellectual control under stress and associated Ror-

schach factors." *J. Consult. Psychol.* **17**: 247-253 (1953). B26,577/53

Careful personal studies and a review of the literature suggest that, contrary to the claims of Meyer Williams, there is no relationship between Rorschach variables and performance under stress (13 refs.).

Westrope, M. R.: "Relations among Rorschach indices, manifest anxiety, and performance under stress." *J. Abnorm. Soc. Psychol.* **48**: 515-524 (1953). J13,304/53

Berger, D.: "The Rorschach as a measure of real-life stress." *J. Consult. Psychol.* **17**: 355-358 (1953). E50,139/53

Broida, D. C., Thompson, G. G.: "The relationship between certain Rorschach 'insecurity' hypotheses and children's reactions to psychological stress." *J. Pers.* **23**: 167-181 (1954). E51,005/54

A statistically significant "relationship was found between the Rorschach insecurity hy-

potheses and behavior hypothesized as indicating insecurity in the psychological stress situation" (18 refs.).

Stopol, M. S.: "Rorschach performance in relation to two types of stress." *J. Consult. Psychol.* **18**: 11-15 (1954). J11,478/54

No specific Rorschach measure was found to be a suitable indicator of stress resistance in general. The pertinent literature is reviewed (19 refs.).

Lofchie, S. H.: "The performance of adults under distraction stress: a developmental approach." *J. Psychol.* **39**: 109-116 (1955) (21 refs.). J13,195/55

Tong, J. E., Murphy, I. C.: "Rorschach indices and autonomic stress reactivity." *J. Clin. Psychol.* **16**: 324-328 (1960).

J23,257/60

Cohen, D. B.: "Transient stress, rater bias, and Rorschach interpretation." *J. Clin. Psychol.* **29**: 345-347 (1973). J19,612/73

Problem Solving (including Pursuit Meter Test). Various psychogenic and even physical stressors interfere with the solving of a great variety of problems that have been selected to test not only the stressor effect of solving the problem but the ability to do so. Among these, the following have enjoyed particular popularity: the SAM Rotary Pursuit Test with Divided Attention, the Hoagland-Werthessen Pursuit Meter test and the WCST. The pursuit meter tests are based on the ability to track a moving target, thus imitating the problem of fighter pilots. Digit span tests require the subject to repeat an increasingly long number of digits, forward and backward, often in the presence of disturbing circumstances. In addition, arithmetic calculation tasks performed under unfavorable circumstances have been employed to test stress resistance, using corticoids, FFA, blood pressure, electrolytes, cholesterol, neck muscle potentials, finger movements, heart rate, blockade of alpha rhythm in the EEG and so on as indicators.

Problem Solving (including Pursuit Meter Test). Hoagland, H., Pincus, G., Elmadjian, F.: "Stressful psychomotor performance and adrenal cortical function in man." *Fed. Proc.* **5**: 48 (1946).

A95,861/46

In men breathing air low in oxygen, performance (as scored on the Hoagland pursuit meter) shows a decline roughly parallel to the degree of lymphopenia and the rise in urinary 17-KS.

Deese, J., Lazarus, R. S.: *The Effects of Psychological Stress upon Perceptual-Motor Performance*, p. 15. Research Bulletin 52-19. Human Resources Research Center. San Antonio, Texas: Lackland Air Force Base, 1952.

G27,359/52

Description of the "SAM Rotary Pursuit Test With Divided Attention" for the measurement of performance, especially under the influence of stress caused by failure, in Air Force trainees.

Ross, B. M., Rupel, J. W., Grant, D. A.: "Effects of personal, impersonal, and physical stress upon cognitive behavior in a card sorting problem." *J. Abnorm. Soc. Psychol.* **47** Supp.: 546-551 (1952). B29,005/52

A study of the effect of various stressors ("heckling," electric shock and auditory distraction) upon performance in the WCST. "Electric shock, the physical threat, alone or in combination with other factors, was the only variable which degraded performance on

the WCST to a statistically significant extent" (16 refs.).

Hoagland, H., Bergen, J. R., Bloch, E., Elmadjian, F., Gibree, N. R.: "Adrenal stress responses in normal men." *J. Appl. Physiol.* 8: 149-154 (1955). C12,916/55

Manipulation of the Hoagland-Werthessen pursuit meter was used as a stress test. Young men (sixteen to twenty years) "appear to call very little on adrenal cortical mechanisms to meet stresses which enhance adrenocortical responses of older men. Eosinopenia correlates better with the urinary excretion" of EP than with that of 17-KS. Both are regarded as indicators of adrenocortical activity.

Davidson, W. Z., Andrews, T. G., Ross, S.: "Effects of stress and anxiety on continuous high-speed color naming." *J. Exp. Psychol.* 52: 13-17 (1956). J13,313/56

Reynolds, G. S.: "The effects of stress upon problem-solving." *J. Gen. Psychol.* 62: 83-88 (1960). J10,610/60

Brief review and personal observations on the effects of psychogenic stress upon performance in problem-solving tests (9 refs.).

Capretta, P. J., Berkun, M. M.: "Validity and reliability of certain measures of psychological stress." *Psychol. Rep.* 10: 875-878 (1962). J10,365/62

Anxious individuals appear to have special difficulty repeating digits backward. This was tested on a "three-rope toggle bridge 200 ft. long and 50 ft. above a rocky ravine, over which Ss, wearing headsets with earphone and microphone, were run individually. They were stopped midway for a recorded test (administered over the headsets) of immediate backward digit memory span." Controls were tested on the same kind of bridge approximately 1 ft. off the ground.

Renner, J., Renner, V.: "Effects of stress on group versus individual problem solving." *Psychol. Rep.* 30: 487-491 (1972). J20,570/72

Kakizaki, T.: "Stress response during mental task. 2. Biochemical response of human subjects under arithmetical calculation tasks." *Ind. Health (Kawasaki)* 9: 105-112 (1971). J10,263/71

Kakizaki, T.: "3. Three factors affecting the stress responses in man under arithmetical calculation tasks." *Ind. Health (Kawasaki)* 9: 153-161 (1971). H79,739/71

Kakizaki, T.: "4. A principal factor inducing the stress responses in man under arithmetical calculation tasks." *Ind. Health (Kawasaki)* 9: 162-170 (1971).

J10,264/71

Kakizaki, T.: "5. Effect of unpleasant feeling toward task performance on the stress response to arithmetical calculation tasks." *Ind. Health (Kawasaki)* 11: 8-18 (1973).

J10,265/73

Kakizaki, T.: "6. Effect of unpleasant feeling due to pure sound noise on the stress response during arithmetical calculation tasks." *Ind. Health (Kawasaki)* 11: 77-83 (1973).

J10,266/73

Detailed description of a test in which responses (corticoid, FFA, blood pressure, electrolytes, blood proteins, cholesterol and so on) are used as indicators of the stress produced by arithmetic calculations. Both the difficulty and the duration of the task are of significance, but curiously, several interfering unpleasant factors (for example, sound) do not significantly affect the results.

O'Hanlon, J. F., Horvath, S. M.: "Interrelationships among performance, circulating concentrations of adrenaline, noradrenaline, glucose, and the free fatty acids in men performing a monitoring task." *Psychophysiology* 10: 251-259 (1973). J3,116/73

In young men performing an exacting vigilance test, basal levels of blood EP and NEP were inversely related to glucose. EP initially increased during the test but later returned to its basal level in proportion to performance. NEP was not related to performance. Glucose and FFA were elevated both during the task and throughout a control period spent watching slide projections.

Trumbo, D. A.: "Some laboratory tasks for the assessment of stressor effects." *Psychiatr. Neurol. Neurochir.* 76: 199-207 (1973).

J5,079/73

Brief survey of the literature on various performance tasks that have been recommended to assess the severity of stress (vigilance, tracking, reaction time, serial reactions and so on).

Shearer, E., Fulkerson, F. E.: "The effects of physical and psychological stress on the performance of high- and low-anxious Ss on a difficult verbal discrimination task." *Bull. Psychonomic Soc.* 1: 255-256 (1973).

H91,958/73

Studies with the TMAS on performance in verbal discrimination tasks.

Temperature. A standardized pain stimulus may be used to quantify a subject's responsiveness to a stressor. For example, the application of heat to the forehead produces lymphopenia as well as changes in cutaneous conductance and EEG, and these have been employed to test the stress resistance of psychoneurotics. For such purposes, a special thermal stimulator was designed which has shown that schizophrenics exhibit a relative lack of discrimination among various pain intensities.

In this connection, the well-known "cold pressor test" might also be mentioned, especially since, in addition to causing a rise in blood pressure, the application of cold also produces other manifestations of stress, such as changes in heart rate, cutaneous conductance and so on.

Temperature. Malmo, R. B., Shagass, C., Davis, J. F., Cleghorn, R. A., Graham, B. F., Goodman, A. J.: "Standardized pain stimulation as controlled stress in physiological studies of psychoneurosis." *Science* **108**: 509-511 (1948). B47,043/48

In psychoneurotics, heat applied to the forehead caused stress as indicated by lymphopenia as well as by GSR and EEG changes. It is concluded that pain tests "may profitably be employed in more extensive analyses of disturbances in mental patients undergoing stress."

Malmo, R. B., Shagass, C.: "Physiologic studies of reaction to stress in anxiety and early schizophrenia." *Psychosom. Med.* **11**: 9-24 (1949). B47,045/49

Quantifiable stress was produced in man by

a standardized series of painful stimulations administered by means of a Hardy-Wolff thermal stimulator. Used as indicators of stress were finger movements, neck muscle potentials, GSR, heart rate, blocking of the α -rhythm in the EEG and so on. Schizophrenics showed a relative lack of discrimination among various pain intensities.

Lacey, J. I., Lehn, R. van: "Differential emphasis in somatic response to stress. An experimental study." *Psychosom. Med.* **14**: 71-81 (1952). J13,182/52

Measurements of heart rate, blood pressure and palmar conductance as indicators of stress during the "cold pressor test," with a discussion of the methodological and theoretical implications.

Cutaneous Conductance, Sweating, GSR. An increased secretion by the sweat glands, especially palmar sweating, is a very popular index of psychogenic stress. It can be measured by colorimetric techniques but is measured more accurately by GSR, both of which reflect cutaneous conductance. It is not yet quite clear to what extent changes in the conductance of the skin tissues themselves contribute to those induced by an increase of sweat.

In any event, the GSR has proven to be an adequate indicator of stress produced by anxiety, the viewing of cruel or sexually arousing films, the threat of electroshocks, stress interviews and so on.

Cutaneous Conductance, Sweating, GSR. Furer, M., Hardy, J. D.: "The reaction to pain as determined by the galvanic skin response." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 72-89. Baltimore: Williams & Wilkins, 1950. B51,896/50

Extensive studies on man exposed to pain (heat) in hot or cold environments as well as after induced anxiety led to the conclusion that the GSR is a good index of stress under these conditions (35 refs.).

Bixenstine, V. E.: "A case study of the

use of palmar sweating as a measure of psychological tension." *J. Abnorm. Soc. Psychol.* **50**: 138-143 (1955). B29,398/55

Description of a colorimetric method for measuring palmar sweating objectively. The test is recommended as a counterpart to the GSR measurements to indicate psychogenic tension.

Beam, J. C.: "Serial learning and conditioning under real-life stress." *J. Abnorm. Soc. Psychol.* **51**: 543-551 (1955). J10,605/55

The stress of academic examinations seri-

ously interfered with serial learning of a list of nonsense syllables. Stress was appraised by the palmar sweat index.

Wang, G. H.: "The galvanic skin reflex. A review of old and recent works from a physiologic point of view. Part one." *Am. J. Phys. Med.* **36**: 295-320 (1957). C42,560/57

Wang, G. H.: "Part two." *Am. J. Phys. Med.* **37**: 35-57 (1958). C42,560/58

Extensive review of the history, physical anatomic basis, measurement techniques and interpretation of the GSR (about 140 refs.).

Kimmel, H. D., Hill, F. A.: "A comparison of two electrodermal measures of response to stress." *J. Comp. Physiol. Psychol.* **54**: 395-397 (1961). J23,526/61

Speisman, J. C., Osborn, J., Lazarus, R. S.: "Cluster analyses of skin resistance and heart rate at rest and under stress." *Psychosom. Med.* **23**: 323-343 (1961).

D10,039/61

Harrison, J., MacKinnon, P. C. B., Monk-Jones, M. E.: "Behaviour of the palmar sweat glands before and after operation." *Clin. Sci.* **23**: 371-377 (1962).

D50,488/62

The "palmar sweat index," based on the number of active sweat glands in a limited area of the middle finger-pad, was found to be low in preoperative patients. "It is considered that the depression is associated with pituitary-adrenal activity consequent upon psychic stress."

Kozarovitskii, L. B.: "Dynamics of skin-galvanic reactions in control panel operators during their work of regulating airplane traffic." *Zh. Vyssh. Nerv. Deiat.* **14**: 387-396 (1964) (Russian). J23,845/64

MacKinnon, P. C. B.: "Hormonal control of the reaction of the palmar sweat index to emotional stress." *J. Psychosom. Res.* **8**: 193-195 (1964). G24,072/64

Harrison, J.: "The behaviour of the palmar sweat glands in stress." *J. Psychosom. Res.* **8**: 187-191 (1964). G24,073/64

Mordkoff, A. M.: "The relationship between psychological and physiological response to stress." *Psychosom. Med.* **26**: 135-150 (1964). G12,092/64

During viewing of *Subincision*, a "stressor film" depicting puberty rites of an Australian aboriginal tribe (crude operations performed with a piece of flint on the penis and scrotum

of adolescent boys), the ratings of psychologic impact upon the audience were closely related to such physiologic indices of stress as GSR, heart rate and respiration (21 refs.).

Zuckerman, M., Levine, S., Biase, D. V.: "Stress response in total and partial perceptual isolation." *Psychosom. Med.* **26**: 250-260 (1964). J7,193/64

Studies on female undergraduates showed that, as indicated by GSR (recorded by the Tissue Resistance Monitor), "1½ hr. total isolation is more stressful than partial isolation. Verbal indices indicate that all types of isolation are equally stressful. The results indicate that a social set theory is not sufficient to explain the stressful effects of perceptual restriction."

Ferreira, A. J., Winter, W. D.: "Age and sex differences in the palmar sweat print." *Psychosom. Med.* **27**: 207-211 (1965).

J22,919/65

Bonier, R. J., Hanley, C.: "Relationship among PGR indices." *J. Psychosom. Res.* **9**: 285-289 (1965).

J22,871/65

The PGR is defined as the "psychogalvanic reflex" and is discussed as an indicator of stress.

Katkin, E. S.: "Relationship between manifest anxiety and two indices of autonomic response to stress." *J. Pers. Soc. Psychol.* **2**: 324-333 (1965).

J8,700/65

Comparative studies on the effect of stress (threat of shock) on basal skin resistance and GSR in relation to the TMAS. "Changes in basal resistance may reflect epidermal activity associated with cognitive responses to the interview situation, while GSR nonspecifics reflect sweat gland activity associated with emotional responses to the threatening instructions." The literature and various psychogenic stress tests are reviewed.

Miller, L. H., Shmavonian, B. M.: "Reproducibility of two GSR indices as a function of stress and cognitive activity." *J. Pers. Soc. Psychol.* **2**: 753-756 (1965).

J8,698/65

With GSR used as an indicator of psychogenic stress during stress interviews, "it was concluded that the changes following the interview could not be attributed solely to the interview."

Lazarus, R. S., Opton, E. M. Jr.: "The study of psychological stress: a summary of theoretical formulations and experimental findings." In: Spiellberger, C. D., *Anxiety*

and Behavior, pp. 225-262. New York and London: Academic Press, 1966.

J10,620/66

Detailed description of the authors' use of films, occasionally combined with tape recording, in order to produce psychogenic stress. GSR and heart rate proved to be helpful objective indicators of autonomic activity, yet the two were not necessarily parallel. This may be due to differences in endocrine sensitivity.

Kafka, E., Reiser, M. F.: "Defensive and adaptive ego processes. Their relationship to GSR activity in free imagery experiments." *Arch. Gen. Psychiatry* **16**: 34-40 (1967).

J22,695/67

Stern, R. M., Gaupp, L., Leonard, W. C.: "A comparison of GSR and subjective adaptation to stressful stimuli." *Psychophysiology* **7**: 3-9 (1970).

J23,694/70

Folkins, C. H.: "Temporal factors and the cognitive mediators of stress reaction." *J. Pers. Soc. Psychol.* **14**: 173-184 (1970).

J20,845/70

Studies on the effect of anticipated electric shock upon GSR and cardiac rhythm in man.

Kaiser, C., Roessler, R.: "Galvanic skin responses to motion pictures." *Percept. Mot. Skills* **30**: 371-374 (1970).

H45,603/70

Kilpatrick, D. G.: "Differential responsiveness of two electrodermal indices to psychological stress and performance of a complex cognitive task." *Psychophysiology* **9**: 218-226 (1972).

J19,072/72

O'Malley, J. M.: "Palmar sweating as a function of failure in preschool children." *Psychol. Rep.* **30**: 279-285 (1972).

J20,569/72

Christie, M. J.: "Electrodermal activity and the stress response. A review." *Acta Med. Pol.* **14**: 343-355 (1973).

J16,612/73

Extensive historical review showing that "electrodermal activity can be used in several ways to provide information about aspects of the stress response" (36 refs.).

Christie, M. J., Venables, P. H.: "Change in palmar skin potential level during relaxation after stress." *J. Psychosom. Res.* **18**: 301-306 (1974).

J16,582/74

"A noise-avoidance task was used as a laboratory stressor, and rate of reduction in the negativity of palmar skin potential level (SPL) as an index of speed of relaxation. SPL was monitored from 12 male subjects during relaxation periods before and after the task, and compared with similar records from 12 control subjects who were not exposed to this stressor. The rate of reduction in negativity of post-stressor SPL was significantly slower than in the pre-stressor condition; there was no such difference in the data from control subjects."

Froese, A. P., Cassem, N. H., Hackett, T. P., Silverberg, E. L.: "Galvanic skin potential as a predictor of mental status, anxiety, depression and denial in acute coronary patients." *J. Psychosom. Res.* **19**: 1-9 (1975).

J22,159/75

Adrenocortical Function Tests. A variety of tests have been designed to examine the functional reactivity of the hypothalamus-pituitary-adrenocortical axis. Some of these have been discussed in detail elsewhere in this volume, for example, the inhibition of ACTH production by the corticoid feedback mechanism. In clinical medicine, dexamethasone is most commonly used for this purpose and it has been shown that in some diseases (for example, in certain psychiatric disturbances) the feedback mechanism is defective.

On the other hand, injections of EP or bacterial pyrogens normally stimulate CRF release and consequently increase the production of ACTH and of glucocorticoids, as long as the structures of the hypothalamus-pituitary-adrenocortical axis are intact.

Metyrapone reduces cortisol production by inhibition of 11β -hydroxylation. Thus, the biosynthesis of cortisol, the principal adrenal glucocorticoid in man, is blocked at the 11-desoxycortisol level, a compound which has practically no suppressing effect upon ACTH release. Normally, administration of metyrapone causes a compensatory increase in ACTH release and the secretion of 11-desoxycorticosterone (a 17-OHCS) in the urine. In patients with diseases of the hypothalamus-pituitary axis who are unable to respond with this compensatory reaction, the diminution or absence of increased

17-OHCS excretion after metyrapone is of diagnostic value. Although this is not strictly speaking a "stress test," it does deserve mention here because it assesses the functional activity of structures indispensable for a normal response to stressors.

Adrenocortical Function Tests. Faurbye, A., Vestergaard, P., Kobbernagel, F., Nielsen, A.: "Adrenal cortical function in chronic schizophrenia (stress, adrenaline-test, ACTH-test)." *Acta Endocrinol. (Kbh.)* 8: 215-246 (1951). B63,996/51

In man, EP treatment and the production of fever by injections of killed *B. faecalis alcaligenes* are regarded as adequate "stress tests," as indicated by the increase in uric acid and potassium excretion, as well as the hematologic changes that result.

Elmadjian, F., Hope, J. M., Lamson, E. T.: "Excretion of epinephrine and norepinephrine under stress." *Rec. Prog. Horm. Res.* 14: 513-553 (1958). C57,735/58

Observations on people exposed to various types of stressors "support the hypothesis that active aggressive emotional displays are related to increased excretion of NE, whereas tense, anxious, but passive, emotional displays are related to increased excretion of E in association with normal excretion of NE."

Jovy, D., Brüner, H., Klein, K. E., Wegmann, H. M.: "Adaptive responses of adrenal cortex to some environmental stressors, exercise and acceleration." In: Martini, L. and

Pecile, A., *Hormonal Steroids. Biochemistry, Pharmacology, and Therapeutics*, p. 545. New York and London: Academic Press, 1965.

E5,499/65

Plasma corticoid and eosinophil determinations in healthy young men exposed to several stressors encountered during space flights (hypoxia, cold, heat, acceleration, muscular work). The results of exposure to these stressors, alone or in various combinations, are taken as an expression of the individual sensitivity towards stress, and offer a criterion of practical importance.

Jenkins, J. S.: "The pituitary-adrenal response to pyrogen." In: James, V. H. T. and Landon, J., *Memoirs of the Society for Endocrinology*, No. 17, pp. 205-212. Cambridge: Cambridge University Press, 1968.

E7,508/68

In man the stressor effect of bacterial pyrogens provides a useful test of pituitary-adrenal reactivity, as indicated by the resulting increase in plasma cortisol. "If our present views on the pituitary site of its action are correct, the pyrogen test would seem to be complementary to such procedures as the vasopressin test, where the site of action seems to lie in the hypothalamus."

Multifactorial Stress Tests. As we explained before, on the basis of present-day knowledge, it is virtually impossible to recommend or even imagine any single indicator that would truly reflect stress, or the "nonspecific response of the organism to any demand made upon it." This may become possible after we have identified the "first mediator" (if it is a single substance) which relays the message from any peripheral tissue to the neurohormonal regulators of defense that a condition of stress exists.

Most of the "stress tests" now in use actually reflect only psychogenic stress and are not applicable to the estimation of such somatic stress situations as those caused by loss of blood, chemical toxicants or extremes of temperature. This is particularly obvious in the case of the Rorschach test, problem solving, or stress interviews. In addition, several tests are presently used to measure the specific effects of certain stressors; for example, the GSR would show a misleadingly high response to heat stress because sweating is specifically stimulated by high temperatures. Probably, direct determination of "stress hormones," such as catecholamines, ACTH or corticoids in the blood and/or urine, as well as the eosinopenia of stress, are least conducive to such misinterpretations.

In view of these factors, which diminish the significance of stress tests based upon the determination of any individual indicator, several batteries or combinations of tests have been recommended. In these, the average value of the most reliable indicators of nonspecific responses is considered to reflect stress as such.

Of course these tests are laborious because numerous endpoints must be determined to eliminate, as far as possible, distortions occasioned by specific responses. However, at the present time, multifactorial stress tests are still the best, especially if they include the many reliable indicators of nonspecific reactions, such as determinations of ACTH, corticoids, catecholamines, blood eosinophils and plasma FFA.

Another type of multifactorial stress test is based upon exposure of a subject to a great variety of stressors to determine his general resistance. However, these examinations are rarely meaningful except within a limited field. For example, it is possible to select a number of stressors likely to be encountered in aviation, business life or muscular exercise and for practical purposes, these will give a fairly instructive picture of a candidate's probable suitability for a particular task but not of his stress resistance in general.

Multifactorial Stress Tests. Rodnick, E. H., Rubin, M. A., Freeman, H.: "Related studies on adjustment. Reactions to experimentally induced stresses." *Am. J. Psychiatry* **99**: 872-880 (1943). B26,250/43

Comparative studies on the value of a battery of tests to measure stress in a camp devoted to instruction for industrial occupations.

Pincus, G., Hoagland, H., Freeman, H., Elmadjian, F.: "Adrenal function in mental disease." *Rec. Prog. Horm. Res.* **4**: 291-322 (1949). B41,235/49

Rather than using any single indicator of stress, the authors recommend a "total response index" (TRI). "This is obtained by employing the data of the principal indices of adrenocortical activity, namely 17-ketosteroid and neutral reducing lipide outputs, the potassium, sodium, and uric acid excretions, and the blood lymphocyte changes. The value is constructed for each individual by averaging the stress and poststress percentage increases of the urinary determinations with twice the stress and poststress lymphocyte percentage decreases" (20 refs.).

Parsons, O., Phillips, L.: "Some problems associated with development of stress scores for the individual." *J. Appl. Physiol.* **6**: 691-695 (1954). J13,191/54

Observations on the correlation between 17-KS excretion, eosinopenia, and psychomotor performance tests following exposure to various stressors (air blasts, intense light, sound and so on) have led to attempts to develop meaningful "stress scores."

Kraft, J. A.: "Measurement of stress and fatigue in flight crews during confinement." *J. Aviat. Med.* **30**: 424-430 (1959).

C70,483/59

Description of an elaborate facility for the

automatic measurement and registration of various stress indices (skin temperature, heart rate, respiratory cycle, muscular tension, GSR and so on) as they are affected by the stressors to which flight crews and astronauts are likely to be exposed (for example, gravity forces, loneliness, confinement, isolation, sensory deprivation).

Dykman, R. A., Ackerman, P. T., Galbrecht, C. R., Reese, W. G.: "Physiological reactivity to different stressors and methods of evaluation." *Psychosom. Med.* **25**: 37-59 (1963). J23,479/63

Thiesen, J. W., Forgas, R. H., Spaner, F. E.: "An objective method of assessing a stress syndrome related to achievement motivation." *Percept. Mot. Skills* **19**: 183-197 (1964). G35,813/64

A multifactorial battery of stress tests "indicate that the sustained heart-rate response, as utilized in this procedure, is a sensitive and convenient measure of stress associated with achievement motivation. It is suggested that the test battery and methodology described may be useful in research concerning striving-induced stress and its role in psychosomatic disorders."

Thiesen, J. W., Brown, K. D., Forgas, R. H., Evans, S. M., Williams, G. M., Taylor, J.: "Further data on a stress syndrome related to achievement motivation: relationships with age and basal serum cholesterol level." *Percept. Mot. Skills* **20**: 1277-1292 (1965). G35,812/65

Verification of a multifactorial stress test based on heart rate acceleration. "While a tendency toward higher over-all heart rates with increased age was observed, the principal specific finding was a positive association of basal serum cholesterol level with poststress heart rate, independent of age. Indi-

viduals with higher serum cholesterol levels showed less complete recovery following stress and higher initial heart rates, but they did not necessarily show a stronger immediate response to the stressors."

Klein, K. E., Brüner, H., Ruff, S.: "Untersuchungen zur Belastung des Bordpersonals auf Fernflügen mit Düsenmaschinen" (Evaluation of resistance to stress in air crew members on transatlantic jet flights). *Z. Flugwisschft.* **14**: 109-121 (1966).

G42,395/66

An attempt to evaluate resistance to fatigue using blood circulation, pulse rate, ECG, oral temperature and motor coordination as indices.

Fleishman, E. A.: "Performance assessment based on an empirically derived task taxonomy." *Hum. Factors* **9**: 349-366 (1967).

J7,673/67

Technique for the assessment of general performance based on an empirically developed task taxonomy. Allegedly, it is suitable for appraising the effect of stress upon efficiency in general.

Hale, H. B., Anderson, C. A., Williams, E. W., Tanne, E.: "Endocrine-metabolic effects of unusually long or frequent flying missions in C-130E or C-135B aircraft." *Aerosp. Med.* **39**: 561-570 (1968).

G63,855/68

"Flight-stress appraisal was made by means of a battery of urinary determinations (epinephrine, norepinephrine, 17-OHCS, urea, uric acid, phosphorus, magnesium, sodium, and potassium) for flyers who participated in (a) 20-hour missions in C-130E aircraft (flights from New Zealand to Antarctica, and back), (b) 6-day missions in C-135B aircraft (earth-circling missions) or (c) 7-week missions in C-135B aircraft (overfrequent transoceanic and transconti-

nental flying). The adrenal medulla (judging by urinary epinephrine) consistently showed flight-sensitivity, but other endocrine-metabolic functions varied in ways indicative of adaptation." East- and westbound earth-circling missions did not elicit essentially different degrees of flight-stress as indicated by the above-mentioned indices.

Mefferd, R. B. Jr., Hale, H. B., Shannon, I. L., Prigmore, J. R., Ellis, J. P. Jr.: "Stress responses as criteria for personnel selection: baseline study." *Aerosp. Med.* **42**: 42-51 (1971).

G99,772/71

Exploratory studies on the feasibility of using a battery of tests for the selection of stress-resistant personnel for Air Force duty. Moderate hypoxia was employed as a stressor, and various psychologic and metabolic changes were used as indicators. A number of potentially useful indices are listed, but no definite combination of these is recommended as an overall stress resistance test.

Wardwell, W. I.: "A study of stress and coronary heart disease in an urban population." *Bull. N.Y. Acad. Med.* **49**: 521-531 (1973).

J3,167/73

A technique for the assessment of stress is developed by combined evaluation of socio-economic status, social stress, physical illness, emotional stability and behavioral pattern in an urban population.

Smith, J. J., Bonin, M. L., Wiedmeier, V. T., Kalbfleisch, J. H., McDermott, D. J.: "Cardiovascular response of young men to diverse stresses." *Aerosp. Med.* **45**: 583-590 (1974).

J13,387/74

Comparative studies on the interpretation of eight stress tests (postural, cold pressor, Valsalva, various exercise stresses) with respect to cardiovascular responses in healthy young men.

Special Instruments. A number of special instruments for the measurement of stress reactions have already been mentioned, for example, various pursuit meters and the machinery necessary for the determination of the EEG, GSR, EMG, and so on.

Here, we merely want to call attention to the polygraphs that simultaneously determine skin temperature, GSR, pulse rate, blood pressure, respiration and so on. A number of lie detectors and "stressalyzers" are based upon this principle. Some of these instruments are highly sophisticated and can even be used for biotelemetry in different operational environments. It is important, however, to select the parameters to be measured according to the type of stress situation for which the candidate is to be appraised.

Special Instruments. Gerard, D. L., Phillips, L.: "Relation of social attainment to psychological and adrenocortical reactions to stress." *Arch. Neurol. Psychiatry* **69**: 350-354 (1953). G85,802/53

A pinball-like device, the Rotter aspiration board, is manipulated by an experimenter so that the subject becomes inept after a period of successful performance. Subjects with high social attainment showed better adaptive responses and less pronounced increases in corticoid excretion than others, because they shifted their goals more realistically after failure.

Baker, L. M., Taylor, W. M.: "The relationship under stress between changes in skin temperature, electrical skin resistance, and pulse rate." *J. Exp. Psychol.* **48**: 361-366 (1954). J13,305/54

Polygraph recordings of skin temperature, GSR and pulse rate are used to appraise the degree of stress elicited by emotional excitement in man.

Tomberg, V. T.: "The monitoring of synergistic stress inducing environmental factors." *3rd Manned Space Flight Convention of NASA & AIAA*, p. 138. Houston, 1964.

G37,471/64

"A Bio-Instrumentation and Monitoring device is described which relates complex environmental variables such as altitude, O₂, CO₂, CO, Temperature-Humidity and radiation dose to the development of psycho-physiological stress for the purpose of controlling the environment in advance." If the astronauts or aircraft flight crews are instrumented, the onset of adverse reactions may be detected early when corrective action is still possible. [The instrument is not described in detail (H.S.).]

Kugelmas, S., Lieblich, I.: "Effects of realistic stress and procedural interference in experimental lie detection." *J. Appl. Psychol.* **50**: 211-216 (1966). J10,619/66

Contemporary professional lie detectors are based on "a limited number of polygraph instruments which usually include the following channels: (a) blood pressure and pulse rate, (b) respiration, and (c) galvanic skin response (GSR). The procedure for measuring blood pressure includes the use of a cuff placed around the upper arm of the subject." The GSR appears to be the most reliable of these indices, but reactivity is probably related to ethnic origin.

Fascenelli, F. W., Cordova, C., Simons, D. G., Johnson, J., Pratt, L., Lamb, L. E.: "Biomedical monitoring during dynamic stress testing: I. Instrumentation and normal values." *Aerosp. Med.* **37**: 911-922 (1966).

J22,765/66

Dean, R. D.: "The use of environmental stress in conjunction with simulation testing." *IEEE Trans. Aerosp. Electron. Syst.* **3**: 688-696 (1967).

J21,362/67

"The Boeing Multiple-Stress Laboratory is capable of exposing subjects to heat, noise, vibration, and altitude, while measuring their performance and physiology." In this laboratory, it is possible to simulate flights in various types of fixed-wing aircraft, helicopters and three-stage boosters.

Roessler, R.: "Psychophysiological indices of stress tolerance." *Biomed. Sci. Instrum.* **3**: 17-28 (1967).

J23,434/67

Ellestad, M. H.: "Telemetry in monitoring stress electrocardiograms." *Biomed. Sci. Instrum.* **3**: 249-256 (1967).

J23,433/67

Description of an instrument that records by telemetry a patient's ECG and blood pressure while he is exercising on a treadmill.

Fuchs-Schmuck, A., Naumann, H. J.: "Arbeitsphysiologische Belastungsuntersuchungen mit dem Kreislaufkontrollgerät 'Physiomat'" (Physiologic work stress studies using the blood circulation control device "Physiomat"). *Dtsch. Gesundheitsw.* **23**: 1280-1283 (1968).

J23,686/68

Rosenbrock, F.: "Hardware problems in ergonomics measurements." *Ergonomics* **14**: 617-623 (1971).

J19,713/71

Multichannel automatic data acquisition and processing instruments are described for the objective measurement of work loads on ATCs, using physiologic variables such as ECG, EMG, EOG (electro-oculogram), respiration and so on. "To correlate these variables with factors of stress and strain a coding is described, which renders the evaluation of a multi-dimensional work process study automatically and synchronously with the physiological data."

Buck, L.: *Performance Data for the NRC Stressalyzer*, p. 66. National Research Council Pamphlet. Res. Lab. Techn. Rep. LTR-CS-69. Ottawa, 1972.

J12,632/72

"The NRC Stressalyzer is a step-input pursuit tracking task used in studying human perceptual-motor skill." The paper sketches

the development of this instrument and defines the measures obtained from it.

Křišťian, L., Dvořák, M., Žáček, I., Pokorný, F.: "Experience with the application of biotelemetry (ECG, EMG) under strenuous working conditions in various operational environments." *Biotelemetry Int. Symp.*, pp. 289-297 (1972). H80,195/72

Buck, L., Leonardo, R.: *Sleep Patterns and Psychomotor Performance of Aircrew Flying the North Pacific*, p. 22. National Research Council, Div. Mech. Eng. Rep. LTR-CS-97. Ottawa, 1973. J10,491/73

Preliminary data on stress levels in aircrews flying the North Pacific, which are measured by means of the "stressalyzer." This is an instrument which permits objective assessment of a step-tracking task in which the subject pursues a light as it moves among five horizontally aligned positions. "The task is subject-paced, target movement depending on pointer alignment, and the coupling between control wheel and pursuit pointer is inverse, the two moving in opposite directions. The instrument yields a number of performance indices relating to the speed and accuracy of decision and movement." Due to various technical difficulties the application of the machine to this particular task did not yield definitive results.

Mitchell, B. W., Siegel, H. S.: "Physiological response of chickens to heat stress measured by radio telemetry." *Poultry Sci.* **52**: 1111-1119 (1973). J22,022/73

Hatch, T. F.: "Design requirements and limitations of a single-reading heat stress meter." *Am. Ind. Hyg. Assoc. J.* **34**: 66-72 (1973). J19,382/73

Pikus, V. G., Korotich, A. F., Batrakov, V. N.: "Instrument for investigating the parameters of human attention." *Med. Tekh.* No. 3: 53-55 (1973) (Russian). In English translation: *Biomed. Eng. (N.Y.)* **7** No. 3: 185-187 (1974). J18,102/73

Description of an instrument which, "in addition to automation of the process of investigation, objective recording of the results obtained, and possibility of investigation both under sparing conditions (without distracting external stimuli) and under conditions of graduated noises, also permits studying the parameters of human attention in a state of emotional stress." During investigation, the introduction of various noises allows determination of the stability of the subjects' attention. "This test is used widely in psycho-

physiological selection of railroad engineers, pilots, and cosmonauts."

Fraser, B. A., Buck, L., McKendry, J. B. R.: "Psychomotor performance during insulin-induced hypoglycemia." *Can. Med. Assoc. J.* **110**: 513-518 (1974).

H82,550/74

In man, hypoglycemia-producing doses of insulin impair performance on the stressalyzer (subject-paced, step-input, pursuit-tracking tasks). The authors state that "in the numerous reports concerning effects of stress on performance of tasks requiring psychomotor ability it is evident that stress situations usually result in deterioration in the quality of performance. In this study the stress applied was insulin-induced lowering of the plasma glucose. In seven of eight subjects in whom reduced plasma glucose was temporally correlated with signs and symptoms suggesting hypoglycemia, speed of performance on the stressalyzer deteriorated concomitantly owing principally to increased movement times and to a lesser extent to increased reaction times."

Other Stress Tests. Chalke, F. R. C.: "The Harrower Stress Tolerance Test." *Psychosom. Med.* **8**: 215-216 (1946).

B26,505/46

Validation experiments indicate the value of the *HSTT* in screening persons susceptible to specific disturbing situations and in differentiating normal subjects from neurotics.

Weller, E.: "Über den 'Operations-Stress,' seine Diagnostik und Prophylaxe. Eine Untersuchung mit besonderer Berücksichtigung des Histamin-Erythem-Testes" (On "operation stress," its diagnosis and prophylaxis. A study with special reference to the *histamine-erythema test*). *Ärztl. Forsch.* **13**: 559-569 (1959). C80,994/59

Observations on patients with stress induced by anesthesia and surgery indicated that "the histamine sensitivity of the skin, the individual histamine index, shows a reciprocal ratio to the individual efficiency of the adrenal cortex, and can serve as a gauge for the evaluation of stress-tolerance due to operation."

Arima, J. K.: "Performance of normal males on the *Halstead Tactual Performance Test* under severe environmental stress." *Percept. Mot. Skills* **21**: 83-90 (1965).

J23,599/65

Erickson, J. M., Pugh, W. M., Gunderson,

E. K. E.: "Status congruency as a predictor of job satisfaction and life stress." *J. Appl. Psychol.* **56**: 523-525 (1972). J10,599/72

Description of a "*status congruency*" test to measure the extent to which an individual's occupation and reward coincide with that of his peers. Deviation from such congruency can to some extent predict job satisfaction and life stress.

Schneider, R. A.: "Newer insights into the role and modifications of olfaction in man through clinical studies." *Ann. N.Y. Acad. Sci.* **237**: 217-223 (1974). H93,890/74

Perception and adaptation to an odor (*olfactometer test*) can be used as an indicator of stress caused by daily life events. In a group of women, "those who failed to adapt (or rarely did) had the greatest incidence of stress on the day of the test or the day preceding. The correlation was significant but

was unrelated either to initial threshold level or to nasal mucous membrane function. It would seem appropriate, in the biological sense, that adaptation be inhibited under circumstances of stress if odors are capable of initiating the 'alarm reaction' of Selye."

Hartley, L. R., Adams, R. G.: "Effect of noise on the Stroop test." *J. Exp. Psychol.* **102**: 62-66 (1974). J17,211/74

In the *Stroop color interference test*, "color names written in inks of different hues, excluding ink of the hue the name indicates, are presented to Ss who are required to name the hue of the ink and not the color name." Brief exposure to noise is beneficial, whereas prolonged exposure to intense noise damages performance, in that elimination of the irrelevant interfering feature (color name) is more difficult during stress.

Body Temperature

Stress, especially if it is severe, characteristically interferes with the regulation of body temperature. Curiously, the direction of the change produced largely depends upon the species. Thus, for example, it has long been known that in man a great variety of infections, intoxications and injuries tend to elicit fever, whereas in the rat, even the first observations on the alarm reaction revealed an almost constant occurrence of hypothermia during acute stress caused by virtually any agent.

It is also common knowledge that even in man, severe stress, especially if conducive to shock, induces heat loss that must be countered by keeping the patient covered in warm surroundings.

Some psychoneurotic individuals are predisposed to "stress-hyperthermia" which has been ascribed to a cortico-hypothalamic imbalance.

Several investigators have tried to determine the relative role of decreased heat production and increased heat loss during severe stress conducive to hypothermia, but this problem has not been definitely solved; the relative importance of the two factors probably varies depending upon circumstances.

Body Temperature

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

First detailed description of the alarm reaction to stressors mentioning an initial drop in body temperature as one of the characteristic changes.

Goodell, H., Graham, D. T., Wolff, H. G.: "Changes in body heat regulation associated with varying life situations and emotional states." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 418-432. Baltimore: Williams & Wilkins, 1950.

B51,917/50

Friedman, M.: "Hyperthermia as a manifestation of stress." In: Wolff, H. G., Wolf,

S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 433-444. Baltimore: Williams & Wilkins, 1950. B51,918/50

"Approximately 45 per cent of psychoneurotic individuals exhibiting somatic reference of their disorder exhibit the phenomenon of neurogenic hyperthermia, as defined." This stress hyperthermia is ascribed to "cortico-hypothalamic imbalance."

Bartlett, R. G. Jr., Bohr, V. C., Helmenstine, R. H., Foster, G. L., Miller, M. A.: "Evidence of an emotional factor in hypothermia produced by restraint." *Am. J. Physiol.* **179**: 343-346 (1954).

J25,354/54

Brodie, D. A., Valitski, L. S.: "Production of gastric hemorrhage in rats by multiple stresses." *Proc. Soc. Exp. Biol. Med.* **113**: 998-1001 (1963). E28,039/63

"Gastric hemorrhage was produced in 93% of rats subjected to cold + restraint stress for 60 minutes." This combination of stressors also elicited a marked depression of body temperature lasting three hours after the stress. "Anticholinergics, ganglionic blocking agents, certain central nervous system depressants and epinephrine reduced the incidence of hemorrhage."

Foss, C. R., Horvath, S. M.: "Reactions of wild and albino mice in response to forced swimming." *Proc. Soc. Exp. Biol. Med.* **120**: 588-592 (1965). F59,402/65

The ability of wild and domestic albino mice to swim until exhaustion was much shorter in water of 20°C than at 37°C. The drop in colonic temperature was an excellent indication of exhaustion in temperatures of 28°C or less but remained normal or even rose at higher temperatures. There was no significant difference in either colonic temperature or endurance between the two strains.

Strydom, N. B., Wyndham, C. H., Williams, C. G., Morrison, J. F., Bredell, G. A. G., Joffe, A.: "Oral/rectal temperature differences during work and heat stress." *J. Appl. Physiol.* **20**: 283-287 (1965).

G27,148/65

Studies on the relationship of the BMR to oral and rectal temperatures under different conditions. [Despite the title, the authors made no effort to show a relationship to stress, and presumably studied the specific effects of work at different temperatures (H.S.).]

Wyndham, C. H., Williams, C. G., Morrison, J. F., Bredell, G. A. G.: "A comparison of multi-stress tests on the sweat rate/rectal temperature relationship." *Int. Z. Angew. Physiol.* **23**: 305-321 (1967). G45,958/67

Fiorica, V., Higgins, E. A., Iampietro, P. F., Lategola, M. T., Davis, A. W.: "Physiological responses of men during sleep deprivation." *J. Appl. Physiol.* **24**: 167-176 (1968). G55,182/68

Metabolic studies on resistance to cold in man after eighty-four to eighty-six hours of sleep deprivation showed no very constant and significant deviations from the norm.

Yokoi, Y.: "Effect of heat and cold stress on thermal responses to antipyretic drugs." *Fed. Proc.* **28**: 1115-1117 (1969).

H13,183/69

Prioux-Guyonneau, M.: "Répercussions de la contrainte sur la régulation thermique du rat blanc maintenu à différentes températures ambiantes" (Repercussions of restraint on thermal regulation of white rats kept at different environmental temperatures). *C.R. Soc. Biol. (Paris)* **164**: 72-75 (1970).

J21,917/70

Adams, T., Morgan, M. L., Hunter, W. S., Holmes, K. R.: "Temperature regulation of the unanesthetized cat during mild cold and severe heat stress." *J. Appl. Physiol.* **29**: 852-858 (1970) (24 refs.). G80,331/70

Harris, D. A., Hale, H. B., Hartman, B. O., Martinez, J. A.: "Oral temperature in relation to inflight work/rest schedules." *Aerospace Med.* **41**: 723-727 (1970). G83,677/70

Hagberg, B.: "Emotionally released hyperthermia in cerebral palsy." *Neuropaediatrica* **1**: 295-306 (1970).

J21,364/70

Oyama, J., Platt, W. T., Holland, V. B.: "Deep-body temperature changes in rats exposed to chronic centrifugation." *Am. J. Physiol.* **221**: 1271-1277 (1971).

J19,653/71

In rats, the stressor effect of centrifugation causes a rapid fall in deep-body temperature monitored continuously by implant biotelemetry.

Yordanova, L., Gotsev, T.: "Alterations in the enzyme activity of students with increased body temperature during examinations." *J. Physiol. (Paris)* **63**: 463-464 (1971).

J20,215/71

Among students under "examination stress," the most outstanding objective

changes were tachycardia, hypertension, dilatation of the pupils, increased intraocular pressure, sweating, alterations in erythrocytes and platelets, a rise in body temperature and in the blood levels of carbonic anhydrase and cholinesterase.

Oyama, J., Chan, L.: "Oxygen consumption and carbon dioxide production in rats during acute centrifugation stress and after adaptation to chronic centrifugation." *Fed. Proc.* **32**: 392 (1973). H67,544/73

In rats, stress produced by continuous centrifugation causes a pronounced hypothermia and a decrease in the BMR. However, upon

continued exposure to the stressor, the BMR rises above normal when adaptation occurs. The authors "conclude that the principal factor responsible for the centrifugation stress-induced hypothermia in rats is a decrease in their rate of heat production."

Wells, C. L., Horvath, S. M.: "Heat stress responses related to the menstrual cycle." *J. Appl. Physiol.* **35**: 1-5 (1973). J4,516/73

The few differences occurring during the menstrual cycle phase had a minimal influence upon the ability of normal women "to regulate body temperature when exposed to environmental heat stress."

Cardiovascular System, including Blood Pressure, ECG

The cardiovascular system is particularly sensitive to stress although the intensity and quality of its response is highly dependent upon special conditioning circumstances. Thus, stress is usually associated with a rise in blood pressure and pulse rate, but in severe stress conducive to shock, blood pressure characteristically falls and the heart rate may be decreased. Similarly, whether a stressor causes vasoconstriction or vasodilatation depends upon circumstances.

After hypophysectomy or adrenalectomy, virtually any type of stress induces hypotension. Hence, it may be assumed that pituitary and adrenal hormones play an important role in conditioning the response of the cardiovascular system. Many of the early animal experiments on the mechanism through which stressors, corticoids and catecholamines influence vascular responses during systemic stress were performed on the mesoappendix vessels of the rat. This work confirmed that both adrenalectomy and stress diminish the responsiveness of the vessels to the topical application of NEP, and it has been suggested that the beneficial effect of corticoids in stress is largely due to the restoration of normal vascular contractility. Glucocorticoids even act topically in sensitizing small splanchnic vessels to NEP after adrenalectomy in the rat.

As we shall see later in the section on Diseases of Adaptation, various stressors can produce hypertension and different types of cardiac arrhythmias in both man and experimental animals.

In man, psychogenic stress often causes an increase in forearm blood flow.

Cardiovascular System, including Blood Pressure, ECG

(See also our earlier stress monographs, p. xiii, and cf. ECG under Stress Tests)

Morris, D. P.: "Blood pressure and pulse changes in normal individuals under emotional stress; their relationship to emotional

instability." *Psychosom. Med.* **3**: 389-398 (1941). B26,186/41

In student nurses undergoing examinations and student pilots performing various flying exercises for the first time, a rise in blood pressure was quite constant, but the pulse rate was more variable and sometimes actually decreased. Pallor, tremor, flushing, excessive sweating, restlessness and apprehensive

facial expression were also studied as possible indicators of stress, but the results proved more difficult to interpret.

Fritz, I., Levine, R.: "Action of adrenal cortical steroids and nor-epinephrine on vascular responses of adrenalectomized rats." *Am. J. Physiol.* **163**: 713 (1950).

B54,186/50

By use of the mesoappendix preparation of the rat, it is shown that vasoconstriction following topical application of NEP is impaired by formaldehyde-induced stress, especially after adrenalectomy, but can be restored by topical application of adrenocortical extract. These and other experiments support the concept that corticoids are necessary for the normal response of small vessels to vasoconstrictors.

Fritz, I., Levine, R.: "Action of adrenal cortical steroids and nor-epinephrine on vascular responses of stress in adrenalectomized rats." *Am. J. Physiol.* **165**: 456-465 (1951).

B58,944/51

In adrenalectomized rats the blood vessels of the mesoappendix become refractory to topical application of NEP. Stress induced by subcutaneous formaldehyde does not impair circulation in the mesoappendix of the normal rat, but it does cause sluggishness of flow and eventually stasis prior to death after adrenalectomy. These changes can be prevented by Dibenamine, which also prolongs the survival time after formaldehyde treatment of adrenalectomized rats. Apparently, corticoids are necessary to permit the blood vessels to respond normally to NEP, and at the same time they protect against toxic amounts of NEP.

Kuhl, W. J. Jr., Ralli, E. P.: "Effect of acute stress upon blood constituents, white cells, and urine constituents in normal individuals." *Proc. Assoc. for the Study of Internal Secretions—33rd. Meeting*, p. 51. Atlantic City, N.J., 1951. Also in: *J. Clin. Endocrinol. Metab.* **11**: 776 (1951).

B58,505/51

Normal men immersed in cold water (9.5°C) for eight minutes showed: "1—A decrease in temperature (immediate, 1 and 2 hours); 2—An increase in systolic and diastolic blood pressure (immediate) and a decrease (2 hours); 3—A decrease in heart rate (1, 2, and 4 hours); 4—An increase in neutrophiles (immediate); 5—A decrease in lymphocytes (2 hours); 6—A decrease in eosinophiles (2 hours); 7—A decrease in serum

chloride (immediate); 8—An increase in total proteins (immediate and 4 hours); 9—A decrease in serum water (immediate); 10—An increase in total cholesterol (4 hours); 11—An increase in the urine uric acid/creatinine ratio (2 and 4 hours)." All of these changes were significant and ascribed to stress, but no one indicator gave uniformly positive results.

Ramey, E. R., Goldstein, M. S., Fritz, I., Levine, R.: "Relation of nor-epinephrine and other autonomic agents to vascular collapse of stressed adrenalectomized animal." *Fed. Proc.* **10**: 108 (1951). B57,125/51

In dogs, adrenalectomy decreases the pressor response to NEP. This cannot be corrected by DOC, but adrenocortical extract largely restores normal responsiveness. Glucocorticoids can even act topically in sensitizing small splanchnic vessels to NEP.

Levine, R., Goldstein, M. S., Ramey, E. R., Fritz, I.: "Studies on the mode of action of cortisone in stress situations." *Bull. N. Eng. Med. Cent.* **13**: 114-120 (1951).

B65,214/51

Studies on the Chambers-Zweifach mesoappendix preparation suggest that the beneficial effect of adrenocortical extract in stress is due largely to restoration of normal vascular contractility.

Bernreiter, M.: "Cardiac arrhythmias in physical or emotional stress." *Mo. Med.* **53**: 19-20 (1956). C11,328/56

Case reports showing that violent arguments with superiors, witnessing a serious car accident, or lifting a heavy weight may cause ventricular or paroxysmal auricular tachycardia, complete heart block and even death. It is concluded that "physical exertion and emotional stress may lead to almost all types of cardiac arrhythmias and death in the abnormal as well as the normal heart. An attempt is made to describe some of these phenomena that occur during the alarm reaction and their possible relationship to the production of ectopic rhythms."

Fencl, V., Hejl, Z., Jirka, J., Madlafousek, J., Brod, J.: "Changes of blood flow in forearm muscle and skin during an acute emotional stress (mental arithmetic)." *Clin. Sci.* **18**: 491-498 (1959). C81,538/59

Bello, C. T., Sevy, R. W., Ohler, E. A., Papacostas, C. A., Bucher, R. M.: "Renal hemodynamic responses to stress in normotensive and hypertensive subjects." *Circulation* **22**: 573-582 (1960). C92,607/60

Comparison of renal and cardiovascular responses in normo- and hypertensive patients.

Paterson, J. C.: "Stress, intimal hemorrhage, and coronary occlusion." *J. Occup. Med.* **3**: 59-63 (1961). D82,819/61

In man, various stressors may cause intimal hemorrhages with coronary occlusion.

Grandpierre, R., Angiboust, R., Chatelier, G.: "Variations de la fréquence cardiaque du Rat blanc soumis à différents facteurs d'agression" (Variations in the cardiac rate of the white rat subjected to different stress factors). *C.R. Soc. Biol. (Paris)* **155**: 2164-2166 (1961). E41,693/61

In rats, intense stress produced by sound or hypoxia invariably causes bradycardia ascribed to an "adrenergic reflex mechanism."

Sipple, W. C., Polis, B. D.: "The electrocardiogram as an indicator of acceleration stress." *IRE Trans. Bio-med. Electron.* **8**: 189-191 (1961). J22,386/61

By use of a transistor amplifier, it was possible to determine the ECG of rats under intense acceleration stress. "A physiological end point for the tolerance of the rat to 20 G (positive acceleration) was defined as the time to reduce the heart rate of the animal from an initial state ranging from seven to nine beats per second to a final moribund state of 2 beats per second."

Hudak, W. J., Buckley, J. P.: "Production of hypertensive rats by experimental stress." *J. Pharm. Sci.* **50**: 263-264 (1961).

D10,013/61

Rats maintained on 0.9 percent sodium chloride as a drinking solution were exposed to different types of stress (bright lights, noxious sounds, vibration) administered under varying conditions to prevent acclimation. Blood pressures rose to 150 mm. Hg after about twenty-five weeks. Sodium chloride by itself had no such effects. Earlier literature on stress-induced experimental hypertension is reviewed.

Glover, W. E., Greenfield, A. D. M., Shanks, R. G.: "The contribution made by adrenaline to the vasodilation in the human forearm during emotional stress." *J. Physiol. (Lond.)* **164**: 422-429 (1962).

D47,670/62

During psychogenic stress, there is often an increase in forearm blood flow. Experiments in which the suppression of this response by dichloroisopropyl-NEP was explored gave re-

sults too variable to ascertain whether the EP release is responsible for this effect.

Stokvis, B., Liem, S. T., Bolten, M. P.: "Das Verhalten der Herzfrequenz während experimentell erzeugtem Stress" (The behavior of the heart rate during experimentally-produced stress). *Z. Psychosom. Med.* **8**: 234-254 (1962). J23,198/62

Bach, J. L.: "Stress and the human heart." *New Physician* **11**: 395-397 (1962). J23,570/62

Cortes, F. M.: "Acute atrial overloading, a response to stress." *Am. J. Med. Sci.* **245**: 443-450 (1963). G22,392/63

Marino, A., Galdi, R., Parise, A., Mastursi, M.: "Stress psicologico e alterazioni ecografiche da ipertensina" (Psychologic stress and ECG changes due to hypertension). *Arch. It. Sci. Farmacol.* **13**: 206-208 (1963).

G19,378/63

Aceto, M. D. G., Kinnard, W. J., Buckley, J. P.: "Effect of compounds on blood pressure and behavioral responses of rats chronically subjected to an avoidance-escape situation." *Arch. Int. Pharmacodyn. Ther.* **144**: 214-225 (1963). E23,944/63

Mordkoff, A. M.: "The relationship between psychological and physiological response to stress." *Psychosom. Med.* **26**: 135-150 (1964). G12,092/64

During viewing of *Subincision*, a "stressor film" depicting puberty rites of an Australian aboriginal tribe (crude operations performed with a piece of flint on the penis and scrotum of adolescent boys), the ratings of psychologic impact upon the audience were closely related to such physiologic indices of stress as GSR, heart rate and respiration (21 refs.).

Brod, J.: "Circulation in muscle during acute pressor responses to emotional stress and during chronic sustained elevation of blood pressure." *Am. Heart J.* **68**: 424-426 (1964). F20,205/64

Študent, V.: "Blood pressure changes under experimental stress in aggressive and anxious-depressive patients." *Activ. Nerv. Sup.* (Praha) **7**: 200-201 (1965).

J23,491/65

Whittow, G. C., Sturkie, P. D., Stein, G. Jr.: "Cardiovascular changes in restrained chickens." *Poultry Sci.* **44**: 1452-1459 (1965). J23,501/65

Border, J. R., Gallo, E., Schenk, W. G.:

"Alterations in cardiovascular and pulmonary physiology in the severely stressed patient: a rational plan for the management of hypotension." *J. Trauma* **6**: 176-193 (1966).

J23,154/66

Rautaharju, P. M., Wolf, H., Piironen, P., Äikäs, E., Karvonen, M. J.: "Thermal stress and the electrocardiogram: a technical study." *J. Appl. Physiol.* **21**: 1875-1879 (1966). F93,465/66

In man, exposure to heat "produced a decrease in magnitude of the horizontal plane ventricular gradient and large but inconsistent shifts in its spatial orientation. QRS area vectors were unchanged and no significant effects were noted in the fine structure of the QRS. The R-R intervals shortened by a factor of 1.7 during the heat stress and the variability of the R-R intervals reduced by a factor of 4.4; these changes far surpass those expected from temperature coefficient effects alone."

Burns, N. M., Baker, C. A., Simonson, E., Keiper, C.: "Electrocardiogram changes in prolonged automobile driving." *Percept. Mot. Skills* **23**: 210 (1966). J23,665/66

Lazarus, R. S., Opton, E. M. Jr.: "The study of psychological stress: a summary of theoretical formulations and experimental findings." In: Spiellberger, C. D., *Anxiety and Behavior*, pp. 225-262. New York and London: Academic Press, 1966.

J10,620/66

Detailed description of the authors' use of films, occasionally combined with tape recording, in order to produce psychogenic stress. GSR and heart rate proved to be helpful objective indicators of autonomic activity, yet the two were not necessarily parallel. This may be due to differences in endocrine sensitivity.

Priem, H.: "Diferencias de la presión arterial, base de la regulación de trastornos vegetativos" (Differences in arterial pressure, basis of the regulation of vegetative disorders). *An. Esp. Odontoestomatolog.* **26**: 177-190 (1967). G39,889/67

Review of blood pressure changes in man during the alarm reaction.

Kuklová-Štúrová, B., Oravec, D.: "Reaction of the vegetative nerve system to emotional stress situations in the orto-klinostatic electrocardiogram." *Cas. Lék. Čes.* **106**: 1253-1258 (1967) (Czech). G57,693/67

Correlation of the ECG changes produced

by stress during the different stages of the G.A.S.

Thackray, R. I., Pearson, D. W.: "The effects of cognitive appraisal of stress on heart rate and task performance." *Federal Aviation Administration, Aviation Med. pamphlet*, pp. 1-6. Washington, D.C., 1968. G65,881/68

Measurement of tachycardia produced by fear of an electric shock which might or might not be given, depending upon performance on a pursuit rotor. Male undergraduates were divided into those who did and those who did not fear shocks. "High fear of shock subjects revealed significantly greater heart rate acceleration and performance impairment, but only under the condition in which the subjects were told that receipt of shock would be contingent on prior performance level."

Fröberg, J., Karlsson, C. G., Levi, L., Lidberg, L., Seeman, K.: "Conditions of work and their influence on psychological and endocrine stress reactions." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 8: 1-19 (1969). G69,180/69

In Swedish officers deprived of sleep for seventy-five hours and performing on an electronic shooting range or engaged in military staff work, EP and NEP excretion was increased, as were erythrocyte sedimentation and the amount of PBI, whereas serum iron was decreased. Some subjects developed ECG anomalies, particularly ST-T depression, and it took several days of rest for the ECG patterns to return towards normal. Stressors imitating situations in civilian life produced essentially similar changes proportional to their severity.

Kasl, S. V., Cobb, S.: "Blood pressure changes in men undergoing job loss: a preliminary report." *Psychosom. Med.* **32**: 19-38 (1970) (30 refs.). J12,249/70

Bellet, S., Roman, L.: "Stress electrocardiography in the diagnosis of arrhythmias." *Geriatrics* **25**: 102-107 (1970).

H31,290/70

Emotional stress precipitates arrhythmias in predisposed patients, presumably because of the release of catecholamines and cortisol.

Balážová, E., Baláž, V.: "The effect of metabolic adaptation in the heart and muscle of rats to hyperthermic stress in a water bath." *Fysiatr. Věstn.* **48**: 9-13 (1970) (28 refs., Slovak). J21,998/70

Delius, W., Kellerová, E.: "Reactions of

- arterial and venous vessels in the human forearm and hand to deep breath or mental strain." *Clin. Sci.* **40**: 271-282 (1971). J20,745/71
- Mancia, G., Baccelli, G., Zanchetti, A.: "Hemodynamic responses to different emotional stimuli in the cat: patterns and mechanisms." *Am. J. Physiol.* **223**: 925-933 (1972). H61,195/72
- Navakatikian, A. O., Kundiev, I. I., Lysina, G. G., Tomashevskaya, L. I., Derkach, V. S., Kapshuk, A. P., Kovaleva, A. I., Stanislavskaya, T. D., Osinskaia, L. S., Parliuk, A. F.: "The effect of mental work with different degrees of nervous-emotional stress on the cardiovascular system." *Kardiologiya* **13** No. 3: 50-56 (1973) (Russian). J20,555/73
- Rowell, L. B.: "Regulation of splanchnic blood flow in man." *Physiologist* **16**: 127-142 (1973). J19,556/73
- Corley, K. C., Shiel, F. O., Mauck, H. P., Greenhoot, J.: "Electrocardiographic and cardiac morphological changes associated with environmental stress in squirrel monkeys." *Psychosom. Med.* **35**: 361-364 (1973). J19,680/73
- Lirman, A. V., Bakman, S. M., Bakman, A. M.: "Electrocardiographic characteristics of stress." *Vopr. Med. Zh.* No. 8: 24-26 (1973) (Russian). J22,380/73
- Caraffa-Braga, E., Granata, L., Pinotti, O.: "Changes in blood-flow distribution during acute emotional stress in dogs." *Pflügers Arch.* **339**: 203-216 (1973). J2,392/73
- Jönsson, L., Johansson, G.: "Cardiac muscle cell damage induced by restraint stress." *Virchows Arch. [Zellpathol.]* **17**: 1-12 (1974). H99,221/74
- Obrist, P. A., Lawler, J. E., Howard, J. L., Smithson, K. W., Martin, P. L., Manning, J.: "Sympathetic influences on cardiac rate and contractility during acute stress in humans." *Psychophysiology* **11**: 405-427 (1974). J14,567/74
- Fenz, W. D., Jones, G. B.: "Cardiac conditioning in a reaction time task and heart rate control during real life stress." *J. Psychosom. Res.* **18**: 199-203 (1974). J15,137/74
- Levinsky, R. A., Lewis, R. M., Lawrie, D. J., Entman, M. L.: "The effects of coronary artery stenosis on coronary blood flow in resting and stressed dogs" (abstracted). *Clin. Res.* **22**: 284A (1974). H90,125/74
- James, F. W.: "Effects of physical stress on adolescents with normal or abnormal cardiovascular function." *Postgrad. Med.* **56**: 53-59 (1974). J18,232/74
- The cardiovascular effects of physical exercise have been studied in adolescents, "with special emphasis on the observed changes in heart rate, blood pressure, and stress electrocardiogram."
- Simonov, P. V., Frolov, M. V., Sviridov, E. P.: "Characteristics of the electrocardiogram under physical and emotional stress in man." *Aviat. Space Environ. Med.* **46**: 141-143 (1975). J22,134/75

Muscular System

[See also Bruxism, and Muscular Function under Stress Tests]

The behavior of the muscular system during stress was studied mainly in connection with the rigidity and tension developing in striated muscles under the influence of psychogenic stressors. This includes bruxism, hyperkinesia (in the form of a tendency to move about without any particular destination), violent gesticulation and even painful muscular cramps.

Muscular hyperactivity can be objectively demonstrated by the EMG and occasionally has been used as a stress test.

Since very little is known about structural changes in the musculature during stress, the few observations along these lines are arbitrarily included in this section otherwise devoted to function.

Muscular System

(See also our earlier stress monographs, p. xiii, and cf. Muscular Function under Stress Tests)

Duncan, C. H., Stevenson, I. P., Wolff, H. G.: "Life situations, emotions, and exercise tolerance." *Psychosom. Med.* **13**: 36-50 (1951). B77,470/51

"In all patients, both with and without structural heart disease, who presented complaints of exercise intolerance a significant portion of the symptomatology was dependent on anxiety, resentment, and cardiac hyperactivity incident to stressful life situations. With the achievement of a state of relative security and relaxation there was diminution in the cardiac activity at rest and improvement in exercise tolerance."

Malmo, R. B., Shagass, C., Davis, J. F.: "Electromyographic studies of muscular tension in psychiatric patients under stress." *J. Clin. Exp. Psychopathol.* **12**: 45-66 (1951). C90,082/51

Psychoneurotic and psychotic patients responded to various stressors (pain, discrimination, mirror drawing) with greater muscular tension (EMG) than did normal controls.

Perry, H. T., Lammie, G. A., Main, J., Teuscher, G. W.: "Occlusion in a stress situation." *J. Am. Dent. Assoc.* **60**: 626-633 (1960). D83,557/60

Various stress situations produce increased tension in the muscles of mastication.

Grainger, H. C.: "Psychic stress and the tonic muscle spindle." *J. Am. Coll. Neuro-psych.* **1**: 1-8 (1962). J23,789/62

Sainsbury, P.: "Muscle responses: muscle tension and expressive movement." *J. Psychosom. Res.* **8**: 179-185 (1964). G24,074/64

Heath, H. A., Oken, D., Shipman, W. G.: "Muscle tension and personality. A serious second look." *Arch. Gen. Psychiatry* **16**: 720-726 (1967). J22,684/67

Little, K. E.: "Toward more effective manipulative management of chronic myofascial strain and stress syndromes." *J. Am. Osteopath. Assoc.* **68**: 675-685 (1969).

J23,819/69

Detailed survey of the osteopathic treatment of myofascial derangements consequent to stress.

Yemm, R.: "Variations in the electrical activity of the human masseter muscle occurring in association with emotional stress." *Arch. Oral Biol.* **14**: 873-878 (1969).

J22,569/69

Yemm, R.: "Masseter muscle activity in stress: adaptation of response to a repeated stimulus in man." *Arch. Oral Biol.* **14**: 1437-1439 (1969).

J22,568/69

Ward, V. G.: "Occult mood in musculoskeletal diseases." *Postgrad. Med.* **48**: 156-160 (1970).

J21,193/70

"Emotional stress may initiate or aggravate muscular pain," especially in patients with osteoarthritis.

Lader, M. H., Mathews, A. M.: "Electromyographic studies of tension." *J. Psychosom. Res.* **15**: 479-486 (1971) (45 refs.).

J20,329/71

Yemm, R.: "A comparison of the electrical activity of masseter and temporal muscles of human subjects during experimental stress." *Arch. Oral Biol.* **16**: 269-273 (1971).

J20,749/71

Boman, K.: "Effect of emotional stress on spasticity and rigidity." *J. Psychosom. Res.* **15**: 107-112 (1971).

G82,946/71

Yemm, R.: "Comparison of the activity of left and right masseter muscles of normal individuals and patients with mandibular dysfunction during experimental stress." *J. Dent. Res.* **50**: 1320-1323 (1971).

J19,856/71

In patients under psychogenic stress, EMGs showed similar patterns on left and

right masseter muscles, despite tenderness in only one of them. It is suggested that "stress-induced muscle activity is a contributory factor in the etiology of mandibular dysfunction."

Wesemeier, H., Bergmann, V.: "Elektronenmikroskopische Untersuchungen am Musculus longissimus dorsi bei Fleischschweinen nach experimenteller Belastung" (Examination by electron microscopy of the longissimus dorsi muscle in meat pigs subjected to experimental stress). *Arch. Exp. Vet. Med.* **26**: 477-490 (1972). J20,225/72

EM changes in the skeletal musculature of pigs exposed to forced exercise, heat, or hemorrhage. Abnormalities in mitochondria, sarcoplasmic reticulum, and ground substance "were regularly found in individual pigs after each exposure to stress; they

evidently represent a faulty individual adaptation to stress situations."

Vecchiet, L., Dolce, V., Fini, F., Branzi, G. C.: "On the muscular pain in the stress trials." *J. Sports Med. Phys. Fitness* **13**: 26-31 (1973). J11,168/73

In healthy young subjects, muscular work of a certain intensity always causes pain, and "the Authors believe that the painful sensation produced by stresses is a constant symptom with well-defined characteristics." [The fact that no other stressor was tested suggests that they were dealing with a specific effect (H.S.).]

Vinogradova, O. L., Kotz, J. M., Rodionov, L. M.: "Experimental analysis of the causes of increase in the muscle endurance during emotional stress." *Fiziol. Zh. SSSR* **60**: 321-328 (1974) (Russian). J23,153/74

Blood Coagulation

The earliest experiments of Cannon showed that fear, rage, asphyxia and pain cause a discharge of EP, and like the injection of EP itself, they accelerate blood coagulation.

Since that time, much work has been done to explore the effect of stress upon the blood clotting mechanism. Undoubtedly, stress can enhance blood coagulation and this effect is usually held responsible for stress-induced coronary thromboses. However, fibrinolysis is also accelerated after surgery or even by anxiety during the preoperative period. An increased fibrinolytic activity has also been observed in human blood after stressful muscular exercise, emotional arousal or exposure to heat.

In rabbits, a curious syndrome of "hemorrhagic death" occurs with application of stressors following treatment with indirect anticoagulants (dicumarol, phenylindandione) but not after treatment with heparin. In themselves, alleged stressors (electric shocks, high-pitched sound) cause no change in the coagulation system of the rabbit, although they do increase prothrombin time in rats.

In a large group of accountants, an acceleration of blood clotting consistently occurred at the time of maximum occupational stress, that is, when tax reports became due.

In man, various surgical operations and other traumatic injuries enhance thrombocyte aggregation; this may be another factor predisposing to thromboembolism or disseminated intravascular coagulation. The stress-induced increase in FFA may also play a role in this response. However, hyperventilation and some other stressors allegedly cause a decrease in platelet aggregation.

ADP-induced platelet aggregation in rats was markedly delayed during the first hours after scalds, concurrently with a transient appearance of a plasma inhibitor. Such changes may contribute to the hypercoagulability that is characteristic of burned or traumatized patients.

Some systematic studies have dealt with the effect of stress upon individual blood coagulation factors but these data are too complex to be discussed here and will have to be looked up in the original literature.

Blood Coagulation

(See also our earlier stress monographs, p. xiii)

Cannon, W. B.: "The stimulation of adrenal secretion by emotional excitement." *Proc. Am. Phil. Soc.* **1**: 226-227 (1911).

35,529/11

Cannon, W. B.: "The emergency function of the adrenal medulla in pain and the major emotions." *Am. J. Physiol.* **33**: 356-372 (1914).
57,873/14

Review on the earliest animal experiments showing that fear, rage, asphyxia and pain cause a discharge of EP from the adrenal medulla, and that this response is mediated through the splanchnic nerves. Direct stimulation of the latter exerts the same effect. The resulting glycogenolysis and increase in blood sugar furnish energy. At the same time, blood circulation is improved. Stimulation of the splanchnics also hastens blood coagulation and thereby protects against bleeding in the event of injury. All these changes are "directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve."

Macfarlane, R. G., Biggs, R.: "Observations on fibrinolysis. Spontaneous activity associated with surgical operations, trauma, &c." *Lancet* December 14, 1946, pp. 862-864.
B26,947/46

In man, fibrinolysis occurs not only after surgery but even during the preoperative period, presumably under the influence of anxiety and drug treatment. "The activation of the proteolytic system of normal blood, almost certainly responsible for the phenomenon of fibrinolysis, may be a part of the 'alarm reaction' of Selye."

Latner, A. L.: "Anxiety as a cause of fibrinolysis." *Lancet* February 1, 1947, pp. 194-195.
B26,725/47

Various stressors, particularly anxiety, anesthesia and surgery, increase the fibrinolysin content of the blood and produce fibrinolysis.

Schneider, R. A.: "The relation of stress to clotting time, relative viscosity and certain other biophysical alterations of the blood in

the normotensive and hypertensive subject." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 818-831. Baltimore: Williams & Wilkins, 1950.

B51,946/50

Review of the literature on the shortening of blood clotting time and the associated biophysical alterations caused by physical exercise or stress interviews. These changes occur in normotensive people only when pressor responses are manifest during stress and appear to be related to the rise in blood pressure. Normally, this response is useful in that it shortens bleeding from wounds sustained in combat, but in hypertensive subjects it may predispose to coronary or cerebral thromboses.

Schneider, R. A., Zangari, V. M.: "Variations in clotting time, relative viscosity, and other physicochemical properties of the blood accompanying physical and emotional stress in the normotensive and hypertensive subject." *Psychosom. Med.* **13**: 290-303 (1951).

B62,983/51

Review of the blood clotting changes induced in normotensive and hypertensive individuals by various stressors (30 refs.).

Dreyfuss, F.: "Coagulation time of the blood, level of blood eosinophils and thrombocytes under emotional stress." *J. Psychosom. Res.* **1**: 252-257 (1956). C26,923/56

In medical students during final examinations, eosinopenia and accelerated blood clotting were not accompanied by significant variations in the platelet count.

Jaques, L. B., Mogenson, G. J., Fisher, L. M.: "The relation of stress to hemorrhage and prothrombin time following anticoagulants." *Trans. R. Soc. Can.* **50** Sect. V: 9-16 (1956).
C28,187/56

In rabbits a high incidence of hemorrhagic death occurs after exposure to stressors together with indirect anticoagulants (dicumarol, phenindione) but not after treatment with heparin. In themselves, stressors (electric stimulation, high-pitched sound) cause no change in the coagulation system of the rabbit, but they do increase prothrombin time in rats.

Friedman, M., Rosenman, R. H., Carroll,

V.: "Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress." *Circulation* **17**: 852-861 (1958).

C56,083/58

In a large group of accountants, "each subject's highest serum cholesterol consistently occurred during severe occupational or other stress, and his lowest at times of minimal stress. The results could not be ascribed to any changes of weight, exercise, or diet. Marked acceleration of blood clotting time consistently occurred at the time of maximum occupational stress, in contrast to normal blood clotting during periods of respite."

Friedman, M., Uhley, H. N.: "Role of the adrenal in hastening blood coagulation after exposure to stress." *Am. J. Physiol.* **197**: 205-206 (1959). C71,261/59

In rats, repeated electroshocks caused depletion of adrenal cholesterol and acceleration of blood clotting time. The latter was not affected by adrenalectomy.

Sawyer, W. D., Fletcher, A. P., Alkjaersig, N., Sherry, S.: "Studies on the thrombolytic activity of human plasma." *J. Clin. Invest.* **39**: 426-434 (1960). J11,002/60

In man, such stressors as muscular exercise or emotional arousal enhance thrombolytic activity.

Ogston, D., McDonald, G. A., Fullerton, H. W.: "The influence of anxiety in tests of blood coagulability and fibrinolytic activity." *Lancet* September 15, 1962, pp. 521-523. D32,583/62

In man, minor degrees of anxiety decreased recalcified-plasma clotting time and increased fibrinolytic activities.

Bedrak, E., Beer, G., Furman, K. I.: "Fibrinolytic activity and heat stress." *Isr. J. Exp. Med.* **11**: 1-6 (1963). G9,119/63

"Single acute exposures of normal resting men to environmental heat stress without physical activity caused increased fibrinolytic activity in both whole blood and plasma systems. With more prolonged heat stress exposures, proportionately greater activity was observed in the whole blood system." The literature on fibrinolytic activity after application of various stressors is reviewed.

Chubaty, W. M., Jaques, L. B.: "Non-specific resistance in spontaneous hemorrhage." *Can. J. Biochem.* **41**: 1079-1080 (1963). D62,264/63

Gabbiani, G.: "Sensitization by stress for renal lesions resembling those of generalized Schwartzman phenomenon." *Med. Exp. (Basel)* **11**: 209-216 (1964). G11,111/64

Aleksandrowicz, J. W., Dzikowski, H., Schiffer, Z.: "Effect of mental stress on blood coagulation." *Pol. Med. Sci. Hist. Bull.* **7**: 103-104; 112 (1964). G19,178/64

Hardaway, R. M., Johnson, D. G., Houchin, D. N., Jenkins, E. B., Burns, J. W., Jackson, D. R.: "Influence of stress on fibrinogen." *J. Trauma* **4**: 673-676 (1964). G32,926/64

In dogs, various stressors elevate the blood fibrinogen level.

Jaques, L. B.: "Stress and multiple-factor etiology of bleeding." *Ann. N.Y. Acad. Sci.* **115**: 78-96 (1964). F16,537/64

Patsch, J.: "Konstitution, Stress und Blutgerinnung" (Constitution, stress and blood coagulation). *Wien Med. Wochenschr.* **114**: 457-459 (1964). F15,289/64

In patients belonging to various constitutional types and having differently formed Turkish saddles, the effect of stressors (noise, cold) upon blood coagulation varies in an allegedly predictable manner.

Lucas, O. N., Millar, G. J., Jaques, L. B.: "Experimental hemorrhage due to stress followed by anticoagulant in rats: lack of protection by CNS depressants." *Acta Physiol. Lat. Am.* **15**: 285-291 (1965). G36,024/65

Gabbiani, G., Selye, H., Tuchweber, B.: "Adrenal localization of a thrombohemorrhagic phenomenon." *Endocrinology* **77**: 177-182 (1965). G19,450/65

In rats pretreated with ACTH, glucocorticoids or restraint, a single intravenous injection of thorium dextrin (an RES-blocking agent) produces thrombohemorrhagic necrosis of the adrenals and liver resembling the Schwartzman-Sanarelli phenomenon.

Cittadini, G., Luppino, V., Tomiselli, G.: "Stress da freddo e coagulazione del sangue nel topo albino" (Stress caused by cold and blood coagulation in albino mice). *Boll. Soc. Ital. Biol. Sper.* **41**: 1157-1159 (1965). G36,891/65

McKenzie, J. M., Celander, D. R., Guest, M. M.: "Fibrinogen destruction in the cadaver: effects of antemortem stress and inhibitors." *Am. J. Physiol.* **208**: 1009-1015 (1965). F39,459/65

In dogs, postmortem loss of fibrinogen is normal, but antemortem stress involving little or no tissue trauma may cause postmortem coagulation of the blood.

Fessel, W. J.: "Dextran turbidity: acute distress-phase reaction." *Nature* **205**: 771-773 (1965). F32,709/65

Among patients treated for various types of psychogenic stress, heavy turbidity in the plasma occurs after additional dextran therapy. This response can also be induced experimentally by exposing subjects to stressful mental experiences. "The presence of so much fibrinogen in the precipitate suggests the possibility that the increased levels of dextran turbidity in mental disease and emotional stress result from activation of various serum enzyme systems which cause changes in the internal structure of blood proteins. Plasmin, which affects the fibrinogen molecule, is activated by various agents including emotional stress, physical stress, adrenal steroids, adrenaline, acetylcholine and histamine, and some evidence suggests that plasmin may be under reflex control. Other serum enzymes are also activated by stress, which is known to influence a variety of blood proteins" (20 refs.).

Latour, J. G., Renaud, S.: "Blood platelet fluctuation consecutive to trauma and surgical intervention in the rat, a possible stress effect." *Can. J. Physiol. Pharmacol.* **44**: 581-588 (1966). F68,011/66

It has repeatedly been observed in man that, following surgical interventions, thrombocytopenia occurs during the first two days and thrombocytosis after five to eight days. These changes have now been reproduced in the rat by various stressors, and are therefore ascribed to stress itself.

Shadomy, S., Zeiger, E.: "Demonstration of a hemorrhagic vascular factor in sera from stressed animals." *Am. J. Physiol.* **210**: 838-846 (1966). F63,564/66

Renaud, S., Latour, J. G.: "Role of the pituitary-adrenocortical system in the stress-induced blood platelet fluctuation." *Can. J. Physiol. Pharmacol.* **44**: 589-596 (1966). F68,012/66

Murray, R. H.: "Effects of thermal transients to 205°C on blood coagulation and clot lysis." *J. Appl. Physiol.* **21**: 1218-1222 (1966). G55,628/66

In man, "there was significant enhancement of fibrinolytic activity following the

heat stress, explaining delayed bleeding episodes following earlier exposures in this environment."

Nikolaeva, L. F.: "The alteration of thrombogenetic properties of the blood in repeated reproduction of stress in rabbits." *Kardiologiya* **7** No. 1: 21-24 (1967) (Russian). J23,748/67

Cash, J. D., Allan, A. G. E.: "Effect of mental stress on the fibrinolytic reactivity to exercise." *Br. Med. J.* May 27, 1967, pp. 545-548. F80,143/67

Beard, E. L., Busuttil, R. W., Gottschalk, S. K.: "Stress induced release of plasminogen activator from lysosomes." *Thromb. Diath. Haemorrh.* **21**: 20-25 (1969). H9,860/69

Klement, A. A., Portnoi, M. V., Vedenskii, A. N.: "Surgical treatment of thrombosis due to physical stress (the Paget-Schroetter syndrome)." *Vestn. Khir.* **103** No. 11: 75-80 (1969) (Russian). J21,847/69

Maliugina, I. B.: "Fibrinolytic activity of tissues in a formalin-induced 'stress' reaction." *Farmakol. Toksikol.* **33**: 441-443 (1970) (Russian). J20,642/70

Deriagina, G. P.: "Effect of emotional stress on indices of blood coagulation, lipid metabolism and functional state of the adrenal glands in healthy persons and in patients with ischemic heart disease." *Kardiologiya* **11** No. 7: 42-46 (1971) (Russian). J21,257/71

Kudriashov, B. A., Bazaian, G. G., Liapina, L. A., Syshina, N. P.: "Restriction of epinephrine-heparin and fibrinogen-heparin complex formation under stress conditions in the blood of animals maintained on an atherogenic diet." *Kardiologiya* **11** No. 10: 58-65 (1971) (Russia). J20,546/71

Chattopadhyay, S., Johnson, D. D., Millar, G. J., Jaques, L. B.: "The effect of stress and warfarin on the adrenal gland in relation to spontaneous hemorrhage, as judged by measurement of adrenal ascorbic acid and serum corticosterone." *Thromb. Diath. Haemorrh.* **26**: 275-288 (1971). H50,193/71

Landaburu, R. H., Castellanos, D. E., Giavedoni, E., Presti, C. A. lo: "Neurohumoral control of blood coagulation. I. Effects of adrenergic drugs or ACTH administration and stress." *Acta Physiol. Lat. Am.* **21**: 64-73 (1971). G91,199/71

In rats, "hypercoagulation due to stress or adrenergic stimulation appears to occur with participation of the central nervous system and hypophysis. Both effects are eliminated by hypophysectomy. However, no suppressive effect is obtained by adrenalectomy."

Mannucci, P. M., Ruggeri, Z. M., Gagnatelli, G.: "Nervous regulation of factor-VIII levels in man." *Br. J. Haematol.* **20**: 195-207 (1971). J20,543/71

Kudriashov, B. A., Bazaian, G. G., Liapina, L. P.: "Non-enzymatic fibrinolytic activity of the plasma of animals under chronic stress." *Kardiologija* **12** No. 10: 100-104 (1972) (Russian). J20,553/72

Engquist, A., Winther, O.: "Variations of plasma cortisol and blood fibrinolytic activity during anaesthetic and surgical stress." *Br. J. Anaesth.* **44**: 1291-1297 (1972).

J672/72

In man, during thirty to ninety-three minutes of "surgical stress, enhancement of fibrinolysis was significantly correlated with an increase of plasma cortisol levels."

Ruxin, R. L., Bidder, T. G., Agle, D. P.: "The influence of autonomic arousal on blood clotting time in patients receiving electroconvulsive treatments." *J. Psychosom. Res.* **16**: 185-192 (1972). J19,669/72

In patients, electroconvulsive treatments raised plasma FFA, but the observations "do not support previous reports demonstrating a direct relationship between arousal and decreased clotting time. Furthermore, they provide no evidence for the hypothesis that emotional factors may influence the pathogenesis of vascular disease or play a part in hemostasis during stress through changes in blood coagulability" (37 refs.).

Zwiener, U., Hindersin, P.: "Die Wirkung von Schmerzreizen auf die Fibrinolyse- und Gerinnungsaktivität postoperativ und bei erhöhter immunologischer Abwehrlage" (The effect of pain on fibrinolysis and coagulation activity after surgery and during increased immunologic defense reactions). *Folia Haematol. (Leipz.)* **98**: 330-337 (1972).

J7,670/72

It is now well established that the most diverse stressors can influence fibrinolytic activity. In rabbits exposed to surgery, "psychic factors of stress only cause inconstant, weak and short-time increases of fibrinolysis as in healthy animals, however they seem to

be able to induce a total plasmalysis when an increased postoperative tendency for fibrinolysis exists. Even increased immunological defense reactions are connected with a significantly higher tendency of fibrinolysis without total plasmalysis occurring here after pain stimulation."

Larcan, A., Stoltz, J. F., Voiry, A. M., Streiff, F.: "Modifications of the electric charge of platelets during various medical stresses." *Acta Univ. Carol. [Med. Monogr.] (Praha)* **53-54**: 455-459 (1972).

H86,544/72

"The electrophoretic mobility of platelets during certain stresses (infarction, arterial thrombosis, endotoxic shock, acute hemolysis) is markedly decreased."

Zwiener, U., Hindersin, P.: "Zur Dynamik von Veränderungen in der fibrinolytischen Plasmaaktivität nach Schmerzreizung" (Painful stimuli causing changes in the fibrinolytic activity of plasma). *Folia Haematol. (Leipz.)* **98**: 322-329 (1972).

H79,337/72

In rabbits, strong painful stimuli often cause acute short-term increases in fibrinolytic activity, with a subsequent drop below the initial values. Similar changes have previously been noted after exposure to other stressors (37 refs.).

Lasierra, J., Ferreira, I. J., Mostacero, C., Viladés, E.: "Changes in platelet aggregation during voluntary hyperventilation." *Rev. Esp. Fisiol.* **28**: 255-259 (1972).

H79,324/72

During respiratory alkalosis induced by voluntary hyperventilation in man, there is a decrease of platelet aggregation. Since various stressors, including anxiety, exert similar effects, the authors "are tempted to see in the decrease of platelet aggregation during respiratory alkalosis a physiological and defence response... [which] ...may be considered as a way to protect somehow the subject from the risk of thrombosis."

Rompel, K., Pfeiffer, H., Höbel, W., Heene, D. L.: "Gerinnungsveränderungen nach akuten apoplektischen Insulten" (Coagulation changes after acute apoplectic strokes). *Med. Klin.* **68**: 1729-1732 (1973).

H81,159/73

After acute apoplectic strokes, the resulting "hyperfibrinogenemia is possibly caused by the unspecific stress situation."

Stremmel, W.: "Stressinduzierte Stoffwechselveränderungen und gesteigerte Throm-

bozyten-Aggregation nach Operationen und Traumen" (Stress-induced metabolic changes and enhanced thrombocyte aggregation after surgery and trauma). *Münch. Med. Wochenschr.* **115**: 416-421 (1973). H68,723/73

In man, various surgical operations and other traumatic injuries enhance thrombocyte aggregation and may cause postoperative thromboembolism or disseminated intravascular coagulation. The stress-induced increase in FFA may play a role in this response (40 refs.).

Uzhanskii, I. G.: "Stress and hemolysis." *Probl. Gemat. Pereliv. Krovi* **18** No. 11: 13-15 (1973) (Russian). J24,004/73

Haft, J. I., Fani, K.: "Intravascular platelet aggregation in the heart induced by stress." *Circulation* **47**: 353-358 (1973). G99,534/73

In rats, immersion in cold water causes platelet aggregation in myocardial vessels, as shown by EM. "It is concluded that stress, probably via catecholamine secretion that enhances platelet stickiness, can induce intravascular platelet aggregation. It is possible that this mechanism plays a part in the relationship between stress and acute clinical myocardial infarction."

Chernigovskaya, S. V., Cherkovich, G. M., Uzunyan, L. A.: "Effect of emotional stress on blood-clotting system indices in monkeys." *Bull. Éksp. Biol. Med.* **75** No. 3: 29-32 (1973) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **75**: 250-253 (1973).

H92,268/73

"Prolonged emotional stress causes a marked rise in the blood fibrinogen level of healthy monkeys and of monkeys fed for a long time (3 years) with cholesterol."

Gordon, J. L., Bowyer, D. E., Evans, D. W., Hutchinson, M. J.: "Human platelet reactivity during stressful diagnostic procedures." *J. Clin. Pathol.* **26**: 958-962 (1973). H83,536/73

In conscious patients, cardiac catheterization and other stressful procedures caused a rise in the platelet aggregation response to ADP, with a concurrent increase in plasma FFA. "It is suggested that catecholamines released due to emotional stress may be responsible for the increased platelet responses to ADP and that this could influence the development of thrombosis and atherosclerosis."

Landaburu, R. H., Castellanos, D. E.: "Further evidence for a humoral control of

factor VIII plasma levels." *Thromb. Diath. Haemorrh.* **30**: 460-470 (1973).

H85,654/73

Review of the literature and personal observations on the effect in various species of stressors and EP upon blood clotting, and particularly the factor VIII plasma level.

Jaques, L. B.: "Spontaneous hemorrhage and stress." *Clin. Sci.* **10**: 171-187 (1973).

H82,949/73

In rabbits, commonly employed doses of phenindione and other anticoagulants produced no sign of hemorrhage, and the same was true of a number of stressors (insulin, hypertonic sodium chloride, nervous stimuli and so on) when given alone. However, when the anticoagulants were administered after the stressors, extensive hemorrhages and mortality developed. This "hemorrhage syndrome meets Selye's major criterion for stress, namely 'nonspecificity.'" In fact, the author states that this "hemorrhage syndrome was found by us to provide a quantitative objective assessment of severe stress in animals" (15 refs.).

Maass, B., Jacobi, E., Esser, G.: "Thrombozytenadhäsivität unter Lärmeinwirkung" (Noise affecting thrombocyte adhesiveness). *Dtsch. Med. Wochenschr.* **98**: 2153-2155 (1973).

H78,870/73

Various forms of auditory stress increase thrombocyte adhesiveness and thereby may predispose to thrombosis in man (27 refs.).

Metze, R., Linke, P.-G., Hoffmann, H.-D.: "Veränderungen des Blutgerinnungssystems bei Belastung" (Changes in blood coagulation under stress). *Med. Sport* **13**: 284-289 (1973).

J15,365/73

Both physical and psychogenic stressors, which stimulate the sympathetic nervous system, cause an activation of the clotting and fibrinolytic processes in man (38 refs.).

Haft, J. I., Fani, K.: "Stress and the induction of intravascular platelet aggregation in the heart." *Circulation* **48**: 164-169 (1973).

J5,700/73

In rats, NEP and various stressors enhance intravascular platelet aggregation and may thereby predispose to myocardial infarction (36 refs.).

Jacey, M. J., Madden, R. O., Tappan, D. V.: "Hemostatic alterations following severe dysbaric stress." *Aerosp. Med.* **45**: 1062-1066 (1974).

J16,190/74

In rats, "acute decompression stress pro-

duced a transient decrease in clotting time. Circulating platelet population was unchanged during the early phase of recovery from severe decompression but had declined significantly by 2 d post-surfacing and then returned to control levels by the end of the observation period. Associated with the thrombocytopenic episode was a tendency toward platelet aggregation." A significant hyperfibrinogenemia developed on the day after the "dysbaric stress," with subsequent normalization. Alterations in prothrombin time or partial thromboplastin time were not found (24 refs.).

Egan, E. L., Bowie, E. J. W., Kazmier, F. J., Gilchrist, G. S., Woods, J. W., Owen, C. A. Jr.: "Effect of surgical operations on certain tests used to diagnose intravascular coagulation and fibrinolysis." *Mayo Clin. Proc.* **49**: 658-664 (1974) (66 refs.).

H93,315/74

Casellas, E., Smith, L., D'Aoust, B. G.: "Effects of stress on salmonid blood clotting mechanisms" (abstracted). *Physiologist* **17**: 371 (1974). H89,978/74

Ferguson, E. W., Guest, M. M.: "Exercise, physical conditioning, blood coagulation and fibrinolysis." *Thromb. Diath. Haemorrh.* **31**: 63-71 (1974). H87,867/74

In healthy young men, "immediately after exercise, a marked increase in fibrinolytic activity and an acceleration of most clotting assays were observed. After physical conditioning there was a decrease in the level of fibrinolytic activity at rest and after exercise, but the reactivity of the fibrinolytic system, i.e., the percent increase in fibrinolytic activity in response to exercise, was unaltered. Following physical conditioning, the clotting times of certain assays were less accelerated."

Britton, B. J., Hawkey, C., Wood, W. G., Peele, M.: "Stress. A significant factor in venous thrombosis?" *Br. J. Surg.* **61**: 814-820 (1974). H95,489/74

Herman, C. M., Oshima, G., Erdös, E. G.: "The effect of adrenocorticosteroid pretreatment on kinin system and coagulation response to septic shock in the baboon." *J. Lab. Clin. Med.* **84**: 731-739 (1974) (40 refs.).

J18,036/74

Pina-Cabral, J. M., Rodrigues, C.: "Blood catecholamine levels, factor VIII and fibrinolysis after therapeutic electroshock." *Br. J. Haematol.* **28**: 371-380 (1974).

J18,676/74

Observations on patients undergoing therapeutic electroshock "suggest that while catecholamines are probably not responsible for plasminogen activator release during stress, adrenergic mediation of the concomitant increase in factor VIII is highly probable."

Teshima, H., Inoue, S., Ago, Y., Ikemi, Y.: "Plasminic activity and emotional stress." *Psychother. Psychosom.* **23**: 218-228 (1974).

J16,685/74

Angioneurotic or Quincke's edema often occurs immediately after psychogenic stress. This may be related to increased plasmin activity, found in animals following exposure to various stressors or EP.

Eurenius, K., Rothenberg, J.: "Platelet aggregation after thermal injury." *J. Lab. Clin. Med.* **83**: 355-363 (1974).

J10,809/74

As judged by ADP-induced platelet aggregation in rats, platelet function was markedly depressed during the first hours after scalds, with the concurrent transient appearance of a plasma inhibitor. These changes may contribute to the "hypercoagulability" frequently described in burned or traumatized patients (37 refs.).

Letheby, B. A., Davis, R. B., Larsen, A. E.: "The effect of major surgical procedures on plasma and platelet levels of factor XIII." *Thromb. Diath. Haemorrh.* **31**: 20-29 (1974). H87,866/74

Immunology

Some thirty years ago a great deal was written about the "anamnestic reaction" (reaction of recalling, defined as the enhancement of antibody titer) which follows treatment with a variety of stressors or glucocorticoids in previously immunized ani-

mals. It coincides with lymphopenia and may reflect the liberation of antibodies from disintegrating lymphocytes.

Although little subsequent work has been done to clarify the mechanism and the significance of this reaction, a good deal of evidence has been adduced to show that stress does affect a number of immune responses. It appears to increase resistance to passive anaphylaxis but only in the presence of the adrenals or upon glucocorticoid treatment of adrenalectomized animals (for instance, mice).

Various immune reactions (for example, those responsible for skin homograft rejection) are inhibited by stress, presumably owing to the production of immunosuppressive glucocorticoids. However, susceptibility to poliomyelitis virus, murine sarcoma virus, Coxsackie virus, vesicular stomatitis virus and various bacteria is enhanced.

The increased susceptibility of mice to vesicular stomatitis and polio viruses induced by sound stress may be due to a concurrent inhibition of interferon production.

Some observations suggest that the effect of stressors and glucocorticoids upon immune responses is mediated through "suppressor T-cell" activity. In the bones, stress inhibits thymidin incorporation into T-cell and B-cell-mitogen stimulated lymphocytes, and this suppression can be further accentuated by glucocorticoids. However, T-cells, which are directly concerned with cell-mediated immunity, are more readily inhibited by glucocorticoids than are B-cells, which control humoral antibody production. Hence, the immunosuppressive effect of stress and glucocorticoids is probably one of the characteristic consequences of thymic lymphatic involution and lymphopenia which have long been recognized as typical stress effects.

Immunology

(See also our earlier stress monographs, p. xiii, and cf. the section on Glycoproteins)

Long, C. N. H.: "Recent studies on the function of the adrenal cortex." *Bull. N.Y. Acad. Med.* **23**: 260-282 (1947).

B35,087/47

Review of the literature and personal observations concerning the lymphopenia and the "anamnestic reaction" produced by stressors and corticoids.

Teodori, C. V., Shwartzman, G.: "Endocrine factors in pathogenesis of experimental poliomyelitis in hamsters. Role of inoculatory and environmental stress." *Proc. Soc. Exp. Biol. Med.* **91**: 181-187 (1956).

J15,624/56

In hamsters, susceptibility to inoculation with poliomyelitis virus is greatly influenced by various stressors (20 refs.).

Rasmussen, A. F. Jr., Marsh, J. T., Brill, N. Q.: "Increased susceptibility to herpes simplex in mice subjected to avoidance-learn-

ing stress or restraint." *Proc. Soc. Exp. Biol. Med.* **96**: 183-189 (1957) (12 refs.).

C42,309/57

Rasmussen, A. F. Jr., Spencer, E. S., Marsh, J. T.: "Decrease in susceptibility of mice to passive anaphylaxis following avoidance-learning stress." *Proc. Soc. Exp. Biol. Med.* **100**: 878-879 (1959). C67,867/59

Mice subjected to "avoidance-learning stress" in a shuttlebox became unusually resistant to passive anaphylactic shock.

Johnsson, T., Lavender, J. F., Marsh, J. T.: "The influence of avoidance-learning stress on resistance to Coxsackie virus in mice" (abstracted). *Fed. Proc.* **18**: 575 (1959). C66,433/59

Luca, R. de, Caruso, P.: "Modificazioni del lisozima serico e della properdina dopo eletroshock" (Modifications of the serum lysozyme and properdin content after electroshock). *First Symp. Internaz. Lisozima*, pp. 3-5. Milan, April, 1959. D16,164/59

In five patients, the serum properdin values rose during the first two hours following electroshock and then returned to normal,

whereas the lysozyme concentration increased up to twenty-four hours and longer.

Wistar, R. Jr., Hildemann, W. H.: "Effect of stress on skin transplantation immunity in mice." *Science* **131**: 159-160 (1960).

C79,322/60

In mice the stress induced by chronic avoidance-learning moderately but significantly depressed the immune reaction responsible for skin homograft rejection (shuttlebox technique).

Hagiwara, M.: "Effects of stress on the experimental herpes simplex of rabbit's cornea." *Acta Soc. Ophthalmol. Jap.* **65**: 1117-1128 (1961) (Japanese).

E86,592/61

In rabbits, various stressors diminish resistance to a herpes virus inoculated into the cornea.

Enerbäck, L., Lundin, P. M., Mellgren, J.: "Pituitary hormones elaborated during stress. Action on lymphoid tissues, serum proteins, and antibody titres." *Acta Pathol. Microbiol. Scand.* **51** Supp. 144: 141-144 (1961).
J23,262/61

Brief review of the role played by the G.A.S. in immune reactions.

Gourwitch, G., Klimentova, A., Kocorine, I.: "La réaction plasmocytaire dans le syndrome général de l'adaptation" (The plasmocytic reaction in the general adaptation syndrome). *Rev. Can. Biol.* **20**: 805-811 (1961).
J22,947/61

Treadwell, P. E., Rasmussen, A. F. Jr.: "Role of the adrenals in stress induced resistance to anaphylactic shock." *J. Immunol.* **87**: 492-497 (1961).
D11,452/61

In mice, shuttlebox stress increased resistance to passive anaphylaxis but only in the presence of the adrenals. Cortisol restored this response in adrenalectomized mice and increased the effect of stress above normal in intact controls (17 refs.).

Luca, R. de, Caruso, P., Bombara, G., Morabito, D.: "Sul comportamento di taluni sistemi immunitari naturali in corso di sindrome generale di adattamento. Nota I" (On the behavior of some natural immunity systems in the general adaptation syndrome. Note I). *Boll. Soc. Ital. Biol. Sper.* **37**: 33-36 (1961).
D60,016/61

Review and personal observations on the relationship between immunity and the G.A.S.

Luca, R. de, Caruso, P., Bombara, G., Morabito, D.: "Sul comportamento di taluni sistemi immunitari naturali in corso di sindrome generale di adattamento. Nota II" (On the behavior of some natural immunity systems in the general adaptation syndrome. Note II). *Boll. Soc. Ital. Biol. Sper.* **37**: 36-38 (1961).
D16,165/61

In rats exposed to cold, the blood properdin levels dropped considerably with the concurrent development of other typical alarm reaction manifestations.

Luca, R. de, Caruso, P., Bombara, G., Morabito, D.: "Sul comportamento di taluni sistemi immunitari naturali in corso di sindrome generale di adattamento. Nota III" (On the behavior of some natural immunity systems in the general adaptation syndrome. Note III). *Boll. Soc. Ital. Biol. Sper.* **38**: 38-40 (1961).
D60,134/61

Levine, S., Strelbel, R., Wenk, E. J., Harman, P. J.: "Suppression of experimental allergic encephalomyelitis by stress." *Proc. Soc. Exp. Biol. Med.* **109**: 294-298 (1962).
D23,507/62

Various stressors, particularly restraint, suppressed allergic encephalomyelitis in rats.

Chiovato, I.: "Stress e poteri immunitari. Comportamento del potere fagocitario nello shock da eviscerazione" (Stress and immunologic capacity. Behavior of the phagocytic capacity in the shock of evisceration). *Rass. Med. Sper.* **9**: 70-73 (1962).
J23,139/62

Alexander, C.: "Stress, immunity and the thymus." *N.Z. Med. J.* **61**: 274-278 (1962) (18 refs.).
J23,212/62

Fessel, W. J.: "Mental stress, blood proteins, and the hypothalamus." *Arch. Gen. Psychiatry* **7**: 427-435 (1962). D69,380/62

Review of the literature on alterations in blood proteins with accelerated blood clotting time in man under the influence of various emotional and physical stressors. The diencephalon and hypothalamus affect blood proteins in immunologic mechanisms. In the present experiments on man, severe mental stress was noted to cause a rise in 4S and 19S class serum proteins. "It is speculated that functional behavior disturbances are but one expression of a general metabolic disorder which is contributed to by the effects of both stress and hypothalamic-hypophyseal action" (61 refs.).

- Rasmussen, A. F., Hildemann, W. H., Sellers, M.: "Malignancy of polyoma virus infection in mice in relation to stress." *J. Natl. Cancer Inst.* **30**: 101-112 (1963). D57,134/63
- Stress caused by avoidance learning or high frequency sound had no significant effect upon the development of malignant tumors in mice infected with polyoma virus.
- Johnsson, T., Lavender, J. F., Hultin, E., Rasmussen, A. F. Jr.: "The influence of avoidance-learning stress on resistance to Coxsackie B virus in mice." *J. Immunol.* **91**: 569-575 (1963). G37,497/63
- Mice inoculated with Coxsackie B1 virus became particularly susceptible to infection during avoidance learning stress. Furthermore, "a significantly higher virus titer could be demonstrated in the pancreas, liver, heart and muscle of stressed mice as compared to unstressed mice."
- Marsh, J. T., Lavender, J. F., Chang, S. S., Rasmussen, A. F.: "Poliomyelitis in monkeys: decreased susceptibility after avoidance stress." *Science* **140**: 1414-1415 (1963). D69,198/63
- In *M. cynomolgus* monkeys, "avoidance stress" prior to inoculation with type I poliovirus protected against the fatal effect of the infection. The circulating lymphocytes decreased significantly during stress. These findings contrast sharply with earlier observations in which stressors diminished the resistance of mice to virus infection. However, the schedule of exposure to stress may be important (10 refs.).
- Jensen, M. M., Rasmussen, A. F.: "Stress and susceptibility to viral infections. II. Sound stress and susceptibility to vesicular stomatitis virus." *J. Immunol.* **90**: 21-23 (1963). D54,098/63
- Mice exposed to the stress of high intensity sound for three hours became especially susceptible to vesicular stomatitis virus. "The same was true after adrenalectomy as long as inoculation occurred before stress. Mice inoculated after stress became more resistant to the virus than the control."
- Heiskala, H., Heiskala, M.: "The effect of excessive sensory stimulation on experimentally induced tuberculosis." *Acta Tuberc. Pneumol. Scand.* **43**: 59-67 (1963). E27,288/63
- In guinea pigs infected with tuberculosis, the stress of auditory stimulation aggravates the course of the disease (17 refs.).
- Bauer, H., Horowitz, R. E., Watkins, K. C., Popper, H.: "Immunologic competence and phagocytosis in germfree animals with and without stress." *J.A.M.A.* **187**: 715-718 (1964). F2,297/64
- Yamada, A., Jensen, M. M., Rasmussen, A. F. Jr.: "Stress and susceptibility to viral infections. III. Antibody response and viral retention during avoidance learning stress." *Proc. Soc. Exp. Biol. Med.* **116**: 677-680 (1964). F17,038/64
- In mice the stressor effect of avoidance learning caused no difference in the immune response to vesicular stomatitis virus, but disappearance of the virus from the site of inoculation was significantly retarded.
- Friedman, S. B., Ader, R., Glasgow, L. A.: "Effects of psychological stress in adult mice inoculated with Coxsackie B viruses." *Psychosom. Med.* **27**: 361-368 (1965). J15,626/65
- In mice exposed to various environmental stressors, susceptibility to infection with Coxsackie B2 virus was greatly increased.
- Johnsson, T., Rasmussen, A. F. Jr.: "Emotional stress and susceptibility to poliomyelitis virus infection in mice." *Arch. Gesamte Virusforsch.* **17**: 392-397 (1965). G36,032/65
- In mice the stress induced by avoidance learning increased susceptibility to poliomyelitis virus.
- Chang, S. S., Rasmussen, A. F. Jr.: "Stress-induced suppression of interferon production in virus-infected mice." *Nature* **205**: 623-624 (1965). F32,471/65
- The increased susceptibility of mice to vesicular stomatitis and polyoma viruses induced by sound stress may be due to the concurrent impairment of interferon production.
- Kretschmar, W.: "The effects of stress and diet on resistance to *Plasmodium berghei* and malarial immunity in the mouse." *Ann. Soc. Belge Méd. Trop.* **45**: 325-340 (1965). G36,020/65
- Pitkin, D. H.: "Effect of physiological stress on the delayed hypersensitivity reaction." *Proc. Soc. Exp. Biol. Med.* **120**: 350-351 (1965). F57,023/65
- Mice sensitized to 1-chloro-2,4-dinitrobenzene are partially protected by various stressors against delayed hypersensitivity reactions to the same antigen.
- Felsenfeld, O., Hill, C. W., Greer, W. E.: "Response of *Cercopithecus aethiops* to

cholera vibrio lipopolysaccharide and psychological stress." *Trans. R. Soc. Trop. Med. Hyg.* **60**: 514-518 (1966). J24,875/66

"The capability of the serum to neutralize the toxicogenicity of the vibrios, in animals under [psychogenic] stress, developed more slowly than in the control group."

Trapani, I. L.: "Altitude, temperature and the immune response." *Fed. Proc.* **25**: 1254-1259 (1966). F69,414/66

Filipp, G.: *Pathogenese und Therapie allergischer Reaktionen. Grundlagenforschung und Klinik* (Pathogenesis and therapy of allergic reactions. Theory and practice), p. 767. Stuttgart: Ferdinand Enke Verlag, 1966.

E6,824/66

Monograph on the pathogenesis of allergic reactions, with several sections on the G.A.S. Stress influences the immune system in various ways, since activation of the hypothalamus-pituitary-adrenocortical axis mobilizes corticoids and catecholamines, causes involution of the thymicolympathic apparatus, and brings about "anamnestic reactions" which reactivate pre-existent immune responses. Furthermore, histamine metabolism is largely dependent upon the above-mentioned stress hormones, and cortisone, as well as catecholamines, has long been shown to affect allergies of various kinds. Presumably, the so-called "nonspecific irritation therapy" (injection of foreign proteins, bacterial polysaccharides, etc.) also plays a role in this respect.

Hill, C. W., Greer, W. E., Felsenfeld, O.: "Psychological stress, early response to foreign protein, and blood cortisol in vervets." *Psychosom. Med.* **29**: 279-283 (1967).

G48,085/67

In vervet monkeys (*Cercopithecus aethiops*) exposed to psychogenic stress (noise, light, handling), serum cortisol levels rose considerably, and antibody formation to bovine serum albumin was diminished and delayed.

Weinmann, C. J., Rothman, A. H.: "Effects of stress upon acquired immunity to the dwarf tapeworm, *Hymenolepis nana*." *Exp. Parasitol.* **21**: 61-67 (1967).

J22,590/67

"Severe and prolonged fighting among male mice hindered development of acquired immunity in stressed animals and increased the reinfection rate in mice with well-established acquired immunity. Stress induced by repeated association with strange mice also

enhanced reinfection rates in immune mice. Severe nutritional stress rendered most immune mice susceptible to reinfection but cold stress did not significantly increase reinfection rates."

Fischer, G.; Dostal, V.: "Einfluss von kältestress auf die Vakzine-Infektion bei Ratten" (Influence of cold-induced stress on vaccinia infections in rats). *Z. Immun. Forsch.* **133**: 313-316 (1967). F87,491/67

In rats, stress induced by cold diminishes the local reaction and increases antibody production after vaccinia infections.

Belfer, M. L.: "Stress-tempered antibiotic response." *N. Engl. J. Med.* **279**: 1002 (1968). J21,992/68

Jensen, M. M.: "The influence of stress on murine leukemia virus infection." *Proc. Soc. Exp. Biol. Med.* **127**: 610-614 (1968). F96,630/68

Jensen, M. M.: "Transitory impairment of interferon production in stressed mice." *J. Infect. Dis.* **118**: 230-234 (1968).

G58,629/68

Avoidance learning in a shuttlebox apparatus caused "transitory impairment of interferon production by forms of stress which were mediated primarily through the central nervous system and which were considered comparable to psychological or the nonspecific stress response of Selye." Possibly, excess glucocorticoid production mediates this reaction.

Thaxton, P., Sadler, C. R., Glick, B.: "Immune response of chickens following heat exposure or injections with ACTH." *Poultry Sci.* **47**: 264-266 (1968). G58,548/68

In chickens exposed to heat, treatment with ACTH or cortisone before antigen injection depresses the antibody response to sheep red blood cells. Such treatment also interferes with the development of the bursa of Fabricius and the spleen. This "might be explained by an interference with phagocytosis or immunoglobulin producing cells brought about by direct effect of the treatment or by some humoral substance like corticosterone."

Abeatici, S., Lamarca, S., Canino, V., Sassi, I., Calvi, A.: "Influenza dello stress sulla reazione di rigetto di omotriplanti cutanei (ricerche sperimentali)" (Influence of stress on the rejection reaction of skin transplants [experimental research]). *Chir. Patol. Sper.* **16** Supp. 6: 14-27 (1968). H27,346/68

In rats exposed to the stress of centrifugation, it was shown that under the influence of "the alarm stimulus, the survival of the cutaneous homografts is significantly higher than that observed in the control animals."

Horwitz, K. B., Ball, R. J., Schmidt, J. P.: "Resistance to infection of mice and hamsters following short term acceleration stress." *Aerosp. Med.* **40**: 1248-1251 (1969).

H44,833/69

Brief exposure to acceleration significantly protected mice but not hamsters against subsequent infection with *Clostridium tetani* or *S. typhimurium*. Cortisol secretion was not demonstrable in the stressed mice. It is suggested that the previously documented effect of stress and cortisol in lowering resistance to infection does not occur following very short exposure.

Friedman, S. B., Glasgow, L. A., Ader, R.: "Psychosocial factors modifying host resistance to experimental infections." *Ann. N.Y. Acad. Sci.* **164**: 381-393 (1969).

H19,303/69

Mettrop, P. J. G., Visser, P.: "Exteroceptive stimulation as a contingent factor in the induction and elicitation of delayed-type hypersensitivity reactions to 1-chloro-2,4-dinitrobenzene in guinea pigs." *Psychophysiology* **5**: 385-388 (1969).

J19,071/69

In guinea pigs exposed to repeated electroshocks, delayed hypersensitivity reactions to 1-chloro-2,4-dinitrobenzene were aggravated.

Levine, S., Strelbel, R.: "Allergic encephalomyelitis: inhibition of cellular passive transfer by exogenous and endogenous steroids." *Experientia* **25**: 189-190 (1969).

H8,867/69

In rats, dexamethasone or endogenous hypersecretion of syntoxic corticoids during stress prevents the passive transfer of allergic encephalomyelitis.

Levina, L. A., Ozeretskovskii, N. A.: "Assessment of paratyphoid B vaccines with known reactogenicity with the aid of laboratory tests." *Zh. Mikrobiol. Epidemiol. Immunobiol.* **46** No. 5: 47-53 (1969) (Russian).
J25,151/69

Rasmussen, A. F. Jr.: "Emotions and immunity." *Ann. N.Y. Acad. Sci.* **164**: 458-462 (1969).

H19,304/69

Review of the literature and personal observations on the effect of stress upon im-

mune mechanisms, including those against tumorigenic viruses, and the possible participation of interferon in these phenomena (22 refs.).

Solomon, G. F.: "Stress and antibody response in rats." *Int. Arch. Allergy Appl. Immunol.* **35**: 97-104 (1969). G64,541/69

"Overcrowding stress but not the stress of apprehension-electric shock administered for a week prior to immunization with a potent bacterial antigen, flagellin, and continued during the course of observation significantly reduced both primary and secondary antibody response in inbred male rats. The stress of remaining on a small platform (with rapid eye-movement sleep deprivation) or medium sized platform (without REM deprivation) over a pan of water significantly reduced primary but not secondary response" (31 refs.).

Anderlik, P., Bános, Z., Szeri, I., Koltay, M., Virág, I.: "Response to stressors of mice undergoing graft-versus-host reaction." *Experientia* **26**: 94-95 (1970).

H21,168/70

In mice, intravenous injection of homologous splenic cells causes lymphopenia with body weight loss. Following such treatment, these animals no longer respond to a second stressor with further lymphopenia.

Thaxton, P., Siegel, H. S.: "Adrenocortical function and immunodepression in young chickens." *Poultry Sci.* **49**: 1444 (1970).

J11,183/70

The immune titers developed by young chickens following challenge with sheep red blood cells were depressed by exposure to heat or ACTH. This immunodepression could in turn be at least partially blocked by metyrapone, which interferes with corticoid synthesis.

Friedman, S. B., Glasgow, L. A., Ader, R.: "Differential susceptibility to a viral agent in mice housed alone or in groups." *Psychosom. Med.* **32**: 285-299 (1970).

G76,988/70

"In two strains of mice, individually housed animals were more susceptible to encephalomyocarditis (EMC) virus than those housed in groups." Interferon and antibody levels following virus inoculation did not explain the differences in resistance. Corticosterone levels at the peak of the circadian rhythm were higher in individually housed mice.

Kurochkin, V. I.: "Properdin concentration and protein composition of the lymph

and blood in stress." *Biull. Éksp. Biol. Med.* **71**: 12-13 (1971) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **71**: 10-11 (1971).

J21,620/71

"After fractures of the tibia and fibula in rabbits the properdin concentration in the lymph draining from the injured limb is reduced, while the total protein concentration is increased. The properdin, total protein, and albumin levels in the blood are lowered under these circumstances."

Portugalov, V. V., Kaplanskii, A. S., Duranova, G. N.: "The condition of immunocompetent organs in the presence of hypokinesia." *Vestn. Akad. Med. Nauk SSSR* **26** No. 10: 29-34 (1971) (Russian). Engl. trans.: *Vestn. USSR Acad. Med. Sci.* **26**: 40-46 (1971). J20,535/71

The thymicolympathic and splenic involution associated with stress (restraint) is accompanied by a decrease in the production of immunocompetent cells, but this paradoxically fails to diminish the antibody content of the blood.

Ermolov, V. I.: "Effects of disturbance of the normal course of pregnancy in dogs on development of natural immunity in the progeny." *Biull. Éksp. Biol. Med.* **71** No. 3: 64-66 (1971) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **71** No. 3: 285-287 (1971).

J21,617/71

In dogs exposed to stressors during pregnancy, "the immunologic properties of the blood of the fetuses and newborn puppies were appreciably weakened. The phagocytic response was depressed most sharply, and this was accompanied by a decrease in the digestive power of the leukocytes. Weakening of the immunobiological properties led to the appearance of inflammation in the lungs and intestine by the action of the automicroflora and was responsible for death of a large proportion of the newly born animals."

Olinescu, A., Olinescu, E., Istrate, N., Oprisan, R., Potorac, E.: "Modificari ale răspunsului imun la soareciile de laborator supuși acțiunii factorului stress-ant de transport" (Changes in the immune response of laboratory mice undergoing transport stress). *Microbiologia* (Bucur.) **16**: 417-422 (1971) (Roumanian). J19,887/71

In mice, "transport stress" decreases the titer of antibodies and increases mortality following inoculation with pathogenic organisms.

Noble, G. A.: "Leishmania braziliensis:

physical and chemical stress in hamsters." *Exp. Parasitol.* **29**: 30-32 (1971).

G81,736/71

In hamsters, various stressors, and particularly restraint, significantly diminished resistance to inoculation with *Leishmania braziliensis*.

Gisler, R. H., Bussard, A. E., Mazié, J. C., Hess, R.: "Hormonal regulation of the immune response. I. Induction of an immune response in vitro with lymphoid cells from mice exposed to acute systemic stress." *Cell. Immunol.* **2**: 634-645 (1971).

G88,149/71

Observations on mice exposed to the stressor effect of acceleration or ether anesthesia "showed a close relationship between depletion of small lymphocytes in the peripheral areas of the follicles and in the marginal zones of the spleen and diminished immune reactivity of the corresponding cell suspensions in vitro."

Gisler, R. H., Schenkel-Hulliger, L.: "Hormonal regulation of the immune response. II. Influence of pituitary and adrenal activity on immune responsiveness in vitro." *Cell. Immunol.* **2**: 646-657 (1971).

G88,150/71

In mice, stress (acceleration, ether) or ACTH decreases antigen production by explanted spleen cells *in vitro*. Pretreatment with STH counteracts this effect and accelerates recovery of corticoid-induced depression of immune reactivity (30 refs.).

Cianci, P., Donahoo, S., Minogue, T., Staver, R.: "Stress as a factor in the development of clinical malaria: a comparative study of malarial incidence in RVN casualties." *Milit. Med.* **137**: 113-114 (1972). G89,300/72

In military personnel, malaria often "appeared after the added stress of surgery and anesthesia, including minor procedures."

Mullane, J. F., Wilfong, R. G., LaForce, F. M., Huber, G. L.: "Effect of acute stress on pulmonary host defenses." *Clin. Res.* **20**: 580 (1972). H54,070/72

Zdrodovskii, P. F., Gurvich, G. A.: *Physiologic Basis and Regulation of Immune Reactions*, p. 88. Moskva: Meditsina, 1972 (Russian). E9,933/72

Monograph on the regulation of immunologic mechanisms. The G.A.S. is intimately involved in the first anamnestic reactions. For example, in rats previously immunized

with paratyphoid, the G.A.S. (produced by cold) first leads to a "passive anamnestic reaction" in which the preformed agglutinins are liberated owing to lysis of plasmocytes in the involuting lymph nodes. Later, during the stage of resistance, there is an "active anamnestic reaction," ascribed to increased synthesis, under the influence of anabolic hormone production, which follows the initial glucocorticoid discharge. Several other experiments are cited in support of the concept that the G.A.S., through the effect of adaptive hormones upon antibody formation, represents an important aspect of immunologic defense, even in the adult organism. On the other hand, it has previously been demonstrated that immunologic challenge can act as a stressor provoking the manifestations of the G.A.S.

Seifter, E., Rettura, G., Zisblatt, M., Levenson, S. M., Levine, N., Davidson, A., Seifter, J.: "Enhancement of tumor development in physically-stressed mice inoculated with an oncogenic virus." *Experientia* **29**: 1379-1382 (1973). H80,975/73

In rats, restraint by a partial body cast produced typical manifestations of systemic stress, and at the same time it increased susceptibility to the tumorigenic action of murine sarcoma virus. In the restrained animals, "there appeared to be a smaller number of small lymphocytes due to stress and a proliferation of epithelioid elements. Hassall bodies were also involved in agreement with earlier findings of Selye. If stress or cortisone treatment results in impaired function of these structures, then the endocrine function of the thymus gland as well as its role in providing circulating cells would be disturbed." In any event, the response of the thymus during stress is assumed to increase susceptibility to the virus through interference with immune reactions.

Amkraut, A. A., Solomon, G. F., Kasper, P., Purdue, A.: "Stress and hormonal intervention in the graft-versus-host response." *Adv. Exp. Med. Biol.* **29**: 667-674 (1973). J24,477/73

The authors quote literature which indicates that stress generally suppresses immune reactions. They then add, "We have shown such suppressive effects on antibody formation and have also reported stress-induced increases in tumor size, which are probably a consequence of immunosuppression."

Gross, W. B., Siegel, P. B.: "Effect of

social stress and steroids on antibody production." *Avian Dis.* **17**: 807-815 (1973). J22,009/73

Stalheim, O. H. V.: "Failure to reproduce acute porcine leptospirosis by physiologic stress or concurrent infections." *Am. J. Vet. Res.* **34**: 1257-1260 (1973). J22,019/73

Jensen, M. M.: "Possible mechanisms of impaired interferon production in stressed mice." *Proc. Soc. Exp. Biol. Med.* **142**: 820-823 (1973). H66,962/73

In mice, avoidance-learning and confinement stress inhibited interferon production following endotoxin injections. "Neither the blocking of alpha adrenergic receptors with phenoxybenzamine nor the antagonism of serotonin with methysergide influenced this response. The spleen did appear to play a role in this response, as no difference in interferon production was seen between stressed and control splenectomized mice."

Ježkova, Z., Petz, R.: "Effect of experimental stress on the immunological response in experimental atherosclerosis in rabbits" (Author's translation). *Čas. Lék. Čes.* **113** (42): 1279-1283 (1974) (Czech). J24,350/74

Brown, K. I., Nestor, K. E.: "Implications of selection for high and low adrenal response to stress." *Poultry Sci.* **53**: 1297-1306 (1974). J21,587/74

In turkeys, exposure to stressors increases susceptibility to viral diseases and resistance to bacterial infections.

Tizard, I. R., Ellicott, D. I.: "Cell-mediated hypersensitivity to *Pasteurella hemolytica* in normal and cold-stressed mice." *Can. J. Comp. Med.* **38**: 44-48 (1974). J21,563/74

Hamid, J., Sayeed, A., McFarlane, H.: "The effect of 1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2-dichloroethane (o,p'-DDD) on the immune response in malnutrition." *Br. J. Exp. Pathol.* **55**: 94-100 (1974). H86,118/74

In rats, o,p'-DDD caused a loss of body weight as well as involution of the thymus, spleen and adrenals. In malnourished rats the adrenal atrophy was particularly marked and was associated with a diminution of plasma corticoids and a decrease in the impairment of the immune response normally occasioned by this drug.

Folch, H., Waksman, B. H.: "The splenic suppressor cell. I. Activity of thymus-depen-

dent adherent cells: changes with age and stress." *J. Immunol.* **113**: 127-139 (1974).

J13,910/74

Review and personal observations on the effect of various stressors, glucocorticoids, and age upon "suppressor T cell" activity, which may play a decisive part in stress-induced changes of immunologic defense (81 refs.).

Gisler, R. H.: "Stress and the hormonal regulation of the immune response in mice." *Psychother. Psychosom.* **23**: 197-208 (1974).

J16,683/74

In mice, various stressors and ACTH decreased immune reactivity of the spleen cells in vitro, while raising plasma corticosterone levels. "Restraint stress significantly increased the homing of ^{51}Cr -labeled lymph node cells from normal nu/+ mice (B and T cells) to spleen and bone marrow. In contrast, homing of nu/nu lymph node cells (B cells) to lymph nodes and spleen was decreased in stressed recipients, and an increased proportion of cells was found in the liver. Hypophysectomy of cell donors resulted in a persistent depression of immune responsiveness, which was restored by treatment with somatotrophic hormone (STH). STH presumably accelerates recovery from stress-induced immunosuppression. Moreover, exogenous STH interfered with the effect of increased endogenous corticosterone" (43 refs.).

Palmlad, J., Cantell, K., Strander, H., Fröberg, J., Karlsson, C. G., Levi, L.: "Stressor exposure and human interferon production." *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 35: 1-8 (1974).

J17,329/74

In women exposed to a seventy-seven-hour vigil and showing hormonal changes characteristic of stress, the ability of the blood cells to produce interferon following addition of Sendai virus to blood samples rose considerably.

Ahmed, A., Herman, C. M., Knudsen, R. C., Sode, J., Strong, D. M., Sell, K. W.: "Effect of exogenous and endogenous glucocorticosteroids on the in vitro stimulation of lymphocytes from sedated and awake-restrained healthy baboons." *J. Surg. Res.* **16**: 172-182 (1974).

J12,487/74

In baboons the stress of squeeze-cage manipulation and restraint decreases the relative and total blood lymphocyte counts. There is also an associated suppression of methyl- ^3H -thymidine incorporation by unstimulated as

well as by T-cell mitogen- and B-cell mitogen-stimulated lymphocytes. Subsequent injection of methylprednisolone blocks this inhibition of incorporation; however, exogenous corticoids affect the thymus-derived T-cells more than the bursa of Fabricius equivalent B-cells. The T-cells seem to be directly concerned with the cell mediated immunity and the B-cells with the production of humoral antibodies. Hence, the immunosuppressive effect of stress and glucocorticoids is probably one of the characteristic consequences of the thymicolympathic involution and lymphopenia that have been recognized as a typical stress effect since the first formulation of the G.A.S. concept.

Hamilton, D. R.: "Immunosuppressive effects of predator induced stress in mice with acquired immunity to *Hymenolepis nana*." *J. Psychosom. Res.* **18**: 143-150 (1974).

J15,134/74

"Predator stressed groups showed a high level of reinfection, high plasma corticosterone levels, increased adrenal gland weights, and decreased body weight gains in proportion to increasing frequency of exposure" (21 refs.).

Blumöhr, T., Klöcking, R., Sprössig, M.: "Veränderungen der Plasmakreatinkinaseaktivität durch Coxsackievirusinfektion bei Mäusen" (Coxsackie virus infection causing plasma creatine kinase changes in mice). *Pathol. Microbiol.* (Basel) **40**: 241-250 (1974).

H89,273/74

In mice, swimming (allegedly owing to its stressor effect) predisposes to Coxsackie virus infection and raises plasma creatine kinase activity. Causal connections between these changes are suspected but not proven.

Dressler, D. P., Skornik, W. A.: "Pulmonary bacterial susceptibility in the burned rat." *Ann. Surg.* **180**: 221-227 (1974).

J15,111/74

Exposure of burned and control rats to *P. aeruginosa* and *S. aureus* showed that susceptibility to pulmonary infection is greatly increased within twenty-four hours of thermal injury.

Cormane, R. H.: "A molecular explanation of stress dermatitis." *Psychother. Psychosom.* **23**: 188-196 (1974).

J16,682/74

In contact dermatitis, deposition mechanisms of immune complexes are "hastened by release of vasoactive amines and hormones due to psychological reasons, stress, or trauma. As a consequence of the aforemen-

tioned sequence of events, it is understandable that release of sympathomimetic amines and hormones along with the presence of antigen may perpetuate or even worsen cell-mediated immunity."

Solomon, G. F., Amkraut, A. A., Kasper, P.: "Immunity, emotions and stress, with special reference to the mechanisms of stress effects on the immune system." *Psychother. Psychosom.* **23**: 209-217 (1974).

J16,684/74

Review of the literature and experiments on rats suggest that stress and CNS lesions "affect thymus-derived lymphocytes (T-cells) and play a role in cell-cell interaction or the release of mediators from reacting lymphocytes. Ultimately, we may find that stress affects the macrophage, a hormone-sensitive cell that plays a role in afferent, central and efferent limbs of the immune system" (no refs.).

Howard, R. J., Simmons, R. L.: "Acquired immunologic deficiencies after trauma and surgical procedures." *Surg. Gynecol. Obstet.* **139**: 771-782 (1974). H95,043/74

In man, "surgical trauma is associated with a number of temporary deficits in the immune system which might conceivably lead to increased susceptibility to infection or tumor spread" (109 refs.).

Wagner, V., Andrlíková, J., Pálek, V.: "Immunoglobulins under the influence of nonspecific factors. II. The influence of work-stress on levels of immunoglobulins (IgG, IgA, IgM) of miners in uranium mines." *Z. Immunitätsforsch.* **148**: 356-365 (1975). J23,619/75

In miners, prolonged exposure to work stress caused "a significant decrease of all 3 classes of Ig. In the group exposed for a shorter time only the IgG decreased significantly."

Death

Sudden death has been observed repeatedly as a consequence of violent arguments with superiors or the emotional upset of witnessing serious accidents. It is usually ascribed to paroxysmal auricular tachycardia, complete heart block or ventricular fibrillation. However, in addition to painful psychogenic stressors, sudden reunion with long-lost relatives, triumphs, or the happy ending of some event which is particularly meaningful to the patient may also lead to sudden death.

Among primitive tribes in New Zealand and Haiti, death induced by "black magic," especially "voodoo" death, is a well-known phenomenon. Presumably it results from a sudden, particularly intense catecholamine discharge. Among animals, intense overactivity of the parasympathetic nervous system allegedly may cause sudden death.

In cockroaches, fighting can result in the death of the subordinates even without any evidence of physical damage. This has been described as "death from stress."

Some authors believe that even certain cases of "crib death" are due to unpredictable stress reactions.

Death

(See also our earlier stress monographs, p. xiii)

Weiss, S.: "Instantaneous 'physiologic' death." *N. Engl. J. Med.* **223**: 793-797 (1940). B23,665/40

Sudden death may often occur under the influence of an acute stressor in the absence of any detectable morphologic change. It is

considered that in these cases the immediate cause of death is usually fatal syncope with asystole of various types and ventricular fibrillation (20 refs.).

Cannon, W. B.: "'Voodoo' death." *Am. Anthropol.* **44**: 169-181 (1942).

B26,335/42

Death induced by spells, sorcery or "black magic" among primitive tribes, especially

"voodoo" death among the natives of New Zealand and Haiti, is ascribed to sudden extreme fear, probably causing overexcitement of the sympathetico-adrenal medullary system. Many pertinent cases are described and analyzed.

Bernreiter, M.: "Cardiac arrhythmias in physical or emotional stress." *Mo. Med.* **53**: 19-20 (1956). C11,328/56

Case reports showing that violent arguments with superiors, witnessing a serious car accident, or lifting a heavy weight may cause ventricular or paroxysmal auricular tachycardia, complete heart block and even death. It is concluded that "physical exertion and emotional stress may lead to almost all types of cardiac arrhythmias and death in the abnormal as well as the normal heart. An attempt is made to describe some of these phenomena that occur during the alarm reaction and their possible relationship to the production of ectopic rhythms."

Sandberg, A. A., Eik-Nes, K., Migeon, C. J., Samuels, L. T.: "Metabolism of adrenal steroids in dying patients." *J. Clin. Endocrinol. Metab.* **16**: 1001-1016 (1956).

C20,121/56

In agonal patients the plasma clearance of intravenous radiocortisol was delayed, and terminal subjects excreted most of the 17-OHCS in conjugated form. These and other findings are interpreted as indicating that "elevated plasma corticoid levels in dying patients are due to impaired metabolism of these steroids in the presence of continued production and secretion of steroids by the adrenal cortex at normal or reduced rates."

Richter, C. P.: "On the phenomenon of sudden death in animals and man." *Psychosom. Med.* **19**: 191-198 (1957).

J24,112/57

The phenomenon of sudden death has been described in man, rats and many other animals as being due primarily to overactivity of the parasympathetic system, with consequent failure of the heart.

Finkel, I. I., Kovanev, V. A.: "The role of the stress reaction in the postoperative mortality of the patients with acquired cardiac affections." *Arkh. Patol.* **25** No. 5: 19-26 (1963) (Russian). G29,660/63

Sudden death during the first three days after an operation, especially among patients with rheumatic cardiac affections, is usually associated with morphologic changes in the endocrine and other internal organs, referred

to by the authors as "nonspecific manifestations of the general adaptational syndrome."

Elkington, A. R., Steele, P. R., Yun, D. D.: "Scared to death?" *Br. Med. J.* August 7, 1965, pp. 363-364. J22,826/65

Report on "an apparently healthy middle-aged woman dying with massive adrenal haemorrhage, following a relatively minor operation, who was subsequently found to have had forebodings of death." The authors suggest that emotional plus traumatic stress may have been the cause of sudden death here.

Ewing, L. S.: "Fighting and death from stress in a cockroach." *Science* **155**: 1035-1036 (1967). J22,668/67

In the cockroach *Nauphoeta cinerea*, fighting may result in death in subordinates without evidence of external damage. "The situation is likened to death from stress as found in mammals."

Bishop, L. F., Reichert, P.: "Emotion and heart failure." *Psychosomatics* **12**: 412-415 (1971). H51,328/71

Stimulating review of the electrolyte and hormonal changes associated with sudden cardiac failure following exposure to psychogenic stressors.

Elkinton, J. R.: "Scared to death?" *Ann. Intern. Med.* **74**: 789-790 (1971). J20,741/71

Porter, A. L., McCarthy, C. D., Pearman, H. E.: "Effect of stressful physical illness on future time perspective." *J. Clin. Psychol.* **27**: 447-448 (1971). J20,216/71

A variety of particularly stressful diseases, and especially myocardial infarction, shorten life expectancy in man.

Engel, G. L.: "Sudden and rapid death during psychological stress. Folklore or folk wisdom?" *Ann. Intern. Med.* **74**: 771-782 (1971). G83,212/71

Excellent and detailed review of the socio-logic-demographic literature shows that the causes of sudden death in man may be classified into eight categories: "1) on the impact of the collapse or death of a close person; 2) during acute grief; 3) on threat of loss of a close person; 4) during mourning or on an anniversary; 5) on loss of status or self-esteem; 6) personal danger or threat of injury; 7) after the danger is over; 8) reunion, triumph, or happy ending" (89 refs.).

Nahum, L. H.: "Emotional stress and sud-

den death." *Conn. Med.* **35**: 558-560 (1971). J20,214/71

Halpern, W. I.: "Some psychiatric sequelae to crib death." *Am. J. Psychiatry* **129**: 398-402 (1972). J19,544/72

Unexplained infant death has not been shown to be related to stress in the usual sense of the word, but it causes unpredictable stress reactions in the mother. When she discovers the dead child, the mother will at times use a young sibling as a scapegoat.

Tejmar, J.: "Berlin wall and sudden death." *Ann. Intern. Med.* **78**: 620 (1973). J19,555/73

Sudden death during joyful meetings after long years of separation has been described, but it is undoubtedly a very rare occurrence.

Lown, B., Verrier, R., Corbalan, R.: "Psychologic stress and threshold for repetitive ventricular response." *Science* **182**: 834-836 (1973). H77,441/73

Psychogenic stressors reduce the threshold of the dog's ventricle for repetitive responses and indicate "electrical instability and a predisposition to ventricular fibrillation, the mechanism of sudden death."

Pruitt, R. D.: "Death as an expression of functional disease." *Mayo Clin. Proc.* **49**: 627-663 (1974). H93,314/74

General review of death, including "Voo-

doo Death" and death from fright (as, for example, among canaries who were exposed to but could not be reached by a leopard), explained by nervous reflexes, especially those regulating heartbeat (excellent bibliography).

Opie, L. H.: "Sudden death and sport." *Lancet* February 1, 1975, pp. 263-266. H98,865/75

"Of 21 sudden deaths in sportsmen, 18 were thought to be caused by heart-attacks either during or after sport." Psychologic factors were considered to be important in eight cases.

Schmidt, R. T.: "Personality and fainting." *J. Psychosom. Res.* **19**: 21-25 (1975). J22,160/75

Vasodepressor fainting often occurs in response to stressful situations in predisposed individuals. It may be precipitated by "a situation, which elicits little emotional response from most people, [but which] can be extremely unpleasant for the fainter. The injury threatened may be minimal, but the related psychic stress is great. Chronic fainters learn to anticipate fainting and avoid precipitating stresses." This differs from hysterical fainting, in which pulse and blood pressure remain normal. "A vasodepressor reaction leads to collapse of the circulatory system, which sometimes resembles shock and has been known to result in death."

Varia

The abstract section contains data on changes in respiration, voice, blood-brain barrier, ultrasonic vocalizations, smell, sweating (for which see also GSR under Stress Tests), handwriting, and drug clearance, among other functional alterations induced by stress.

Varia

(See also our earlier stress monographs, p. xiii)

Legruen, A.: "Fatigue, exhaustion, manager's disease. Findings from students' handwriting." *Prax. Kinderpsychol. Kinderpsychiatr.* **11**: 5-10 (1962). J24,360/62

Mordkoff, A. M.: "The relationship between psychological and physiological response to stress." *Psychosom. Med.* **26**: 135-150 (1964). G12,092/64

During viewing of *Subincision*, a "stressor film" depicting puberty rites of an Australian aboriginal tribe (crude operations performed with a piece of flint on the penis and scrotum of adolescent boys), the ratings of psychologic impact upon the audience were closely related to such physiologic indices of stress as GSR, heart rate and respiration (21 refs.).

Friedhoff, A. J., Alpert, M., Kurtzberg, R. L.: "An electro-acoustic analysis of the effects of stress on voice." *J. Neuropsychiatry* **5**: 266-272 (1964). F14,620/64

After they were exposed to various stressors, "changes in the *voice* of experimental subjects probably revealed changes of the emotions more directly than the usually recorded or measured blood pressure and skin resistance. By recording changes which are in the voice electronically, some of the cues that reflect emotions have been objectively measured by the authors."

Angel, C., Burkett, M. L.: "Adrenalectomy, stress and the *blood-brain barrier*." *Dis. Nerv. Syst.* **27**: 389-393 (1966).

G39,712/66

Rubenstein, L.: "Electro-acoustical measurement of vocal responses to limited stress." *Behav. Res. Ther.* **4**: 135-138 (1966).

J22,890/66

Observations in man showed that, "within the limits of the experiments, the *voice* responds to limited stress by changes which could be detected electro-acoustically but which could not be perceived by the listener."

Wyndham, C. H., Williams, C. G., Morrison, J. F., Bredell, G. A. G.: "A comparison of multi-stress tests on the *sweat rate/rectal temperature relationship*." *Int. Z. Angew. Physiol.* **23**: 305-321 (1967).

G45,958/67

Iroshnikova, G. P.: "The blood cholesterol level and bile acids excretion depending on the degree and duration of functional stress of the nervous system." *Kardiologija* **8** No. 4: 48-54 (1968) (Russian).

J23,895/68

"Prolonged functional stress of the nervous activity, not leading to the development of neurosis, may cause in rabbits an alteration of the *cholesterol metabolism*, this being manifested by an increased excretion of *bile acids* and wave-like fluctuation of the blood cholesterol level. The blood cholesterol content manifests a tendency to rise with increase of the functional stress."

Selzer, M. L.: "Alcoholism, mental illness, and stress in 96 *drivers* causing fatal accidents." *Behav. Sci.* **14**: 1-10 (1969).

J16,328/69

Angel, C.: "Starvation, stress and the *blood-brain barrier*." *Dis. Nerv. Syst.* **30**: 94-97 (1969).

G64,873/69

Myers, R. D., Sharpe, L. G.: "Cerebrospinal fluid production during temperature stress and feeding in the conscious monkey." *Experientia* **25**: 497-498 (1969).

H13,633/69

Various stressors increase *CSF* production.

Baekeland, F.: "Laboratory studies of effects of presleep events on *sleep* and dreams." *Int. Psychiatry Clin.* **7**: 49-58 (1970) (56 refs.).

J21,252/70

Carr, W. J., Martorano, R. D., Krames, L.: "Responses of mice to odors associated with stress." *J. Comp. Physiol. Psychol.* **71**: 223-228 (1970).

G75,361/70

"Male mice respond to an *olfactory* signal emitted by stressed mice."

Bullard, R. W., Dill, D. B., Yousef, M. K. el: "Responses of the burro to desert heat stress." *J. Appl. Physiol.* **29**: 159-167 (1970).

G78,189/70

Donkeys are extremely resistant to "desert heat stress," presumably because of a particularly efficient *sweating* and rehydration mechanism which largely depends upon EP secretion. Intradermal injection of EP causes local sweating in this species.

Grandjean, E. P.: "Fatigue." *Am. Ind. Hyg. Assoc. J.* July-August, 1970, pp. 401-411.

J16,329/70

Review of neurophysiologic interrelations regulating *fatigue*, especially in connection with particularly stressful mental or monotonous work (27 refs.).

Popov, V. A., Simonov, P. V., Frolov, M. V., Khachaturians, L. S.: "Frequency spectrum of *speech* as a criterion of the degree and nature of emotional stress." *Zh. Vyssh. Nerv. Deiat.* **21**: 104-109 (1971) (Russian).

J23,860/71

Nitschke, W., Bell, R. W., Zachman, T.: "Distress *vocalizations* of young in three inbred strains of mice." *Dev. Psychobiol.* **5**: 363-370 (1972).

J23,571/72

Simonov, P. V., Frolov, M. V.: "Utilization of human *voice* for estimation of man's emotional stress and state of attention." *Aerosp. Med.* **44**: 256-258 (1973).

H91,919/73

Dumont, M., Erlinger, S.: "Influence of hydrocortisone on bile formation in the rat." *Biol. Gastroenterol. (Paris)* **6**: 197-203 (1973).

J10,513/73

In the rat, cortisol stimulates the bile-acid independent fraction of canalicular *bile flow* (21 refs.).

Meng, K., Loew, D.: "Mikropunktionsversuch über die Ursachen des akuten Nierenversagens beim experimentellen Verbrü-

hungsschock" (Micropuncture experiments on the causes of acute *renal* failure in experimental burn shock). *Langenbecks Arch. Chir.* **333**: 245-255 (1974). J14,130/74

Gentry, W. D., Shows, W. D., Thomas, M.: "Chronic low back pain: a psychological profile." *Psychosomatics* **15**: 174-177 (1974). H96,179/47

Various stressful life situations predispose to *low back pain* (14 refs.).

Loew, D., Meng, K.: "Untersuchungen über das akute Nierenversagen beim Verbrennungsschock der Ratte" (Experiments on the acute *renal* failure in burn shock in the rat). *Langenbecks Arch. Chir.* **335**: 295-307 (1974). J14,960/74

Carpenter, M., Musacchia, X. J.: "The effect of chronic heat stress on *intestinal* function in the rat" (abstracted). *Physiologist* **17**: 371 (1974). H89,977/74

Fröhlich, H.: "Steuermechanismen der Motilität des nichtgraviden Uterus *in situ*" (Extensive review of various mechanisms with a special section on psychogenic stressors regulating *uterine motility*). *Wien Klin.*

Wochenschr. **86** Supp. 24: 1-28 (1974) (299 refs.). H90,700/74

Swartz, R. D., Sidell, F. R., Cucinell, S. A.: "Effects of physical stress on the disposition of drugs eliminated by the liver in man." *J. Pharmacol. Exp. Ther.* **188**: 1-7 (1974). H81,251/74

In man, stressors which reduce *liver* plasma flow (heat, exercise, fluid deprivation) delayed the plasma clearance of drugs normally eliminated by the liver.

Bell, R. W., Nitschke, W., Bell, N. J., Zachman, T. A.: "Early experience, ultrasonic vocalizations, and maternal responsiveness in rats." *Dev. Psychobiol.* **7**: 235-242 (1974). J12,730/74

Exposure of neonatal rats to cold and several other stressors induces *ultrasonic vocalization* and agitation of their mothers. "If the pup is mildly stressed he displays a pattern of ultrasonic signaling which elicits adaptive maternal responsiveness. If the pup is too severely stressed he displays persistent signaling which agitates the mother, preventing an adaptive pattern of behavior, and resulting in a prolonged response to stress in the pup."

IV. DISEASES OF ADAPTATION

Generalities

Soon after the description of the G.A.S., the concept of stress-induced diseases or "diseases of adaptation" was formulated; it appeared then that stress (particularly maladaptation to stress) played a decisive role in a number of maladies. At times these maladies have been referred to as "diseases of our civilization." This is hardly justifiable; stress and demands for adaptation, as well as faulty responses to such demands, have existed since time immemorial, although the stressors of our era are of course very different from those that affected man in prehistoric times or in antiquity.

Diseases of adaptation are essentially always pluricausal or multifactorial. As we pointed out before, no agent alone produces stress without also eliciting specific manifestations of its own and the latter are necessarily superimposed upon the former. Conversely, all pathogens make some nonspecific demands, hence they all produce stress in addition to their specific pathogenic effects, and there is an element of stress in every disease. It is customary, however, to speak of diseases of adaptation only in referring to those maladies in which stress plays the predominant pathogenic role, although its manifestations are modified not only by the specific effects of the pathogen but also by external and internal conditioning factors that determine disease susceptibility.

Among the most important diseases of adaptation in this sense, we shall discuss shock, peptic ulcers, various cardiovascular diseases (particularly hypertension and cardiac infarcts), psychiatric disturbances (including toxicomanias), certain immune diseases and so on. In many of these maladies, inappropriate (excessive or insufficient) corticoid secretion plays an important part.

In the 1950s, it was claimed that "the tissues of the organism with a normal pituitary-adrenal system are never subjected to a plethora of cortical hormones as implied in the 'Diseases of Adaptation' thesis of Selye" because at that time it was thought that the corticoid feedback mechanism worked perfectly even during stress (Sayers). However, it is now generally accepted that a stress-induced excess of corticoids or catecholamines does play a role in the development of many diseases, although this factor may be more or less important within the framework of a given "pathogenic situation" (Ingle, Thorn *et al.*).

During the 1960s, the view gained some momentum, especially in Germany, that stress hormones are not involved in the production of morbid lesions, but that non-specific changes of resistance are due to "vegetative total reorientation," which is in essence a modification of the relative predominance of sympathetic or parasympathetic nervous impulses (Hoff). There can be no doubt that changes in the activity of the ANS also play an important role in diverse stress-induced diseases, but the "vegetative

tonus" is much more difficult to quantify than the hormone level of the blood and urine. The concept of "vegetative total reorientation" proved to be very difficult to substantiate by quantitative observations, and hence much more work has been done on the hormonal than on the nervous components involved in the pathogenesis of stress diseases.

Finally, it should be pointed out that embryonic and immediately postnatal development of diseases of adaptation may also cause permanent malformations and that many of the manifestations of aging are probably the accumulated result of all the maladaptations to stress experienced during a lifetime.

Generalities

(See also our earlier stress monographs, p. xiii)

Selye, H.: "The general adaptation syndrome and the diseases of adaptation." *J. Clin. Endocrinol.* **6**: 117-230 (1946).

B1,204/46

First detailed review of the G.A.S. and the diseases of adaptation, presented as a special number of the *Journal of Clinical Endocrinology* (over 700 refs.).

Wolff, H. G.: "Life stress and bodily disease—a formulation." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 1059-1094. Baltimore: Williams and Wilkins, 1950.

B51,960/50

Sayers, G.: "Pituitary regulation of adrenal cortical activity." In: Soskin, S., *Progress in Clinical Endocrinology*, pp. 122-130. New York: Grune & Stratton, 1950.

B47,555/50

The author recapitulates his arguments in favor of enhanced "utilization" of corticoids during stress, which would prevent the development of diseases of adaptation owing to conditioning that increases sensitivity to pathogens. "It appears that the tissues of the organism with a normal pituitary-adrenal system are never subjected to a plethora of cortical hormones as is implied in the 'diseases of adaptation' thesis of Selye" (26 refs.).

Thorn, G. W., Jenkins, D., Laidlaw, J. C.: "The adrenal response to stress in man." *Rec. Prog. Horm. Res.* **8**: 171-215 (1953).

B73,567/53

Extensive review lecture on clinical indices of adrenal responses to stress in man and the role of the G.A.S. in the pathogenesis of diseases of adaptation. Special emphasis is placed upon reactivity to infusions of ACTH, corticoids and EP, and upon the diagnostic value of blood eosinophils and 17-KS excretion as indicators of adrenocortical participation in stress responses (47 refs.).

Ingle, D. J., Baker, B. L.: "A consideration of the relationship of experimentally produced and naturally occurring pathologic changes in the rat to the adaptation diseases." *Rec. Prog. Horm. Res.* **8**: 143-169 (1953).

B73,566/53

Detailed review and critique of the concept that stressors and hormones produced during stress can be decisive factors in the production of the "diseases of adaptation."

Finlay, B., Gillison, K., Hart, D., Mason, R. W. T., Mond, N. C., Page, L., O'Neill, D.: "Stress and distress in general practice." *Practitioner* **172**: 183-196 (1954).

J25,479/54

Conn, J. W.: "Man's endocrine and metabolic responses to stressing circumstances: clinical implications." *Hawaii Med. J.* **14**: 19-26 (1954).

D88,031/54

Mach, R. S.: "Glandes surrénales et agression" (Adrenal glands in relation to stress). *Helv. Med. Acta* **22**: 279-287 (1955).

C15,620/55

Ischlondsky, N.: "La lutte contre les maladies attribuées aux effets nocifs des 'stresses' de la vie moderne" (The struggle against diseases attributed to the noxious ef-

fects of the stresses of modern life). *Bull. Acad. Nat. Méd.* (Paris) **123**: 560-566 (1959).

J23,254/59

Fruhling, L., Oppermann, A., Korn, R.: "Anatomie pathologique du syndrome général d'adaptation en pathologie humaine" (Pathologic anatomy of the general adaptation syndrome in human pathology). *Ann. Anat. Pathol.* **4**: 515-540 (1959).

C68,239/59

Crane, W. A. J., Wilgram, G. F., Ingle, D. J.: "The role of the adrenal cortex in the aetiology of various diseases." *Scott. Med. J.* **5**: 437-447 (1960).

D350/60

Review of the concept of the "diseases of adaptation," with special emphasis upon the conditioning influence of corticoids.

Charvát, J.: "Disease of adaptation." *Patol. Fiziol. Éksp. Ter.* **5** No. 6: 5-14 (1961) (Russian).

D64,945/61

Futer, D. S.: "Critical notes of a clinician on Selye's adaptation syndrome." *Zh. Nevropatol. Psichiatr.* **62**: 1253-1261 (1962) (Russian).

J24,044/62

Cope, C. L.: *Adrenal Steroids and Disease*, p. 827. Philadelphia and Montreal: J B Lippincott, 1964.

E4,976/64

Monograph on the role of corticoids in adaptation and disease, with a special section on the diseases of adaptation.

Hoff, F.: "Krankheit und Adaptation" (Disease and adaptation). *Med. Welt* No. 1: 1-10 (1964).

F508/64

Detailed description of a lecture in which stress and the G.A.S. are considered to play no role in the pathogenesis of disease. In particular, the so-called stress hormones are not involved in the production of morbid lesions. Nonspecific changes of resistance are due to "vegetative total reorientation" ("vegetative Gesamtumschaltung"), which is a modification of the relative predominance of sympathetic and parasympathetic nervous impulses as described by the author many years ago. The concept of stress is superfluous, and to a large extent is based merely on linguistic innovations applied to the author's theory of vegetative total reorientation.

Jasmin, G.: *Endocrine Aspects of Disease Processes* (Proc. of the Conf. held in honor of Hans Selye, Mont Tremblant, Qué.), p. 456. St. Louis, Mo.: Warren H Green, 1968.

E7,612/68

Proceedings of a symposium on endocrine

aspects of disease, with several references to stress and the diseases of adaptation.

Levi, L.: "Definition and evaluation of stress" *Lab. Clin. Stress Res.* (Stockh.) Rep. No. 25: 1-11 (1971). Also in: *Thromb. Diath. Haemorrh.* 7-14 (1972).

G87,068/1971, 1972

Review on the hormonal, nervous and cardiovascular indices of stress if defined as "the nonspecific response of the body to any demand."

Tinbergen, N.: "Ethology and stress diseases." *Science* **185**: 20-27 (1974).

H87,100/74

In this Nobel lecture the author points out that, more than half a century ago and without any medical training, F. M. Alexander developed a technique for correcting various somatic and mental disorders by improvement of body posture and avoidance of faulty use of our neuromuscular system. "Misuse, with all its psychosomatic, or rather somatopsychic, consequences must therefore be considered a result of modern living conditions of a culturally determined stress." There is considerable evidence that arthritis, respiratory troubles, asthma, hypertension, gastrointestinal disorders, various gynecologic derangements, sexual failures, migraine, and depression (all diseases not caused by identifiable pathogens), as well as suicide, are actually due to stress. These diseases can be corrected by proper ethologic counseling. "It is stress in the widest sense, the inadequacy of our adjustability, that will become perhaps the most important disruptive influence in our society."

Aakster, C. W.: "Psycho-social stress and health disturbances." *Soc. Sci. Med.* **8**: 77-90 (1974).

J10,857/74

A review of the literature on psychosocial factors in disease leads to a rather far-reaching conclusion: "the results are taken as support of the hypothesis that illnesses are the more or less automatic result of a failure to adjust to stress."

Kagan, A.: "Psychosocial factors in disease: hypotheses and future research." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 41-57. Springfield, Ill.: Charles C Thomas, 1974.

E10,681/74

Classen, H. G.: "Stress, Distress und Adaptationskrankheiten" (Stress, distress and the general adaptation diseases). *Gynäkol. Balneotherap.* November, 1974, pp. 1-23.

J18,275/74

Shock

Perhaps shock is the most typical stress disease, since it can be produced by virtually any pathogen as long as its effect is sufficiently severe. However, this condition has already been previously discussed in the sections on trauma, hemorrhage, and various intoxications (Chapter II), all of which can elicit shock.

Shock

(See also our earlier stress monographs, p. xiii)

Wiggers, C. J.: *Physiology of Shock*, p. 459. Cambridge, Mass.: Harvard University Press, 1950. B68,707/50

Technical treatise on shock, with a few pages on its relationship to the alarm reaction.

Levij, I. S., Fuente, A. A. de la: "A post-mortem study of gastric and duodenal peptic lesions. Part I. Frequency and distribution by age and sex. Part II. Correlations with other pathological conditions." *Gut* 4: 349-359 (1963). E35,115/63

Statistical studies on clinical material suggest that "the correlation of acute peptic lesions with acute pathological conditions of the central nervous system may be explained by the mechanism of stress. In cases with a severe stress condition, shock is usually present, and in shock there is stasis of blood and haemoconcentration. In the mucous membrane of the stomach and the duodenum, small infarctions are formed, which are di-

gested as a result of the concomitant hyperacidity of the gastric contents in shock."

Bednarek, J. M., Matsumoto, T.: "Use of steroids in surgery." *Int. Surg.* 59: 584-589 (1974). H97,116/74

Motsay, G. J., Romero, L. H., Lillehei, R. C.: "Use of corticosteroids in the treatment of shock." *Int. Surg.* 59: 593-600 (1974). H97,118/74

Menguy, R., Masters, Y. F.: "Mechanism of stress ulcer. III. Effects of hemorrhagic shock on energy metabolism in the mucosa of the antrum, corpus, and fundus of the rabbit stomach." *Gastroenterology* 66: 1168-1176 (1974). J13,617/74

Menguy, R., Masters, Y. F.: "Mechanism of stress ulcer: influence of hypovolemic shock on energy metabolism in the gastric mucosa" (abstracted). *Digestion* 10: 233 (1974). H91,851/74

In rats, hypovolemic shock produced by hemorrhage results in gastric ulcers, presumably owing to shock-induced ischemia with diminution of energy metabolism in the mucosa.

GASTROINTESTINAL DISEASES OF ADAPTATION

Peptic Ulcers

Acute gastroduodenal peptic ulcers or bleeding surface erosions known as "stress ulcers" are among the most characteristic manifestations of stress induced by trauma in man as well as in various other mammals. The abundant literature on this topic furnishes much detail on the histologic structure, distribution, and occurrence of stress ulcers, both after surgical interventions and as a consequence of accidental wounds (especially those sustained in combat). Their development has been investigated by light microscopy, EM and even by sequential photographic studies of the gastric mucosa before and after bleeding. Complications, such as sepsis and emotional arousal, may increase the incidence and aggravate the intensity of stress ulcers. Cranial injuries

appear to be particularly likely to elicit such lesions, but among the many mechanisms mentioned as possible causes, none appears to be supported by fully convincing arguments.

There is still some controversy about whether the acute hemorrhagic gastric erosions produced by sudden stress in man and in experimental animals are truly comparable to the classic, chronic peptic ulcers of clinical medicine. It is highly likely that the two lesions merely represent the acute and chronic stage of the same derangement.

In any event, the fact that extensive skin burns can produce duodenal ulcers in man was described by Swan in 1823, Cooper in 1839, and Long in 1840, although the discovery is usually attributed to Curling, whose monograph was published in 1842.

This observation has often been confirmed, not only after burns but also upon exposure to other severe stressors, such as surgery (especially brain lesions), massive infections, acute anxiety ("air raid ulcers") and so on. On the other hand, common, everyday stressful life events may be conducive to chronic peptic ulcers.

A statistical study on Polish miners revealed that hereditary predisposition and nightshift work increase the incidence of peptic ulcers.

According to one statistical study, 32.5 percent of ATCs suffered from duodenal or gastric ulcers.

In a patient with a gastric fistula, it was possible to establish that spontaneously-occurring day-to-day stress situations are associated with increased acidity and decreased mucoprotein concentrations in the gastric juice; this rendered the mucosa extremely fragile, leading to the appearance of small erosions and hemorrhagic spots. Other extensive psychologic and psychoanalytic studies have likewise revealed the importance of mental stress in regulating gastric secretion and ulcer formation. Predisposition to anxiety is one of the principal characteristics of the so-called "peptic ulcer personality."

Allegedly, both acute and chronic stress stimulates pepsin secretion by the stomach via the hypothalamus-pituitary-adrenocortical axis, that is, independently of the vagus nerve.

In patients with CNS injury, the serum gastrin level is unusually high and corresponds to their extraordinary predisposition to stress-ulcer formation.

Anxiety stimulates gastric hydrochloric acid and enzyme secretion but causes ulceration only in predisposed individuals. Hence, here again, we are dealing with a pluricausal pathogenic situation.

A great deal has been written about the relative ulcerogenic effect of various occupations but there is no conclusive evidence that executives have a higher ulcer incidence than their subordinates. As we said in connection with so many stress manifestations, it is not what happens to you but the way you take it that really counts. In some people, the responsibility of giving orders, in others the obligation to follow them, is more stressful. Hence, the best way to avoid stress ulcers is to develop a philosophy of life that permits friction-free interpersonal relations. The frequent combination of peptic ulcers in the upper intestinal tract with ulcerative colitis and other diseases of adaptation likewise argues in favor of a common etiology, namely, stress.

Anatomic studies revealed that stasis and minute infarctions in the mucosa of the stomach and duodenum are usually associated with peptic ulcers and presumably are of pathogenic significance.

There is ample evidence that children are at least as subject to stress ulcer formation as adults.

In one series of women with chronic peptic ulcers, the symptoms regularly disappeared during pregnancy.

Among the therapeutic measures recommended for stress ulcers, ingestion of milk and antacids proved to be particularly efficacious, but a detailed description of the clinical problems would be beyond the scope of this monograph.

Peptic Ulcers

(See also our earlier stress monographs, p. xiii, and *cf.* Psychosomatic Diseases of Adaptation as well as Gastrointestinal System under Morphologic Changes)

Generalities. Gray, S. J., Benson, J. A. Jr., Reifenstein, R. W., Spiro, H. M.: "Chronic stress and peptic ulcer. I. Effect of corticotropin (ACTH) and cortisone on gastric secretion." *J.A.M.A.* **147**: 1529-1537 (1951). B59,935/51

Selye, H.: "The general-adaptation-syndrome and the gastrointestinal diseases of adaptation." *Am. J. Proctol.* **2**: 167-184 (1951). B61,231/51

Review of stress in the pathogenesis of gastrointestinal disease, particularly peptic ulcers, ulcerative colitis, nontropical sprue, appendicitis, various forms of regional and necrotizing enteritis, and gastrointestinal allergies (146 refs.).

Woldman, E. E.: "Acute ulcers of upper gastrointestinal tract. Their relation to systemic stress and adrenal damage." *J.A.M.A.* **149**: 984-987 (1952). B71,586/52

Nine hundred and forty-three consecutive necropsies performed in a hospital indicated 136 cases of acute ulcers and 108 cases of focal hemorrhages in the mucosa of the upper gastrointestinal tract, all of which were ascribed to the alarm reaction phase of the G.A.S.

Gray, S. J., Ramsey, C. G., Reifenstein, R. W.: "Clinical use of the urinary uropepsin determination in medicine and surgery." *N. Engl. J. Med.* **251**: 835-843 (1954). C1,309/54

Extensive studies in man "support the concept that acute and chronic stress stimulates the stomach and increases uropepsin excretion by way of a humoral mechanism involving the hypothalamic-pituitary-adrenal-gastric axis that is independent of the vagus nerve or the gastric antrum" (25 refs.).

Shay, H., Sun, D. C. H.: "Stress and gastric secretion in man. I. A study of the mechanisms involved in insulin hypogly-

cemia." *Am. J. Med. Sci.* **228**: 630-642 (1954). C38,532/54

Vargas, L., Orrego, H., Feuereisen, L. de: "Increased intermedin-like activity in the blood of patients with duodenal ulcer." *J. Clin. Endocrinol. Metab.* **16**: 662-667 (1956). C15,079/56

In about two-thirds of patients with duodenal ulcers the MTH content of the blood was increased. This was not the case in gastric ulcer patients.

Breckenridge, I. M., Walton, E. W., Walker, W. F.: "Stress ulcers in the stomach." *Br. Med. J.* December 19, 1959, pp. 1362-1364. C79,323/59

Diegel, G.: "Utilization of the teaching of the adaptation syndrome in diseases of the digestive tract." *Landarzt* **37**: 997-999 (1961). J24,603/61

Oppen, R. A. M. van, Kortlandt, J. G. A.: "Stress ulcers." *Arch. Chir. Neerl.* **13**: 360-370 (1961). D34,420/61

Review on the pathogenesis and treatment of stress ulcers in man (37 refs.).

Cailar, J. du, Jaquenoud, P.: "Pathologie gastrique et agression aiguë" (Gastric pathology and acute stress). *Agressologie* **4**: 621-653 (1963). G10,972/63

Report on a discussion (with the participation of seven specialists) concerning the pathogenesis of stress ulcers in man and experimental animals.

Gray, S. J.: "Stress and the gastrointestinal tract. Endocrine aspects of peptic ulcer disease." *Am. J. Gastroenterol.* **41**: 243-247 (1964). G10,507/64

Galindez, R. E.: "La hemorragia ulcerosa gastroduodenal dentro del síndrome general de adaptación de Selye" (Gastroduodenal ulcerative hemorrhage within Selye's general adaptation syndrome). *Medicina (Méx.)* **44**: 33-37 (1964). J24,551/64

Schattenfroh, C.: "Das Stress-Ulcus, Klinik und Begutachtung" (Stress ulcer, clinical aspects and expert opinion). *Chirurg.* **37**: 338-343 (1966). G42,453/66

Brihaye, J., Kiekens, R., Voort, G. van der: "Las ulcérations digestives dans les états de stress" (Stress and ulcers of the digestive system). *Acta Chir. Belg.* Supp. I: 1-166 (1966). G39,794/66

Extensive review on the G.A.S., with special reference to stress ulcers and other intestinal disturbances that occur during stress in man.

Wolf, S.: "Stress and the gut." *Gastroenterology* 52: 288-289 (1967).

G77,842/67

Müller, E., Sailer, R., Kremer, K.: "Das akute gastro-duodenale Stress-Ulkus in der Chirurgie" (The acute postoperative gastro-duodenal stress ulcer). *Dtsch. Med. Wochenschr.* 92: 516-522 (1967) (35 refs.).

F78,781/67

Mouillé, P.: "Les ulcérations digestives dans les états de stress" (Digestive ulcerations in stress states). *Presse Méd.* 75: 1523-1525 (1967).

G48,127/67

Spirgi, E., Rossetti, M.: "Über 58 Fälle von Stressulcera" (Stress ulcers. 58 case reports). *Helv. Chir. Acta* 35: 44-51 (1968).

G54,851/68

Review on the clinical and anatomic features of stress ulcers in man (58 personal observations, few refs.).

Skillman, J. J., Bushnell, L. S., Goldman, H., Silen, W.: "Respiratory failure, hypotension, sepsis, and jaundice. A clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach." *Am. J. Surg.* 117: 523-530 (1969) (26 refs.).

J18,262/69

Eckert, N.: "Das Stressulkus als Ursache einer akuten gastrointestinalen Blutung am Ende der Schwangerschaft bei Eklampsie" (Stress ulcer as a cause of acute gastrointestinal hemorrhage at the end of pregnancy with eclampsia). *Zentralbl. Gynaekol.* 91: 1478-1483 (1969).

G72,012/69

Skillman, J. J., Silen, W.: "Acute gastroduodenal 'stress' ulceration: barrier disruption of varied pathogenesis?" *Gastroenterology* 59: 478-482 (1970).

J25,007/70

Rostad, H.: "Stress-ulcus-blödning" (Stress-ulcer-hemorrhage). *Nord. Med.* 84: 1236-1239 (1970) (33 refs., Norwegian with extensive English summary).

H31,391/70

Zer, M., Assudi, A., Dintsman, M.:

"Stress ulcer." *Harefuah* 81: 381-382 (1971) (Hebrew). J23,975/71

Crawford, F. A., Hammon, J. W. Jr., Shingleton, W. W.: "The stress ulcer syndrome. A clinical and pathologic review." *Am. J. Surg.* 121: 644-649 (1971).

G84,520/71

In man, "stress ulcers are common after surgery, trauma, burns, and other stressful situations. This is especially true when steroids are being administered and the complication of sepsis is introduced.... Vagotomy plus gastric resection has been the most successful surgical procedure."

Sós, J., Gáti, T., Csalay, L., Dézsi, I.: *Pathology of Civilization Diseases*, p. 174. Budapest: Akadémiai Kiadó, 1971.

E8,933/71

Many maladies due largely to stress are considered to be "diseases of civilization." A special section is devoted to the role of corticoids and stress in the development of peptic ulcers.

Girvan, D. P., Passi, R. B.: "Acute stress ulceration with bleeding or perforation." *Arch. Surg.* 103: 116-121 (1971).

G85,398/71

Among thirty patients with acute stress ulceration, gastric and duodenal localizations were found with equal frequency, but gastric ulcers were more likely to be multiple.

Atik, M., Matini, K.: "Platelet dysfunction: an important factor in massive bleeding from stress ulcer." *J. Trauma* 12: 834-846 (1972).

G96,123/72

Wolfman, E. F. Jr.: "Gastroduodenal stress ulcers." *Calif. Med.* 116: 62-63 (1972).

J19,879/72

Davenport, H. W.: "Why the stomach does not digest itself." *Sci. Am.* 226: 87-93 (1972).

J11,147/72

Semipopular description of the manner in which the mucosa lining protects the stomach against self-digestion. [How the crater of a chronic gastric ulcer is protected, despite the absence of a mucosa, is not considered (H.S.).]

Robbins, R., Ijdadi, F., Stahl, W. M., Essiet, G.: "Studies of gastric secretion in stressed patients." *Ann. Surg.* 175: 555-562 (1972) (30 refs.).

G89,646/72

Lucas, C. E., Sugawa, C., Friend, W., Walt, A. J.: "Therapeutic implications of disturbed gastric physiology in patients with

stress ulcerations." *Am. J. Surg.* **123**: 25-34 (1972). G88,179/72

Skillman, J. J., Silen, W.: "Stress ulcers." *Lancet* December 16, 1972, pp. 1303-1306 (36 refs.). H62,747/72

Krück, F.: "Pathogenese und Pathophysiologie des stressulkus" (Pathogenesis and pathophysiology of the stress ulcer). *Med. Klin.* **68**: 1389-1393 (1973). H40,146/73

The author believes that it is incorrect to speak of "stress ulcers" without specifying the type. He distinguishes between (1) Curling's ulcer after lesions in the CNS or psychic stress, in which cholinergic mediation leads to over-secretion of acid and pepsin with normal mucus production, (2) Curling's ulcer after burns, especially when complicated by septicemia, hypervolemia and circulatory disturbances, (3) steroid ulcer after treatment with ACTH or glucocorticoids, with quantitative and qualitative diminution of mucus production and (4) ulcers after other stress situations in which blood loss, shock, ischemia and other humoral factors are of central importance (32 refs.).

Hunt, T. K.: "Injury and repair in acute gastroduodenal ulceration." *Am. J. Surg.* **125**: 12-18 (1973). G98,868/73

A review of the literature suggests that "the conditions most commonly associated with acute ulcer disease are burns, shock, severe trauma, sepsis, steroid hormone therapy, hypothalamic stimulation due to brain injury or tumor, and uremia" (30 refs.).

Schmidt-Wilcke, H. A.: "Die akuten Magenschleimhautblutungen" (Acute gastric hemorrhage). *Internist* (Berlin) **14**: 259-264 (1973). H72,799/73

Review of the literature and theoretical considerations on the pathogenesis of stress ulcers (30 refs.).

Wangesteen, S. L., Golden, G. T.: "Acute 'stress' ulcers of the stomach: a review." *Am. Surg.* **39**: 562-567 (1973).

J6469/73

Seidel, W., Lorenz, W., Doenicke, A., Mann, G., Uhlig, R., Rohde, H.: "Histaminfreisetzung beim Menschen und Stressulkus-Pathogenese" (Histamine liberation in man and the pathogenesis of stress ulcers). *Z. Gastroenterol.* **11**: 297-300 (1973).

J24,571/73

In man, the plasma histamine content rises under the influence of various stressors and

may play an important role in the pathogenesis of stress ulcers.

Silen, W.: "Stress ulcers." *Med. Trial Techn. Q.* **20**: 254-266 (1974).

J23,293/74

General characterization of stress ulcers, mainly for the benefit of attorneys.

Silen, W.: "Potpourri dissected." *N. Engl. J. Med.* **291**: 974-975 (1974).

H94,319/74

"Massive upper gastrointestinal bleeding." *Br. Med. J.* March 9, 1974, pp. 403-404.

H85,393/74

Brief editorial on the causes and treatment of "stress ulceration" in the stomach (13 refs.).

Menguy, R., Masters, Y. F.: "Mechanism of stress ulcer. II. Differences between the antrum, corpus, and fundus with respect to the effects of complete ischemia on gastric mucosal energy metabolism." *Gastroenterology* **66**: 509-516 (1974).

J12,433/74

Walt, A. J.: "'Stress ulcer': an unresolved puzzle." *J. Trauma* **14**: 539-540 (1974).

J13,319/74

Sibilly, A., Boutelier, P.: "Les complications digestives du stress" (The digestive complications of stress). *J. Chir. (Paris)* **108**: 117-134 (1974).

J17,165/74

Brief review on stress-induced pancreatitis and gastroduodenal ulcers in man.

History. Cooper, S.: "Pathology of burns and scalds." *Lond. Med. Gaz.* **23**: 837-838 (1839).

72,145/1839

In an eight-year-old girl who died about five weeks after severe scalds of the chest, an ulcer "about the size of a shilling" was noted in the duodenum just beyond the pylorus. Duodenal ulcers were also found after scalds and burns in other children.

Long, J.: "On the post-mortem appearances found after burns." *Lond. Med. Gaz.* **25**: 743-750 (1840).

B4,643/1840

One of the first descriptions of perforating duodenal ulcers, seen in eleven patients who died from extensive burns. "I have been induced to give the two cases of perforation of the duodenum in detail, as I believe they are unique; indeed I am not aware of any case being recorded, of perforation of the gastro-intestinal tube occurring after a burn, except the one I have quoted from Liston, which approximates to my two cases by the perforation being near the pylorus,

and by the change which had taken place in the duodenum."

Brinton, W.: *On the Pathology, Symptoms and Treatment of Ulcer of the Stomach.* London: John Churchill, 1857.

E3,954/1857

The author concludes that "mental anxiety ... so frequently coincides with ulcer that we are fully entitled to regard it as a more or less immediate cause."

Billroth, T.: "Aus klinischen Vorträgen. I. Ueber Duodenalgeschwüre bei Septicämie" (From clinical lectures. About duodenal ulcers in septicemia). *Wien. Med. Wochenschr.* **17:** 705-709 (1867). 23,917/1867

Description of patients with duodenal ulcers following septicemia as a consequence of operations on the thyroid or other causes. The so-called Curling's ulcer after extensive skin burns is also ascribed to the associated blood poisoning, that is, to sepsis.

Bardeen, C. R. "A study of the visceral changes in extensive superficial burns." *J. Exp. Med.* **2:** 501-514 (1897).

B19,954/1897

Autopsy report on several patients who died from severe skin burns revealed gastric or duodenal ulcers and thymicolumphatic atrophy, as well as hepatic and renal changes. Patients who died during the first few hours showed predominantly edematous lymphatic organs. "These lesions of the lymphatic tissue furnish most important additional evidence of a toxæmia after superficial burns."

Guilbert, J., Bounous, G., Gurd, F. N.: "Role of intestinal chyme in the pathogenesis of gastric ulceration following experimental hemorrhagic shock." *J. Trauma* **9:** 723-743 (1969). J10,786/69

Allegedly, gastric ulcers and intestinal hemorrhagic necrosis following extensive burns were observed by Dupuytren (1823), Swan (1823), Cooper (1839) and Long (1840), before Curling (1842) described the lesions which now bear his name. The literature on these and many subsequent observations on peptic ulceration following surgical interventions is reviewed up to recent times, when ulcers were recognized as part of the G.A.S. (98 refs.).

Hinchey, E. J., Hreno, A., Benoit, P. R., Hewson, J. R., Gurd, F. N.: "The stress ulcer syndrome." In: Welch, C. E., *Advances in Surgery*, Vol. 4, p. 325-392. Chicago: Year Book Medical Publ., 1970. J19,355/70

History and clinical characteristics of the stress ulcer syndrome, with comments on its pathogenesis and therapy (185 refs.).

Skillman, J. J.: "Pathogenesis of peptic ulcer: a selective review." *Surgery* **76:** 515-523 (1974). J16,101/74

←Trauma. Fletcher, D. G., Harkins, H. N.: "Acute peptic ulcer as a complication of major surgery, stress, or trauma." *Surgery* **36:** 212-226 (1954). C6,820/54

In man, acute peptic ulcers developed following major surgery, trauma, burns and various other stressors (46 refs.).

Davis, R. A., Wetzel, N., Davis, L.: "Acute upper alimentary tract ulceration and hemorrhage following neurosurgical operations." *Surg. Gynecol. Obstet.* **100:** 51-58 (1955). C10,925/55

Rishholm, L.: "Acute upper alimentary tract ulceration and haemorrhage following surgery or traumatic lesions." *Acta Chir. Scand.* **110:** 275-283 (1956). C12,797/56

Dunn, L. J., Nash, L. D.: "Stress ulcers of the stomach following obstetric and gynecologic surgery." *Am. J. Obstet. Gynecol.* **90:** 1288-1292 (1964). G22,222/64

Kelly, T. R., Schlueter, T. M.: "Stress ulcer following unrelated major surgery." *Am. Surg.* **30:** 338-340 (1964).

F10,634/64

Fogelman, M. J., Garvey, J. M.: "Acute gastroduodenal ulceration incident to surgery and disease. Analysis and review of eighty-eight cases." *Am. J. Surg.* **112:** 651-656 (1966). G41,532/66

Review of eighty-eight cases of acute stress ulcer which developed after surgical trauma, sepsis, and miscellaneous diseases. "Acute stress ulceration is usually present in the form of a single ulcer, either gastric or duodenal" (28 refs.).

Wense, G., Kreuzer, W.: "Stress ulcer" (The stress ulcer). *Bull. Soc. Int. Chir.* **27:** 513-520 (1968). G66,162/68

Stress ulcers frequently occur after traumatic surgical operations and may be associated with greatly increased 17-OHCS excretion.

Eiseman, B., Heyman, R. L.: "Stress ulcers; a continuing challenge." *N. Engl. J. Med.* **282:** 372-374 (1970). H21,079/70

The common occurrence of "stress ulcers" in combat casualties stimulated a review on

the pathology and etiology of this lesion, with special reference to the roles of mucus, gastric-cell growth, histamine and therapeutic measures.

Kunzman, J.: "Management of bleeding stress ulcers." *Am. J. Surg.* **119**: 637-639 (1970). G75,612/70

"Bleeding stress ulcers developed in seventy-four young men without previous ulcer disease and with major injuries received in the Vietnam war." Among various therapeutic procedures (vagotomy, pyloroplasty), rapid, aggressive treatment for the underlying illness was most effective.

Reding, R., Festge, A.: "Über das Auftreten postoperativer und posttraumatischer akuter Erosionen und Ulzerationen des Magens und Zwölffingerdarms" (The occurrence of acute postoperative and posttraumatic erosions and ulcerations of the stomach and duodenum). *Zentralbl. Chir.* **95**: 582-588 (1970). J21,698/70

Lucas, C. E., Sugawa, C., Riddle, J., Rector, F., Rosenberg, B., Walt, A. J.: "Natural history and surgical dilemma of 'stress' gastric bleeding." *Arch. Surg.* **102**: 266-273 (1971). G82,156/71

In patients undergoing major surgery or having septic complications, gastrointestinal bleeding was commonly observed. "Sequential photographic studies of the gastric mucosa performed prior and subsequent to bleeding revealed a wide spectrum of erosions limited to the body of the stomach. Gastric hypersecretion was present in most patients." Determinations of gastric mucus, as well as histologic and EM studies are also reported.

Lev, R., Molot, M. D., McNamara, J., Stremple, J. F.: "'Stress' ulcers following war wounds in Vietnam. A morphologic and histochemical study." *Lab. Invest.* **25**: 491-502 (1971). G87,574/71

Histologic study of stress ulcers following combat wounds in Vietnam. There was "acute inflammation and fibrin in the fresher ulcers and larger erosions. Chronic inflammatory cells, granulation tissue, and advanced epithelial repair were found in the older, deeper ulcers. In noneroded areas, patches of cuboidal surface epithelium with reduced cytoplasmic mucin and, elsewhere, foci of mucous cell hyperplasia were found. The cuboidal epithelium was interpreted as a form of chronic regenerative response to sustained injury. Mast cells were decreased in the areas of regeneration. It is concluded that

stress ulcers are accompanied by the usual type of inflammation and repair, that the injurious stimulus responsible for mucosal damage acts over a prolonged period from the time of original trauma (and/or associated surgery) onward, and that reduction in cytoplasmic mucus and degranulation of mucosal stromal mast cells may contribute to increased susceptibility to mucosal ulceration" (33 refs., excellent photographs).

Stremple, J. F., Molot, M. D., McNamara, J. J., Mori, H., Glass, G. B. J.: "Posttraumatic gastric bleeding. Prospective gastric secretion composition." *Arch. Surg.* **105**: 177-185 (1972). G93,305/72

In nine of fifty combat casualties, bleeding ulcers developed although steroid excretion remained within the normal range. Total gastric juice sialic acid output was independent of bleeding but the total "leak" of plasma protein was greater in the gastric ulcer group. "Initial decreased acid output, accompanied by plasma protein 'leakage' into the gastric lumen, is consistent with back diffusion of H⁺ ions soon after trauma," as has been postulated for stress ulcers occurring in the G.A.S. (33 refs.).

Fischer, R. P., Stremple, J. F.: "Stress ulcers in post-traumatic renal insufficiency in patients from Vietnam." *Surg. Gynecol. Obstet.* **134**: 790-794 (1972). H54,661/72

Stress ulcers are common during posttraumatic renal insufficiency among patients wounded in Vietnam. However, "sepsis, rather than renal insufficiency, probably is the reason for the high incidence of ulcers in these patients."

Fischer, H.: "Das Stress-Ulcus, eine Gefahr für den Unfallverletzten" (The stress ulcer, a danger to the accident victim). *Monatschr. Unfallheilk.* **75**: 124-130 (1972). G90,741/72

Histologic characterization of stress ulcers after severe trauma. There is much necrosis and relatively little inflammation with fibrosis.

Glass, G. B. J., Stremple, J. F.: "Stress ulcers." *Lancet* June 30, 1973, pp. 1506-1507. H71,825/73

Among soldiers wounded in battle, gastric bleeding and gastric or duodenal ulcers are common and are associated with increased nonsulfated glycoprotein secretion into the gastric juice.

Marchal, G., Balmes, M., Vergue, J., Selami, A.: "Les hémorragies par ulcération

de stress" (Hemorrhage due to stress ulcers). *Ann. Chir.* **27**: 1266-1268 (1973).

J10,030/73

Statistical studies on the frequency of "stress ulcers" in man after various surgical interventions.

Sibilly, A., Krivošić, I.: "Troubles digestifs post-agressifs. II. L'ulcère de stress chez les traumatisés crâniens" (Gastrointestinal disorders after injury. II. Stress ulcers after cranial trauma). *Ann. Anesth. Franç.* **15**: 28-31 (1974). J14,623/74

Bowen, J. C., Fleming, W. H.: "A prospective study of stress ulceration in Vietnam." *South Med. J.* **67**: 156-160 (1974).

J10,402/74

Among soldiers who sustained trauma in Vietnam, those with multiple injuries had the highest incidence of stress ulcers. Of twenty-eight substances mentioned as possible mediators of such lesions (electrolytes, steroids, free acid, lactate, gastrin, histamine, 5-HT, renin and so on), none could be identified as the specific etiologic factor.

←Burns. Harkins, H. N.: "Acute ulcer of the duodenum (Curling's ulcer) as a complication of burns: relation to sepsis." *Surgery* **3**: 608-641 (1938) (134 refs.).

E87,072/38

Pruitt, B. A. Jr., Foley, F. D., Moncrief, J. A.: "Curling's ulcer: a clinical-pathology study of 323 cases." *Ann. Surg.* **172**: 523-539 (1970) (35 refs.). H46,172/70

Czaja, A. J., McAlhany, J. C., Pruitt, B. A. Jr.: "Acute gastroduodenal disease after thermal injury. An endoscopic evaluation of incidence and natural history." *N. Engl. J. Med.* **291**: 925-929 (1974). H94,314/74

←Nervous Stimuli. Stewart, D. N., Winser, D. M. de R.: "Incidence of perforated peptic ulcer. Effect of heavy air-raids." *Lancet* February 28, 1942, pp. 259-261. A56,376/42

During heavy air raids over London, the incidence of perforating peptic ulcers increased considerably, presumably as a consequence of emotional stress.

Selye, H.: "Perforated peptic ulcer during air-raid." *Lancet* February 20, 1943, p. 252. A56,386/43

The frequent occurrence of perforated peptic ulcers during air raids over London in 1942 is ascribed to stress. These "air-

raid ulcers" correspond to those produced by various other stressors in the original experiments on the alarm reaction.

Mahl, G. F.: "Anxiety, HCl secretion, and peptic ulcer etiology." *Psychosom. Med.* **12**: 158-169 (1950). D77,743/50

Considerations on an anxiety hypothesis of peptic ulcer etiology and its relation to an oral dependency hypothesis in man (47 refs.).

Wolf, S., Glass, G. B. J.: "Correlation of conscious and unconscious conflicts with changes in gastric function and structure. Observations on the relations of the constituents of gastric juice to the integrity of the mucous membrane." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 665-676. Baltimore: Williams & Wilkins, 1950. B51,936/50

In a patient with a gastric fistula, the various functions of the stomach as well as the naked eye appearance of its mucosa were studied in relation to "spontaneously occurring day to day stresses in the life situation.

... The individual concentrations of pepsin, lysozyme and mucoprotein in the gastric juice appeared to have little bearing on the fragility of the membrane, but when acidity was high and mucoproteose concentration low in association with significant and sustained emotional conflict the gastric mucosa was extraordinarily fragile, leading to the ready appearance of small erosions and hemorrhagic spots."

Hamilton, M.: "The personality of dyspeptics with special reference to gastric and duodenal ulcer." *Br. J. Med. Psychol.* **23**: 182-198 (1950). B64,696/50

A paper based on an M. D. thesis, dealing with statistical studies which suggest that the most characteristic feature of the "peptic ulcer personality" is an anxiety neurosis.

Margolin, S. G., Orringer, D., Kaufman, M. R., Winkelstein, A., Hollander, F., Janowitz, H., Stein, A., Levy, M. H.: "Variations of gastric functions during conscious and unconscious conflict states." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 656-664. Baltimore: Williams & Wilkins, 1950. B51,935/50

Psychoanalytic study of the mental stress factors influencing gastric secretion in man.

Mahl, G. F., Brody, E. B.: "Chronic anxiety symptomatology, experimental stress, and HCl secretion." *Arch. Neurol. Psychiatry* **71**: 314-325 (1954). J13,190/54

Review of the literature on the effect of stress upon gastric acidity in animals and man. In patients, chronic anxiety is associated with increased gastric hydrochloric acid secretion and may be related to ulcerogenesis (18 refs.).

Wolff, P., Levine, J.: "Nocturnal gastric secretions of ulcer and nonulcer patients under stress." *Psychosom. Med.* **17**: 218-226 (1955). J13,311/55

Weiner, H., Thaler, M., Reiser, M. F., Mirsky, I. A.: "Etiology of duodenal ulcer. I. Relation of specific psychological characteristics to rate of gastric secretion (serum pepsinogen)." *Psychosom. Med.* **19**: 1-10 (1957). C31,678/57

Studies on more than two thousand army inductees revealed that, independently, "neither a high rate of gastric secretion nor a specific psychodynamic constellation" caused peptic ulcers. "Together, however, these two parameters constitute the essential determinants in the precipitation of peptic ulcer on exposure to social situations noxious to the specific individual" (24 refs.).

Sawrey, W. L., Conger, J. J., Turrell, E. S.: "An experimental investigation of the role of psychological factors in the production of gastric ulcers in rats." In: Reed, C. F., Alexander, T. E. et al., *Psychopathology. A Source Book*, pp. 200-208. Cambridge, Mass.: Harvard University Press, 1958.

C60,677/58

Experiments indicate "(a) that conflict per se contributes significantly to ulcer formation, (b) that hunger and shock also contribute significantly, but only in interaction, (c) that thirst does not contribute significantly, (d) that weight loss alone cannot account for the differences in ulcer formation between conflict and nonconflict groups, and (e) that weight loss is significantly related to the variables of shock, hunger, and thirst, though in the case of the latter two, only through interaction. However, the weight loss in these cases is not directly related to ulcer formation."

Dunn, J. P., Cobb, S.: "Frequency of peptic ulcer among executives, craftsmen, and foremen." *J. Occup. Med.* **4**: 343-348 (1962). J4,086/62

Statistical studies on several Pittsburgh companies showed that foremen suffered from peptic ulcer more frequently than craftsmen or executives. The data do not support the widely held notion that ulcer

disease is unusually high among executives. "Though both the prevalence and the incidence of peptic ulcer within the several groups correlated well with the level of serum pepsinogen it remains an enigma that the mean pepsinogen levels should be lowest for the foremen and highest for the executives."

Susser, M., Stein, Z.: "Civilisation and peptic ulcer." *Lancet* January 20, 1962, pp. 115-119. D46,685/62

"The immediate effects of war are evident in the rise in perforations and deaths from peptic ulcer which followed air-raids and the stress of war." Statistical studies suggest that with "the sharp rise in morbidity and mortality during this century, peptic ulcer, particularly of the duodenum, has earned a place as one of the 'diseases of civilisation'."

Ayers, A. W., Burr, H. B., Tuttle, W. B.: "Personality concomitants of peptic ulcer among managerial, supervisory, and pre-supervisory personnel." *J. Occup. Med.* **5**: 252-258 (1963) (26 refs.). E57,199/63

Hoffmann, G. L., Englund, P. M.: "The ulcerogenic spouse." *Ariz. Med.* **20**: 252-253 (1963). J23,630/63

Alp, M. H., Court, J. H., Grant, A. K.: "Personality pattern and emotional stress in the genesis of gastric ulcer." *Gut* **11**: 773-777 (1970). G78,877/70

Weiner, H. (ed.): *Advances in Psychosomatic Medicine. 6. Duodenal Ulcer*, p. 200. Basel, München and Paris: S. Karger, 1971. E10,332/71

Collection of nine publications (each followed by a discussion) concerned mainly with the role of psychologic factors in the development of duodenal ulcers in man. Animal experiments and basic research on pathogenesis are also considered.

Grayson, R. R.: "Air controllers syndrome: peptic ulcer in air traffic controllers." *Ill. Med. J.* **142**: 111-115 (1972). G99,015/72

In a large group of ATCs, 32.5 percent suffered from duodenal or gastric ulcers. "Peptic ulcer in this series is concluded to be a stress-related disease, the stress being occupational."

Apter, A., Hurst, L. A.: "Personality and duodenal ulcer." *S. Afr. Med. J.* **47**: 2131-2133 (1973). J8,550/73

Among patients who underwent major sur-

gery, careful comparison of thirty with duodenal ulcers against thirty controls showed no characteristic personality traits which would distinguish the two groups. Hence, the authors conclude that duodenal ulcer is a psychosomatic disease and "a reaction to stress, independent of static personality traits or specific types of emotional conflict."

Bowen, J. C., Fleming, W. H., Thompson, J. C.: "Increased gastrin release following penetrating central nervous system injury." *Surgery* **75**: 720-724 (1974). J12,555/74

In patients with CNS injuries, serum gastrin levels are unusually high. This corresponds to their extraordinary predisposition to stress ulcer formation.

Crocq, L., Rabarihoela, O., Molinie, C., Essioux, H., Cristau, P., Laverdant, C.: "Etude psychosomatique des ulcères duodénaux chez le jeune adulte en milieu militaire" (Psychosomatic study of duodenal ulcer in young adults during military service). *Sem. Hôp. Paris* **51**: 465-469 (1975).

J23,316/75

←Age. Chenoweth, A. I., Dimick, A. R.: "Stress ulcer in infants and children." *Ann. Surg.* **161**: 977-984 (1965) (22 refs.). G30,907/65

Weidenmann, W.: "Die Problematik der schweren Magenblutung im Kindesalter" (Problems of severe gastric hemorrhage in childhood). *Zentralbl. Chir.* **90**: 2321-2327 (1965). F60,332/65

Following severe stress, bleeding peptic ulcers may develop even in very young infants.

Krakowski, A. J.: "Psychophysiological gastrointestinal disorders in children." *Psychosomatics* **8**: 326-330 (1967).

F91,348/67

The most common stress-induced gastrointestinal lesions in children are gastritis, peptic ulcer, ulcerative colitis and diarrhea.

Grosz, C. R., Wu, K. T.: "Stress ulcers: a survey of the experience in a large general hospital." *Surgery* **61**: 853-857 (1967).

G47,260/67

Stress ulcers were found to be most prevalent in the fifty-six- to sixty-five-year age group.

Beraud, C., Campo-Paysaa, A., Savioz, C., Andre, M.: "Ulcères de stress post-opératoires chez l'enfant. (A propos de trois observations)" (Postoperative stress-ulcers in

children. [3 case reports]). *Lyon Méd.* **222**: 1041-1054 (1969). G72,323/69

Krasna, I. H., Schneider, K. M., Becker, J. M.: "Surgical management of stress ulcerations in childhood: report of five cases." *J. Pediatr. Surg.* **6**: 301-306 (1971).

J20,566/71

Detailed clinical study of stress ulcers in infants and children.

Jacobs, S. (ed.): "Stress ulcer in an octogenarian." *J. Louisiana Med. Soc.* **124**: 44-49 (1972). J19,598/72

Pfeiffer, C. J., Fodor, J., Geizerova, H.: "An epidemiologic study of the relationships of peptic ulcer disease in 50-54 year old, urban males with physical, health and smoking factors." *J. Chron. Dis.* **26**: 291-302 (1973). J7,638/73

A study on 402 males aged fifty to fifty-four years, randomly selected from the population of Prague, showed no clearcut correlation between the incidence of peptic ulcer and the ordinary stresses of urban life, although a review of the literature strongly suggests such a relationship (34 refs.).

Spada, A., Damilano, C.: "Ulcere da stress in neonati immaturi" (Stress ulcers in immature newborns). *Minerva Med.* **64**: 3676-3682 (1973). H66,649/73

Review and personal observations on stress ulcers in neonates (42 refs.).

Deckelbaum, R. J., Roy, C. C.: "Peptic ulcer disease: a clinical study in 73 children." *Can. Med. Assoc. J.* **111**: 225-228 (1974).

H89,198/74

Report on seventy-three children with peptic ulcers. "Secondary or stress ulcers accounted for more than one third of the patients, but the true prevalence of this entity is likely higher, for clinical recognition is rare in the absence of a complication, and prodromal symptoms are distinctly uncommon. The stress ulcer is shallow, without underlying induration, and hence difficult to recognize in X-ray pictures."

Franken, E. A. Jr.: "Gastrointestinal bleeding in infants and children. Radiologic investigation." *J.A.M.A.* **229**: 1339-1340 (1974). H90,754/74

A brief review of stress-induced gastric ulcers in children.

Voorhis, C. C., Law, E. J., Macmillan, B. G.: "Operative treatment of Curling's ulcer in children: report of four cases with three

survivors." *J. Trauma* **14**: 175-182 (1974).
J10,330/74

Bertin, P., Bienaymé, J., Lepintre, J., Delalande, C., Pellerin, D.: "Les ulcérations digestives aiguës de stress chez l'enfant. A propos de 36 observations" (Thirty-six observations on acute stress ulcers of the digestive system in children.) *Ann. Chir.* **28**: 21-33 (1974). J11,214/74

←Various Other Stimuli. Leśniok, A., Bajdur, M., Sosnierz, D.: "Role of some etiopathogenetic factors in gastric and duodenal peptic ulcers in miners." *Med. Pracy* **21**: 202-208 (1970) (Polish). J16,123/70

In Polish miners, hereditary predisposition and night shift work were found to increase the incidence of peptic ulcers.

Thieme, R., Theisinger, W.: "Stressulkus im Wochenbett (Ein kasuistischer Beitrag)" (Stress ulcer during the puerperium [A case report]). *Zentralbl. Gynaekol.* **93**: 894-897 (1971). G84,873/71

In general, patients with peptic ulcers tend to be free of symptoms during pregnancy. In one woman, however, a perforating duodenal ulcer developed after delivery.

Treatment. Salasin, R. G., Bowers, W. F.: "Hemorrhage from stress ulcer treated by resection." *Surgery* **34**: 821-825 (1953) (28 refs.). G86,654/53

Bryant, L. R., Griffen, W. O. Jr.: "Vagotomy and pyloroplasty. An inadequate operation for stress ulcers?" *Arch. Surg.* **93**: 161-170 (1966). J17,153/66

In man, partial gastrectomy with vagotomy is recommended as the initial operation when treating hemorrhage associated with stress ulcerations."

Rosoff, C. B., Goldman, H.: "Effect of the intestinal bacterial flora on acute gastric stress ulceration." *Gastroenterology* **55**: 212-222 (1968). G60,200/68

In rats, polymyxin B offers significant protection against acute stress ulcers elicited by restraint, probably because this nonabsorbable antibiotic reduces the coliform bacteria in the intestine. "This change in the flora results in a decrease in the motor tone of the stomach and cecum, and in the volume and concentration of gastric acid produced in response to the stress of immobilization. The protection offered by the coliform-poor state is eliminated when endotoxin is given to antibiotic-treated animals." Conversely, systemic administration of endotoxin increases

both gastric acid and stress ulcers. "It is suggested that, under the conditions induced by stress, detoxification mechanisms suffer and permit absorbed bacterial products to reach the systemic circulation and stimulate the hypothalamus."

Kirtley, J. A., Scott, H. W. Jr., Sawyers, J. L., Graves, H. A. Jr., Lawler, M. R.: "The surgical management of stress ulcers." *Ann. Surg.* **169**: 801-809 (1969). G66,269/69

Douglass, H. O. Jr., LeVeen, H. H.: "Stress ulcers. A clinical and experimental study showing the roles of mucosal susceptibility and hypersecretion." *Arch. Surg.* **100**: 178-181 (1970). G72,800/70

In surgical patients, "gastroduodenal ulceration occurs in direct proportion to the degree of stress. The relative frequency of ulceration on thoracic and vascular surgical wards confirms previous reports... The therapy of stress ulcer by gastric resection markedly reduced the probability of further ulcer complications in long-term follow-up."

Lucas, C. E., Sugawa, A., Walt, A. J.: "Prospective analysis of factors influencing the development of stress ulceration." *Surg. Forum* **21**: 308-310 (1970). J10,787/70

Brief résumé on the development of stress ulcers in men, most of whom had concomitant gastric hypersecretion and signs of cellular hypoxia. "These changes occurred despite a variety of preventive antacid regimens."

Kunzman, J.: "Management of bleeding stress ulcers." *Am. J. Surg.* **119**: 637-639 (1970). G75,612/70

"Bleeding stress ulcers developed in seventy-four young men without previous ulcer disease and with major injuries received in the Vietnam war." Among various therapeutic procedures (vagotomy, pyloroplasty), rapid, aggressive treatment for the underlying illness was most effective.

Chernov, M. S., Hale, H. W. Jr., Wood, M.: "Prevention of stress ulcers." *Am. J. Surg.* **122**: 674-677 (1971). G86,818/71

Following severe surgical trauma or burns, serum vitamin A levels dropped sharply in man. Allegedly, "treatment with high doses of parenteral vitamin A reduces the risk of gastroduodenal ulceration in these severely stressed patients" (23 refs.).

Crawford, F. A., Hammon, J. W. Jr., Shingleton, W. W.: "The stress ulcer syndrome. A clinical and pathologic review." *Am. J. Surg.* **121**: 644-649 (1971). G84,520/71

In man, "stress ulcers are common after surgery, trauma, burns, and other stressful situations. This is especially true when steroids are being administered and the complication of sepsis is introduced.... Vagotomy plus gastric resection has been the most successful surgical procedure."

Assudi, A., Zer, M., Dintsman, M.: "Gastrectomy in childhood for massive bleeding from stress ulcer." *Harefuah* **81**: 373-374 (1971) (Hebrew). J23,861/71

Chong, G. C., Kelly, K. A.: "Surgical management of acute gastric and duodenal stress ulcers." *Surg. Clin. N. Am.* **51**: 863-870 (1971). J20,177/71

Larena, A., Zimmermann, F., Zehle, A.: "Behandlung der 'Stress-Ulkus'-Blutung durch Magenunterkühlung" (Treatment of "stress-ulcer" hemorrhage using cryotherapy). *Fortschr. Med.* **90**: 1005-1008 (1972). H68,729/72

Gastric cooling is not a particularly efficient way of combatting bleeding from stress ulcers.

Chernov, M. S., Cook, F. B., Wood, M., Hale, H. W. Jr.: "Stress ulcer: a preventable disease." *J. Trauma* **12**: 831-833 (1972). G96,122/72

"Large doses of vitamin A reduce the risk of stress ulcer in injured patients."

Raithel, D., Mühe, E., Decker, D.: "Zur Therapie des Stressulcus" (Therapy of stress ulcer). *Chirurg.* **43**: 328-331 (1972). G92,453/72

"Gastric resection was shown to be the treatment of choice."

Byrne, J. J., Guardione, V. A.: "Surgical treatment of stress ulcers." *Am. J. Surg.* **125**: 464-467 (1973). J2,450/73

Athanasoulis, C. A., Brown, B., Shapiro, J. H.: "Angiography in the diagnosis and management of bleeding stress ulcers and gastritis." *Am. J. Surg.* **125**: 468-473 (1973). J2,451/73

Taylor, P. C., Loop, F. D., Hermann, R. E.: "Management of acute stress ulcer after cardiac surgery." *Ann. Surg.* **178**: 1-5 (1973). J4,304/73

Sibilly, A., Krivošić, I.: "L'ulcère de stress chez les traumatisés crâniens" (Stress ulcers in patients with cranial trauma). *Ann. Chir.* **27**: 1240-1244 (1973). J10,029/73

The common gastroduodenal ulcers in patients with cranial traumas can be prevented by oral administration of hypertonic glucose.

Rendall, M.: "The use of antacids in an intensive care unit." *J. Int. Med. Res.* **2** Supp. 2: 23-28 (1974). H97,987/74

Clinical and experimental studies on the use of antacids in the treatment of acute "stress ulcers" in man and rabbits.

Markoff, N., Infanger, K., Cahannes, M., Herwig, W.: "Prophylaxe und Therapie der Stresserosionen und des Stressulkus mit Gefarnil (Gefarnyl-Gefarnesylazetat)" (Prophylactic treatment of bleeding stress erosions and ulcers with Gefarnil [Gefarnyl-Gefarnesylacetate]). *Praxis* **63**: 1573-1576 (1974). J21,448/74

Usardi, M. M., Franceschini, J., Mandelli, V., Daturi, S., Mizzotti, R.: "Prostaglandins VIII: a proposed role for PGE₂ in the genesis of stress-induced gastric ulcers." *Prostaglandins* **8**: 43-51 (1974). J18,077/74

"A protective effect on stress-induced gastric ulcers has been demonstrated for PGE₂ and PGF_{2α} in rats."

Hinsdale, J. G., Engel, J. J., Wilson, D. E.: "Prostaglandin E in peptic ulcer disease." *Prostaglandins* **6**: 495-500 (1974).

J13,965/74

Patients with peptic ulcers have a deficiency in the prostaglandin E concentration of plasma and gastric juice. This may indicate that treatment of peptic ulcers by prostaglandin E represents a substitutive type of therapy (12 refs.).

Ammann, J., Schöll, H., Vogt, B.: "Die selektive intraarterielle Vaso-pressininfusion bei der Behandlung von Blutungen des oberen Gastrointestinaltrakts" (The treatment of upper gastrointestinal bleeding by selective intra-arterial vasopressin infusion). *Helv. Chir. Acta* **41**: 147-150 (1974).

J13,039/74

In patients who developed stress ulcers after extensive surgery, the much-recommended intra-arterial vasopressin infusion was only moderately successful.

Winawer, S. J., Sherlock, P., Sonenberg, M., Vanamee, P.: "Beneficial effect of human growth hormone on stress ulcers." *Arch. Intern. Med.* **135**: 569-572 (1975).

J23,616/75

"Human growth hormone was effective in healing erosions and controlling hemorrhage in six of eight patients with stress ulcers."

Experimental Peptic Ulcers

Production of Experimental Peptic Ulcers. The occurrence of acute hemorrhagic gastric and upper-intestinal ulcers was described as one of the characteristic manifestations of the alarm reaction in the first publication in which the latter was reported. Ever since then, a large number of investigators have examined the production of experimental peptic ulcers by the most diverse stressors in rats and other species.

Unlike thymicolumphatic involution, eosinopenia, lymphopenia and many other characteristics of stress, the causation of peptic ulcers does not depend upon the presence of the pituitary or the adrenals, since they occur even after hypophysectomy or adrenalectomy. In fact, it appears that in the absence of the pituitary-adrenal axis, animals become particularly sensitive to the production of gastrointestinal erosions by stress, perhaps as a consequence of their greatly increased responsiveness to any aggression. Undoubtedly, these gastrointestinal ulcerations are part of the damage, not of the defense, elicited by stressors.

Curiously, a great excess of glucocorticoids can also provoke peptic ulcers, or at least condition the mucosa for their production during stress in both experimental animals and man. Here, the pathogenic situation is particularly complicated, but present evidence suggests that any decrease in the vitality of the gastric mucosa predisposes it to erosion by the digestive juices contained in the stomach. For example, in rabbits, the gastric wall usually digests itself and perforates after death. Apparently, hitherto unidentified vital mechanisms must continuously be at work to protect the gastric mucosa against self-digestion. This protection is impaired during severe stress, perhaps owing to the decrease in blood pressure, temperature, metabolism and so on. In addition, autonomic nervous impulses, especially cholinergic secretory stimuli, appear to participate in the production of these ulcers. Here, corticoids can play a dual role by protecting the mucosa when they antagonize shock and by predisposing it to ulceration when given in large amounts that suppress defensive phenomena in general, particularly protective granuloma formation in the connective tissue under the mucosa. That is why the crater of chronic ulcers often perforates in patients given large amounts of corticoids (for example, for rheumatoid arthritis). A better understanding of this complex pathogenesis, in which a general decrease in vitality, secretory autonomic impulses and corticoids participate, helps to explain many of the apparently paradoxical reports in the literature (for example, the fact that under varying circumstances corticoids can prevent or produce ulcers).

A great deal has been said about the experiments on "executive monkeys." Rhesus monkeys were placed in restraining chairs where some of them could, while others could not, prevent electric shocks by pressing a lever. Unexpectedly, those that had "executive control" over their stressor developed gastric and duodenal ulcers even more frequently than did the controls. These findings have been regarded as illustrating the high stressor effect of decision making, but this interpretation is not unanimously accepted.

Comparison of ulcer production in rats by avoidable and unavoidable electroshocks led to the concept that alterations in feedback from responding can considerably influence ulcer formation. This may explain the "executive monkey" phenomenon.

Gastric ulcers developed in rats exposed to various stressors, especially if they were sacrificed only two hours after the stress period. Presumably, reversal from stressful to ordinary conditions is also an ulcerogenic factor.

EM studies have shown that, in rats, gastric ulcers produced by a response-avoidance procedure or restraint begin with an initial surface breakthrough involving only a few cells and then the mucosal lesions increase by erosion of the more vulnerable lateral and basal cell surfaces.

Although acute stress ulcers are usually localized in the gastric mucosa, especially in rats, this is not always the case. Both acute and chronic duodenal ulcers may also develop during stress.

It has been claimed that the ulcer-producing agent can be transmitted through the blood in rats united by parabiosis since erosions occur in both partners even if only one is restrained on a mobile cart which the unrestrained partner is free to pull about. However, it may be assumed that under these conditions both animals are under considerable stress.

Certain drugs appear to have a specific ulcerogenic tendency. Thus, in the rat (which, as we have said, is normally rather resistant to duodenal ulcer production) propionitrile, and even more consistently, cysteamine produces perforating duodenal ulcers. The relationship of these to typical stress ulcers remains to be clarified, but the cysteamine-induced duodenal ulcers of the rat generally respond to the same therapeutic agents as the spontaneous duodenal ulcers of man; hence "they represent a useful model to detect antiulcer agents, and to study the mechanism of duodenal ulcer formation."

Large doses of digitoxin (like propionitrile and cysteamine) allegedly produce duodenal ulcers, but in our experience this has occurred only exceptionally.

Sensitization, Prophylaxis and Treatment of Experimental Stress Ulcers. Among the factors conditioning the gastric mucosa for stress-induced ulceration, I already alluded briefly to the role of corticoids and autonomic nervous impulses; these influence the resistance and secretory activity of the gastric mucosa.

In dogs, gastroduodenal ulcers were produced by electroshock stress, especially after reserpine sensitization. This synergistic effect was ascribed to the peptic action of gastric juice upon a mucosa damaged by angiitis.

Experiments on stress-induced ulcers in the rat have shown that fasting, cold and various other agents that aggravate stress in general also increase the tendency to develop gastrointestinal ulcers, whereas local application of antacids or glucose exerts a prophylactic effect.

The ulcers produced by stressors differ qualitatively from those elicited by the histamine liberator 48/80 in that the latter are readily prevented by glucocorticoids although these can themselves provoke gastric erosions if administered in very high doses.

Vagotomized rats are relatively resistant to stress ulcer formation, whereas—as previously stated—hypophysectomy or adrenalectomy predisposes to it.

The healing of the restraint-induced gastric ulcers is delayed by glucocorticoids in the rat presumably because of interference with the production of the protective granuloma in the ulcer crater.

Among other drugs that prevent stress ulcer formation in rats, we may mention anti-cholinergics, CNS depressants, fusaric acid (a dopamine hydroxylase inhibitor), nicotinic acid, chlorpromazine, asiaticoside (which also prevents cysteamine-induced duodenal ulcers) and prostaglandins. On the other hand, the ulcerogenic effect of stress-

ors is aggravated in rats by acetylsalicylic acid or large doses of reserpine (which is ulcerogenic in itself).

Curiously, atropine and other anticholinergic agents protect against ulcers when given in small doses; at the same time, they may produce ulcers in the proventriculus, which is normally unaffected by stress.

Calcitonin offers considerable protection against restraint-induced gastric ulcers.

Diazepam, vagotomy and particularly, combined application of both agents, offer considerable protection against stress-induced gastric ulcers in the rat. Presumably, the two act through different mechanisms.

Experimental Peptic Ulcers

(See also our earlier stress monographs, p. xiii)

Generalities. Gray, S. J., Ramsey, C. G.: "Adrenal influences upon the stomach and the gastric responses to stress." *Rec. Prog. Horm. Res.* **13:** 583-617 (1957).

C38,192/57

Review of the literature and personal observations on the participation of corticoids in stress-induced peptic ulcers. "The adrenal-gastric relationship may be considered to be either on a 'permissive' or 'conditioned' basis in accord with the recent hypotheses of Ingle and of Selye. Under normal circumstances the stomach enjoys a semi-autonomous role relative to the adrenal cortex, requiring the presence of normal adrenocortical function for acid-peptic activity. During conditions of stress, however, the stomach is more directly under adrenocortical control" (70 refs.).

Roger, M., Alexy, G.: "Experimentelle Magengeschwüre durch verschiedenartige chirurgische Eingriffe" (Experimental stomach ulcer caused by different surgical procedures). *Z. Gesamte Exp. Med.* **138:** 57-61 (1964). F7,455/64

In rats, the stress of surgical interventions, hemorrhage or tourniquet readily produces gastric ulcers (18 refs.).

Sawrey, J. M., Sawrey, W. L.: "Age, weight, and social effects on ulceration rate in rats." *J. Comp. Physiol. Psychol.* **61:** 464-466 (1966). J22,889/66

Lorenz, W., Feifel, G.: "Neue Gesichtspunkte zur Pathogenese des Stress- und Steroidulkus" (New viewpoints in the etiopathology of stress- and steroid-induced ulcer). *Dtsch. Med. Wochenschr.* **95:** 1848-1850 (1970). H30,240/70

Kilmore, M. A., Noel, W. K., Terry,

W. H.: "Interactions of stress, food intake, and drug in producing peptic ulcers." *Res. Commun. Chem. Pharmacol.* **4:** 391-404 (1972). H59,523/72

Bounous, G.: "Tryptic enteritis: its role in the pathogenesis of stress ulcer and shock." *Can. J. Surg.* **12:** 397-409 (1969) (92 refs.). H36,642/69

Hase, T., Moss, B. J.: "Microvascular changes of gastric mucosa in the development of stress ulcers in rats." *Gastroenterology* **65:** 224-234 (1973). J5,152/73

Observations on rats exposed to "rotational stress" in a centrifuge followed by injection of India ink or silicone rubber into the gastric vasculature indicate that "mucosal ischemia is caused by contraction of connecting arterioles, and that persistent, focal ischemia of the gastric mucosa triggers tissue damage and development of stress ulcer" (20 refs.).

Mullane, J. F., Wilfong, R. G., Phelps, T. O., Fischer, R. P.: "Metabolic acidosis, stress and gastric lesions in the rat." *Arch. Surg.* **107:** 456-459 (1973). J5,966/73

In rats the acidosis induced by restraint and ingestion of ammonium chloride was compared with that in patients with renal failure. "These studies suggest that metabolic acidosis may account in part for gastric lesions associated with renal failure."

Horowitz, M. I., Slomiany, B. L., Slomiany, A.: "Changes in gastric mucosa lipid profile with development of stress-ulcer in rats." *Fed. Proc.* **33:** 259 (1974). H83,955/74

Desiderato, O., MacKinnon, J. R., Hissom, H.: "Development of gastric ulcers in rats following stress termination." *J. Comp. Physiol. Psychol.* **87:** 208-214 (1974). J5,848/74

In rats exposed to various stressors, gastric ulcers developed most readily if the rats were sacrificed about two hours after the termination of the stress period. Apparently, sudden reversal from stressful to ordinary conditions, rather than the delay *per se* is the major ulcerogenic factor.

Harding, R. K., Morris, G. P.: "An ultrastructural study of stress ulcers in the rat" (abstracted). *Proc. Can. Fed. Biol. Soc.* **17**: 165 (1974). H92,179/74

Menguy, R., Masters, Y. F.: "Gastric mucosal energy metabolism and 'stress ulceration.'" *Ann. Surg.* **180**: 538-548 (1974) (29 refs.). J18,523/74

Slomiany, A., Slomiany, B. L., Horowitz, M. I.: "Studies on changes in lipid profiles of the rat gastric mucosa with stress ulcers." *Clin. Chim. Acta* **59**: 215-226 (1975). J21,844/75

←Neuropsychologic Stimuli. Brady, J. V.: "Ulcers in 'executive' monkeys." *Sci. Am.* **199**: 95-99 (1958). B28,871/58

Rhesus monkeys were placed in restraining chairs where some of them could, and others could not, prevent electric shocks by pressing a lever. Those that had control over the situation, the "executive monkeys," developed gastric and duodenal ulcers while the controls did not. Unexpectedly, even prolonged periods of this type of stress were not ulcerogenic, and "periodic emotional stress apparently causes ulcers only if its period coincides with that of some natural rhythm of the gastrointestinal system."

Levrat, M., Lambert, R.: "Experimental ulcers produced in rats by modification of environment." *Gastroenterology* **37**: 421-426 (1959). C77,394/59

Production of gastric ulcers in rats by the stress of placement in a shaking cage and intermittent photic stimulation.

Paré, W.: "The effect of conflict and shock stress on stomach ulceration in the rat." *J. Psychosom. Res.* **6**: 223-225 (1962). J19,162/62

Polish, E., Brady, J. V., Mason, J. W., Thach, J. S., Niemeck, W.: "Gastric contents and the occurrence of duodenal lesions in the rhesus monkey during avoidance behavior." *Gastroenterology* **43**: 193-201 (1962). J23,014/62

Foltz, E. L., Millett, F. E.: "Experimental

psychosomatic disease states in monkeys. I. Peptic ulcer—'executive monkeys.'" *J. Surg. Res.* **4**: 445-453 (1964) (39 refs.).

D18,871/64

Pearl, J. M., Ritchie, W. P. Jr., Gilsdorf, R. B., Delaney, J. P., Leonard, A. S.: "Hypothalamic stimulation and feline gastric mucosal cellular populations. Factors in the etiology of the stress ulcer." *J.A.M.A.* **195**: 281-284 (1966). F60,597/66

In cats, "low intensity stimulation of the anterior hypothalamus resulted in a marked hyperplasia of all gastric mucosal cellular elements within 48 to 72 hours. This was sustained until ulceration occurred producing a mixed picture of fibrosis and hyperplasia. If the vagus nerve was sectioned prior to stimulation, no hyperplasia was noted."

Weiss, J. M.: "Effects of coping responses on stress." *J. Comp. Physiol. Psychol.* **65**: 251-260 (1968). G56,996/68

Observations on rats comparable to the "executive monkey" experiments in which electric shocks could or could not be prevented by the animal. Conditions determining gastric ulcer formation are examined.

Muggenburg, B. A., Kowalczyk, T., Olson, W.: "Effect of ambient temperature on gastric lesions and gastric secretion in swine." *Am. J. Vet. Res.* **32**: 603-608 (1971). J17,593/71

In pigs exposed to the recording of a pig in distress, ambient temperature influences gastric secretion and the development of stress ulcers.

Weiss, J. M.: "Effects of coping behavior in different warning signal conditions on stress pathology in rats." *J. Comp. Physiol. Psychol.* **77**: 1-13 (1971). G86,209/71

Weiss, J. M.: "Effects of punishing the coping response (conflict) on stress pathology in rats." *J. Comp. Physiol. Psychol.* **77**: 14-21 (1971). G86,210/71

Weiss, J. M.: "Effects of coping behavior with and without a feedback signal on stress pathology in rats." *J. Comp. Physiol. Psychol.* **77**: 22-30 (1971). G86,211/71

Paré, W. P.: "Conflict duration, feeding schedule, and strain differences in conflict-induced gastric ulcers." *Physiol. Behav.* **8**: 165-171 (1972). H73,769/72

Allen, H. M.: "Gastrointestinal erosions in wild rats subjected to 'social stress.'" *Life Sci. [I]* **11**: 351-356 (1972). G90,995/72

Weiss, J. M.: "Influence of psychological variables on stress-induced pathology." In: Porter, R. and Knight, J., *Physiology, Emotion and Psychosomatic Illness*, pp. 253-278. Amsterdam, London and New York: Associated Scientific, 1972. J15,758/72

In rats exposed to electroshocks, predictability, avoidability and escapability of the stressor had a considerable influence upon the severity of tissue pathology. The theory is developed which holds "that ulceration is a function of two variables: the number of coping attempts an animal makes and the informational feedback it receives from making the coping attempts. Experiments have been carried out which show that alterations in feedback from responding greatly increase or decrease ulceration. The theory also explains a well-known paradoxical finding, the 'executive monkey' phenomenon."

Mikhail, A. A.: "Stress and ulceration in the glandular and nonglandular portions of the rat's stomach." *J. Comp. Physiol. Psychol.* **85**: 636-642 (1973). J8,643/73

Allegedly, "conditioned fear and conflict produce ulceration in the nonglandular portion of the stomach (rumen), while immobilization produces ulceration in the glandular portion (corpus)" in rats.

Freimark, S. J.: "Effects of electrical stimulation of the brain on the formation of acute gastric lesions." *Physiol. Behav.* **11**: 855-859 (1973). J8,677/73

In rats on a schedule of food-reinforced bar pressing, exposure to an unpredictable number of electric shocks induced the formation of gastric ulcers. High but not low frequency electric stimulation of the medial forebrain bundle attenuated the gastric changes produced by unpredictable footshock. Electric stimulation of the brain was used as a positive reinforcing event, since previous studies have shown it to be effective in this respect.

Morris, G. P., Harding, R. K.: "Topography and fine structure of acute fundic mucosal erosions in the rat." *Lab. Invest.* **30**: 639-646 (1974). J12,845/74

"Acute focal mucosal lesions occurred in rats following exposure to a response-avoidance schedule of 3 to 12 hours' duration. The topography of the fundic mucosa of experimental, yoked control, and normal animals was compared in the scanning electron microscope. Transmission electron microscopy was employed to substantiate and clarify the re-

sults of these topographic studies." The authors believe that "after an initial surface breakthrough involving a small number of cells, mucosal lesions increase in area, primarily by erosion of the more vulnerable lateral and basal cell surfaces."

→Electric Stimuli. Sawrey, W. L., Weisz, J. D.: "An experimental method of producing gastric ulcers." *J. Comp. Physiol. Psychol.* **49**: 269-270 (1956). G46,668/56

Gastric ulcers developed in fasted rats kept in a cage where they received an electric shock every time they approached receptacles containing food or water.

Brodie, D. A., Hanson, H. M., Sines, J. O., Ader, R.: "Current research on gastric ulcers." *J. Neuropsychiatry* **4**: 388-408 (1963). J2,287/63

Symposium on the experimental production of stress ulcers, particularly by restraint and electroshock, in the stomach of the rat. The influence of diet, vagotomy, adrenalectomy, corticoids, hypophysectomy, anticholinergic drugs and so on, upon these erosions is discussed (54 refs.).

Selzer, M. L.: "Stress ulcers and renal disease following electric convulsive therapy." *Psychiatr. Q.* **37**: 509-517 (1963).

J24,548/63

Moreva, E. V.: "Biochemical changes in the brain during reflexes causing degeneration of the gastric mucosa." *Biull. Èksp. Biol. Med.* **62** No. 7: 49-52 (1966) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **62**: 772-774 (1966). J24,289/66

In rats stressed by combined electroshock and restraint, the development of gastric lesions was accompanied by a "reduction in the level of bound acetylcholine mainly in the hypothalamic region and by a decrease in the amount of free acetylcholine mainly in the cerebral hemisphere." The GABA level of the brain was likewise diminished.

Weiss, J. M.: "Somatic effects of predictable and unpredictable shock." *Psychosom. Med.* **32**: 397-408 (1970). G77,862/70

Observations on rats exposed to electroshock show that "the same physical stressor can be markedly altered by psychologic factors such as predictability."

Gliner, J. A.: "Predictable vs. unpredictable shock: preference behavior and stomach ulceration." *Physiol. Behav.* **9**: 693-698 (1972). J444/72

In rats, unpredictable electroshock caused a greater incidence of gastric ulcers than did predictable shock.

Freimark, S. J.: "Effects of electrical stimulation of the brain on the formation of acute gastric lesions." *Physiol. Behav.* **11**: 855-859 (1973). *J8,677/73*

In rats on a schedule of food-reinforced bar pressing, exposure to an unpredictable number of electric shocks induced the formation of gastric ulcers. High but not low frequency electric stimulation of the medial forebrain bundle attenuated the gastric changes produced by unpredictable foot-shock. Electric stimulation of the brain was used as a positive reinforcing event since previous studies have shown it to be effective in this respect.

Wald, E. D., Mackinnon, J. R., Desiderato, O.: "Production of gastric ulcers in the unrestrained rat." *Physiol. Behav.* **10**: 825-827 (1973). *J3,751/73*

In unrestrained rats, gastrointestinal ulcers developed following six hours of exposure to intermittent electroshocks.

Hara, M.: "Gastroduodenal ulcers in dogs produced by electric stress after reserpine." *Nihon Univ. J. Med.* **16**: 119-128 (1974). *J15,282/74*

An article on production of gastroduodenal ulcers by electric stimulation and reserpine in pretreated dogs. The reserpine-stress-induced ulcer is ascribed to the peptic action of gastric juice upon a mucosa damaged by angiitis. Special attention is given to the Japanese literature which is unavailable in English (24 refs.).

←**Restraint.** Rossi, G., Bonfils, S., Lief-fogh, F., Lambling, A.: "Technique nouvelle pour produire des ulcérations gastriques chez le rat blanc: l'ulcère de contrainte" (A new method of producing gastric ulcers in the white rat: the restraint ulcer). *C.R. Soc. Biol. (Paris)* **150**: 2124-2126 (1956).

J3,771/56

Stress ulcers were produced in rats restrained in a wire grill tube for twenty hours.

Brodie, D. A., Hanson, H. M.: "A study of the factors involved in the production of gastric ulcers by the restraint technique." *Gastroenterology* **38**: 353-360 (1960).

C87,271/60

Mice, rats, guinea pigs and hamsters showed a high incidence of gastric ulcers fol-

lowing restraint, whereas rabbits and monkeys were much more resistant. Fasting predisposed the rat to this type of stress ulcer. Young rats proved to be more susceptible than old animals. Hypophysectomy and bilateral subdiaphragmatic vagotomy did not significantly reduce the incidence of restraint ulcers, whereas bilateral adrenalectomy considerably increased it.

Hanson, H. M., Brodie, D. A.: "Use of the restrained rat technique for study of the anti-ulcer effect of drugs." *J. Appl. Physiol.* **15**: 291-294 (1960). *C83,740/60*

In rats, atropine and other anticholinergic drugs inhibited restraint-induced gastric ulcers. Among the CNS-active agents, chlorpromazine, benactyzine and pentobarbital had a protective effect, but acetazolamide was inactive in this respect. Prednisolone delayed healing of existent ulcers.

François, G. R., Sines, J. O.: "Stress induced stomach lesion as related to destruction of the sympathetic ganglia." *J. Psychosom. Res.* **5**: 191-193 (1961).

J23,515/61

"Moderate to marked reduction in the number of cells in the cervical ganglia is related to a higher incidence of stomach lesion development in the rat under stress" (caused by restraint).

Brodie, D. A.: "Ulceration of the stomach produced by restraint in rats." *Gastroenterology* **43**: 107-109 (1962). *J16,349/62*

Brodie, D. A., Hanson, H. M., Sines, J. O., Ader, R.: "Current research on gastric ulcers." *J. Neuropsychiatry* **4**: 388-408 (1963). *J2,287/63*

Symposium on the experimental production of stress ulcers, particularly by restraint and electroshock, in the stomach of the rat. The influence of diet, vagotomy, adrenalectomy, corticoids, hypophysectomy, anticholinergic drugs and so on, upon these erosions is discussed (54 refs.).

Guth, P. H., Mendick, R.: "The effect of chronic restraint stress on gastric ulceration in the rat." *Gastroenterology* **46**: 285-286 (1964). *G18,489/64*

Restraint is very useful for producing experimental ulcers in the rat, but after a certain time adaptation occurs and during the phase of resistance the ulcerogenic effect of this stressor diminishes.

Frisone, J. D., Essman, W. B.: "Stress-

induced gastric lesions in mice." *Psychol. Rep.* **16**: 941-946 (1965). G41,731/65

"Immobilization-induced stress contributed little more to the incidence and severity of gastric lesions in mice than did food deprivation alone." Apparently, the gastric ulcers produced by restraint are essentially due to fasting.

Sines, J. O.: "Elevated activation level as a primary characteristic of the restraint stress-ulcer-susceptible rat." *Psychosom. Med.* **28**: 64-69 (1966). G42,964/66

Restraint is most effective in producing gastric ulcers in rats if it is imposed at the peak of their activity, whether spontaneous or artificially induced.

Buchel, L., Gallaire, D.: "Influence de la température ambiante sur la production d'ulcères de contrainte chez le rat" (Influence of surrounding temperature on the production of restraint ulcers in rats). *C.R. Soc. Biol. (Paris)* **160**: 1817-1820 (1966).

F78,016/66

A decrease of the surrounding temperature from 24 to 14°C facilitates the production of restraint ulcers in rats, whether or not they are previously exposed to twenty-four hours of fasting. Yet starvation facilitates and accelerates the development of such restraint ulcers. On the other hand, body temperature does not appear to be the only important factor since rats kept at warm temperatures (28-32°C) still show gastric erosions, whereas treatment with phenobarbital or chloral hydrate during restraint aggravates the hypothermia and yet diminishes ulcer frequency.

Robert, A., Phillips, J. P., Nezamis, J. E.: "Production by restraint, of gastric ulcers and of hydrothorax in the rat." *Gastroenterology* **51**: 75-81 (1966). G40,473/66

In rats, restraint produced gastric ulcers and hydrothorax within four to six hours. Overnight fasting prevented the hydrothorax and reduced the gastric ulcerations (contrary to previous reports). Restraint ulcers and hydrothorax "were also inhibited by crowding of the animals, a rise in ambient temperature, or administration of prednisolone."

Brodie, D. A., Hanson, H. M.: "Restraint-induced gastric lesions." *J. Indian Med. Prof.* **12**: 5601-5606 (1966). J24,576/66

Wilson, T. R.: "Age and susceptibility to gastric ulceration in male and female rats." *Gerontologia (Basel)* **12**: 226-230 (1966). F78,288/66

Young rats are much more susceptible to restraint-induced gastric ulcers than adults.

Mikhail, A. A., Holland, H. C.: "A simplified method of inducing stomach ulcers." *J. Psychosom. Res.* **9**: 343-347 (1966).

J22,879/66

Description of a simplified method of restraint to produce gastric ulcers in the rat.

Luparello, T. J.: "Restraint and hypothalamic lesions in the production of gastroduodenal erosions in the guinea pig." *J. Psychosom. Res.* **10**: 251-254 (1966).

G43,819/66

Guth, P. H., Hall, P.: "Microcirculatory and mast cell changes in restraint-induced gastric ulcer." *Gastroenterology* **50**: 562-570 (1966).

G39,152/66

On the basis of experiments in the rat, a new hypothesis concerning the mechanism of gastric ulcers is formulated: "Stress → gastric mucosal mast cell degranulation with release of vasoactive substances → gastric mucosal vascular engorgement → decreased resistance to acid-pepsin digestion → mucosal ulceration."

Gairard, A., Marnay-Gulat, C., Raoul, Y.: "Essai d'analyse de la contrainte ulcérogène du Rat par l'étude de l'élimination urinaire de divers ions" (Experimental analysis of restraint ulcerogenesis in the rat by study of the urinary elimination of various ions). *C.R. Soc. Biol. (Paris)* **161**: 2132-2136 (1967).

F98,979/67

In rats, restraint ulcers are associated with a decrease in creatinine, chlorine, sodium and calcium excretion. Phosphaturia is increased, whereas potassium elimination does not change.

Lambert, R., Martin, M. S., Martin, F.: "Ulcères gastriques provoqués par contrainte dans un tube métallique chez le Rat" (Gastric ulcers produced by restraint in a metal tube, in the rat). *C.R. Soc. Biol. (Paris)* **161**: 816-818 (1967). F90,113/67

Description of a metallic tube used for the production of stress ulcers in the rat. The occurrence of such lesions is especially common in females.

Kim, Y. S., Kerr, R., Lipkin, M.: "Cell proliferation during the development of stress erosions in mouse stomach." *Nature* **215**: 1180-1181 (1967). F87,558/67

Senay, E. C., Levine, R. J.: "Synergism between cold and restraint for rapid produc-

tion of stress ulcers in rats." *Proc. Soc. Exp. Biol. Med.* **124**: 1221-1223 (1967).

F83,370/67

Technique for the production of acute gastric ulcers in rats within two hours by combined exposure to restraint and cold.

Buchel, L., Gallaire, D.: "Ulcères de contrainte chez le rat. I. Influence, sur la fréquence des ulcères, du jeûne et de la température de l'environnement associés à des immobilisations de durées variables" (Restraint ulcers in the rat. I. Influence of fasting and environmental temperature associated with the restraint of variable duration on the incidence of restraint ulcers). *Arch. Sci. Physiol.* (Paris) **21**: 527-536 (1967).

G53,615/67

In rats, twenty-four hours of fasting increases the incidence of gastric ulcers produced by subsequent restraint. Concurrent exposure to cold further sensitizes the stomach to the development of these stress ulcers.

Guth, P. H., Kozbur, X.: "Pathogenesis of gastric microcirculatory and mast cell changes in restraint stress." *Am. J. Dig. Dis.* **13**: 530-535 (1968).

G58,480/68

Arcari, G., Gaetani, M., Glässer, A. H., Turolla, E.: "Restraint-induced gastric ulcers in the golden hamster." *J. Pharm. Pharmacol.* **20**: 73 (1968).

J22,648/68

Levine, R. J., Senay, E. C.: "Studies on the role of acid in the pathogenesis of experimental stress ulcers." *Psychosom. Med.* **32**: 61-65 (1970).

J21,336/70

Martin, M. S., Martin, F., Lambert, R.: "The effect of ambient temperature on restraint ulcer in the rat." *Digestion* **3**: 331-337 (1970).

H34,597/70

In rats the incidence of gastric ulcers produced by restraint increased considerably as the ambient temperature was lowered from 28 to 19°C. However, no strict correlation was observed between body temperature and the frequency of the gastric lesions. Restraint during the active phase of their diurnal cycle was particularly effective in producing gastric ulcers in the rats, and cold augmented wakefulness.

Baltar-Tojo, L.: "Influencias del sistema nervioso central sobre el aparato digestivo. Ulceras de estómago de origen neurógeno. Estudio especial de la leucotomía en la úlcera por inmovilización en la rata" (The influence of central nervous system upon

digestive tract. Neurogenic peptic ulcer. Special study of leukotomy in ulcers by immobilization in rats). *Rev. Esp. Otoneurooftal.* **29**: 255-313 (1971).

J24,466/71

Discussion of the central regulation of the gastrointestinal tract in health and disease, with special emphasis upon the role of the G.A.S.

Klein, H. J., Gheorghiu, T., Hübner, G., Eder, M.: "Zur Pathogenese stressbedingter Magenulcera. Morphologische und pathophysiologische Untersuchungen an Ratten in Zwangshaltung" (Mechanisms of stress-induced ulcerations in the stomach of restrained rats. A morphologic and functional analysis). *Virchows Arch. [Pathol. Anat.]* **352**: 195-208 (1971).

H39,871/71

Cosen, J. N., Cosen, R. H.: "Les ulcères gastriques produits par l'association de médicaments ulcérogènes et de la contrainte" (Gastric ulcers produced by an association of ulcerogenic drugs and restraint). *Biol. Gastroenterol.* (Paris) **4**: 345-349 (1971).

J20,129/71

Gerety, D. C., Guth, P. H.: "Restraint-induced gastric erosions. Role of acid back-diffusion." *Am. J. Dig. Dis.* **17**: 1012-1018 (1972).

G96,605/72

Herner, D., Caul, W. F.: "Restraint induced ulceration in rats during estrus and diestrus." *Physiol. Behav.* **8**: 777-779 (1972).

G91,270/72

Pyant, R. L. Jr., Mullane, J. F.: "Starvation, glucose ingestion and stress ulcer formation in the rat." *Clin. Res.* **20**: 872 (1972).

H62,440/72

Stress ulcer production by restraint is facilitated in rats by four but not by two days of previous starvation. Oral administration of glucose has a protective effect.

Caul, W. F., Buchanan, D. C., Hays, R. C.: "Effects of unpredictability of shock on incidence of gastric lesions and heart rate in immobilized rats." *Physiol. Behav.* **8**: 669-672 (1972).

G91,264/72

In restraint-conditioned rats, unpredictable electric shocks produced a higher incidence of gastric ulcers than did predictable shocks.

Djahanguiri, B., Taubin, H. L., Landsberg, L.: "Increased sympathetic activity in the pathogenesis of restraint ulcer in rats." *J. Pharmacol. Exp. Ther.* **184**: 163-168 (1973).

H65,010/73

In rats, exposure to cold greatly increased the production of gastric ulcers by restraint. α -Methyldopa, bretylium, phenoxybenzamine and phentolamine all reduced the incidence of such gastric ulcerations. "The results suggest that the increased turnover of norepinephrine may be causally related to the development of restraint ulcers."

Yano, S., Harada, M.: "A method for the production of stress erosion in the mouse stomach and related pharmacological studies." *Jap. J. Pharmacol.* **23**: 57-64 (1973). H85,804/73

Stress ulcers of the stomach can be produced most reliably in mice by immersing them in water of 25°C for eighteen hours in a restraint cage of special design. The technique is said to be particularly useful in the assay of drugs inhibiting such erosions. Curiously, immersion at lower or higher temperatures causes less severe gastric ulcers.

Yamaguchi, T., Tobe, T., Hikasa, Y., Sano, M., Kanato, M.: "Electron microscopic studies on the exocrine cells and the endocrine cells of the rat stomachs after restraint." *J. Clin. Electron Microsc.* **7**: 337-338 (1974). K386/74

"Ulcer formation in the rat stomachs after restraint and effect of vagotomy on prevention of the ulcer have been well known facts. Using electron microscope, the exocrine cells (chief cells and parietal cells) and the endocrine cells (gastrin cells and enterochromaffin cells) of the rat stomachs were studied after restraint or restraint with vagotomy."

Tran, T. A., Gregg, R. V.: "Hypothermia in restraint-induced gastric ulcers in parabiotic rats." *Gastroenterology* **67**: 271-275 (1974). J15,225/74

Buchanan, D. C., Caul, W. F.: "Gastric ulceration in rats induced by self-imposed immobilization or physical restraint." *Physiol. Behav.* **13**: 583-588 (1974). J17,958/74

Even self-immobilization, in which an unrestrained rat avoids footshock by remaining motionless, can produce stress ulcers (24 refs.).

Schwiller, P. O., Schellerer, W., Reitzenstein, M., Hermanek, P.: "Hyperglucagonemia, hypocalcemia and diminished gastric blood flow—evidence for an etiological role in stress ulcer of rat." *Experientia* **30**: 824-826 (1974). H90,543/74

In intact and adrenalectomized rats, re-

straint causes gastric ulcers with a considerable rise in glucagon and a decrease in gastrin attributed to stress.

Bauer, R. F., Ambromovage, A. M.: "The effect of restraint stress on food stimulated gastric secretion in the rhesus monkey." *Fed. Proc.* **33**: 330 (1974). H84,089/74

The increase in volume and acidity of gastric juice following food stimulation is diminished by restraint.

Popperová, E., Nikš, M., Hulín, I.: "Gastric motility and acidity in experimental gastric ulcer." *Folia Fac. Med. Univ. Comeniana Bratisl.* **12**: 55-105 (1974) (Czech, with extensive English summary).

J14,078/74

A detailed study on the mechanism of stress ulcer formation during restraint in the rat. Both the motility and the secretion of the stomach can readily be followed during ulcerogenesis by the technique employed (120 refs.).

Tran, T. A., Gregg, R. V.: "Transmittal of restraint-induced gastric ulcers by parabiosis in rats." *Gastroenterology* **66**: 63-68 (1974).

J9,758/74

In rats, induction of gastric ulcers "in the parabiotic mate of a restrained rat implicates a humoral factor in the etiology" of this lesion. In this experiment, "one rat of a parabiosed pair was restrained for 28 or 30 hr. on a mobile cart which its unrestrained mate was free to pull about. All restrained animals showed gastric ulceration, and 15 of 17 unrestrained mates also developed gastric ulceration" (28 refs.). [It may be assumed, however, that the control animal was also under considerable stress under such conditions (H.S.).]

←Reserpine (See also Drugs under Agents). Blackman, J. G., Campion, D. S., Fastier, F. N.: "Mechanism of action of reserpine in producing gastric haemorrhage and erosion in the mouse." *Br. J. Pharmacol.* **14**: 112-116 (1959). C68,958/59

Gastric hemorrhage and erosion are produced in mice by reserpine through a mechanism involving liberation of 5-HT.

Damrau, F.: "Peptic ulcers induced in white rats by reserpine and stress. The protective action of roterized bismuth subnitrate." *Am. J. Gastroenterol.* **35**: 612-618 (1961). D92,441/61

Harrity, A. L.: "The effects of reserpine

on the psychogenic production of gastric ulcers in rats." *J. Comp. Physiol. Psychol.* **55**: 719-721 (1962). J23,448/62

Observations on rats suggest that "although reserpine does not in itself induce ulceration at low dosages, it does appear to interact with restraint stress to increase ulceration."

Niks, M., Janovjakova, E., Hulin, I.: "Interaction between reserpine and stress in the production of experimental gastric ulcer." *Bratisl. Lék. Listy* **48**: 80-84 (1967).

J24,399/67

Kido, R.: "The hypothalamus and stomach function, with special reference to experimental peptic ulcer induced by administration of reserpine." *Brain Nerve (Tokyo)* **19**: 467-476 (1967) (Japanese). J25,107/67

Doteuchi, M.: "Studies on the experimental gastrointestinal ulcers produced by reserpine and stress. I. Relationship between production of ulcers and changes in tissue monoamines." *Jap. J. Pharmacol.* **17**: 638-647 (1967). F96,238/67

Doteuchi, M. "II. Ulcerogenic activities of reserpine and its analogues." *Jap. J. Pharmacol.* **18**: 130-138 (1968). J16,601/68

Observations on cats suggest that a decrease in peripheral and central monoamines is involved in gastric ulcer formation by reserpine and its analogues in combination with electroshock.

Doteuchi, M. "III. Effects of monoamines and their precursors." *Jap. J. Pharmacol.* **18**: 175-184 (1968). J16,602/68

In cats, gastric ulcer formation by reserpine plus electroshock could be inhibited by 5-hydroxytryptophane, dopa and atropine. These and other observations suggested that a decrease in the monoamine content of the CNS was involved in stress ulcer formation.

Nakane, S., Sakai, T.: "The effect of reserpine on stress-induced stomach ulcer in rats." *Folia Pharmacol. Jap.* **69**: 549-555 (1973) (Japanese). J22,204/73

Gupta, M. B., Tangri, K. K., Bhargava, K. P.: "Mechanism of ulcerogenic activity of reserpine in albino rats." *Eur. J. Pharmacol.* **27**: 269-271 (1974). H89,397/74

In rats, reserpine-induced gastric ulcers were prevented by α -adrenergic blockers, 6-hydroxydopamine and atropine, but not by

adrenalectomy. Presumably, both adrenergic and cholinergic mechanisms are involved in reserpine-induced stress ulcers.

←Other Drugs Producing Peptic Ulcers.
Selye, H., Szabo, S.: "Experimental model for production of perforating duodenal ulcers by cysteamine in the rat." *Nature* **244**: 458-459 (1973). G88,067/73

In rats, cysteamine produces perforating duodenal ulcers with even greater frequency and consistency than does 3,4-toluenediamine or propionitrile. However, to a large extent, these must be due to specific effects of the drugs, since nonspecific stress ulcers are located predominantly in the glandular stomach of this species. Yet this model may be of interest in elucidating the mechanism responsible for stress ulcers, as these are frequently localized in the duodenum in man.

Cheney, D. H., Slogoff, S., Allen, G. W.: "Ketamine-induced stress ulcers in the rat." *Anesthesiology* **40**: 531-535 (1974).

J13,522/74

In rats, restraint produced stress ulcers, whereas at the dose levels given ketamine alone did not, but it did increase the incidence of restraint-induced ulcers from 35 percent to almost 100 percent. This sensitization was counteracted by phenoxybenzamine and halothane, "suggesting that the action of ketamine is mediated by vasoconstriction. Antihistamine pretreatment with promethazine was without effect."

Glass, G. B. J., Pitchumoni, C. S., Kawashima, K.: "Gastric injury from acute and chronic alcohol use: its potentiation by stress" (abstracted). *Clin. Res.* **22**: 558A (1974). H90,434/74

In mice, "acute ethanol excess and stress are more important than underlying gastritis in causing mucosal injury and bleeding."

Robert, A.: "Experimental production of duodenal ulcers." *Biol. Gastroenterol. (Paris)* **7**: 145-161 (1974). J19,366/74

Comparison of various methods for the production of duodenal ulcers in rats, with special emphasis upon those elicited with cysteamine, 3,4-toluenediamine, and other drugs.

Robert, A., Lancaster, C., Nezamis, J., Badalamenti, J.: "A new model to test antiulcer agents, cysteamine-induced duodenal ulcers." *Fed. Proc.* **33**: 310 (1974).

H84,075/74

Cysteamine-induced duodenal ulcers in rats generally respond to the same therapeutic agents as spontaneous duodenal ulcers in man. Hence, "they represent a useful model to detect antiulcer agents, and to study the mechanism of duodenal ulcer formation."

Szabo, S., Dzau, V. J., Feldman, D., Reynolds, E. S.: "Effect of propionitrile and cysteamine on gastric secretion in rats" (abstracted). *Clin. Res.* **22**: 370A (1974).

H90,258/74

"The production of duodenal ulcer in the rat by propionitrile or cysteamine is associated with enhanced gastric secretion and acid output."

Robert, A., Nezamis, J. E., Lancaster, C., Badalamenti, J. N.: "Production of duodenal ulcers in the rat by administration of digitoxin." *Experientia* **30**: 781-783 (1974).

H90,530/74

In rats, large doses of digitoxin (like propionitrile and cysteamine) may produce duodenal ulcers. The role of stress in this response remains to be determined.

Mangla, J. C., Kim, Y., Desbaillets, L. G.: "Carbazochrome salicylate and its role in aspirin-induced gastric irritation in rats." *Am. J. Dig. Dis.* **19**: 830-834 (1974).

J15,798/74

Acetylsalicylic acid produced gastric ulcers in rats. Presumably, these were due to a specific gastrototoxic effect of the drug, since they occurred at dose levels that caused no severe manifestations of stress. Contrary to earlier claims, carbazochrome salicylate complex failed to antagonize these aspirin ulcers (14 refs.).

Greenberg, L., Himal, H. S.: "Hydrochloric acid clearance and endotoxin induced duodenal erosions in dogs." *Surg. Gynecol. Obstet.* **139**: 561-565 (1974).

H92,596/74

In dogs, intravenous endotoxin inhibited transmucosal hydrogen ion passage, bile flow, and pancreatic juice flow, all of which normally clear instilled hydrochloric acid. When bile and pancreatic ducts were ligated and acid instilled, the high concentration of hydrochloric acid remaining in the pouches led to acute duodenal erosions. When no acid was instilled, endotoxin markedly stimulated fluid and electrolyte flow into the lumen and was associated with hemorrhagic necrosis of the duodenal mucosa. The authors conclude that duodenal damage caused by endotoxin may vary from acute focal erosions to hemor-

rhagic necrosis, depending upon the ability of the duodenum to clear hydrochloric acid.

←**Sensitization** (See also preceding sections on the production of experimental peptic ulcers by various means). Dragstedt, L. R., Ragins, H., Dragstedt, L. R., Evans, S. O. Jr.: "Stress and duodenal ulcer." In: Moritz, A. R. and Helberg, D. S., *Trauma and Disease. Selections from the Recent Literature*, p. 792. New York: Central Book (1959).

C44,814/59

After vagotomy, stress and corticoids fail to produce gastric ulcers in dogs.

Sines, J. O.: "Selective breeding for development of stomach lesions following stress in the rat." *J. Comp. Physiol. Psychol.* **52**: 615-617 (1959).

J19,353/59

Selective mating of rats which readily developed gastric ulcers during restraint led to offspring which were even more genetically ulcer-prone.

Brodie, D. A., Hanson, H. M.: "A study of the factors involved in the production of gastric ulcers by the restraint technique." *Gastroenterology* **38**: 353-360 (1960).

C87,271/60

Adrenalectomy greatly sensitizes rats to the production by restraint of gastric ulcers.

Bonfils, S., Dubrasquet, M., Potet, F., Lambling, A.: "Influence de l'hypophysectomie sur l'ulcère expérimental de contrainte. Test de la pente de restriction" (Influence of hypophysectomy on experimental restraint ulcers. The test of graded restriction). *C.R. Soc. Biol. (Paris)* **155**: 1928-1930 (1961).

D21,555/61

Hypophysectomy actually increases the incidence of restraint ulcers in the rat.

Harjola, P. T., Sivula, A.: "Gastric ulceration following experimentally induced hypoxia and hemorrhagic shock: *in vivo* study of pathogenesis in rabbits." *Ann. Surg.* **163**: 21-28 (1966) (22 refs.).

G36,639/66

Kim, Y. S., Lambooy, J. P.: "Riboflavin deficiency and gastric ulcer production in the rat: a procedure for the study of susceptibility to stress-induced gastric ulcers." *J. Nutr.* **91**: 183-188 (1967).

G45,068/67

Riboflavin deficiency increased the susceptibility of rats to stress-induced (rocking cage) gastric ulcers. A comparable degree of general inanition did not have this effect.

Dumas, J., Pérès, G.: "Action du rayonnement ultraviolet sur la formation de l'ulcère

de contrainte chez le rat blanc" (Action of ultraviolet irradiation on the formation of restraint ulcer in the white rat). *C.R. Acad. Sci. (Paris)* **163**: 863-865 (1969).

H19,005/69

Ultraviolet irradiation accelerates the development of stress ulcers by restraint in the rat.

Hase, T., Scarborough, E. S.: "Development of stress ulcer in rats and guinea pigs by mechanical rotation." *J. Appl. Physiol.* **30**: 580-582 (1971). G84,313/71

In guinea pigs and rats, stress ulcers of the stomach can be produced by mechanical rotation in a specially-designed chamber.

Chiu, C.-J., McArdle, A. H., Brown, R. A., Scott, H. J., Gurd, F. N.: "Gastric mucosal changes following burns in rats. A morphological and metabolic approach to the stress ulcer problem." *Arch. Surg.* **103**: 147-152 (1971). G85,399/71

In scalded rats, the ATP content of the gastric mucosa diminishes sharply together with the ability of the lining cells to consume oxygen. These changes precede morphologic alterations.

Nance, F. C., Kaufman, H. J., Batson, R. C.: "The role of the microbial flora in acute gastric stress ulceration." *Surgery* **72**: 68-73 (1972). G91,560/72

Norton, L., Nolan, P., Sales, J. E. L., Eiseman, B.: "A swine stress ulcer model." *Ann. Surg.* **176**: 133-138 (1972).

G93,135/72

Adult pigs are unusually resistant to the production of gastric ulcers by the stress of hemorrhage, whereas young piglets are particularly sensitive (19 refs.).

Sales, J. E. L.: "Ischaemia as a factor in the aetiology of stress ulceration." *Br. J. Surg.* **59**: 309-310 (1972). J19,878/72

In piglets, stress ulcers of the stomach were produced by severe hemorrhage.

Goodman, A. A., Osborne, M. P.: "An experimental model and clinical definition of stress ulceration." *Surg. Gynecol. Obstet.* **134**: 563-571 (1972). H52,672/72

Hemorrhagic shock produced in piglets is a useful model for the study of stress ulcers.

Paré, W. P., Temple, L. J.: "Food deprivation, shock stress and stomach lesions in the rat." *Physiol. Behav.* **11**: 371-375 (1973). J6,693/73

Electroshock did not increase the incidence

of rumenal ulcers in the rat following prolonged fasting.

Mullane, J. F., Smith, J. C., Wilfong, R. G.: "Hypoxia and stress ulcer formation in the rat." *Surgery* **74**: 326-332 (1973).

G98,010/73

In rats, hypoxia increased the incidence of gastric ulcers produced by restraint or EP injections.

Groza, P., Cananau, S. A., Zaharia, B.: "L'apparition des ulcérations gastriques après l'action répétée des accélérations (+ Gz; + Gx)" (Gastric ulcers after repeated acceleration [+ Gz; + Gx]). *Rev. Méd. Aéronaut.* **12**: 399-403 (1973). J9,250/73

Technique for the production of "stress ulcers" in the gastric mucosa of guinea pigs subjected to acceleration.

Richardson, R. S., Norton, L. W., Sales, J. E. L., Eiseman, B.: "Gastric blood flow in endotoxin-induced stress ulcer." *Arch. Surg.* **106**: 191-195 (1973). G99,516/73

In pigs, endotoxin shock invariably caused stress ulcers of the stomach, with changes in the gastric circulation.

Schellerer, W.: "The role of mucosal blood flow in the pathogenesis of stress ulcers." *Acta Hepatogastroenterol. (Stuttg.)* **21**: 138-141 (1974). J13,984/74

In rats the severity and degree of stress-induced gastric ulcers parallel the reduction in blood perfusion of the mucosa (10 refs.).

Rasche, R., Butterfield, W. C.: "The effect of sepsis on acute gastric ulcerations in the rat." *Surgery* **76**: 764-770 (1974).

J17,863/74

Review and personal observations on the effect of sepsis upon clinical and experimental stress ulcers.

Menguy, R., Masters, Y. F.: "Mechanism of stress ulcer. IV. Influence of fasting on the tolerance of gastric mucosal energy metabolism to ischemia and on the incidence of stress ulceration." *Gastroenterology* **66**: 1177-1186 (1974). J13,618/74

Fasting greatly sensitizes the gastric mucosa of the rabbit to the induction of stress ulcers by hemorrhage. These and many other observations suggest that "stress ulceration complicating hemorrhagic shock results from a gastric mucosal energy deficit due to shock-induced mucosal ischemia."

Schulte, W. J., Pintar, K., Barboriak, J. J.: "Development of gastric lesions in food-

restricted rats." *Fed. Proc.* **33**: 259 (1974).
H83,956/74

Technique for the production of stress ulcers in the stomach of rats by exercise and fasting.

Goldenberg, M. M.: "Stress-induced gastric lesions in spontaneously hypertensive rats. Involvement of autonomic neurotransmitter substances." *Am. J. Dig. Dis.* **19**: 353-360 (1974). J12,313/74

Rosolovskii, A. P.: "The effect of the thyroid gland on the appearance of trophic affections of the stomach during the action of stress and steroids." *Probl. Endokrinol.* **20** No. 5: 70-72 (1974) (Russian).

H95,571/74

In rats "the ulcerogenic action of stress and steroids increased considerably in experimental hyperthyroidism, and was markedly diminished in hypothyroidism."

Fischer, R. P., Peter, E. T., Mullane, J. F.: "Experimental stress ulcers in acidotic and nonacidotic renal insufficiency." *Arch. Surg.* **109**: 409-411 (1974). J16,376/74

In rats, acute renal insufficiency with acidosis, hyperkalemia and uremia "enhances restraint-induced stress ulcer formation, possibly by impairing the normal reparative process of the gastric mucosa."

Koch, G., Schumpelick, V., Rehren, D. von: "Einfluss der Splenektomie auf Magensaftsekretion und Ulcusentstehung der Ratte" (The effect of splenectomy on gastric secretion and ulcer formation in rats). *Langenbecks Arch. Chir.* **336**: 15-23 (1974). J15,777/74

Splenectomy increases the incidence of gastric ulcers in both restrained and pylorus-ligated rats.

←**Prophylaxis and Treatment** (See also preceding sections on the production of experimental peptic ulcers by various means). Selye, H., MacLean, A.: "Prevention of gastric ulcer formation during the alarm reaction." *Am. J. Dig. Dis.* **11**: 319-322 (1944). A75,010/44

In rats the gastric ulcers produced by transection of the spinal cord at the height of the seventh cervical vertebra "may be prevented by the prophylactic administration of various food substances, aluminum hydroxide gel and especially by comparatively small doses of dextrose. Dextrose is effective when given either per os or intravenously. It prevents gastric ulcer formation even in doses

insufficient to raise the glucose content of the blood above the normal level for the duration of the experiment. The prophylactic effect of dextrose is nonspecific in the sense that the compound prevents the formation of gastric ulcers by a variety of widely different damaging agents such as formaldehyde injections, exposure to cold or spinal cord transection."

Robert, A., Selye, H.: "Effet de la cortisone et de la STH sur l'ulcère gastrique expérimental" (Effect of cortisone and STH on experimental gastric ulcers). *Ann. Endocrinol.* (Paris) **13**: 845-848 (1952).

B70,246/52

In rats, injection of formaldehyde into the gastric wall rapidly produces bleeding and necrotizing gastric erosions that are aggravated by STH but inhibited by cortisone. This is yet another finding that shows the antagonistic behavior of STH and glucocorticoids.

Atwater, J. S., Carson, J. M.: "Therapeutic principles in management of peptic ulcer. 3. Anticholinergic-tranquilizer combination." *Am. J. Dig. Dis.* **4**: 1055-1065 (1959). J18,431/59

Bonfils, S., Rossi, G., Liefooghe, G., Lambling, A.: "'Ulcère' expérimental de contrainte du rat blanc. I. Méthodes. Fréquence des lésions. Modifications par certains procédés techniques et pharmacodynamiques" (Experimental restraint "ulcer" in the white rat. I. Methods. Frequency of lesions. Modifications by some technical and pharmacodynamic procedures). *Rev. Fr. Etudes Clin. Biol.* **4**: 146-150 (1959). J22,385/59

Description of a modification of Selye's restraint technique for the production of stress ulcers in the rat. Adrenalectomy did not influence, whereas cortisone and vagotomy diminished the incidence of gastroduodenal ulcers.

Bonfils, S., Dubrasquet, M., Lambling, A.: "Les utilisations de la technique de l'ulcère de contrainte du Rat blanc comme test pharmacodynamique" (The use of the restraint ulcer technique in the white rat as a pharmacodynamic test). *Thérapie* **15**: 1096-1110 (1960). J23,582/60

Sines, J. O.: "Experimental production and control of stomach lesions in the rat." *J. Psychosom. Res.* **4**: 297-300 (1960).

J23,258/60

Certain strains of rats are especially susceptible to restraint-induced gastric ulcers.

Such lesions can be controlled by anticholinergics but are increased by large doses of chlorpromazine. This "suggests that stomach lesion development in the rat is at least in part dependent upon parasympathetic hyperactivity."

Selye, H., Jean, P., Cantin, M.: "Prevention by stress and cortisol of gastric ulcers normally produced by 48/80." *Proc. Soc. Exp. Biol. Med.* **103**: 444-446 (1960).

C78,128/60

"Experiments on rats indicate that gastric ulcers produced by various stressors (as part of the alarm reaction) differ qualitatively from those induced by the histamine liberator 48/80. The latter lesions as well as the anaphylactoid inflammation and shock produced by 48/80 can actually be prevented by stressors or cortisol, although these same agents are, in themselves, capable of producing the alarm-reaction type of gastric erosion." Evidently, certain types of gastric ulcers can be prevented by glucocorticoids.

Menguy, R.: "Effects of restraint stress on gastric secretion in the rat." *Am. J. Dig. Dis.* **5**: 911-916 (1960).

C93,988/60

"Previously vagotomized rats were partially protected from stress [restraint] ulcers whereas hypophysectomy or adrenalectomy were without effect" (13 refs.).

Hanson, H. M., Brodie, D. A.: "Use of the restrained rat technique for study of the antiulcer effect of drugs." *J. Appl. Physiol.* **15**: 291-294 (1960).

C83,740/60

In rats, atropine and other anticholinergic drugs inhibited restraint-induced gastric ulcers. Among the CNS-active agents, chlorpromazine, benactyzine and pentobarbital had a protective effect while acetazolamide was ineffective. Prednisolone delayed healing of existent ulcers.

Bonfils, S., Dubrasquet, M., Lambling, A.: "Ulcère expérimental de contrainte. Quelques applications du test de la pente de restriction" (Experimental restraint ulcer. Some uses of the restriction gradient test). *Thérapie* **16**: 384-392 (1961).

J23,583/61

Simler, M., Schwartz, J., Schmid, F.: "Effets du chlorhydrate de morphine sur la prévention de l'ulcère de contrainte chez le Rat" (Effects of morphine hydrochloride on the prevention of restraint ulcers in rats). *C.R. Soc. Biol. (Paris)* **156**: 1495-1497 (1962).

D50,230/62

Chatterjee, M. L., Pal, S., Dey, D.: "Effect of nialamide on stress-induced gastric ulcer and fatty liver in rats." *Bull. Calcutta Sch. Trop. Med.* **10**: 65-66 (1962).

J24,319/62

Buchel, L., Gallaire, D.: "Réduction de la durée de la contrainte pour la production d'ulcères expérimentaux chez le rat. Application à l'étude de substances protectrices" (Reduction of the duration of restraint for the production of experimental ulcers in rats. Application to the study of protective substances). *C.R. Soc. Biol. (Paris)* **157**: 1225-1228 (1963).

E33,965/63

Fifty-day-old rats exposed to 180 minutes of restraint after a 24-hour fast are particularly susceptible to the production of stress ulcers.

Simler, M., Schwartz, J.: "Prévention de l'ulcère de contrainte par les infiltrations procainiques frontales" (Prevention of restraint ulcers by frontal procaine infiltrations). *Rev. Fr. Etudes Clin. Biol.* **8**: 594-597 (1963).

J23,538/63

In rats, "lobectomy does not reduce the incidence of ulcers due to forced restraint: frontal lobe infiltration with procaine, on the other hand, is as effective in protection as various psychotropic drugs." These findings confirm the concept that cortical centers influence autonomic regulation of gastric function.

Sanyal, A. K., Banerji, C. R., Das, P. K.: "Banana and restraint ulcers in albino rats." *J. Pharm. Pharmacol.* **15**: 775-776 (1963).

J23,400/63

"Banana powder, besides its prophylactic value against chemical (phenylbutazone) ulcers as reported earlier... can also afford significant protection against ulcers produced by a stress situation."

Hillyard, I. W., Grandy, R. P.: "The gastric antiulcer activity of chlorbenzoxamine, a non-anticholinergic piperazine compound." *J. Pharmacol. Exp. Ther.* **142**: 358-364 (1963).

E35,711/63

Cahen, R., Pessonner, A.: "Etude de l'allantoïnate de dihydroxyaluminium et de l'allantoïnate de chlorhydroxyaluminium. V. Effet sur la cicatrisation de l'ulcère gastrique" (Study of dihydroxyaluminum allantoinate and chlorhydroxyaluminum allantoinate. V. Effect on cicatrization of gastric ulcers). *Ann. Pharm. Fr.* **21**: 405-411 (1963).

J23,842/63

Bonfils, S., Dubrasquet, M., Lambling, A.: "Dérivés de la phénothiazine et de l'imino-dibenzyle: relation dose-efficacité vis-à-vis de l'ulcère expérimental de contrainte" (Phenothiazine and iminodibenzyl derivatives: dose-effect relationship in experimental restraint ulcers). *Thérapie* **18**: 373-389 (1963). J23,592/63

Haot, J., Djahanguiri, B., Richelle, M.: "Action protectrice du chlordiazepoxide sur l'ulcère de contrainte chez le rat" (Protective action of chlordiazepoxide on restraint ulcer in the rat). *Arch. Int. Pharmacodyn. Ther.* **148**: 557-559 (1964). F9,446/64

Flandre, M. O., Damon, M.: "Action de la 6 alpha-méthyl-prednisolone sur l'ulcère expérimental de contrainte" (Action of 6-alpha-methylprednisolone on experimental restraint ulcer). *Thérapie* **19**: 1471-1474 (1964). G26,436/64

In rats, gastric ulcers produced by restraint are not influenced by 6 α -methylprednisolone.

Takagi, K., Kasuya, Y., Watanabe, K.: "Studies on the drugs for peptic ulcer. A reliable method for producing stress ulcer in rats." *Chem. Pharm. Bull. (Tokyo)* **12**: 465-472 (1964). G33,924/64

In rats, stress ulcers of the stomach were most readily produced by immersion in cold water during restraint on a board. "Anticholinergics or central depressants effectively inhibited the ulceration and combination of both drugs suppressed it more effectively than single administration of each drug."

Frenkl, R., Csaly, L., Makara, G., Harmos, G.: "Antiulcerogenic effect of exercise in rats." *Acta Physiol. Acad. Sci. Hung.* **25**: 97-100 (1964). J16,350/64

"Regular muscular activity has been found to inhibit the development of restraint ulcer in the rat." Reserpine ulcers are similarly influenced, although to a lesser extent.

Foss, D. L., Stavney, L. S., Haraguchi, T., Harkins, H. N., Nyhus, L. M.: "Pathophysiological and therapeutic considerations of Curling's ulcer in the rat." *J.A.M.A.* **187**: 592-594 (1964). F1,660/64

Stress ulcers produced in rats by scalding could be prevented by antacids, bilateral vagotomies and anticholinergic agents.

Thayer, W. R., Toffler, A. H., Chapo, G., Spiro, H. M.: "Inhibition of restraint ulcers

in the rat by pyridoxine deficiency." *Yale J. Biol. Med.* **38**: 257-264 (1965).

G37,375/65

In rats, pyridoxine deficiency decreases the incidence of restraint ulcers and depresses gastric secretion. "It is suggested that since pyridoxine deficiency lowers histamine-forming capacity, this reduction in endogenous histamine leads to a decrease in acid production which then protects against restraint ulcers."

Zabrodin, O. N.: "Analysis of the incidence of destructive changes in the gastric mucosa during combined immobilization and electric stimulation in rats." *Patol. Fiziol. Éksp. Ter.* **9** No. 3: 68 (1965) (Russian).

J24,155/65

Brief discussion of experimental stress ulcers and their response to vagotomy and adrenalectomy in the rat.

Buckley, J. P., Vogen, E. E., Kinnard, W. J.: "Effects of pentobarbital, acetylsalicylic acid, and reserpine on blood pressure and survival of rats subjected to experimental stress." *J. Pharm. Sci.* **55**: 572-575 (1966).

F67,051/66

Chronic exposure of rats to a variety of stressors (strong light, sound, electric shock) produces hypertension which is not prevented by pentobarbital or acetylsalicylic acid but is diminished by reserpine. The ulcerogenic effect of the stressors is aggravated by acetylsalicylic acid.

Reynolds, R. W., Meeker, M. R.: "Thiosemicarbazide injection followed by electric shock increases resistance to stress in rats." *Science* **151**: 1101-1102 (1966).

F62,497/66

In rats, pretreatment with thiosemicarbazide (which lowers GABA concentrations in the brain) offers considerable protection against gastric ulcers produced by electroshock or immobilization.

Watanabe, K.: "Some pharmacological factors involved in formation and prevention of stress ulcer in rats." *Chem. Pharm. Bull. (Tokyo)* **14**: 101-107 (1966). F93,314/66

Buchel, L., Gallaire, D.: "Ulcères de contrainte chez le rat. II. Etude de substances protectrices" (Restraint ulcers in rats. II. Study of protective substances). *Arch. Sci. Physiol.* **21**: 537-552 (1967).

G55,607/67

In rats, restraint-induced ulcers can be

prevented by a variety of anticholinergic, ganglioplegic, tranquilizing, analgesic and hypnotic agents (53 refs.).

Mercier, J., Lumbroso, S.: "Influence exercée par la 1,3-dihydro-7-nitro-5-phényl-2H-1,4-benzodiazépine-2-one (Mogadon) sur l'ulcère de contrainte du rat et de la souris albinos" (Influence exerted by 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazépine-2-one [Mogadon] on stress ulcer in albino rats and mice). *Arch. Int. Pharmacodyn. Ther.* **167**: 35-38 (1967). F81,261/67

"Like Librium, Mogadon exerts a protective action against gastric ulceration in restrained albino rats. Mogadon is only three times more active than Librium in this respect, though it is ten times more potent as a tranquilizing agent."

Ritchie, W. P. Jr., Breen, J. J., Grigg, D. I., Wangensteen, O. H.: "Effect of decreased levels of endogenous gastric tissue histamine on acid secretion and stress ulcer formation in the rat." *Gut* **8**: 32-35 (1967). G44,746/67

"Decreased levels of tissue histamine were found to afford significant protection against the development of restraint-induced ulceration in the glandular portion of the rat's stomach."

Dasgupta, S. R., Mukherjee, B. P.: "Effect of chlordiazepoxide on stomach ulcers in rabbit induced by stress." *Nature* **215**: 1183 (1967). F87,560/67

In rabbits, the gastric ulcers and eosinopenia produced by electroshock or restraint were inhibited by chlordiazepoxide.

Ritchie, W. P. Jr., Breen, J. J., Grigg, D. I.: "Prevention of stress ulcer by reducing gastric tissue histamine." *Surgery* **62**: 596-600 (1967). G59,906/67

Djahanguiri, B., Sadeghi, D., Hemmati, S.: "Système orthosympathique et ulcères gastriques expérimentaux" (The orthosympathetic system and experimental gastric ulcers). *Arch. Int. Pharmacodyn. Ther.* **173**: 154-161 (1968). F99,278/68

In rats, cold increases the ulcerogenic effect of restraint, whereas α -adrenergic blocking agents prevent it.

Takagi, K., Okabe, S.: "The effects of drugs on the production and recovery processes of the stress ulcer." *Jap. J. Pharmacol.* **18**: 9-18 (1968). J23,245/68

Schramm, H.: "Die Beeinflussung des experimentellen Ulkus bei der immobilisierten Ratte durch verschiedene Pharmaka" (The modification of experimental ulcers in immobilized rats by different pharmacologic agents). *Dtsch. Z. Verdau. Stoffwechselkr.* **28**: 305-312 (1968). J23,554/68

Lipkin, M., Ludwig, W.: "Carbenoxolone pretreatment and the production of restraint-stress induced erosions in guinea-pigs." In: Robson, J. M. and Sullivan, F. M., *A Symposium on Carbenoxolone Sodium*, pp. 41-46. London: Butterworths, 1968. J24,402/68

Djahanguiri, B., Sadeghi, D.: "Action préventive de l'acétazolamide sur l'ulcère de contrainte du rat blanc" (Preventive action of acetazolamide on restraint ulcers in white rats). *Acta Gastroenterol. Belg.* **31**: 689-692 (1968). G64,543/68

Levine, R. J., Senay, E. C.: "Histamine in the pathogenesis of stress ulcers in the rat." *Am. J. Physiol.* **214**: 892-896 (1968).

F96,913/68

Studies with brocresine (a potent inhibitor of histidine decarboxylase) and amino-guanidine (an inhibitor of diamine oxidase activity) "support the hypothesis that histamine plays an essential role in the pathogenesis of stress ulcers" produced in the rat by restraint and cooling.

Takagi, K., Okabe, S.: "An experimental gastric ulcer of the rat produced with anticholinergic drugs under stress." *Eur. J. Pharmacol.* **5**: 263-271 (1969).

H9,358/69

In rats the stress ulcers produced by immersion in cold water are prevented by atropine and other anticholinergic agents, but at the same time another type of ulcer appears in the proventriculus.

Brodie, D. A., Lotti, V. J., Bauer, B. G.: "Drug effects on gastric secretion and stress gastric hemorrhage in the rat." *Am. J. Dig. Dis.* **15**: 111-120 (1970). G73,656/70

Brodie, D. A., Hooke, K. F.: "The effect of vasoactive agents on stress-induced gastric hemorrhage in the rat." *Digestion* **4**: 193-204 (1971). H45,858/71

In rats, gastric hemorrhage induced by cold plus restraint is significantly inhibited by vasodepressors and aggravated by vasocon-

strictors (for example, vasopressin, angiotensin, NEP).

Hutcher, N., Silverberg, S. G., Lee, H. M.: "The effect of vitamin A on the formation of steroid induced gastric ulcers." *Surg. Forum* **22**: 322-324 (1971). J17,503/71

In rats, vitamin A significantly reduced methylprednisolone-induced gastric ulcers.

Frenkl, R.: "Humoral mechanism of ulcer-resistance of the organism adapted to physical exercise." *Acta Med. Acad. Sci. Hung.* **28**: 69-73 (1971). G87,952/71

In rats, stress ulcers of the stomach produced in various ways can be prevented with injections of the serum of sportsmen engaged in regular exercise. Inhibition of histamine-stimulated gastric secretion, or of the hypothalamus-pituitary-adrenocortical mediation of stress, is thought to be involved in this antiulcerogenic effect of the serum.

Mullane, J. F., Ritchie, W. P. Jr., Solis, R. T., Wilfong, R. G., Fischer, R. P.: "Experimental biliary obstruction and stress ulcer formation." *J. Surg. Res.* **12**: 180-184 (1972). G96,117/72

In rats the acute stress of restraint in conjunction with liver damage secondary to biliary obstruction produces particularly pronounced ulcers, which are prevented by vagotomy and (to facilitate emptying of the stomach) by pyloroplasty. "The gastric congestion that occurs in the patients with Laennec's and biliary cirrhosis may make their stomachs more susceptible to stress."

Ritchie, W. P. Jr., Roth, R. R., Fischer, R. P.: "Studies on the pathogenesis of 'stress ulcer': effect of hemorrhage, transfusion, and vagotomy in the restrained rat." *Surgery* **71**: 445-451 (1972). G89,104/72

"Restraint-induced ulcers in the rat resemble posttraumatic 'stress ulcers' in man in that they are acute and multiple, occur mainly in the stomach, are confined to the oxyntic cell area, and are not associated with gastric acid hypersecretion." The production of these ulcers is enhanced by hemorrhage and greatly diminished by vagotomy.

Voitk, A. J., Chiu, C. J., Gurd, F. N.: "Prevention of porcine stress ulcer following hemorrhagic shock with elemental diet." *Arch. Surg.* **105**: 473-476 (1972). G93,148/72

In pigs, "prefeeding with the predigested elemental diet protected the gastric mucosa

from the stress ulcers that occurred in nine of ten of the controls."

Requena, R., Forte, R., Knopf, M., Scherrer, J., Kirschner, J., Levowitz, B. S.: "Intracellular potassium and vitamin A in the prevention of stress ulcers." *Surg. Forum* **23**: 388-389 (1972). J21,575/72

Ferguson, W. W., Starling, J. R., Wangenstein, S. L.: "Role of lysosomal enzyme release in the pathogenesis of stress-induced gastric ulceration." *Surg. Forum* **23**: 380-382 (1972). J21,574/72

Restraint-induced gastric ulcers in the rat are accompanied by a reduction of the lysosomal enzyme, cathepsin D, from the gastric mucosa. Methylprednisolone diminishes the stress ulcers and prevents cathepsin D release. "Thus, lysosomal enzymes appear to play a role in the pathogenesis of stress ulcerations."

Perkins, W. E., Vars, L.: "Effects of carbenoxolone sodium on stress-induced gastric damage in rats." *Br. J. Pharmacol.* **47**: 847-849 (1973). H69,528/73

Intraperitoneal carbenoxolone offered significant protection against restraint-induced gastric ulcers in fed, but not in fasted rats.

Goodman, A. A., Osborne, M. P.: "Stress ulcer. A definition, a discussion of other stress-associated upper gastrointestinal lesions, and an experimental model." *Am. J. Surg.* **125**: 461-463 (1973). J2,449/73

Stress ulcers produced in piglets by hemorrhage could not consistently be prevented by vagotomy and pyloroplasty, despite reduction of gastric acid.

Osumi, Y., Takaori, S., Fujiwara, M.: "Preventive effect of fusaric acid, a dopamine- β -hydroxylase inhibitor, on the gastric ulceration induced by water-immersion stress in rats." *Jap. J. Pharmacol.* **23**: 904-906 (1973). H82,948/73

Earlier observations have shown that EP and NEP can inhibit the production of stress ulcers in the stomach of the rat. It has also been noted that most α -adrenergic blocking agents as well as the release of endogenous monoamines by reserpine and tetrabenazine aggravate these lesions, while β -adrenergic blockade inhibits them. In the present experiments, rats immobilized in restraint cages were immersed up to the xyphoid in water at 21°C, causing gastric ulceration within three hours. Tetrabenazine prior to the stress aggravated ulcer

production and elicited a decrease in NEP and dopamine content. Fusaric acid (5-butylpicolinic acid), a potent inhibitor of dopamine- β -hydroxylase, exerted an anti-ulcerogenic effect, presumably due to a decrease in the release of NEP from the CNS.

Rasche, R., Butterfield, W. C.: "Vitamin A pretreatment of stress ulcers in rats." *Arch. Surg.* **106**: 320-321 (1973).

J641/73

Studies on rats that received 10,000 international units of vitamin A prior to an eight-hour period of immobilization in a wire gauze device suggest that this vitamin "exerts a negligible, if any, protective effect on the occurrence of gastric ulceration."

Sibilly, A., Krivošić, I., Foucher, G., Fresnel, P. L., Boutelier, P.: "Prevention locale de l'ulcère gastrique expérimental. (Etude préliminaire)" (Topical prevention of experimental gastric ulcer [Preliminary study]). *J. Chir. (Paris)* **106**: 521-534 (1973).

J10,151/73

In rats the stress ulcers produced by restraint are aggravated by fasting and prevented by oral administration of glucose or aluminum gel. Neutralization of the gastric acid does not seem to be decisive, since aluminum gel protects less than hypertonic glucose; perhaps the latter helps to maintain cell metabolism and the gastric barrier.

Lindenbaum, E. S., Diamond, B., Yaryura-Tobías, J. A.: "Nicotinic acid and restraint induced ulcers." *Acta Physiol. Lat. Am.* **23**: 288-292 (1973).

J9,059/73

In rats, gastric ulcers produced by restraint with food and water deprivation are more effectively inhibited by nicotinic acid than by chlorpromazine.

Schumpelick, V., Paschen, U.: "Vergleich der protektiven Wirkung von Diazepam und Vagotomie auf das Stressulkus der Ratte" (Comparison of the protective activity of diazepam and vagotomy on stress ulcers in rats). *Arzneim. Forsch.* **24**: 176-179 (1974).

H82,750/74

In rats, stress ulcers (produced by restraint) can be inhibited by diazepam pretreatment or vagotomy, but combined application of these agents offers the best protection. "This fact demonstrates a different mode of action. The antiulcerative effect of diazepam is explained by its direct action on the vegetative regulation centers in the hypothalamic and limbic system, leading

to a partial inhibition of the vagally controlled HCl-pepsin component and the splanchnic nerve-dependent vascular factor of ulcerogenesis as well."

Lippmann, W.: "Oral gastric acid secretion-inhibitory activity and anti-ulcer activity of synthetic prostaglandin analogues: C-15 epimers of 15-hydroxy-15-methyl-9-oxoprostanic acid (AY-22,469)." *Prostaglandins* **7**: 223-229 (1974).

J16,177/74

Lippmann, W.: "Inhibition of gastric acid secretion and ulcer formation in the rat by orally-administered 11-deoxyprostaglandin analogues: 15-hydroxy-16,16-dimethyl-9-oxo-prost-5,13-dienoic acids." *Prostaglandins* **7**: 231-246 (1974).

J16,178/74

Ravokatra, A., Nigeon-Dureuil, M., Ratsimamanga, A. R.: "Action d'un triterpénoïde pentacyclique, l'asiaticoside, retirée de *Hydrocotyle Madagascariensis* ou *Centella asiatica*, contre les ulcéractions gastriques du rat Wistar, exposé au froid à + 2°" (The effect of asiaticoside, a pentacyclic triterpenoid, isolated from *Hydrocotyle Madagascariensis* or *Centella asiatica*, on gastric ulcers of Wistar rats exposed to cold at + 2°). *C. R. Acad. Sci. [D]* (Paris) **278**: 1743-1746 (1974).

J12,423/74

Asiaticoside inhibits the development of stress ulcers in rats exposed to cold.

Ravokatra, A., Loiseau, A., Ratsimamanga-Urverg, S., Nigeon-Dureuil, M., Ratsimamanga, A. R.: "Action de l'asiaticoside (triterpène pentacyclique) retiré de l'*Hydrocotyle Madagascariensis* sur les ulcères duodénaux créés par la mercaptoéthylamine chez le rat Wistar mâle" (The effects of asiaticoside [pentacyclic triterpene] extracted from *Hydrocotyle Madagascariensis* on mercaptoethylamine-induced duodenal ulcers in the male Wistar rat). *C. R. Acad. Sci. [D]* (Paris) **278**: 2317-2321 (1974).

J13,441/74

In rats, cysteamine-induced duodenal ulcers can be prevented by asiaticoside. This compound exerts a similar protective effect against peptic ulcers caused by stress.

Bates, R. F. L., Barlet, J. P.: "The preventative effect of porcine calcitonin given by mouth on restraint-induced gastric ulcer in rats." *Horm. Metab. Res.* **6**: 332-333 (1974).

H90,741/74

In rats, restraint-induced gastric ulcers can largely be prevented by calcitonin.

Norton, L., Mathews, D., Avrum, L., Eisenman, B.: "Pharmacological protection against swine stress ulcer." *Gastroenterology* **66**: 503-508 (1974). J12,432/74

In pigs, hemorrhagic shock induces stress ulcers in the stomach that can be prevented by cholestyramine (which binds bile acids), methysergide (a 5-HT antagonist), and methylprednisolone, but only under certain conditions of dosage and timing. Thus the clinical usefulness of this approach is problematic.

Cheney, D. H., Slogoff, S., Allen, G. W.: "Ketamine-induced stress ulcers in the rat." *Anesthesiology* **40**: 531-535 (1974).

J13,522/74

Restraint produced stress ulcers in rats, whereas at the dose levels given ketamine alone did not, but it did increase the incidence of restraint-induced ulcers from 35 to almost 100 percent. This sensitization was counteracted by phenoxybenzamine and halothane, "suggesting that the action of ketamine is mediated by vasoconstriction. Antihistamine pretreatment with promethazine was without effect."

Seiser, R. L., Houser, V. P.: "Effects of scopolamine methylbromide on shock-induced gastric lesions in the unrestrained rat." *Physiol. Behav.* **13**: 147-151 (1974).

J14,551/74

In rats the incidence and severity of gastric ulcers produced by the stress of electroshock avoidance conflict can be significantly decreased by pretreatment with the anticholinergic agent scopolamine methylbromide.

Cheney, C. D., Rudrud, E.: "Prophylaxis by vitamin C in starvation induced rat stomach ulceration." *Life Sci.* **14**: 2209-2214 (1974) (16 refs.). J14,496/74

Dai, S., Ogle, C. W.: "Gastric ulcers induced by acid accumulation and by stress in pylorus-occluded rats." *Eur. J. Pharmacol.* **26**: 15-21 (1974). H85,051/74

In pylorus-ligated rats, restraint decreased the volume and total acid output of gastric secretion. This type of "stress ulceration was prevented only by atropine, but not by antacids or adrenoceptor blocking agents. Increase in gastric motility during stress appears to cause these ulcers." Conversely, the proventricular ulcers produced by pyloric occlusion alone were prevented by atropine and antacids, suggesting their causation by gastric juice.

Moritz, E., Zacherl, H., Onderscheka, K., Helsberg, A.: "Vitamin A und Stressulkus-Prophylaxe" (Vitamin A and prevention of stress ulcers). *Bruns Beitr. Klin. Chir.* **221**: 208-221 (1974). J13,239/74

In rats the incidence of endotoxin-induced stress ulcers of the stomach can be reduced by vitamin A. Despite virtually unchanged plasma and liver levels, the vitamin content of the gastric wall was significantly increased after treatment.

Hemmati, M., Abtahi, F., Farrokhshiar, M., Djahanguiri, B.: "Prevention of restraint and indomethacin-induced gastric ulceration by bile duct or pylorus ligation in rats." *Digestion* **10**: 108-112 (1974). H87,920/74

In rats, restraint- and indomethacin-induced gastric ulcers were prevented by bile duct or pylorus ligation. This protection was abolished by bile administration. Presumably, the presence of bile in the stomach is necessary for the development of this type of ulcer.

Konturek, S. J., Radecki, T., Demitrescu, T., Kwiecień, N., Pucher, A., Robert, A.: "Effect of synthetic 15-methyl analog of prostaglandin E₂ on gastric secretion and peptic ulcer formation." *J. Lab. Clin. Med.* **84**: 716-725 (1974). J18,035/74

"In conscious cats with chronic gastric and pancreatic fistulas, a synthetic 15-methyl analog of prostaglandin E₂, 15/S/15-methyl-E₂-methyl ester, caused a dose-related inhibition of maximal gastric acid and pepsin response to pentagastrin and histamine." These antisecretory and antiulcerogenic effects may be of therapeutic value in man.

Yeomans, N. D., St. John, D. J. B.: "Effect of carbenoxolone sodium on aspirin-induced injury of the rat gastric mucosa." *Am. J. Dig. Dis.* **19**: 217-222 (1974). J12,310/74

Although carbenoxolone protects the rat against stress ulcers (restraint), it does not prevent erosions produced by aspirin.

Emerson, L., Kerkut, G. A.: "Effect of oral administration of degraded carrageenan on the induction of gastric ulcers in rats treated with glucocorticoids." *J. Comp. Pathol.* **84**: 151-159 (1974). J13,062/74

Discussion of the literature concerning the relationship between gastric ulcers produced by stressors and those caused by glucocorticoids. In fasted rats, fluocortolone, difluocortolone, and difluocortolone trimethyl acetate

elicited gastric ulcers that could be inhibited by oral carrageenan.

Shirazi, S. S., Paluska, G., Zike, W. L.: "The role of dexamethasone and 5-fluorouracil in the prevention of stress ulcers" (abstract). *Clin. Res.* **22**: 369A (1974).

H90,255/74

In dogs, gastric "stress ulcers" produced by the combination of bile salts and hemorrhage were not improved by dexamethasone or 5-fluorouracil.

Schumpelick, V., Kauffmann-Mackh, G.: "Der Einfluss des N. Vagus auf die Ulkusentstehung bei portokavalen Anastomose der Ratte" (The influence of the vagus nerve on ulcer formation in rats with portacaval anastomosis). *Brunn's Beitr. Klin. Chir.* **221**: 239-246 (1974).

J13,241/74

In rats with portacaval anastomosis, multiple ulcers occurred following pylorus ligation because of vagal stimulation. This could largely be inhibited by vagotomy, which also diminished the quantity and acidity of the gastric juice (32 refs.).

Mullane, J. F., Pyant, R. L. Jr., Wilfong, R. G., Dailey, W.: "Starvation, glucose and stress ulcers in the rat." *Arch. Surg.* **109**: 416-419 (1974).

H16,378/74

In rats, restraint produces stress ulcers especially during fasting. This effect can be counteracted by oral glucose. "These studies suggest that a critically low glucose or caloric intake may account in part for gastric lesions in the stressed patient."

Wilson, D. E.: "Prostaglandins and stress ulcers." *Prostaglandins* **8**: 52-53 (1974).

J18,078/74

Zike, W. L., Safae-Shirazi, S., Denbesten, L.: "The role of cholestyramine in the prevention of stress ulcers." *J. Surg. Res.* **17**: 315-319 (1974).

J19,651/74

In dogs, stress ulcers produced by hemorrhagic shock plus intragastric instillation of hydrochloric acid and bile salts can be prevented by cholestyramine.

Daturi, S., Franceschini, J., Mandelli, V., Mizzotti, B., Usardi, M. M.: "A proposed role for PGE₂ in the genesis of stress-induced gastric ulcers." *Br. J. Pharmacol.* **52**: 464P (1974).

H97,097/74

Kawarada, Y., Weiss, R., Matsumoto, T.: "Pathophysiology of stress ulcer and its prevention. I. Pharmacologic doses of steroid." *Am. J. Surg.* **129**: 249-254 (1975).

J23,615/75

Decadron (a potent glucocorticoid) given before restraint prevents gastric ulcer formation in the rat.

Kawarada, Y., Lambek, J., Matsumoto, T.: "Pathophysiology of stress ulcer and its prevention. II. Prostaglandin E₁ and microcirculatory responses in stress ulcer." *Am. J. Surg.* **129**: 217-222 (1975).

J21,536/75

Prostaglandin E₁ completely prevented the formation of stress ulcers in the rat but only in doses which were toxic (17 refs.).

Ulcerative Colitis

There appears to be fairly unanimous agreement that, in children as well as in adults, ulcerative colitis is often related to stressful life situations. In children, it seems to be associated with aggressive emotions, especially against parents. In adults, stressful situations in the family or on the job appear to be of pathogenic importance, as is grief for real or fantasized objects of loss. Among nomadic Arabs, ulcerative colitis has often been noted upon settlement in Kuwait City, presumably owing to the sudden shift from simple country to complicated urban life. Allegedly, glucocorticoids are of therapeutic value but this claim has not yet received adequate confirmation.

Ulcerative Colitis

(See also our earlier stress monographs, p. xiii)

Groen, J.: "Psychogenesis and psychotherapy of ulcerative colitis." *Psychosom.*

Med. **9**: 151-174 (1947).

B27,185/47

Prugh, D. G.: "Variations in attitudes, behavior and feeling-states as exhibited in the play of children during modifications in the course of ulcerative colitis." In: Wolff,

H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 692-705. Baltimore: Williams & Wilkins, 1950. B51,938/50

In children with ulcerative colitis, there is a fairly constant inverse relationship "between therapeutic release of hostility and aggressive emotions and the intensity of gastrointestinal symptomatology."

Lindemann, E.: "Modifications in the course of ulcerative colitis in relationship to changes in life situations and reaction patterns." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 706-723. Baltimore: Williams & Wilkins, 1950.

B51,939/50

Ulcerative colitis is often aggravated and perhaps produced by stressful life situations such as family difficulties.

Grace, W. J.: "Life situations, emotions and chronic ulcerative colitis." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 679-691. Baltimore: Williams & Wilkins, 1950.

B51,937/50

Stressful experiences are undoubtedly involved in the pathogenesis of ulcerative colitis and tend periodically to aggravate its course.

Selye, H.: "The general-adaptation-syndrome and the gastrointestinal diseases of adaptation." *Am. J. Proctol.* 2: 167-184 (1951).

B61,231/51

Review on the role of stress in the pathogenesis of gastrointestinal disease, particularly peptic ulcers, ulcerative colitis, non-tropical sprue, appendicitis, various forms of regional and necrotizing enteritis, and gastrointestinal allergies (146 refs.).

Jones, F. A.: "Stress and the gut." *Practitioner* 172: 23-28 (1954).

B89,347/54

In man, stress may cause not only peptic ulcers, but also constipation, diarrhea, or ulcerative colitis.

Jackson, M., Plant, A.: "Psychological aspects of ulcerative colitis in childhood." *Arch. Midd. Hosp.* 5: 21-34 (1955). Abstracted in: *Dig. Neurol. Psychiatry* July, 1955, p. 305.

C9,081/55

Moutier, F., Cornet, A., Loiry, E.: "Ulcères gastro-duodénaux et colites ulcéreuses par choc émotionnel" (Gastroduodenal ulcers and ulcerative colitis due to emotional shock). *Presse Méd.* 64: 585-587 (1956).

C15,608/56

Fullerton, D. T., Kollar, E. J., Caldwell, A. B.: "A clinical study of ulcerative colitis." *J.A.M.A.* 181: 463-471 (1962).

D38,251/62

Ulcerative colitis is frequently caused by psychogenic stress. It "occurs in persons with immature or defective egos after real or fantasized object loss and may be viewed as a morbid grief reaction."

Brown, C. H.: "Acute emotional crises and ulcerative colitis. Report of seven cases." *Am. J. Dig. Dis.* 8: 525-536 (1963).

J23,463/63

"Dramatic and shocking emotional stress immediately preceded the onset of ulcerative colitis in 6 patients, and initiated a flare-up in a seventh. The emotional situations and case histories are presented. The onset of ulcerative colitis immediately after such severe emotional trauma suggests that psychogenic factors may be etiologic in some patients" (46 refs.).

Kollar, E. J., Fullerton, D. T., Censo, R. di, Agler, C. F.: "Stress specificity in ulcerative colitis." *Compr. Psychiatry* 5: 101-112 (1964).

J22,977/64

Jackson, D. D., Yalom, I.: "Family research on the problem of ulcerative colitis." *Arch. Gen. Psychiatry* 15: 410-418 (1966).

J8,775/66

Ulcerative colitis appears to be especially common in families that live a socially restricted, over-disciplined and traditional life. However, "it is also important not to overlook the possibility that a chronically ill child is the source of the stress rather than one of its products."

Fazlullah, S.: "Idiopathic ulcerative colitis in tropics. Its pattern and clinical course (A preliminary report)." *Medicus* (Karachi) 33: 13-40 (1966).

F74,076/66

General review on "idiopathic ulcerative colitis" as it occurs in the tropics. Special emphasis is placed upon stress, malnutrition and poor hygienic conditions in its pathogenesis, and glucocorticoid therapy is discussed.

Salem, S. N., Shubair, K. S.: "Non-specific ulcerative colitis in Bedouin Arabs." *Lancet* March 4, 1967, pp. 473-475.

F77,588/67

Ulcerative colitis has been noted in Bedouin and other nomadic Arabs after settlement in Kuwait city. Presumably, "the

sudden shift from a simple life to a complicated one predisposes these people to the disease."

Davidson, M.: "Juvenile ulcerative colitis." *N. Eng. J. Med.* **277**: 1408-1410 (1967). F92,345/67

A review of juvenile ulcerative colitis suggests that it may be emotional in origin, but this view is less enthusiastically supported than it was a few decades ago.

Mendeloff, A. I., Monk, M., Siegel, C. I., Lilienfeld, A.: "Illness experience and life stresses in patients with irritable colon and with ulcerative colitis. An epidemiologic study of ulcerative colitis and regional enteritis in Baltimore, 1960-1964." *N. Engl. J. Med.* **282**: 14-17 (1970). H20,041/70

In the Baltimore area, "subjects with irritable colon had consistently higher scores for various social-cultural factors thought to represent life stresses than either the patients with ulcerative colitis or the general population. The group with ulcerative colitis resembled the general population in this respect, except for being significantly more Jewish." Specific stressor events preceding the outbreak of the disease could not be established, and hence these "studies fail to

support the thesis that ulcerative colitis is a paradigm of psychosomatic illness."

Monk, M., Mendeloff, A. I., Siegel, I., Lilienfeld, A.: "An epidemiological study of ulcerative colitis and regional enteritis among adults in Baltimore. III. Psychological and possible stress-precipitating factors." *J. Chron. Dis.* **22**: 565-578 (1970).

J21,919/70

Paull, A., Hislop, I. G.: "Etiologic factors in ulcerative colitis: birth, death and symbolic equivalents." *Psychiatr. Med.* **5**: 57-64 (1974).

J25,088/74

Kristensen, M., Koudahl, G., Fischerman, K., Jarnum, S.: "High dose prednisone treatment in severe ulcerative colitis." *Scand. J. Gastroenterol.* **9**: 177-183 (1974).

J12,924/74

"High dose prednisone treatment in severe acute attacks of ulcerative colitis is justified." [Since this malady has been considered by others as a disease of adaptation, it must be pointed out that not all the lesions caused by stress are mediated through glucocorticoids, and some (for example, shock or any stress-induced derangement in Addison's disease) respond favorably to this type of therapy (H.S.).]

Varia

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Acute phlegmonous appendicitis produced by intravenous administration of histamine." *Lancet* November 21, 1936, pp. 1210-1211. 66,642/36

In rats, intraperitoneal injections of formaldehyde or histamine affect the appendix selectively and cause phlegmonous and often perforating *appendicitis*. The response is considered to be a special type of alarm reaction.

Selye, H.: "Experimental production and prevention of appendicitis with histamine." *Can. Med. Assoc. J.* **36**: 462-464 (1937).

68,819/37

In certain strains of rats, intravenous injection of histamine causes acute phlegmonous *appendicitis*, which may be prevented by pretreatment with smaller doses of the same substance. Other stressors may also cause similar appendicular lesions.

Prugh, D. G.: "A preliminary report on

the role of emotional factors in idiopathic celiac disease." *Psychosom. Med.* **13**: 220-241 (1951).

B61,229/51

Observations suggesting that "idiopathic celiac disease" is largely due to psychogenic stress situations, and may be viewed as a disease of adaptation (23 refs.).

Selye, H.: "The general-adaptation-syndrome and the gastrointestinal diseases of adaptation." *Am. J. Proctol.* **2**: 167-184 (1951).

B61,231/51

Review on stress in the pathogenesis of gastrointestinal diseases, particularly peptic ulcers, ulcerative colitis, nontropical sprue, *appendicitis*, various forms of regional and necrotizing enteritis, and gastrointestinal allergies (146 refs.).

Hayes D. W.: "The irritable bowel syndrome." *Am. Practit.* **5**: 787-789 (1954).

J25,482/54

The *irritable bowel syndrome* is frequently due to stress (18 refs.).

Gylling, M.: "Stress and appendix: with effect of stress on variations in the weight of the adrenals." *Ann. Chir. Gynaecol. Fenn.* **43** Supp. 3: 1-75 (1954). J25,357/54

Doctoral dissertation in which, on the basis of clinical studies, the author confirms "Selye's concept of the possible significance of stress in producing *appendicitis*." Large portions of the book deal also with the general effects of stress upon thymicolumphatic tissue.

Foltz, E. L., Millett, F. E. Jr., Weber, D. E., Alksne, J. F.: "Experimental psychosomatic disease states in monkeys. II. Gut hypermotility." *J. Surg. Res.* **4**: 454-464 (1964). D18,872/64

"Fatal *intussusception* is reported in a series of five Rhesus monkeys undergoing 'conditioned stress' performance after extensive conditioned training to conditioned avoidance, conditioned punishment and conditioned anxiety, accomplished in chronic restraining chairs."

Heffernon, E. W., Lippincott, R. C.: "The gastrointestinal response to stress (the *irritable colon*)." *Med. Clin. N. Am.* **50**: 591-595 (1966). J23,161/66

Gurd, F. N., McClelland, R. N.: "Trauma workshop report: the gastrointestinal tract in trauma." *J. Trauma* **11**: 1089-1091 (1970). J21,200/70

In man, "intractable *paralytic ileus* is often associated with stress ulceration."

Litarczek, G., Cristeo, I., Panaitescu, E., et al.: "Current aspects of therapy of *post-operative paralysis* of the digestive tract (Problem of stress disease in the digestive area)" (abstracted). *Chirurgia* (Bucur.) **22**: 837-848 (1973) (Roumanian). J24,392/73

Hunt, R. H., O'Brien, I. M., Milton-Thompson, G. J.: "Stress and the enteron." *J. R. Nav. Med. Serv.* **60**: 49-51 (1974). J20,069/74

"The *irritable bowel syndrome* is a common problem in the Royal Navy and Royal Marines, frequently follows dysenteric infections, is often aggravated by stress but is rarely incapacitating."

Thompson, W. G.: "The irritable colon." *Can. Med. Assoc. J.* **111**: 1236-1244 (1974). H96,077/74

Psychogenic stressors are a common cause of the "*irritable colon*" syndrome.

Flury, H., Herzka, H.S.: "Rumination als psychosomatische Krankheit des ersten Lebensjahres" (Rumination as a psychosomatic disease during the first year of life). *Helv. Paediatr. Acta* **29**: 335-348 (1974). J18,691/74

"*Rumination*" in human neonates is the regurgitation and renewed mastication of food, subsequently swallowed again. It is ascribed to psychogenic stress which depends mainly upon the mother's attitude toward the baby (34 refs.).

CARDIOVASCULAR DISEASES (INCLUDING HYPER-TENSION, CARDIAC INFARCTS, PERIARTERITIS NODOSA)

[See also Psychosomatic Diseases, Occupations, Stress Tests, and other sections where cardiovascular changes are likely to play an important role]

Generalities

The cardiovascular diseases in the pathogenesis of which stress appears to play an important role will be discussed conjointly because many of them usually occur in combination (for example, hypertension, arteriosclerosis, myocardial infarcts).

It is difficult to classify the factors involved in the causation of stress-induced cardiovascular disease because of similar overlaps. For example, various stressors may

result in hypertension or cardiac infarction, yet psychogenic stress plays such a preponderant role that it deserves to be discussed in a special section. The conditioning factors that predispose to cardiovascular disease likewise overlap. Undoubtedly, genetic factors are important in determining behavior, the choice of an occupation, the site of residence (urban, rural), or even the type of diet. On the other hand, age, at least the chronologic age of an individual, though a highly important conditioning factor determining predisposition for cardiovascular disease, is largely independent of those just mentioned. Finally, the various indices of stress and cardiovascular disease (pathologic anatomy, chemical changes, blood coagulability) have not only diagnostic value, but also furnish significant data on probably important pathogenetic factors.

Although recognizing the unavoidable overlap in my classification, I feel it is better to list the literature in some more or less logical predetermined order to facilitate orientation; hence, despite its arbitrary nature, I have decided to use the following subdivisions:

- History
- Stressors
 - General
 - Psychogenic
- Conditioning
 - Genetics
 - Diet
 - Occupation, Social Factors including Urbanization
 - Age
- Diagnostic Indicators and Other Changes Characteristic of Stress-induced Cardiovascular Disease
 - Stress Tests
 - Morphology
 - Blood Clotting
 - Hormones
 - Nonhormonal Metabolites
- Experimental Cardiovascular Diseases
 - Hypertension, Arteriosclerosis
 - Hyalinos
 - Infarctoid Necrosis
 - Adrenal Regeneration Hypertension

For a general overview of the subject, the reader is referred to the reviews and monographs listed below.

Generalities

(See also our earlier stress monographs, p. xiii)

Warmbrand, M.: *Add Years to Your Heart*, p. 232. New York: Whittier Books, 1956. C18,796/56

Highly simplified set of practical recommendations for cardiac patients, with a special section on lessons derived from work on the G.A.S.

Kerner, F.: *Stress and Your Heart* (Introduction by Hans Selye), p. 237. New York: Hawthorn Books, 1961. D5,450/61

Practical advice on the avoidance of cardiovascular disease resulting from stress, based principally on the technical monographs of Hans Selye.

Paterson, J. C.: "Stress, intimal hemorrhage, and coronary occlusion." *J. Occup. Med.* 3: 59-63 (1961). D82,819/61

In man, various stressors may cause intimal hemorrhages with coronary occlusion.

Golden, J. S.: "Stress, physical or emotional, and coronary occlusions." *Chicago Med.* **64**: 13-16 (1961). J23,788/61

Bach, J. L.: "Stress and the human heart." *New Physician* **11**: 395-397 (1962).

J23,570/62

Hoffmann, H.: "Herzkranké am Steuer von Kraftfahrzeugen. Untersuchungen über das Kreislaufverhalten im Fahrversuch an gesunden und kranken Kraftfahrzeugführern" (Car driving and cardiac patients. Examination of blood circulation during driving in healthy and sick drivers). *Münch. Med. Wochenschr.* **37**: 1790-1796 (1963).

E28,340/63

In cardiac patients, driving tends to cause ECG anomalies and unusually marked increases in blood pressure. "This shows that at least for the driver with angina pectoris the operation of a vehicle is an irresponsible stress."

Buchem, F. S. P. van: "Stress en cardio-vasculaire afwijkingen" (Stress and cardiovascular disorders). *Ned. T. Geneesk.* **107**: 1668-1672 (1963) (Dutch). E35,518/63

Alekim, M.: "Electrolytes, stress and heart." *Harefuah* **66**: 230-232 (1964) (Hebrew). J24,301/64

Raab, W. (ed.): *Prevention of Ischemic Heart Disease*, p. 466. Springfield, Ill.: Charles C Thomas, 1966. E6,496/66

This book presents the First International Congress on Preventive Cardiology, and is composed of highly technical reports by numerous outstanding cardiologists. Several sections deal particularly with the effects of stress.

Friedberg, C. K.: *Diseases of the Heart*, Vol. 1, p. 929. Philadelphia and London: W B Saunders, 3rd ed., 1966.

E10,673/66

Monograph on cardiovascular diseases with special sections on the role of stress (several hundred refs.).

Selye, H., Côté, G.: "Stress et cardiopathies" (Stress and cardiopathies). *Coeur Med. Interne* **7**: 237-245 (1968).

G46,743/68

Review of the relationship between stress and cardiovascular disease (41 refs.).

Selye, H.: "La evolución del concepto de stress. Stress y enfermedad cardiovascular"

(The evolution of the stress concept. Stress and cardiovascular disease). *Folia Clin. Int. (Barc.)* **19**: 471-489 (1969).

G60,033/69

Review on the evolution of the stress concept, with special reference to cardiovascular disease (64 refs.).

Selye, H.: "A stress elmélet kialakulása. A stress- és a szívér-betegségek" (The evolution of the stress concept. Stress and cardiovascular disease). *Orv. Hetil.* **110**: 2257-2265 (1969) (Hungarian).

G60,034/69

History of the G.A.S. with special reference to observations on the role of stress in cardiovascular disease (64 refs.).

Selye, H.: *Experimental Cardiovascular Diseases*, 2 vols., p. 1155. New York, Heidelberg and Berlin: Springer-Verlag, 1970.

G60,083/70

Extensive two-volume treatise on various cardiovascular diseases that can be produced in animals, with extensive sections on the role of stress.

Raab, W.: *Preventive Myocardiology. Fundamentals and Targets*, p. 227. Springfield, Ill.: Charles C Thomas, 1970.

E8,717/70

Monograph reviewing the many measures (diet, life habits, exercise, and so on) that have been recommended for the prevention of cardiovascular disease in man. Attention is given to interactions between corticoids, catecholamines and diets, especially on the basis of corresponding animal experiments (almost 1,000 refs.).

Lukl, P.: "Stress and heart disease." *Cardiovasc. Clin.* **2**: 143-149 (1971).

J23,698/71

Hlougal, L., Dušek, J.: "Etiopathogenesis and prevention of coronary heart disease." *Acta Univ. Carol. [Med.] (Praha)* **18**: 203-227 (1972).

H93,346/72

Review on CHD with special emphasis upon the role of stress in its production (93 refs.).

Schär, M., Reeder, L. G., Dirken, J. M.: "Stress and cardiovascular health: an international cooperative study. II. The male population of a factory at Zürich." *Soc. Sci. Med.* **7**: 585-603 (1973) (22 refs.).

J15,756/73

Maria, A. N. de, Vera, Z., Amsterdam, E. A., Mason, D. T., Massumi, R. A.: "Dis-

turbances of cardiac rhythm and conduction induced by exercise." *Am. J. Cardiol.* **33**: 732-736 (1974). H86,246/74

Sweet, R. L., Sheffield, L. T.: "Myocardial infarction after exercise-induced electrocardiographic changes in a patient with variant angina pectoris." *Am. J. Cardiol.* **33**: 813-817 (1974). H86,260/74

Beach, J. E., Blair, A. M. J. N., Pirani, C. L., Cox, G. E., Dixon, F. J.: "An unusual form of proliferative arteriopathy in macaque monkeys (Macacca sps)." *Exp. Mol. Pathol.* **21**: 322-338 (1974). J19,230/74

Freeman, Z.: "The effect of stress on the heart." *Med. J. Aust.* **1**: 87-90 (1974). J10,829/74

Review of the literature on stress-induced heart disease with special reference to its medico-legal implications.

Carruthers, M.: *The Western Way of Death. Stress, Tension and Heart Attacks*, p. 142. New York: Pantheon Books, 1974. E10,630/74

Highly simplified popular description of factors influencing predisposition to heart disease with brief sections on urban environment, alcohol, drugs, diets, and various occupational groups, such as accountants, clerical workers, pilots, bus drivers, industrial workers, public speakers, television performers, athletes, and so on.

Amsterdam, E. A., Wilmore, J. H., Maria, A. N. de: "Symposium on exercise in cardiovascular health and disease." *Am. J. Cardiol.* **33**: 713-714 (1974). H86,244/74

Schettler, G.: "Risikofaktoren der Herz- und Gefässkrankheiten" (Risk factors of cardiovascular diseases). *Med. Welt* **25**: 1171-1176 (1974). H89,496/74

General review of stress-induced myo-

cardial infarction with special reference to predisposing factors (no refs.).

Dallocchio, M., Clementy, J., Bricaud, H.: "Face à l'athérosclérose, un impératif: combattre tous les facteurs de risque (hypertension, tabac, hyperlipidémies, sédentarité, stress,...)" (To fight atherosclerosis: combat all risk factors [hypertension, tobacco, hyperlipidemias, sedentarity, stress,...]). *Ent. Bichat*: 35-38 (1974). J17,300/74

Eliot, R. S.: *Stress and The Heart*, Vol. 1, p. 415. Contemporary Problems of Cardiology. Mount Kisco, N.Y.: Futura, 1974. E10,556/74

Monograph containing articles by numerous experts on the role of stress in the production of cardiovascular disease with special reference to hypertension and myocardial infarction. Among the factors involved in the cardiovascular effects of stress, individual chapters deal with the role of occupation, homeostasis, sex, environmental influences, athletics, emotional arousal and stress tests. The therapeutic value of various techniques for relaxation, including Transcendental Meditation, yoga, Zen, sentic cycles, hypnosis, and related practices is examined.

Fiennes, R. N. T. W.: "Stress as a 'hypotensive' condition." *Br. Vet. J.* **130**: 87-88 (1974). J20,867/74

Kannel, W. B., Doyle, J. T., McNamara, P. M., Quicketon, P., Gordon, T.: "Precursors of sudden coronary death. Factors related to the incidence of sudden death." *Circulation* **51**: 606-613 (1975). J23,305/75

Selye, H.: "Stress and cardiovascular disease." *Jubilee Volume in Honor of V. V. Parin* (In press) (Russian). G88,057/

Review on the relationship between stress and cardiovascular disease with special reference to infarctoid necrosis and mineralocorticoid hypertensive disease.

History

Some of the earliest data on stress-induced cardiovascular diseases were mentioned in the section on History. Suffice it to point out here that as early as 1812, Corvisart expressed the view that cardiac disease depends upon the "passions of man" and that the heart can be injured by such efforts as fencing, wrestling, playing wind instruments or emotional arousal associated with anger, fear or despair.

However, it was not until recent times that special attention was given to statistical

studies that would prove the relationship between the stressors of daily life (especially extreme muscular effort), traumatic injuries or intense emotional arousal.

Animal experiments have shown that, following suitable pretreatment, exposure to virtually any severe stressor can precipitate myocardial necroses or hypertensive vascular disease. In other words, here again we are dealing with complex pathogenic situations in which both the conditioning or predisposing factors that induce disease-proneness and the eliciting stressors play equally important roles.

History

(See also our earlier stress monographs, p. xiii)

Corvisart, J. N.: *An Essay of the Organic Diseases and Lesions of the Heart and Great Vessels*. Boston: Bradford and Read, 1812.

E3,955/1812

All heart diseases stem "from the action of the organ and from passions of man." The heart can be injured by crying in infancy, wrestling, fencing, playing wind instruments, laughing, weeping, reading, declamation, anger, madness, fear, jealousy, terror, love, despair, joy, avarice, cupidity, ambition, revenge, and every kind of effort. However, "to conceive man without passions, is to conceive a being without his attributes."

Selye, H.: "Die Entwicklung des Stresskonzeptes. Stress und Herzkrankheiten" (The evolution of the stress concept. Stress and cardiovascular disease). *Med. Welt* **20**: 915-933 (1969).

G60,015/69

History of the G.A.S. with special refer-

ence to experimental cardiovascular diseases (64 refs.).

Selye, H.: "Evolution du concept du stress. Le stress et la maladie cardio-vasculaire" (The evolution of the stress concept. Stress and cardiovascular disease). *Med. Hyg.* (Genève) **27**: 669-675 (1969).

G60,010/69

Review of the evolution of the stress concept, with special reference to its role in the pathogenesis of cardiovascular diseases (64 refs.).

Selye, H.: "The evolution of the stress concept—stress and cardiovascular disease." In: Levi, L., *Society, Stress and Disease. I. The Psychosocial Environment and Psychosomatic Diseases*, pp. 299-311. London, New York and Toronto: Oxford University Press, 1971.

G70,422/71

Review of the evolution of the stress concept, with special reference to experimental models of cardiovascular disease in which stress plays an important role.

Stressors in General

The literature amply illustrates the fact that, in predisposed patients, myocardial infarcts can follow extracardiac surgical interventions and a variety of other physical and mental stressors. There may be a latency period between the stress and the myocardial infarction. Unaccustomed efforts are particularly harmful, which illustrates the importance of adaptation. This is true in both human and experimental pathology.

Similar observations have been made concerning the development of hypertension. Even in workers exposed to continuous industrial noise, the blood pressure shows a great tendency to reach high values and ECG changes have been noted.

Stress may play a role even in the production of endocarditis in that glucocorticoids decrease resistance to infection and catecholamines increase the demands made upon the cardiac valves by raising the blood pressure.

<Stressors in General

(See also our earlier stress monographs, p. xiii)

Thomas, C. B.: "What is the mode of action of thiocyanate compounds in essential hypertension?" *Ann. Intern. Med.* **37**: 106-122 (1952). J12,254/52

Literature and personal observations suggesting that the beneficial effect of thiocyanate in essential hypertension may largely be due to its influence upon the thyroid and adrenal which may counteract the stress factor in the pathogenesis of the disease (49 refs.).

Vowles, K. D. J., Howard, J. M.: "Myocardial and cerebral infarctions as post-operative complications." *Br. Med. J.* May 10, 1958, pp. 1096-1099. G61,934/58

Description of myocardial infarcts following extracardiac surgical interventions.

Oka, M., Nakao, K., Angrist, A.: "Nonspecific aspects of endocarditis. Clinical applications of an experimental study." *N.Y. State J. Med.* **60**: 669-678 (1960). D2,078/60

Stress may play a role in the production of endocarditis in that glucocorticoids decrease resistance to infection and both corticoids and catecholamines make increased demands upon the cardiac valves by raising the blood pressure (62 refs.).

Wolf, S.: "Stress and heart disease." *Mod. Concepts Cardiovasc. Dis.* **29**: 599-604 (1960). G62,498/60

Evaluation of the literature suggests that various stressors may play a pathogenic role in cardiovascular disease (24 refs.).

White, P. D.: "The relation of heart disease to injury, stress and occupation." In: Bisteni, A., Fishleder, B. L. et al., *Cardiologia*, pp. 43-47. Mexico: Editorial Interamericana, 1961. D31,194/61

Cardiac infarcts are precipitated by physical or mental stress only in patients predisposed by preexistent cardiac disease.

Sparkman, D. R.: "Trauma or strain and heart disease. Causal relationship." *Calif. Med.* **94**: 72-76 (1961). D1,913/61

To clarify the problems of the cardiac patient under workmen's compensation laws, a special committee of the Washington State Heart Association reasoned that a "causal relationship of trauma to heart disease may exist under the following circumstances: Sudden death from acute coronary disease (or coronary occlusion with myocardial in-

farction, or acute coronary insufficiency) in which symptoms develop during the course of or immediately following exertion or strain that is both excessive and unusual for the particular individual concerned; this exertion or strain may be either physical or emotional." In the years 1950 to 59, 77 percent of all the claims for cardiac damage made in the state of Washington were for myocardial infarction or acute coronary insufficiency following unusual effort. Since CHD is progressive, it is difficult to ascertain when a given stress at work may have contributed to an eventual infarct. Data are reviewed on steps taken by several states concerning a causal relationship between stress and heart disease (20 refs.).

Shatalov, N. N., Saitanov, A. O., Glotova, K. V.: "On the state of the cardiovascular system under conditions of exposure to continuous noise." *Gig. Tr. Prof. Zabol.* **6**: 10-14 (1962). J6,200/62

"In persons exposed to the effect of continuous industrial medium-frequency and high-frequency noise of intensity 85 to 120 db, functional disturbances of the cardiovascular system were frequently observed. Very often the subjects exhibited an instability of the arterial blood pressure. The electrocardiographic data showed bradycardia with a tendency to retardation of the intravesicular conductivity, plus a depression of the T-wave that was most frequently observed after physical stress and at the end of the work-period."

Roseman, M. D.: "Postoperative myocardial infarction." *Am. J. Proctol.* **13**: 372-376 (1962). D42,980/62

Review on postoperative myocardial infarction in man. Prolonged hypotension with the resulting decrease in cardiac output and coronary insufficiency are regarded as the main pathogenic factors.

Aldrich, C. K.: "Stress factors in heart disease." *Minn. Med.* **46**: 241-244 (1963). J11,744/63

Schlüssel, H.: "Sport und Arteriosklerose" (Sports and arteriosclerosis). *Med. Welt (Stuttg.)* **28**: 1563-1569 (1965).

F46,438/65

Review of animal experiments and observations on man suggesting that muscular work diminishes the severity and intensity of arteriosclerosis.

Larcan, A.: "Pathophysiological basis and practical application of a 'metabolic' therapy

of myocardial infarction." In: Bajusz, E., *Electrolytes and Cardiovascular Diseases. Physiology, Pathology, Therapy. 2. Clinical Aspects*, pp. 277-301. Basel and New York: S. Karger, 1966. E6,377/66

Review of the role played by stress and electrolytes in myocardial infarction, with an interpretation of polarizing therapy.

Rotberg, J. T., Tello G. M. A., Gutiérrez, F. E., Medrano, G. A., Steyer, I., Fishleder, B., Soní, J.: "Isquemia, angor e infarto del miocardio en pacientes con coronariografía normal" (Ischemia, angina, and myocardial infarction in patients with normal coronary angiography). *Arch. Inst. Cardiol. Méx.* **43**: 806-825 (1973). H81,335/73

Review of the literature and personal observations on the role of stress in the development of cardiac infarcts (44 refs.).

Boulard, P.: "Stress et maladies de cœur" (Stress and cardiac diseases). In: *L'Athérosclérose*, pp. 161-166. Paris: Editions Baillière, 1973. J13,729/73

Review on the part played by the stressors of modern life in the production of cardiovascular disease.

Guazzi, M., Fiorentini, C., Polese, A., Magrini, F., Olivari, M. T.: "Stress related and sympathetically mediated ECG relations in the primary hyperkinetic heart syndrome." *8th Ann. Meeting Eur. Soc. Clin. Invest.*, pp. 55-56. Rotterdam, 1974. H85,236/74

Psychogenic Stressors

In man, probably because of his highly developed CNS, psychogenic stressors are among the most frequent causes of cardiovascular disease. A large number of published observations suggest that tensions and threats arising from interpersonal relations in the family or at work are particularly apt to cause hypertension, whereas cardiac infarcts are more often the result of acute, intense mental arousal. In predisposed subjects, events causing anxiety and resentment increase the pulse rate, cardiac output and blood pressure. At the same time, tolerance to exercise is impaired. However, in the few instances when stress has evoked dejection and despair, the cardiovascular response was a hypodynamic one with bradycardia, decreased blood pressure and hypotension.

There appears to be little doubt that emotional stress is one of the most frequent factors in the development of high blood pressure, congestive heart failure or cardiac infarction in predisposed patients. Violent arguments with superiors or members of the family, as well as witnessing a serious car accident or lifting a heavy weight, may cause ventricular tachycardia, paroxysmal auricular tachycardia, complete heart block and even sudden death. In fact, both physical and emotional exhaustion can provoke virtually all types of cardiac arrhythmias (and death) in the normal as well as the abnormal heart.

The many statistical studies conducted in this field show that cardiovascular derangements as well as other diseases of adaptation depend not so much upon the kind of demand made on an individual as upon his reaction to it. There has been much argument about whether executives or subordinates are more subject to stress-induced cardiovascular disease but there appears to be no uniformly applicable answer to this problem. The deciding factor is whether a person finds it more stressful to be responsible for giving orders or for having to obey them. In any event, it is obvious that in subjects under otherwise identical conditions, individual motivation and personality play a decisive role.

In this respect, two types of people have been distinguished: Type A subjects exhibit a behavior pattern characterized primarily by intense ambition, competitive drive, constant preoccupation with job deadlines, a sense of time urgency, restless motor mannerisms and staccato-style verbal responses, whereas Type B individuals

manifest a converse behavior. Sometimes, an additional Type C is recognized as having essentially the characteristics of Type B, but with the added element of chronic anxiety. Type A subjects usually have a high cholesterol level, a shortened blood clotting time and an increased tendency to develop coronary artery disease and arcus senilis. Allegedly, they succumb to coronary artery disease six times more frequently than do Type B individuals.

Friedman and Rosenman called attention to these two types and deserve the greatest credit for having clearly delineated them. However, the authors themselves are the first to point out that, during the nineteenth century, Sir William Osler described a behavior pattern typical of coronary-prone patients. If we accept the tenet that stress, like emotional responsiveness, is equally dependent upon life events and upon our reactions to them, it is evident that the distinction of Types A and B is essentially equivalent to admitting that stress, especially emotional stress, plays a decisive role in the pathogenesis of cardiovascular disease, and is more influential in those who respond to a given event intensely (that is with severe stress) than in unresponsive, phlegmatic persons. Of course, this concept is also very compatible with the hormonal theory in that the tense, excitable Type A person responds more readily with catecholamine and corticoid secretion than does Type B, as we shall see in the section on the role of endocrine responses.

One review of the literature suggests that among the stressors of modern life, fear, hatred, aggression and frustration increase catecholamine and particularly NEP secretion, as well as the plasma levels of FFA and triglycerides. They also augment platelet adhesiveness and hence can lead to thrombosis. It is suggested that "in modern society wrath, reinforced by sloth and gluttony, is the deadliest of the seven sins." Job satisfaction has also been claimed to be inversely related to death from CHD.

It may now be taken as indubitably established that psychogenic stress is a risk factor in myocardial infarction. Indeed, the American Academy of Psychosomatic Medicine formulated a resolution in 1973 "that psychosocial stresses must be included among the recognized high-risk factors in myocardial infarction" and "that the psychiatrist and psychosocial team be formally incorporated as an integral part of the Coronary Care Unit for every patient."

←*Psychogenic Stressors*

(See also our earlier stress monographs, p. xiii)

Saul, L. J.: "Hostility in cases of essential hypertension." *Psychosom. Med.* 1: 153-161 (1939) (12 refs.). B63,551/39

Alexander, F.: "Emotional factors in essential hypertension. Presentation of a tentative hypothesis." *Psychosom. Med.* 1: 173-179 (1939). B63,594/39

Discussion of essential hypertension as a psychosomatic disease (20 refs.).

Wolf, S., Pfeiffer, J. B., Ripley, H. S., Winter, O. S., Wolff, H. G.: "Hypertension as a reaction pattern to stress: summary of experimental data on variations in blood pres-

sure and renal blood flow." *Ann. Intern. Med.* 29: 1056-1076 (1948). B43,405/48

A review of the literature and personal observations led to the conclusion that "hypertension may represent an atavistic protective reaction of mobilization, invoked inappropriately by these subjects to deal with day-to-day stresses and threats arising out of problems of interpersonal relation. It becomes harmful and leads to illness when this essentially emergency pattern is adopted as a way of life" (42 refs.).

Stevenson, I., Duncan, C. H.: "Alterations in cardiac function and circulatory efficiency during periods of life stress as shown by changes in the rate, rhythm, electrocardiographic pattern and output of the heart in

those with cardiovascular disease." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 799-817. Baltimore: Williams & Wilkins, 1950. B51,945/50

"In seventy subjects with a variety of cardiovascular complaints, life stress-evoking anxiety and resentment were met by cardiovascular mobilization. This was characterized by an increase in the heart rate and cardiac output and elevation of the blood pressure. In the few instances where the stress evoked depression and despair the cardiovascular response was a hypodynamic one, with a decrease in the heart rate and cardiac output and usually a lowering of the blood pressure. Tolerance to exercise was impaired during periods of anxiety and resentment related to life stress, with an exaggerated cardiovascular response to the exercise."

Reiser, M. F., Brust, A. A., Shapiro, A. P., Baker, H. M., Ranschoff, W., Ferris, E. B.: "Life situations, emotions and the course of patients with arterial hypertension." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 870-880. Baltimore: Williams & Wilkins, 1950.

B51,948/50

Review of the literature and personal observations demonstrating "the high frequency with which emotionally stressful life situations influence adversely the course of hypertension in terms of its onset, associated symptoms, and complications, and the high frequency with which emotionally relaxing situations such as the Doctor-Patient relationship may improve the patients."

Pfeiffer, J. B. Jr., Wolff, H. G.: "Studies in renal circulation during periods of life stress and accompanying emotional reactions in subjects with and without essential hypertension; observations on the role of neural activity in regulation of renal blood flow." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 929-953. Baltimore: Williams & Wilkins, 1950.

B51,951/50

Reiser, M. F., Rosenbaum, M., Ferris, E. B.: Psychologic mechanisms in malignant hypertension. *Psychosom. Med.* 13: 147-159 (1951). B70,658/51

Hambling, J.: "Emotions and symptoms in essential hypertension." *Br. J. Med. Psychol.* 24: 242-253 (1951). D80,514/51

Jost, H., Ruilmann, C. J., Hill, T. S., Gulo, M. J.: "Studies in hypertension. II. Central and autonomic nervous system reactions of hypertensive individuals to simple physical and psychologic stress situations." *J. Nerv. Ment. Dis.* 115: 152-162 (1952).

J13,184/52

Chambers, W. N., Reiser, M. F.: "Emotional stress in the precipitation of congestive heart failure." *Psychosom. Med.* 15: 38-60 (1953).

G37,177/53

"Emotional stress is a frequent precipitating factor in the development of congestive heart failure in the patient with limited cardiac reserve."

Bernreiter, M.: "Cardiac arrhythmias in physical or emotional stress." *Mo. Med.* 53: 19-20 (1956).

C11,328/56

Case reports showing that violent arguments with superiors, witnessing a serious car accident, or lifting a heavy weight may cause ventricular or paroxysmal auricular tachycardia, complete heart block, and even death. It is concluded that "physical exertion and emotional stress may lead to almost all types of cardiac arrhythmias and death in the abnormal as well as the normal heart. An attempt is made to describe some of these phenomena that occur during the alarm reaction and their possible relationship to the production of ectopic rhythms."

Weiss, E., Dlin, B., Rollin, H. R., Fischer, H. K., Bepler, C. R.: "Emotional factors in coronary occlusion." *Arch. Intern. Med.* 99: 628-641 (1957).

C93,120/57

Studies on forty-three patients with CHD suggest that "among the multiple factors having to do with coronary occlusion, gradually mounting stress of emotional origin may be significant" (21 refs.).

Sprague, H. B.: "Emotional stress and the etiology of coronary artery disease." *Circulation* 17: 1-4 (1958).

C47,825/58

Brief editorial on emotional stress as an etiologic factor in the genesis of coronary artery disease.

Friedman, M., Rosenman, R. H.: "Association of specific overt behavior pattern with blood and cardiovascular findings. Blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease." *J.A.M.A.* 169: 1286-1296 (1959).

C67,550/59

The effect of stress on the development of

CHD was studied in men with three distinct behavioral patterns. "Men of group A exhibited a behavior pattern primarily characterized by intense ambition, competitive 'drive,' constant preoccupation with occupational 'deadlines,' and a sense of time urgency and the men of group B, a converse behavior pattern. Men of group C exhibited a behaviour pattern essentially similar to that exhibited by men of group B, but with the added elements of a chronic anxiety state." An analysis of the results strongly suggested that "the behavior pattern exhibited by the men of group A was of itself largely responsible not only for their higher serum cholesterol and possible hastening of clotting time but also for their markedly increased incidence of both clinical coronary artery disease and arcus senilis."

Weinberg, S. B., Helpern, M.: "Circumstances related to sudden, unexpected death in coronary heart disease." In: Rosenbaum, F. F. and Belknap, F. L., *Work and the Heart*, pp. 288-292. New York: P B Hoeber, 1959.

J11,127/59

Statistical studies on the relative importance of physical and emotional stress in producing fatal CHD in predisposed patients.

Dreyfuss, F.: "Role of emotional stress preceding coronary occlusion." *Am. J. Cardiol.* **3**: 590-596 (1959).

C67,879/59

In twenty-three patients a well-substantiated history of great emotional stress existed prior to myocardial infarction. This was particularly common in young individuals with coronary occlusion (29 refs.).

Simonson, E., Brozek, J.: "Russian research on arterial hypertension." *Ann. Intern. Med.* **50**: 129-193 (1959).

C63,471/59

Review on the etiology of hypertension, with special reference to the Russian literature on neurogenic factors (232 refs.).

Jouve, A., Dongier, M., Delaage, M., Barabino, J.: "Personnalité et stress dans la genèse de l'ischémie cardiaque (Angor et infarctus)." (Personality and stress in the origin of cardiac ischemia [Angina and infarct]). *Rev. Athérosclér. (Paris)* **2**: 154-165 (1960).

J24,543/60

Russek, H. I.: "Emotional stress in the etiology of coronary heart disease." *Minn. Med.* **44**: 155-159 (1961).

J23,523/61

Kanatsoulis, A.: *Psychologie du Cardiaque. Interréactions Psychiques et Cardiovascu-*

laires (Psychology of the cardiac patient. Psychologic and cardiovascular interreactions), p. 138. Paris: G. Doin, 1961.

E10,953/61

Cathey, C., Jones, H. B., Naughton, J., Hammarsten, J. F., Wolf, S.: "The relation of life stress to the concentration of serum lipids in patients with coronary artery disease." *Am. J. Med. Sci.* **244**: 421-441; 445 (1962).

J23,453/62

A relationship exists between emotional conflict and the rises in blood cholesterol immediately preceding myocardial infarction in man.

Kasanen, A., Kallio, V., Forsström, J.: "The significance of psychic and socio-economic stress and other modes of life in the etiology of myocardial infarction." *Ann. Med. Intern. Fenn.* **52** Supp. 43: 1-40 (1963) (121 refs.).

E36,432/63

Friedberg, C. K.: "Physical effort and the emotions in the genesis of coronary occlusion and myocardial infarction." In: James, T. N. and Keyes, J. W., *Henry Ford Hospital International Symposium: The Etiology of Myocardial Infarction*, pp. 427-440. Boston: Little, Brown, 1963.

E568/63

A brief review of the literature leads to the conclusion that "claims of a causal relation of effort and emotion to coronary thrombosis based on the latter's occurrence after a severe or unusual effort, a sudden emotional strain, a period of occupational stress or personal frustration or grief are not founded on adequately controlled observations and fail to exclude other possible factors." It is considered probable that the apparent increase in the incidence of coronary thrombosis during the past few decades is due to better diagnostic techniques. However, there is admittedly no scientific basis for excluding the role of effort and emotion in coronary thrombosis.

Pearson, H. E. S.: "Stress and occlusive coronary artery disease." *Am. Heart J.* **66**: 836-838 (1963).

E35,737/63

The term "stress" is derived from the Latin *stringere* (to draw tight), and hence it necessarily implies a constraining force, such as the grip of emotion. In a pilot investigation, such stresses were found to be greater in coronary patients than in controls.

Pearson, H. E. S.: "Stress and occlusive coronary-artery disease." *Lancet* February 23, 1963, pp. 415-418.

D57,816/63

In a small pilot study based on interviews, emotional stress was found to be significantly greater in coronary patients than in matched controls.

Charvat, J., Dell, P., Folkow, B.: "Mental factors and cardiovascular diseases." *Cardiologia* **44**: 124-141 (1964). G9,635/64

Miller, C. K.: "Psychological correlates of coronary artery disease." *Psychosom. Med.* **27**: 257-265 (1965). J22,925/65

Sherman, M.: *Heart Disease and the Psyche*, p. 175. U.S. Public Health Service Publication No. 1453. Bethesda, Md., 1965. G38,600/65

Review of research projects subsidized by the National Heart Institute of the U.S.A. between 1949 and 1965 to clarify the relationship between heart disease and emotional factors. An extensive section deals with animal experiments on the G.A.S. (over 200 refs.).

Hahn, P., Nüssel, E., Stieler, M.: "Psychosomatik und Epidemiologie des Herzinfarktes" (Psychosomatic and epidemiologic aspects of myocardial infarction). *Z. Psychosom. Med.* **12**: 229-253 (1966).

G57,680/66

Review on the epidemiology of myocardial infarction with special reference to the role of psychogenic stress in its pathogenesis.

Ostow, M.: "Orthostatic hypotension and psychic energizers: a clinical note." *Psychosomatics* **7**: 224-225 (1966). F68,735/66

After patients are treated with MAO inhibitors, both stressors and glucocorticoids combat the resulting orthostatic hypotension. Endogenous glucocorticoid liberation may have a therapeutic effect on this condition.

López-Ramírez, R.: "Factor psíquico en aterosclerosis" (Psychic factors in atherosclerosis). *Prensa Med. Argent.* **53**: 1190-1191 (1966). H4,474/66

Review of the literature indicating that emotional stress enhances the development of atherosclerosis.

Caffrey, B.: "A review of empirical findings." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 119-139 (1967). G58,145/67

Review indicating that personality characteristics and individual responses to stressors in life situations are related to CHD. Experimental work, particularly on infarctoid myo-

cardial necroses elicited by stress, is also carefully considered (76 refs.).

Jenkins, C. D., Rosenman, R. H., Friedman, M.: "Development of an objective psychological test for the determination of the coronary-prone behavior pattern in employed men." *J. Chron. Dis.* **20**: 371-379 (1967). J5,580/67

A "coronary-prone behavior pattern, called Type A, is characterized primarily by excessive drive, aggressiveness, ambition, involvement in competitive activities, frequent vocational deadlines, pressure for vocational productivity, an enhanced sense of time urgency and restless motor mannerisms and staccato style of verbal response. The converse, low coronary-risk behavior pattern, called Type B, is characterized by the relative absence of this interplay of psychological traits and situational pressures. The Type B subject is relaxed and more easy going, seldom becomes impatient and takes more time to enjoy avocational pursuits. He is not easily irritated and works steadily, but without a feeling of being driven by a lack of time. He is not preoccupied with social achievement, and is less competitive in his occupational and avocational pursuits. He moves and speaks in a slower and more smoothly modulated style." Sir William Osler was one of the first to describe a typical behavior pattern in coronary-prone patients, and the types presently outlined can be further divided into subtypes (23 refs.).

Russek, H. I.: "Emotional stress in the etiology of coronary heart disease." *Geriatrics* **22**: 84-89 (1967). F86,596/67

CHD is most likely to occur under the influence of emotional stress in patients on high-fat diets.

Rosenman, R. H.: "Emotional factors in coronary heart disease." *Postgrad. Med.* **42**: 165-172 (1967). G50,093/67

Type A behavior predisposes to CHD, whereas type B behavior protects against it, because the former is much more stressful than the latter.

Sigler, L. H.: "Emotion and atherosclerotic heart disease. I. Electrocardiographic changes observed on the recall of past emotional disturbances." *Br. J. Med. Psychol.* **40**: 55-64 (1967). G49,523/67

"Repeated psychic trauma, in emotionally disturbed individuals, may be one of the underlying causes in the pathogenesis of athero-

sclerotic heart disease and in inducing an acute cardiac insult."

Friedman, M., Rosenman, R. H., Straus, R., Wurm, M., Kositchev, R.: "The relationship of behavior pattern A to the state of the coronary vasculature. A study of fifty-one autopsy subjects." *Am. J. Med.* **44**: 525-537 (1968). J8,971/68

Among more than three thousand men enrolled in a prospective study, fifty-one autopsies were performed to determine the possible relationship between atherosclerosis and behavior during life. "It was found that subjects who while living exhibited a particular behavior pattern (type A) succumbed to coronary artery disease six times more frequently than subjects who exhibited a converse pattern (type B) during their life. The former subjects also exhibited, irrespective of the actual cause of death, severe basic coronary atherosclerosis six times more frequently than the latter subjects." The coronary patients also exhibited a higher "serum cholesterol, triglyceride and beta:alpha lipoprotein ratio than those who died of extracardiac causes."

Mai, F. M. M.: "Personality and stress in coronary disease." *J. Psychosom. Res.* **12**: 275-287 (1968). G63,266/68

Review on the roles of personality and emotional stress in the pathogenesis of coronary disease.

Iglesias, E. H.: "Emoción, angustia, e infarto de miocardio" (Emotion, anxiety, and myocardial infarction). *Galicia Clín.* **40**: 873-882 (1968). G64,509/68

Review of the stress theory of myocardial infarction.

Gonin, A., Aimard, G., Froment, R.: "Role des facteurs neuro-psychiques dans l'expression de la maladie coronarienne constituée" (Role of neuropsychic factors in established coronary disease manifestations). *Coeur Med. Interne* **7**: 265-290 (1968). H861/68

Review of the literature on the role of neuropsychiatric stressors in coronary disease, particularly angina pectoris.

Umidova, Z. I., Arifdzhhanov, A. A., Budianskii, M. V., Korolev, G. P., Tarapata, N. P., Abdullaeva, S. V.: "The picture of arterial hypertension during the Tashkent earthquake." *Ter. Arkh.* **41** No. 6: 38-40 (1969) (Russian). J25,191/69

"The authors saw increase of arterial hy-

pertension during the Tashkent earthquake and believe it to be due first of all to the change of meteorological factors and psycho-emotional stress."

Richter-Heinrich, E., Sprung, H.: "Psychophysiologische Untersuchungen im Anfangsstadium der essentiellen Hypertonie" (Psychophysiological studies of the initial stage of essential hypertension). *Z. Gesamte Inn. Med.* **24**: 17-21 (1969). J21,996/69

Heyden, S.: "Environmental factors." In: Schettler, F. G. and Boyd, G. S., *Atherosclerosis*, pp. 587-631. Amsterdam, London and New York: American Elsevier, 1969.

E8,021/69

The role of emotional factors in CHD is still considered doubtful. A review of available data fails to offer definite proof, especially if animal experiments are disregarded. Besides, the best that man can do is to learn to live with stress, since it is unavoidable in normal life.

Morris, J. N., Gardner, M. J.: "Epidemiology of ischaemic heart disease." *Am. J. Med.* **46**: 674-683 (1969). G67,204/69

Extensive review on the social and medical implications of ischemic heart disease, which is particularly common among men "showing strong drive, competitiveness, time urgency and preoccupation with deadlines, and the frustrations attendant on these" (Type A). This is true especially in early middle age, and results in particularly fatal disease. The incidence is twice that among Type B patients, who do not exhibit such personality traits.

Carruthers, M. E.: "Aggression and atheroma." *Lancet* November 29, 1969, pp. 1170-1171. H19,421/69

Evaluation of the literature shows that various stresses of daily life, especially fear, hatred, aggression and frustration, increase catecholamine and particularly NEP secretion, as well as the plasma levels of FFA and triglycerides. The latter can be deposited in vessel walls, and since they also augment platelet adhesiveness, may lead to thrombosis. "This hypothesis suggests that in modern society wrath, reinforced by sloth and gluttony, is the deadliest of the seven sins."

Zyzanski, S. J., Jenkins, C. D.: "Basic dimensions within the coronary-prone behavior pattern." *J. Chron. Dis.* **22**: 781-795 (1970). J8,980/70

The JAS identifies men with a coronary-prone behavior pattern (Type A) with about 70 percent accuracy. This behavior pattern is composed of at least three independent behavioral syndromes: (1) Hard Driving Temperament, (2) Job Involvement, (3) Speed and Impatience. "A system was constructed for deriving factor scores for individuals on these dimensions, and these scores were demonstrated to be reliable across forms of the test and stable over time. The 3 scores were uncorrelated with each other."

Koster, M., Musaph, H., Visser, P. (eds.): *Psychosomatics in Essential Hypertension*, p. 189. Biblio. Psychiatry No. 144. Basel and New York: S. Karger, 1970. E10,095/70

International symposium organized by the Dutch Society for Psychosomatic Research in 1968. Such topics as the methodology of blood pressure measurements, the role of emotional stress, and various psychosomatic aspects of disease were covered in eight presentations, each followed by a discussion.

Bellet, S., Roman, L.: "Stress electrocardiography in the diagnosis of arrhythmias." *Geriatrics* 25: 102-107 (1970).

H31,290/70

Emotional stress precipitates arrhythmias in predisposed patients, presumably because of the release of catecholamines and cortisol.

Bersay, C.: "Infarctus du myocarde et facteurs psycho-somatiques" (Myocardial infarct and psychosomatic factors). *Coeur Méd. Interne* 9: 323-326 (1970).

J22,115/70

Kobayashi, T., Ishikawa, H., Tawara, I.: "Psychosomatic aspects of angina pectoris." *Scand. J. Rehab. Med.* 2: 87-91 (1970).

J20,212/70

Hambling, J.: "Psychodynamics of sustained high blood pressure." *Psychother. Psychosom.* 18: 349-354 (1970).

J19,063/70

On the role of anxiety and other stressful interpersonal relations in the development of hypertension.

Engel, G. L.: "Sudden and rapid death during psychological stress. Folklore or folk wisdom?" *Ann. Intern. Med.* 74: 771-782 (1971).

G83,212/71

This excellent detailed review of the sociologic-demographic literature shows that the causes of sudden death in man may be classified into eight categories: "1) on the impact of the collapse or death of a close person; 2) during acute grief; 3) on threat

of loss of a close person; 4) during mourning or on an anniversary; 5) on loss of status or self-esteem; 6) personal danger or threat of injury; 7) after the danger is over; 8) reunion, triumph, or happy ending" (89 refs.).

Taggart, P., Gibbons, D.: "The motor-car and the normal and abnormal heart." *Triangle* 10: 63-68 (1971). J16,979/71

ECG studies on ordinary and racing-car drivers "indicate strongly that emotionally induced angina, and borderline left ventricular failure, should be contraindications to holding a driving licence."

Brod, J.: "The influence of higher nervous processes induced by psychosocial environment on the development of essential hypertension." In: Levi, L., *Society, Stress and Disease. I. The Psychosocial Environment and Psychosomatic Diseases*, pp. 312-323. London, New York and Toronto: Oxford University Press, 1971. E9,322/71

Eastwood, M. R., Trevelyan, H.: "Stress and coronary heart disease." *J. Psychosom. Res.* 15: 289-292 (1971). G85,721/71

"In individuals drawn from the general population, 'stress' in the form of confirmed neurotic disorder . . . appears to be significantly associated with presumed coronary heart disease."

Mertens, C., Segers, M. J.: "L'influence des facteurs psychologiques dans la genèse des affections coronariennes" (Influence of psychologic factors on the genesis of coronary diseases). *Bull. Acad. R. Méd. Belg.* 11: 155-221 (1971). G98,104/71

Extensive review of psychologic characteristics among patients with CHD. Several tabular summaries of risk factors and of criteria for scoring are included. Stress is undoubtedly an important predisposing factor.

Rahe, R. H., Lind, E.: "Psychosocial factors and sudden cardiac death: a pilot study." *J. Psychosom. Res.* 15: 19-24 (1971).

G82,942/71

In men with or without a history of CHD, "there was a significant increase in subjects' life change intensities during the final 6 months of their lives compared to chronologically identical time periods 2 and 3 yr prior to death. These life changes increases were threefold in magnitude—greater than those previously reported for Swedish subjects surviving myocardial infarction."

Theorell, T., Rahe, R. H.: "Psychosocial factors and myocardial infarction. I. An in-

- patient study in Sweden." *J. Psychosom. Res.* **15**: 25-31 (1971). G82,943/71
- Bishop, L. F., Reichert, P.: "Emotion and heart failure." *Psychosomatics* **12**: 412-415 (1971). H51,328/71
- Stimulating review of the electrolyte and hormonal changes associated with sudden cardiac failure following exposure to psychogenic stressors.
- Biörck, G., Rahe, R. H., Theorell, T.: "Hjärtinfarkt och 'psykisk' stress—några synpunkter" (Myocardial infarct and 'psychic' stress—some viewpoints). *Läkartidningen* **68**: 4765-4771 (1971) (Swedish). J20,742/71
- Perlman, L. V., Ferguson, S., Bergum, K., Isenberg, E. L., Hammarsten, J. F.: "Precipitation of congestive heart failure: social and emotional factors." *Ann. Intern. Med.* **75**: 1-7 (1971). J21,161/71
- Graff, C., Baumann, R., Ziprian, H., Gödicke, W., Hartrodt, W.: "Das Verhalten vegetativer und biochemischer Parameter bei essentiellen Hypertonikern während psychischer Stresssituationen" (Behavior of vegetative and biochemical parameters in essential hypertension during psychologic stress). *Dtsch. Gesundheitsw.* **26**: 6-11 (1971). J23,697/71
- Cochrane, R.: "High blood pressure as a psychosomatic disorder: a selective review." *Br. J. Soc. Clin. Psychol.* **10**: 61-72 (1971). J20,746/71
- Extensive review of the literature "yields general support to the idea of a link between perceived stress in the environment, a personality overreactive to stress and high blood pressure."
- Rahe, R. H., Paasikivi, J.: "Psychosocial factors and myocardial infarction. II. An outpatient study in Sweden." *J. Psychosom. Res.* **15**: 33-39 (1971). G83,067/71
- Segers, M., Graulich, P., Mertens, C.: "Stress et angoisse dans la pathogénie des affections coronariennes; une perspective psychosomatique" (Stress and anguish in the pathogenesis of coronary diseases; a psychosomatic approach). *Ann. Méd. Psychol.* **130**: 363-374 (1972). G97,976/72
- Theorell, T., Rahe, R. H.: "Behavior and life satisfactions characteristics of Swedish subjects with myocardial infarction." *J. Chron. Dis.* **25**: 139-147 (1972). J20,346/72
- Kerekjarto, M. von: "Psychosomatische Beschwerden bei Hypotonie" (Psychosomatic disturbances in hypotension). *Internist* (Berlin) **14**: 521-524 (1973). H78,896/73
- Statistical studies on psychosomatic complaints among patients suffering from arterial hypertension, hypotension or chronic fatigue related to stress.
- Johns, M. W.: "Stress and coronary heart disease." *Ergonomics* **16**: 683-690 (1973). J8,267/73
- Review of the literature on the role of psychosocial stress in the pathogenesis of CHD. "It seems likely that long-term behavioural arousal, associated with aggressive competition between men, and a sense of urgency interact with other factors such as diet and cigarette smoking to produce the various manifestations of coronary heart disease, but the physiological mechanisms are uncertain."
- Russek, H. I.: "The stress of life." In: Russek, H. I., *The Paul D. White Symposium: Major Advances in Cardiovascular Therapy*, pp. 111-115. Baltimore: Williams & Wilkins, 1973. E10,229/73
- Discussion of the most common emotional stressors and dietary factors conducive to coronary accidents in the North American population.
- Segers, M.-J.: "Auto-évaluation de l'anxiété, de la dépression et facteurs de risque d'affections coronariennes" (Autoevaluation of anxiety, depression, and coronary disease risk factors), p. 47. Thesis, Université Catholique de Louvain, 1973. J10,475/73
- Doctoral dissertation on the roles of anxiety and depression in the production of CHD in man.
- Wardwell, W. I., Bahnsen, C. B.: "Behavioral variables and myocardial infarction in the southeastern Connecticut heart study." *J. Chron. Dis.* **26**: 447-461 (1973). J15,910/73
- A statistical study based on questionnaires led to the conclusion that what counts in the production of CHD "may not be the amount of situational or intrapsychic stress a person is subjected to but the way he copes with it—his defensive style" (28 refs.).
- Wardwell, W. I.: "A study of stress and coronary heart disease in an urban population." *Bull. N.Y. Acad. Med.* **49**: 521-531 (1973). J3,167/73
- Statistical studies, based mainly on ques-

tionnaires about subjective criteria and life habits, support the "contention that a coronary-prone behavior pattern predicts the incidence of coronary heart disease in white males." The decisive factor may be that coronary candidates have an unusually strong "tendency to somaticize affect: that is, the proclivity on the part of some people in contradistinction to others to translate psychological and situational tensions, conflicts, and frustrations in bodily symptoms. The variety of ways in which such stresses are expressed appear to include restless activity, ambitious strivings, bodily symptoms of many different sorts, and pathogenic atherosclerotic and thrombotic processes."

Somerville, W.: "Emotions, catecholamines and coronary heart disease." *Adv. Cardiol.* **8**: 162-173 (1973). J16,987/73

A statistical study shows that "certain experienced motor-car drivers with a history of coronary heart disease when driving in busy traffic develop angina, sinus tachycardia, ectopic beats and various arrhythmias. Healthy racing drivers stimulated by the emotions of competition and danger, develop high-grade sinus tachycardia, raised plasma catecholamines and free fatty acids immediately before and after a race. Public speaking induces in normal persons similar changes in heart rate and rhythm and elevations in plasma catecholamines and free fatty acids. In both drivers and public speakers, triglycerides show a peak elevation 1-2 h after the event. Oxyphenol inhibits the increase in heart rate, plasma catecholamines, free fatty acids and triglycerides."

Theorell, T.: "Psychosocial factors and myocardial infarction—why and how?" *Adv. Cardiol.* **8**: 117-131 (1973). J19,610/73

Burch, G. E., Giles, T.: "Aspects of the influence of psychic stress on angina pectoris." *Am. J. Cardiol.* **31**: 108-110 (1973). H63,705/73

Thiel, H. G., Parker, D., Bruce, T. A.: "Stress factors and the risk of myocardial infarction." *J. Psychosom. Res.* **17**: 43-57 (1973). G98,345/73

Levene, D. L.: "Psychological factors in the genesis of myocardial infarction." *Can. Med. Assoc. J.* **111**: 499-501 (1974). H92,257/74

Review of numerous cases in which psychogenic stress immediately preceded myocardial infarction.

Pfanz, M.: "Psychische und soziale Faktoren bei der Entstehung des Hochdrucks" (Importance of mental and social factors in the genesis of hypertension). *Internist* (Berlin) **15**: 124-128 (1974). H86,142/74

Review of hypertension as a disease largely dependent upon stress, particularly social maladjustment (29 refs.).

Vlachakis, N. D., Schiavi, R., Mendlowitz, M., Guia, D. de, Wolf, R. L.: "Hypertension and anxiety." *Am. Heart J.* **87**: 518-526 (1974). H85,440/74

Liesse, M., Imschoot, K. van, Mertens, C., Lauwers, P.: "Caractéristiques psychologiques et réactions physiologiques au stress de sujets normaux et coronariens" (Psychologic characteristics and physiologic reactions to stress in normal and coronary-prone subjects). *J. Psychosom. Res.* **18**: 49-53 (1974). J12,478/74

From various psychologic tests, it is concluded that "patients with ischemic heart disease do not show an exclusive coronary-prone personality pattern. Different patterns can be identified among them. The common psychological coronary-prone component of these different patterns seems to be the incapacity to cope with anxiety or the inadequacy of their defense-mechanisms."

Corbalan, R., Verrier, R., Lown, B.: "Psychological stress and ventricular arrhythmias during myocardial infarction in the conscious dog." *Am. J. Cardiol.* **34**: 692-696 (1974). H94,394/74

Lenzner, A. S.: "Psychiatry in the coronary care unit." *Psychosomatics* **15**: 70-71 (1974). H87,383/74

It has been so definitely established that stress plays a crucial role in CHD that the Academy of Psychosomatic Medicine formulated the following resolution at its twentieth annual meeting in 1973: "psychosocial stresses must be included among the recognized high risk factors in myocardial infarction . . . [and] . . . the psychiatrist and psychosocial team [must] be formally incorporated as an integral part of the Coronary Care Unit for every patient."

Turner, R., Ball, K.: "Prevention of coronary heart-disease." *Lancet* March 9, 1974, pp. 411-412. H83,448/74

Empirical findings on the prevention of CHD by protection against excessive psychogenic stress.

Friedman, M., Rosenman, R. H.: *Type A*

Behavior and Your Heart, p. 276. New York: Alfred A Knopf, 1974. E10,671/74

Detailed discussion of the authors' definition of Type A and Type B behavior as influencing predisposition to CHD. Emphasis is placed upon the fact that Type A, the coronary-prone patient, is exposed to much more stress than Type B (no refs.).

Rahe, R. H., Romo, M.: "Recent life changes and the onset of myocardial infarction and coronary death in Helsinki." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 105-120. Springfield, Ill.: Charles C Thomas, 1974 (18 refs.).
E10,685/74

Froese, A., Hackett, T. P., Cassem, N. H., Silverberg, E. L.: "Trajectories of anxiety and depression in denying and nondenying acute myocardial infarction patients during hospitalization." *J. Psychosom. Res.* **18**: 413-420 (1974). J19,266/74

Rahe, R. H., Romo, M., Bennett, L., Siltanen, P.: "Recent life changes, myocardial infarction, and abrupt coronary death." *Arch. Intern. Med.* **133**: 221-228 (1974).
J20,915/74

Theorell, T.: "Life events before and after the onset of a premature myocardial infarction." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 101-117. New York, London and Sydney: John Wiley & Sons, 1974.
E10,784/74

Friedman, M., Byers, S. O., Diamant, J., Rosenman, R. H.: "Plasma catecholamine response of coronary-prone subjects (Type A) to a specific challenge." *Metabolism* **24**: 205-210 (1975). H98,918/75

In a nonphysical competitive struggle (puzzle solving), the plasma NEP content of Type A persons rises 30 percent above that of Type B individuals, whereas plasma EP remains essentially unchanged in both groups.

Lundberg, U., Theorell, T., Lind, E.: "Life changes and myocardial infarction: individual differences in life change scaling." *J. Psychosom. Res.* **19**: 27-32 (1975).
J22,161/75

Miller, W. B., Rosenfeld, R.: "A psychophysiological study of denial following acute myocardial infarction." *J. Psychosom. Res.* **19**: 43-54 (1975). J22,162/75

Conditioning

Genetics. Genetic predisposition undoubtedly plays an extremely important role in CHD. Evidence supporting this concept was presented in the previous section in which the constitutional types of predisposed and comparatively resistant individuals were delineated from the psychologic point of view. Of course, various other risk factors, such as a tendency to excessive eating, smoking, high cholesterol and FFA levels, accelerated blood coagulation, disinclination to exercise and so on are also largely dependent upon inherited constitutional factors. In any event, CHD appears to run in families, as do hypertension, the smoking habit, high cholesterol, triglyceride and β -lipoprotein levels and Type A behavior.

Diet. The dietary factors that predispose to cardiovascular disease in general exert the same conditioning effect upon stress-induced hypertension or CHD. The most recognized among these nutritional factors are the foods with high saturated fat content (mainly animal fat) and cholesterol. However, especially in the presence of renal disease and hypertension, excessive sodium intake is also harmful, as is gluttony in general, because the resulting adiposity makes increased demands upon the circulatory system and at the same time augments the stressor effect of exercise.

Occupation, Social Factors including Urbanization. According to large statistical surveys, the incidence of CHD has greatly increased during the present century, and the relative immunity of primitive races disappears when they subject themselves to

civilized life. However, the effect upon statistics of constantly improving diagnostic techniques and more accurate reporting of death from CHD must not be neglected.

It has been claimed that in a series of one hundred young coronary patients, emotional strain of occupational origin was noted in 91 percent, as compared with 20 percent in normal controls.

In another study, myocardial infarction among male employees proved to be inversely proportional to their annual income; however, such findings are difficult to interpret. The demands of top management jobs may be no more stressful than those of low level jobs, but usually, men chosen for advancement are those whose personalities endow them with both executive talent and resistance to CHD in that they are better adjusted to life. In any event, other statistical studies gave opposite results, which were attributed to the greater drive and willingness to accept stressful responsibilities among those who reach higher echelons.

It has also been claimed that geographically and occupationally mobile subjects have a higher CHD incidence than others. This may be ascribed to their need for more frequent readjustment and adaptation to new circumstances.

It is generally agreed that urban life is more conducive to hypertension and CHD than rural settings, but here again it is difficult to distinguish between the relative role played by crowding, differences in diet, occupations, air pollution and so on. In any event, the occupational stressors of industrial society appear to play a dominant role in the high incidence of CHD as well as in establishing a predisposition for it through a rise in plasma lipids, altered hemodynamics, and accelerated blood clotting.

An extensive epidemiologic study on thirty-one thousand men in London showed CHD to be more frequent among those holding sedentary jobs. Bus conductors were found to have less CHD than bus drivers, postmen less than telephonists, executives and clerks. It is implied that these differences are determined by the amount of exercise required by their jobs. Extensive statistical studies among twelve thousand members of fourteen professional groups in the U.S.A. showed that CHD was strikingly related to occupational activity among physicians, lawyers, security analysts and traders.

Yet another statistical study in high and low stress areas of Detroit revealed that social and economic stressors definitely predisposed to increased blood pressure, especially among blacks.

In Israeli kibbutzim, agricultural workers were most likely to experience stress associated with CHD, although the generally-accepted predisposing factors among them did not significantly differ from those in managerial, professional, clerical or factory workers.

Age. It is hardly worth reiterating the well-known fact that the incidence of arteriosclerosis and CHD increases with age. However, among 866 patients eighteen to thirty-nine years old, a fatal coronary attack often occurred during strenuous activity related to combat and other military duties.

There is a general impression, not supported by convincing statistical evidence, that fatal CHD occurs more frequently among young people now than some decades ago.

Allegedly, in juvenile hypertension, excess production of mineralocorticoids—which activate hepatic hypertensinogen formation and catecholamine secretion—is especially important. However, these findings have not yet been confirmed.

<Conditioning

(See also our earlier stress monographs, p. xiii, and cf. individual conditioning factors)

Genetics. Gertler, M. M., White, P. D.: *Coronary Heart Disease in Young Adults. A Multidisciplinary Study*, p. 218. Cambridge, Mass.: Harvard University Press, 1954.

E10,486/54

An excellent multidisciplinary study conducted at the Massachusetts General Hospital with the cooperation of several experienced cardiologists, reviewing the indices characteristic of the "coronary candidate" and the precipitating agents of CHD, including heredity, athletic activity, endocrine factors, diet and blood biochemistry (several hundred refs.).

Kruse, H.: "Committee on cultural, societal, familial, psychological, and genetic influences." *Am. J. Public Health* 50 Supp.: 71-104 (1960). E48,857/60

Extensive review by a committee on cultural, societal, familial, psychologic and genetic influences upon the development of cardiovascular disease, with special reference to stress and the G.A.S.

Mordkoff, A. M., Parsons, O. A.: "The coronary personality: a critique." *Psychosom. Med.* 29: 1-14 (1967) (54 refs.).

J23,148/67

Rosenman, R. H., Friedman, M., Straus, R., Jenkins, C. D., Zyzanski, S. J., Wurm, M.: "Coronary heart disease in the Western Collaborative Group study. A follow-up experience of 4½ years." *J. Chron. Dis.* 23: 173-190 (1970). J9,014/70

In a follow-up study of 3,182 men thirty-nine to fifty-nine years old, "a significantly increased incidence of CHD was found to be associated with parental history of CHD, elevated systolic or diastolic blood pressure, cigarette smoking, higher serum levels of cholesterol, triglyceride and beta lipoproteins, and the Type A behavior pattern."

Diet. Lipman, D. G.: "Stress and hypertension: use of antistress diet and antihistamine." *J. Am. Geriatr. Soc.* 8: 177-184 (1960). C81,912/60

Detailed description of a diet which allegedly alleviates stress-induced hypertension, especially when given in combination with an antihistaminic.

Bajusz, E.: *Nutritional Aspects of Cardiovascular Diseases*, p. 244. London: Crosby Lockwood & Son, 1965. E5,013/65

Monograph on the influence of diet upon the development of cardiovascular disease, with special emphasis on nutritional factors determining predisposition to stress-induced experimental cardiac necroses.

Russek, H. I.: "Role of emotional stress in the etiology of clinical coronary heart disease." *Dis. Chest.* 52: 1-9 (1967).

F85,321/67

A careful survey of the literature and personal observations lead to the conclusion that "the concept of any disease arising from a single cause is obsolete and misleading. Much evidence now suggests that most of the lethality of a high fat diet in Western society may actually be dependent on the 'catalytic' influence of stressful living." This is particularly true of CHD (36 refs.).

Raab, W.: *Preventive Myocardiology. Fundamentals and Targets*, p. 227. Springfield, Ill.: Charles C Thomas, 1970.

E8,717/70

Monograph reviewing the many measures (diet, life habits, exercise, and so on) that have been recommended for the prevention of cardiovascular disease in man. Attention is given to interactions between corticoids, catecholamines and diets, especially on the basis of corresponding animal experiments (almost 1,000 refs.).

Occupation, Social Factors including Urbanization. Stewart, I. McD. G.: "Coronary disease and modern stress." *Lancet* December 23, 1950, pp. 867-870.

B54,219/50

Review of the literature suggests that the incidence of CHD has greatly increased during the present century. The immunity enjoyed by primitive races disappears when they subject themselves to civilized life with its associated mental stresses and richness of diet. "It is, in fact, reasonable to identify sufferers from coronary disease as the selected victims of modern stress."

Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., Parks, J. W.: "Coronary heart-disease and physical activity of work." *Lancet* November 21 and 28, 1953, pp. 1053; 1111; 1120. D85,741/53

An extensive epidemiologic study on thirty-one thousand men aged thirty-five to sixty-four years was performed in London,

showing that physically active men apparently have a lower incidence of CHD in middle age than those holding sedentary jobs. "Transport workers, postal workers, and Civil Service executive officers and clerks were observed during 1949-50. Bus conductors (on double-decker vehicles) were found to have less coronary heart-disease than bus drivers, and postmen less than telephonists, executive officers, and clerks."

Sigler, L. H.: "Cardiac disability and death caused by strains: problem in workmen's compensation." *J.A.M.A.* 154: 294-299 (1954). B89,752/54

Russek, H. I., Zohman, B. L.: "Relative significance of heredity, diet and occupational stress in coronary heart disease of young adults. Based on an analysis of 100 patients between the ages of 25 and 40 years and a similar group of 100 normal control subjects." *Am. J. Med. Sci.* 235: 266-277 (1958). A352/58

Hereditary predisposition and high-fat diets are undoubtedly important conditioning factors in CHD. However, in one hundred young coronary patients, "severe emotional strain of occupational origin was observed in 91% of the test subjects as compared with 20% of normal controls. Emotional stress associated with job responsibility appears far more significant in the etiologic picture of coronary disease in young adults than heredity or a prodigiously high-fat diet." Smoking "would appear to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease."

Lee, R. E., Schneider, R. F.: "Hypertension and arteriosclerosis in executive and non-executive personnel." *J.A.M.A.* 167: 1447-1450 (1958). C81,673/58

The authors were surprised to learn that, among more than one thousand subjects in business, hypertension and cardiovascular disease (arteriosclerosis, CHD, myocardial infarction) were disproportionately low in the executive group. They noted that "stress is a relative matter and that the disruption of the harmonious balance between a man and his environment can result from either the demands of the environment or the failure of the man to measure up to them. Success in a career goes hand in hand with good health. The executive, as part of his training, learns to judge the amount of occupational stress he

can stand and to appreciate the value of outside avenues of expression."

Rosenman, R. H., Friedman, M.: "The possible relationship of occupational stress to clinical coronary heart disease." *Calif. Med.* 89: 169-174 (1958). C61,455/58

Review of the literature and personal observations showing that the predisposing factors for CHD (increased plasma lipids, intimal damage, altered hemodynamics, accelerated blood clotting) are affected by various types of stressors. "It is suggested that the increasing occupational stress unique to industrialized society plays a dominant role in the high incidence of clinical coronary heart disease."

Russek, H. I.: "Role of heredity, diet, and emotional stress in coronary heart disease." *J.A.M.A.* 171: 503-508 (1959).

C74,784/59

In ninety-one of one hundred patients, prolonged emotional strain related to occupational responsibilities preceded a coronary attack. Smoking is particularly frequent among coronary patients, but it may be a manifestation of inner stress rather than an etiologic factor. Furthermore, much of our envied leisure time is regimented by participation in social, educational and civic events which "may represent a poor antidote for the emotional stresses of daily business competition."

Mortensen, J. M., Stevenson, T. T., Whitney, L. H.: "Mortality due to coronary disease analyzed by broad occupational groups." *Arch. Ind. Hyg.* 19: 1-4 (1959).

E57,220/59

A statistical study shows that "in the Bell Telephone System there is no material difference in coronary mortality between the top management group and the craftsmen and laborers group, but there is a marked difference between top management and middle management which is not explainable from presently available data. The popular notion that high executive positions are associated with high coronary mortality is likely due to the greater publicity connected with such deaths rather than to statistical facts."

Master, A. M.: "The role of effort and occupation (including physicians) in coronary occlusion." *J.A.M.A.* 174: 942-948 (1960).

J7,796/60

A general review of epidemiologic data

does not convince the author that the frequency of CHD has reached epidemic proportions or is elicited by the stress of modern life. He believes that its apparently greater incidence is due to increased population age and improved diagnostic techniques.

Russek, H. I.: "Emotional stress and coronary heart disease in American physicians, dentists and lawyers." *Am. J. Med. Sci.* **243**: 716-725 (1962). D34,808/62

Questionnaires sent to ten thousand physicians, dentists and attorneys aged forty to sixty-nine showed a definite positive correlation between occupational stress and CHD. "General practitioners in each field showed coronary heart disease prevalence rates 2 to 3 times those of the specialists selected for survey. No consistent relationship was found for prevalence rates of reported hypertension and occupational stress." Correlations of the data with the diets of these subjects "lend support to clinical and experimental studies which suggest that emotional stress is an important accelerating factor in atherogenesis when the diet is relatively high in animal fat" (28 refs.).

Pell, S., D'Alonzo, C. A.: "Acute myocardial infarction in a large industrial population. Report of a 6-year study of 1,356 cases." *J.A.M.A.* **185**: 831-838 (1963).

E26,954/63

The age-adjusted incidence of myocardial infarction among male employees was inversely proportional to their annual income. These results are difficult to interpret because "the demands of a top-management job may be no more stressful than situations commonly encountered by persons in lower job levels, at work and at home. Secondly, men chosen for advancement may be those whose personal qualities are characteristic of both executive talent and resistance to coronary disease. It is conceivable, for example, that in selecting persons to assume greater responsibilities, supervisors and managers, knowingly or unknowingly, may tend to choose the better adjusted individuals, who by virtue of their personality and psychic state are better able to cope with life's stresses in general."

Syme, S. L., Hyman, M. M., Enterline, P. E.: "Some social and cultural factors associated with the occurrence of coronary heart disease." *J. Chron. Dis.* **17**: 277-289 (1964).

J11,128/64

Systematic studies on the incidence of

CHD in North Dakota (performed irrespective of diet, body weight, blood pressure, smoking or parental longevity) showed that "geographically mobile subjects had a ratio twice that of geographically stable subjects; occupationally mobile men had a ratio three times higher than that of occupationally stable men."

Wardwell, W. I., Hyman, M., Bahnsen, C. B.: "Stress and coronary heart disease in three field studies." *J. Chron. Dis.* **17**: 73-84 (1964).

G1,335/64

Brief statistical study indicating a high probable correlation between CHD and social, cultural and even religious factors. Although further proof is necessary, the study suggests that in the U.S.A., "coronary heart disease may be viewed as an alternative to certain personality disorders, particularly for native-born American middle class Protestants, who are culturally not permitted to be weak or to fail to compete successfully" (35 refs.).

Russek, H. I.: "Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups." *J.A.M.A.* **192**: 189-194 (1965).

F36,826/65

Statistical studies on twelve thousand professional men in fourteen occupational categories in the United States. On the basis of questionnaires evaluated by specialists in each field, CHD was "strikingly related to the relative stressfulness of occupational activity" among physicians, lawyers, security analysts and traders. High fat diets and smoking were associated with a high incidence of CHD in combination with emotional stress. Smoking was most frequent in stressful occupations, but unexpectedly CHD was more common among nonsmokers than among persons who once smoked but gave it up. Possibly, "the ability to stop smoking may imply a resilient personality response to stress and diminished vulnerability to atherogenic influences."

Smith, T.: "A review of empirical findings." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 23-39 (1967).

J10,923/67

Brief review suggesting that modern urban industrialized society is associated with a greater incidence of hypertension and CHD than rural settings. Migrants have an unusually high incidence of these diseases both at their place of origin and at their destination (26 refs.).

Marks, R. U.: "A review of empirical findings." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 51-107 (1967). J10,924/67

Extensive review of the demographic variables, particularly urbanization, in relation to CHD (154 refs.).

Jenkins, C. D.: "Appraisal and implications for theoretical development." *Milbank Mem. Fed. Q.* **45** No. 2, Part 2: 141-150 (1967). J10,925/67

Brief review on the role of socioenvironmental stressors in the pathogenesis of CHD.

Scheinman, H. Z.: "Coronary atherosclerosis in military pilots: I. Relationship to flying and aviation accidents." *Aerosp. Med.* **39**: 1348-1351 (1968). G85,445/68

Autopsies on 206 military pilots "demonstrate that the amount of flying time (when the age factor is considered) and type of aircraft are neither statistically related nor contributory to the severity of coronary atherosclerosis." It is concluded that drastic elimination of older aircrew will not significantly reduce aviation accidents.

French, J. R. P., Caplan, R. D.: "Psychosocial factors in coronary heart disease." *Proc. Ann. Conf. NASA Clin. Dir., Environm. Health Off. Med. Program Advisors*, pp. 26-72 (1969). J16,126/69

Matsumoto, Y. S.: "Social stress and coronary heart disease in Japan." *Milbank Mem. Fed. Q.* **48**: 9-36 (1970).

G73,150/70

In Japan the incidence of arteriosclerotic CHD is extremely low as compared to its incidence among the white North American population. "Although the diet factor remains dominant in current thinking, the stress hypothesis merits the most intensive probing as alternate or associated explanations of observed relations and differentiations" (87 refs.).

Gutmann, M. C., Benson, H.: "Interaction of environmental factors and systemic arterial blood pressure: a review." *Medicine* (Baltimore) **50**: 543-553 (1971).

G33,290/71

Excellent epidemiologic and experimental study showing that hypertension is related to environmental conditions requiring continuous behavioral and physical readjustments, especially with regard to urbanization. "Operant conditioning techniques may be useful in training humans to lower their blood pressure in environmental situations previously

associated with pressor responses" (85 refs.).

Sales, S. M., House, J.: "Job dissatisfaction as a possible risk factor in coronary heart disease." *J. Chron. Dis.* **23**: 861-873 (1971). J10,970/71

Statistical studies show that "job satisfaction is negatively related to a group's rate of death from coronary heart disease."

Jenkins, C. D.: "Psychologic and social precursors of coronary disease. Parts 1 & 2." *N. Eng. J. Med.* **284**: 244-255; 307-317 (1971) (96 & 162 refs.). H35,196/71

Harburg, E., Erfurt, J. C., Chape, C., Hauenstein, L. S., Schull, W. J., Schork, M. A.: "Socioecological stressor areas and black-white blood pressure: Detroit." *J. Chron. Dis.* **26**: 595-611 (1973). J8,243/73

Comparative studies in high- and low-stressed areas of Detroit revealed that social and economic stress definitely predisposes to increased blood pressure, especially in blacks.

Reeder, L. G., Schrama, P. G. M., Dirken, J. M.: "Stress and cardiovascular health: an international cooperative study. I." *Soc. Sci. Med.* **7**: 573-584 (1973). J15,755/73

The data obtained from questionnaires used in the Los Angeles Heart Study's SSS correlate well with a similar psychosomatic stress scale developed in the Netherlands. An extensive study on postal and telegraph workers indicated that "a relatively low job level was related to a relatively high number of EKG abnormalities. These latter findings may be predictive of future coronary artery disease in this group" (53 refs.).

Shirom, A., Eden, D., Silberwasser, S., Kellermann, J. J.: "Job stresses and risk factors in coronary heart disease among five occupational categories in kibbutzim." *Soc. Sci. Med.* **7**: 875-892 (1973). J8,517/73

Among 762 adult male kibbutz members in Israel, agricultural workers were most likely to experience stress associated with CHD. Yet such cardiac lesions and acknowledged risk factors predisposing for them "did not significantly differ among managerial and professional workers, clerical workers, craftsmen, factory workers and agricultural workers."

House, J. S.: "Occupational stress and coronary heart disease: a review and theoretical integration." In: O'Toole, J., *Work and the Quality of Life. Resource Papers for Work in America*. (In Press). J16,202/75

Age. Yater, W. M., Traum, A. H., Brown, W. G., FitzGerald, R. P., Geisler, M. A., Wilcox, B. B.: "Coronary artery disease in men eighteen to thirty-nine years of age. Report of eight hundred sixty-six cases, four hundred fifty with necropsy examinations." *Am. Heart J.* **36**: 334-372; 481-526; 683-722 (1948). C45,577/48

Extensive clinical and anatomical studies on coronary arteriosclerosis and cardiac infarcts in 866 patients eighteen to thirty-nine years of age, in whom the fatal coronary attack occurred most frequently during strenuous activity related to combat and other military duties (162 refs.).

Kappert, A.: "Der jugendliche Hochdruck" (Juvenile hypertension). *Schweiz. Med. Wochenschr.* **82**: 821-825 (1952).

J7,692/52

Review on juvenile hypertension with reference to the possible role of stress. This view is supported not only by the production of mineralocorticoid hypertension with DOC in rats, but also by the fact that both glucocorticoids and mineralocorticoids can activate hepatic formation of hypertensinogen, and that

stress is well known to cause catecholamine secretion and a rise in blood pressure.

Hauss, W. H.: "Tissue alterations due to experimental arteriosclerosis." In: Vogel, H. G., *Connective Tissue and Ageing* (Int. Congr. Ser. No. 264), pp. 23-33. Amsterdam: Excerpta Medica, 1973. J14,882/73

In rats the emotional stress produced by restraint elicits typical mesenchymal reactions in the blood vessel walls with increased ³⁵S-sulfate and ³H-thymidine incorporation. Essentially similar changes occur after exposure to other stressors, and these are considered to be the first step in the arteriosclerotic process characteristic of aging. "The deformation of the structure of the arterial wall participates essentially in the development of lipidosis, fibrinosis, and cell necroses. Aggregation of thrombocytes and thrombosis in the arterial wall results from the frequent reduplication of intima cells."

Hrubec, Z., Zukel, W. J.: "Epidemiology of coronary heart disease among young army males of World War II." *Am. Heart J.* **87**: 722-730 (1974). H86,845/74

Diagnostic Indicators and Other Changes Characteristic of Stress-Induced Cardiovascular Disease

In practice it is virtually impossible to separate diagnostic indicators from other changes characteristic of stress-induced cardiovascular disease that are not particularly helpful in diagnosis. Since all these also help to analyze the pathogenesis of such maladies, they will be discussed here conjointly.

Stress Tests. Tests commonly employed to evaluate the stress resistance of patients with cardiovascular disease have already been discussed in the section on Stress Tests in general. They are based mainly on resistance to muscular exercise (bicycle ergometer, treadmill, step tests) although "stress interviews" and cold pressor tests also have some diagnostic value. Furthermore, in early hypertensive patients, psychogenic stress (for example, arithmetic under time pressure) causes an unusual rise in pulse rate, blood pressure, blood glucose, oxygen consumption, muscular tone, plasma NEP, FFA, cortisol and renin activity.

Morphology. Histologic evidence suggests that the development of coronary thrombosis is often very gradual taking several days before pain and occlusion become manifest.

In patients who died from CHD following severe stress, there was extensive fuchsinophilic degeneration of the myocardium (similar to that seen in experimental animals during the ESCN), indicating a necrosis "of metabolic origin."

A review of the literature also suggested that various nonvascular noxious factors

interfering with myocardial metabolism play a decisive role in CHD. This is true especially of the production of microfocal necroses which coincide with or aggravate the pathogenic effects of primarily vascular disturbances.

"Stress polycythemia" is manifested by a normal erythrocyte mass, but a high hematocrit reading secondary to contracted plasma volume. This condition can be elicited by a variety of stressors and may be related to certain types of hypertension.

Blood Clotting. The frequent lack of correlation between coronary thrombosis and myocardial infarction or "sudden coronary heart death," which was repeatedly emphasized in the earlier literature, has again been demonstrated on the basis of an extensive review. "In more than 50% of the examined acute-recent infarct and sudden coronary heart death cases, an acute-recent occlusion was not detected." In other patients, it took place in an already almost completely stenotic vessel so that it could have little effect; hence, special attention must be given to the "infarctoid myocardial necroses" such as have been produced in animals by combined treatment with steroids and stressors.

Cardiac catheterization and other stressful procedures caused a rise in the platelet aggregation response to ADP, concurrently with an increase in plasma FFA. It is suggested that catecholamines, released during emotional stress, may be responsible for enhanced platelet aggregation and the development of thrombosis as well as atherosclerosis.

Hormones. There can hardly remain any doubt today about the participation of hormones in the development of stress-induced cardiovascular disease. Evidence in favor of this view has come from observations in man and from animal experiments. Here, we shall limit ourselves to clinical findings, since a special section is devoted to experimental cardiovascular diseases.

Catecholamines liberated from sympathetic nerve endings and the adrenal medulla cause a dramatic rise in blood pressure. Hence, their role in hypertension has long been suspected, and the production of what we have called "mineralocorticoid hypertension" in DOC-treated animals has led to many clinical studies on this and related steroids in patients with various forms of hypertension.

The relevant literature has become too voluminous to be discussed here in detail; besides, a large part of it has already been analyzed in "our earlier stress monographs" (p. xiii).

Suffice it to say here, that an increase in the plasma and urinary concentration of catecholamines, of several mineralocorticoids (DOC, 18-OH-DOC, aldosterone) and renin has repeatedly, though not consistently, been noted in hypertensive patients. There is good reason to believe that both hypertension and CHD can be elicited during stress through a rise in the secretion of any of these humoral substances, and are often caused by the concurrent overproduction of several among them; one or the other can play the predominant role, depending upon conditioning factors.

For a detailed discussion of hormonal participation in the pathogenesis of hypertension and other cardiovascular diseases the reader must be referred to pertinent reviews and monographs, but it may be useful to summarize at least a few of the more salient facts.

There is good evidence that catecholamines and corticoids mutually enhance each other's pressor effects and that the hypertensive actions of mineralocorticoids are augmented by a high sodium intake. The latter also predisposes the kidney to damage,

especially by mineralocorticoids, including renin-stimulated mineralocorticoid secretion. Thus, a vicious circle may develop in which mineralocorticoids elicit renal injury and the resulting rise in renal pressor substances augments mineralocorticoid secretion, which further damages the kidney until fatal malignant hypertension ensues.

In predisposed persons, virtually any kind of stressor causes a rise in blood pressure as well as in catecholamine and corticoid secretion; furthermore, the therapeutic efficiency of both adrenergic blocking agents (for example, propranolol) and antimineralcorticoids (for example, spironolactone) supports this hypothesis. It is still difficult, however, to explain the occasional instances of hypertension in which the blood level of renin is subnormal. According to some investigations, this "hyporeninemic hypertension" is probably a pluricausal disease of variable etiology, often dependent upon increased production of some mineralocorticoid which decreases renin secretion.

A prolonged increase in blood pressure undoubtedly damages the vessel walls and contributes to the development not only of arteriosclerosis but even of the hyalinizing arterial lesions characteristic of malignant hypertension and periarteritis nodosa. All of this presumably can enhance the narrowing of cardiac arteries, and by damaging their endothelium, eventually results in thrombosis. The latter is further facilitated by the well-known decrease in blood clotting time produced by catecholamines.

Nevertheless, an ever-increasing body of evidence suggests that many types of myocardial necrosis are not due to coronary thrombosis but to metabolic necroses of the myocardium in which corticoids and sodium play decisive roles, as we shall see in the section Experimental Cardiovascular Diseases. Furthermore, not all cases of sudden death produced by acute stress are due to myocardial necrosis; they may be of purely functional origin, for example, ventricular fibrillation.

Nonhormonal Metabolites. The nonhormonal metabolic changes associated with stress-induced cardiovascular disease are often those characteristic of stress itself, such as a rise in serum FFA and cholesterol; these are highly subject to the conditioning influence of the diet. Allegedly, hypertensive patients also tend to have especially high adrenal cholesterol levels.

Diagnostic Indicators and Other Changes Characteristic of Stress-Induced Cardiovascular Disease

(See also our earlier stress monographs, p. xiii)

Stress Tests. Wolf, S., Cardon, P. V. Jr., Shepard, E. M., Wolff, H. G.: *Life Stress and Essential Hypertension. A Study of Circulatory Adjustments in Man*, p. 253. Baltimore: Williams & Wilkins, 1955. E145/55

Monograph on the role of stress in the production of essential hypertension in man. Principal emphasis is placed upon stress interviews and a cold pressor test as diagnostic indices. Adrenocortical participation is only briefly considered (158 refs.).

Payne, R. M., Horwitz, L. D., Mullins, C. B.: "Comparison of isometric exercise and

angiotensin infusion as stress test for evaluation of left ventricular function." *Am. J. Cardiol.* 31: 428-433 (1973). H68,564/73

Baumann, R., Ziprian, H., Gödicke, W., Hartrodt, W., Naumann, E., Läuter, J.: "The influence of acute psychic stress situations on biochemical and vegetative parameters of essential hypertensives at the early stage of the disease." *Psychother. Psychosom.* 22: 131-140 (1973). J10,171/73

In early hypertensive patients, psychogenic stress (arithmetic under time pressure) caused: a rise of the pulse rate, an increased systolic and diastolic blood pressure; a prolonged persistence of increased pulse rate and blood glucose; elevated "oxygen consumption and muscular tonus (both the initial values and the values after stress situations were higher in hypertensives than in

the control group); a rise of noradrenalin, free fatty acids, cortisol and renin activity (orthostasis effect) in the plasma. In contrast to the control group, the adaptation of hypertensives to repeated experimental stress situations was markedly disturbed."

Theorell, T., Rahe, R. H.: "Psychosocial characteristics of subjects with myocardial infarction in Stockholm." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 90-104. Springfield, Ill.: Charles C Thomas, 1974. E10,684/74

CHD is discussed as a stress disease, mainly on the basis of the SRE questionnaire (44 refs.).

Ander, S., Lindstrom, B., Tibblin, G.: "Life changes in random samples of middle-aged men." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 121-124. Springfield, Ill.: Charles C Thomas, 1974. E10,686/74

The SRE questionnaire correlates fairly well with CHD in this retrospective study.

Imschoot, K. van, Liesse, M., Mertens, C., Lauwers, P.: "Caractéristiques psychologiques et réactions physiologiques au stress de sujets normaux et coronariens. II" (Psychologic characteristics of normal subjects and coronary patients, and their physiologic reaction to stress. II). *J. Psychosom. Res.* **18**: 75-87 (1974). J14,110/74

According to several physiologic tests, coronary patients respond to stressors less markedly than others, perhaps because they live under permanent stress, are accustomed to stress, or because their responses are impaired (38 refs.).

Gould, K. L., Hamilton, G. W., Lipscomb, K., Ritchie, J. L., Kennedy, J. W.: "Method for assessing stress-induced regional malperfusion during coronary arteriography. Experimental validation and clinical application." *Am. J. Cardiol.* **34**: 557-564 (1974). H92,788/74

Helfant, R. H., DeVilla, M. A., Meister, S. G., Banka, V. S.: "Isometric handgrip stress in evaluation of left ventricular performance in patients with coronary heart disease" (abstracted). *Clin. Res.* **22**: 279A (1974). H90,122/74

Morphology. Danilova, K. M.: "Morphological tests of the stress reaction in human myocardium." *Arkh. Pathol.* **25** No. 7: 42-49 (1963) (Russian). G29,912/63

In patients who died following severe stress, fuchsinophilic degeneration of the myocardium was usually severe and accompanied by diffuse necrosis "of metabolic origin."

Myasnikov, A. L.: "Myocardial necroses of coronary and noncoronary genesis." *Am. J. Cardiol.* **13**: 435-440 (1964).

F7,701/64

A review of the literature and personal observations led the author to conclude: "it has become quite clear that various nonvascular noxious influences directly interfering in myocardial metabolism (such as anoxemic, hormonal and neurogenic) are of outstanding importance in the origin of myocardial necroses, either as primary or as contributory factors. This applies in particular to the multiple, microfocal type of necroses, frequently developing by coincidence with, or aggravation of, the pathogenic effects of primarily vascular disturbances." The role of stress hormones and electrolytes is particularly emphasized.

Sośnierz, M., Wieczorek, M.: "The influence of stress on the pathomorphologic state of the heart." *Patol. Pol.* **17**: 361-368 (1966) (Polish). F86,559/66

In a series of ninety-two patients who died of various diseases, fuchsinophilic degeneration of the myocardium was constant among old people and absent in neonates. The intensity of fuchsinophilia was particularly high in patients who died under very stressful circumstances.

Emery, A. C. Jr., Whitcomb, W. H., Frohlich, E. D.: "'Stress' polycythemia and hypertension." *J.A.M.A.* **229**: 159-162 (1974).

H87,420/74

"'Stress' polycythemia is a term that refers to a disorder manifested by a normal red blood cell mass, but a high hematocrit reading secondary to a contracted plasma volume. The latter has been ascribed to a wide variety of stressful factors including emotional stress, chronic anxiety, alcoholism, and a variation of the normal state. Hypertension (perhaps too long associated with 'stress') has been closely associated with 'stress' polycythemia" (30 refs.).

Postnov, V. V., Strakhov, E. V., Glukhovets, B. I., Gorkova, S. I.: "Hypothalamic neurosecretory nuclei and nucleus habenularis of epithalamus in essential hypertension." *Virchows Arch. [Pathol. Anat.]* **364**: 275-283 (1974). H95,408/74

"In patients with essential hypertension, morphological signs of functional hypertrophy were observed in the nucleus habenularis of the epithalamus."

Blood Clotting. Paterson, J. C.: "Relation of physical exertion and emotion to precipitation of coronary thrombi." *J.A.M.A.* **112**: 895-897 (1939). B29,339/39

Histologic evidence suggests that the development of coronary thrombosis is a gradual process, sometimes taking several days before pain and occlusion are manifest. Therefore, events immediately preceding the attack are not of etiologic significance. "The pathologic appearances in a series of fatal cases of coronary thrombosis suggest strongly that excessive exercise and emotional stress are intimately concerned in the mechanism of coronary artery thrombosis."

Stoica, E., Costa-Foru, D., Cherculescu, F.: "The reactivity of the clotting mechanism and fibrinolysis in cerebral thrombotic disease." *J. Neurol. Sci.* **4**: 491-500 (1967). J22,642/67

"Emotional stress induced a sustained hypercoagulability only in patients with occlusive cerebral softening (verified by angiography) and in those with peripheral atherosclerosis obliterans; concomitantly, in these patients an unresponsiveness of the fibrinolytic system to stress was observed."

Baroldi, G.: "Lack of correlation between coronary thrombosis and myocardial infarction or sudden 'coronary' heart death." *Ann. N.Y. Acad. Sci.* **156**: 504-525 (1969). G79,107/69

Extensive review of the literature on sudden death due to coronary infarction showing that "in more than 50% of the examined acute-recent infarct and sudden coronary heart death cases, an acute-recent occlusion was not detected. In most of the remaining cases, the acute-recent thrombosis had little if any effect, either because it took place in highly stenotic vessels (more than 65%) with enlarged anastomotic circulation, or because the acute-recent thrombosis was not coeval with the myocardial damage." Hence, special attention is called to the "infarctoid myocardial necroses," such as have been produced in animals by combined treatment with various diets, hormones, and subsequent exposure to stressors.

Gordon, J. L., Bowyer, D. E., Evans, D. W., Hutchinson, M. J.: "Human platelet

reactivity during stressful diagnostic procedures." *J. Clin. Pathol.* **26**: 958-962 (1973). H83,536/73

In conscious patients, cardiac catheterization and other stressful procedures caused a rise in the platelet aggregation response to ADP, with a concurrent increase in plasma FFA. "It is suggested that catecholamines released due to emotional stress may be responsible for the increased platelet responses to ADP and that this could influence the development of thrombosis and atherosclerosis."

Haft, J. I., Fani, K.: "Intravascular platelet aggregation in the heart induced by stress." *Circulation* **47**: 353-358 (1973). G99,534/73

In rats, immersion in cold water causes platelet aggregation in myocardial vessels, as shown by EM. "It is concluded that stress, probably via catecholamine secretion that enhances platelet stickiness, can induce intravascular platelet aggregation. It is possible that this mechanism plays a part in the relationship between stress and acute clinical myocardial infarction."

Levites, R., Haft, J. I.: "Effects of exercise-induced stress on platelet aggregation" (abstracted). *Clin. Res.* **22**: 285A (1974). H90,126/74

Hormones. Demura, R. K.: "Pituitary-adrenocortical function in essential hypertension." *J. Jap. Soc. Intern. Med.* **51**: 93 (1962). J11,873/62

The plasma 17-OHCS level is increased in patients with essential hypertension.

Raab, W.: "Neurogenic multifocal destruction of myocardial tissue. (Pathogenic mechanism and its prevention)." *Rev. Can. Biol.* **22**: 217-239 (1963). E21,307/63

Enhanced catecholamine and corticoid secretion can produce myocardial necrosis, presumably by increasing the sodium and decreasing the potassium content of the myocardium. "The first immediate specific effect upon the heart muscle which all stresses have in common is due to the reflex-mediated influx of catecholamines into the myocardial tissue."

Raab, W.: "The nonvascular metabolic myocardial vulnerability factor in 'coronary heart disease.' Fundamentals of pathogenesis, treatment, and prevention." *Am. Heart J.* **66**: 685-706 (1963). E31,416/63

Review on the role of stress, catechol-

amines and corticoids in the genesis of myocardial infarction.

Raab, W.: "Emotional and sensory stress factors in myocardial pathology." *Am. Heart J.* **72**: 538-564 (1966). F70,981/66

Perusal of the "world literature provides abundant experimental and clinical evidence for a potentially cardiotoxic overproduction of sympathogenic catecholamines and adrenocortical steroids, resulting from emotional and sensory stress-induced stimulations of the central nervous system and the pituitary gland. Fear, anger, and frustration, as well as, to a lesser extent, optical, acoustical, and thermal annoyances act as the most common potentially pathogenic stimuli." In addition, stress-induced sympathetic and adrenocortical stimulation also affect the myocardium indirectly through blood pressure elevation and other hemodynamic effects (305 refs.).

Raab, W.: "Correlated cardiovascular adrenergic and adrenocortical responses to sensory and mental annoyances in man. A potential accessory cardiac risk factor." *Psychosom. Med.* **30**: 809-818 (1968).

G64,304/68

"Standardized mild sensory and mental annoyances, comparable to those frequently occurring in civilized everyday life (noise, flickering light, mental arithmetic), were found to provoke significant elevations of the plasma cortisol level, paralleled by manifestations of cardiac sympathetic stimulation, particularly in emotionally excitable individuals. The pattern of cardiovascular adrenergic responses proved rather constant when repeated within 4-5 years." These neurogenic and hormonal stress responses may play an important role in CHD.

Nestel, P. J.: "Blood-pressure and catecholamine excretion after mental stress in labile hypertension." *Lancet* April 5, 1969, pp. 692-694. H9,851/69

Psychogenic stress increased blood pressure as well as EP and NEP excretion in hypertensives more than in normotensives, although the resting catecholamine levels were essentially the same in both groups.

Bellet, S., Roman, L., Kostis, J.: "The effect of automobile driving on catecholamine and adrenocortical excretion." *Am. J. Cardiol.* **24**: 365-368 (1969). H16,504/69

In patients with CHD and in controls, "excretion of both catecholamines and 11-OHCS was found to be significantly in-

creased during a two hour period of driving compared with a two hour control period. These results suggest that automobile driving represents a mental stress.... The electrocardiographic changes (ischemic type of S-T segment depression or frequent premature ventricular contractions, or both) which occur during driving in subjects with coronary artery disease are induced by this stress."

McDonald, L., Baker, C., Bray, C., McDonald, A.: "Plasma-catecholamines after cardiac infarction." *Lancet* November 15, 1969, pp. 1021-1023. H18,916/69

In racing drivers, plasma NEP levels were greatly raised immediately after the race. Following cardiac infarction, "patients with atrial dysrhythmias or early ventricular dysrhythmias had higher noradrenaline concentrations in their plasma. There was no such difference for patients with late ventricular dysrhythmias, and adrenaline levels were unremarkable. The raised noradrenaline levels are not thought to be related to stress because six other patients undergoing the stressful procedure of cardiac catheterisation had low levels."

Carruthers, M. E.: "Aggression and atherosclerosis." *Lancet* November 29, 1969, pp. 1170-1171. H19,421/69

Evaluation of the literature shows that various stresses of daily life, especially fear, hatred, aggression and frustration, increase catecholamine and particularly NEP secretion, and raise the plasma levels of FFA and triglycerides. The latter can be deposited in vessel walls, and since they also augment platelet adhesiveness, may lead to thrombosis. "This hypothesis suggests that in modern society wrath, reinforced by sloth and gluttony, is the deadliest of the seven sins."

Lorimer, A. R., Macfarlane, P. W., Provan, G., Duffy, T., Lawrie, T. D. V.: "Blood pressure and catecholamine responses to 'stress' in normotensive and hypertensive subjects." *Cardiovasc. Res.* **5**: 169-173 (1971). J21,255/71

When exposed to the stressor effect of a monotonous but attention-demanding task (sorting steel balls), patients with sustained hypertension exhibited approximately the same increase in catecholamine production as normotensive controls.

Gödicke, W., Graff, C., Baumann, R., Naumann, E., Ziprian, H.: "Die Beeinflussung der Serumlipide, des Plasma-Kortisol und der 3-Methoxy-4-hydroxy-mandelsäure-Aus-

scheidung bei essentiellen Hypertonikern durch eine experimentell erzeugte psychische Stress-Situation" (Influence of experimentally-produced mental stress on serum lipids, plasma cortisol and 3-methoxy-4-hydroxy-mandelic acid excretion in essential hypertension). *Dtsch. Gesundheitsw.* **26**: 1973-1976 (1971). J23,736/71

Hypertensive patients "manifested a significant rise of the free fatty acids, of triglycerides, of phospholipids and of cortisol in the serum and plasma, as well as an increased 3-methoxy-4-hydroxy-mandelic acid excretion in the urine. The results indicate that essential hypertonics react more sensitively to psychic stress than normotonics."

Jäättelä, A., Tammisto, T., Nikki, P., Takki, S.: "Effect of operative stress on plasma catecholamines in treated and untreated hypertensive patients." *Ann. Clin. Res.* **4**: 84-88 (1972). H75,923/72

In hypertensive patients pretreated with methyldopa, the mean arterial pressure and plasma NEP fell at the time of operative stress. On the whole, the blood pressure and heart rate seemed more stable in treated than in untreated hypertensives.

Argüelles, A. E., Hoffman, C., Chekherdemian, M., Cervetto, A.: "Corticoadrenal and adrenergic overactivity in male patients with chronic myocardial infarction." *J. Steroid Biochem.* **4**: 427-432 (1973).

J16,684/73

Even long after recovery, patients who suffered myocardial infarction show an increased EP secretion in response to audio-genic stress, and a high basic plasma 11-OHCS concentration. This endocrine derangement may predispose to myocardial necrosis of the ESCN type.

O'Boyle, A., Gannon, D., Hingerty, D.: "Sympatho-adrenal response to stress." *J. Ir. Med. Assoc.* **66**: 699-704 (1973).

J10,153/73

Review of the sympathoadrenal participation in stress, with personal observations "on cardiac infarct patients, normal and toxemic pregnant subjects and on subjects undergoing various forms of athletic stress."

Esler, M. D., Nestel, P. J.: "High catecholamine essential hypertension: clinical and physiological characteristics." *Aust. N.Z.J. Med.* **3**: 117-123 (1973).

J3,376/73

In 20 percent of patients with sustained essential hypertension, urinary NEP levels

were elevated. "Plasma volume, the responsiveness of the sympathetic nervous system, renin-angiotensin status, indices of emotional stress, and 'hyperkinetic circulatory state,' all proved to be unrelated to basal noradrenaline excretion. Urinary noradrenaline was related only to the level of the blood pressure, being highest in patients with more severe hypertensive disease."

Oparil, S., Haber, E.: "The renin-angiotensin system. (Second of two parts)." *N. Engl. J. Med.* **291**: 446-457 (1974).

H90,100/74

A review of the renin-angiotensin system in hypertension, with special reference to the role of electrolytes and mineralocorticoids (376 refs.).

Ledingham, J. M.: "Ätiologie und Pathogenese der Hypertonie" (Etiology and pathogenesis of hypertension). *Internist* (Berlin) **15**: 114-123 (1974).

H86,141/74

Review of hypertension as a stress-induced disease in which increased catecholamine and mineralocorticoid production often plays a role and emotional factors are particularly common eliciting agents.

Distler, A.: "Ist die essentielle Hypertonie noch eine Krankheitseinheit? Abgrenzung der hyporeninämischen Hypertonie" (Is essential hypertension still a disease entity? Definition of hypo-reninemic hypertension). *Internist* (Berlin) **15**: 146-154 (1974).

H86,145/74

Hypo-reninemic hypertension is probably a pluricausal disease of variable etiology, although in many cases it depends on increased production of some mineralocorticoids (69 refs.).

Kimura, K.: "Pathophysiological significance of sympathetic activity in cardiovascular diseases." *Jap. Circ. J.* **38**: 181-194 (1974).

H88,882/74

In essential hypertension, urinary catecholamine excretion after exercise is somewhat above normal, and the responsiveness of the adrenergic system to neurogenic stressors is also elevated in CHD. The excessive vascular responses are readily suppressed by β -adrenergic blocking agents.

Vlachakis, N. D., Guia, D. de, Mendlowitz, M., Antram, S., Wolf, R. L.: "Hypertension and anxiety. A trial with epinephrine and norepinephrine infusion." *Mt. Sinai J. Med.* **41**: 615-625 (1974).

J16,758/74

In patients, anxiety and anxiety hyperten-

sion may be attributable as much to increased vascular responsiveness to EP as to excessive EP secretion (25 refs.).

Baumann, R.: "Theoretische und klinische Aspekte der zerebroviszeralen Regulationskrankheit arterielle essentielle Hypertonie. I. Zu Problemen der Adaptations-Maladaptionsprozesse und der pathogenetischen Effizienz des psychoemotionalen Stresses" (Theoretical and chemical analyses of cerebro-visceral regulation of essential arterial hypertension. I. Problems of adaptation-maladaptation processes and the pathogenetic efficiency of psycho-emotional stress). *Dtsch. Gesundheitsw.* **29**: 673-676 (1974).

J15,328/74

Baumann, R.: "II. Hämodynamische und biochemische Regulationsstörungen des jugendlichen Hypertoniens unter Stressexposition" (II. Hemodynamic and biochemical disturbances in young male hypertensive patients under stress). *Dtsch. Gesundheitsw.* **29**: 721-733 (1974).

J15,329/74

In young hypertensive patients with or without latent diabetes, emotional stress produced a rise in plasma FFA, NEP and renin (63 refs.).

Klein, R. F., Garrity, T. F., Gelein, J.: "Emotional adjustment and catecholamine excretion during early recovery from myocardial infarction." *J. Psychosom. Res.* **18**: 425-435 (1974) (35 refs.).

J19,268/74

Naftchi, N. E., Wooten, G. F., Lowman, E. W., Axelrod, J.: "Relationship between serum dopamine- β -hydroxylase activity, catecholamine metabolism, and hemodynamic changes during paroxysmal hypertension in quadriplegia." *Circulat. Res.* **35**: 850-861 (1974).

H97,485/74

Observations on patients "indicate that hypertension in quadriplegia, whether spontaneous or induced, is caused by increased release of norepinephrine and that the half-life of dopamine- β -hydroxylase released during stress is shorter than that previously reported."

Beevers, D. G., Nelson, C. S., Padfield, P. L., Barlow, D. H., Duncan, S., Greaves, D. A., Hawthorne, V. M., Morton, J. J., Young, G. A. R., Young, J.: "The prevalence of hypertension in an unselected population, and the frequency of abnormalities of potassium, angiotensin II and aldosterone in hypertensive subjects." *Acta Clin. Belg.* **29**: 276-280 (1974).

J21,482/74

An epidemiologic study of three thousand subjects aged forty-five to sixty-four revealed no cases of primary hyperaldosteronism among those having the most severe hypertension. A frequency distribution curve for plasma angiotensin II concentration in this group showed "no evidence of a subpopulation of subjects with low levels." However, occasionally, patients with high plasma angiotensin II or aldosterone were noted.

Palem-Vliers, M., Genard, P., Eechaute, W.: "La détection de la 18-hydroxy-11-désoxcorticostérone et de deux substances inconnues dans les urines de malades hypertendus. Isolement d'une de ces substances" (Detection of 18-hydroxy-11-desoxycorticosterone and two unknown substances in the urine of hypertensive patients. Isolation of one of these substances). *Acta Clin. Belg.* **29**: 281-282 (1974).

J21,483/74

Cope, C. L., Loizou, S.: "Deoxycorticosterone excretion in normal, hypertensive and hypokalaemic subjects." *Clin. Sci. Mol. Med.* **48**: 97-105 (1975).

J21,280/75

Radioimmunoassays did not detect a constant increase in the urinary DOC excretion of hypertensive patients. However, "of nine subjects showing hypokalaemia, eight had elevated excretion of deoxycorticosterone with values from 263 to 5515 pmol (87-1820 ng) daily. Seven of these were hypertensive and two were normotensive."

Nonhormonal Metabolites. Hammarsten, J. F., Cathey, C. W., Redmond, R. F., Wolf, S.: "Serum cholesterol, diet and stress in patients with coronary artery disease." *J. Clin. Invest.* **36**: 897 (1957).

D32,061/57

In survivors of myocardial infarction, serum cholesterol values were routinely taken and stressful life events registered. "It was striking that 19 of the 20 occasions of high cholesterol corresponded with periods that had been separately judged as particularly stressful for the individuals concerned."

Jolliffe, N.: "Fats, cholesterol, and coronary heart disease. A review of recent progress." *Circulation* **20**: 109-127 (1959).

G61,930/59

In a review on the role of fats and cholesterol in CHD, emphasis is placed upon stress which raises both serum cholesterol and FFA. It is doubtful whether the stressors of ancient times (constant fight for physical

survival) were more damaging in this respect than those of urbanization. Mortality rates from CHD were no higher in England than in the U.S.A. during the Battle of Britain, and they actually decreased in Norway during the German occupation. However, these results were greatly influenced by conditioning factors such as wartime nutrition and hence are difficult to interpret (85 refs.).

Wolf, S., McCabe, W. R., Yamamoto, J., Adsett, C. A., Schottstaedt, W. W.: "Changes in serum lipids in relation to emotional stress during rigid control of diet and exercise." *Circulation* **26**: 379-387 (1962).

J10,367/62

Striking increases in serum cholesterol and triglycerides occurred in people kept on a constant diet and exposed to various situations inducing anxiety, including difficulties in the family, on the job and so on. Stressful interviews caused such changes within sixty minutes. "No inferences are drawn with respect to the significance of emotional stress in the pathogenesis of coronary atherosclerosis or myocardial infarction, but it is clear that the mechanisms that govern the serum concentration of certain lipids are connected with and capable of responding to impulses from the higher centers of the brain."

Jayle, M. F.: "Rôle du métabolisme des glycoprotéines dans la biogénèse de l'athérosclérose. Concept sur le 'syndrome général de l'agression'" (Role of the metabolism of glycoproteins in the biogenesis of atherosclerosis. Concept of the "general stress syndrome"). *Ann. Thér.* **14**: 11-22 (1963).

G63,439/63

Under various stress conditions, the plasma levels of fibrinogen and of the glycoproteins haptoglobin and seromucoid are characteristically increased; this may play an important part in stress-induced atherosclerosis. The common denominator of the diseases of adaptation and of stress responses may be a rise in these compounds, which might thus correspond to the "first mediator." This interpretation might act as a valid focal point of Selye's "unitary concept" although the claims concerning the central role of the pituitary-adrenal axis are rejected.

Thomas, C. B., Ross, D. C.: "Observations on some possible precursors of essential hypertension and coronary artery disease. VIII. Relationship of cholesterol level to certain habit patterns under stress." *Bull. Johns Hopkins Hosp.* **113**: 225-238 (1963).

E29,405/63

Among medical students exposed to diverse psychogenic stressors, a questionnaire showed marked individual differences in responses.

Frequency distribution of positive responses to habits of nervous tension items by 1085 medical students

Habits of Nervous Tension	Positive Responses	
	No.	(%)
Exhaustion	157	(14.5)
Exhilaration	227	(20.9)
Depressed feelings	216	(19.9)
Uneasy or anxious feelings	526	(48.5)
General tension	871	(80.3)
Increased activity	709	(65.3)
Decreased activity	55	(5.1)
Increased urge to sleep	154	(14.2)
Increased difficulty in sleeping	483	(44.5)
Increased urge to eat	200	(18.4)
Loss of appetite	402	(37.0)
Nausea	66	(6.1)
Vomiting	10	(0.9)
Diarrhoea	163	(15.0)
Constipation	48	(4.4)
Urinary frequency	341	(31.4)
Tremulousness	172	(15.9)
Anger	233	(21.5)
Gripe sessions	173	(15.9)
Concern about physical health	47	(4.3)
Tendency to recheck work	254	(23.4)
Urge to confide	293	(27.0)
Urge to be alone	221	(20.4)
Irritability	97	(8.9)
Philosophic effort	255	(23.5)
Total	6373*	

* 5.9 positive responses per subject (range 0 to 21).

(Adapted from *Bulletin Johns Hopkins Hospital* **113** (1963) by permission.)

The blood cholesterol levels usually increased, but the reverse also occurred occasionally. "Subjects in the lower cholesterol group more often reported loss of appetite, exhaustion, nausea and anxiety when under

stress; in addition, urge to be alone, tremulousness and depression were more frequent than expected, although these items only approached significance. The only item with a significant positive relationship to higher cholesterol levels was urge to eat" (35 refs.).

Hoch-Ligeti, C.: "Adrenal cholesterol concentration in cases of suicide." *Br. J. Exp. Pathol.* 47: 594-598 (1966). F65,019/66

The highest adrenal cholesterol concentrations were found in patients who committed suicide and in hypertensives, being much above those of persons who died in accidents. Presumably the changes are related to stress.

Chapman, J. M., Reeder, L. G., Massey, F. J. Jr., Borun, E. R., Picken, B., Browning, G. G., Coulson, A. H., Zimmerman, D. H.: "Relationships of stress, tranquilizers, and serum cholesterol levels in a sample population under study for coronary heart disease." *Am. J. Epidemiol.* 83: 537-547 (1966).

J15,961/66

Válek, J., Kuhn, E.: "Stress-induced changes of carbohydrate and lipid metabolism in coronary heart disease." *Psychother. Psychosom.* 18: 275-280 (1970).

J19,062/70

Bajusz, E., Rona, G.: *Recent Advances in Studies on Cardiac Structure and Metabolism. I. Myocardiology* (3rd Ann. Meeting Int. Study Group for Research in Cardiac Metabolism, Stowe, Vt., 1970), p. 835. Baltimore, London and Tokyo: University Park Press, 1972.

E9,671/72

Monograph in which many contributors present their data concerning myocardial metabolism and pathology. Special attention is given to the roles of dietary factors, corticoids, catecholamines and stress (several hundred refs.).

Seelig, M. S., Heggtveit, H. A.: "Magnesium interrelationships in ischemic heart disease: a review." *Am. J. Clin. Nutr.* 27: 59-79 (1974).

J10,135/74

A review of clinical data and earlier animal experiments showing the prophylactic value of magnesium salts against stress-induced and other types of infarctoid myocardial necrosis. "Its role in maintaining normal rhythmicity in the heart in the face of an ischemic insult may well explain the difference in sudden cardiac death rates in hard and soft water areas. Therapeutic use of magnesium in acute ischemic heart disease may well be justified" (228 refs.).

Theories. Brunner, H. R., Gavras, H., Laragh, J. H.: "Specific inhibition of the renin-angiotensin system: a key to understanding blood pressure regulation." *Prog. Cardiovasc. Dis.* 17: 87-98 (1974).

J16,270/74

With inhibitors of various parts of the renin-angiotensin system being used, blood pressure regulation is viewed and described in Figure 4 (p. 793).

Two models of renal hypertension served for the development of this concept. "Established two-kidney Goldblatt hypertension (one renal artery clipped, contralateral kidney intact) was found to be renin-dependent, since angiotensin II blockade induced a marked fall in blood pressure. Clinical counterparts to this predominantly "vasoconstrictor" type of hypertension are renovascular hypertension with unilateral renal artery stenosis, malignant and essential hypertension with high renin levels, and possibly normotensive situations with reduced "effective" blood volume such as cirrhosis and congestive heart failure.

"Chronic one-kidney Goldblatt hypertension (one renal artery clipped, contralateral nephrectomy) under conditions of unrestricted sodium intake appeared on the other hand to be predominantly sodium-volume-dependent, so that angiotensin II blockade did not alter the pressure level. However, sodium (and volume) depletion did not lower the blood pressure either in this model but resulted instead in a compensatory rise of renin release, and thus in a transition from a sodium-volume to vasoconstrictor-maintained type of hypertension. Accordingly, under conditions of sodium depletion, angiotensin II blockade did markedly reduce the blood pressure. Clinical counterparts to this model in which simultaneous sodium depletion plus blockade of the renin system are necessary to reduce blood pressure appear to be most patients with normal renin essential hypertension, chronic renal failure with normal or low renin levels, renovascular hypertension with bilateral renal artery stenoses, and possibly coarctation of the aorta.

"In contrast to these two model situations, low-renin essential hypertension as well as the hypertension induced by an excess of various mineralocorticoids appears to represent a pure volume type of hypertension, in which a diuretic-induced volume reduction does not result in a compensatory rise in renin release and a shift to vasoconstrictor

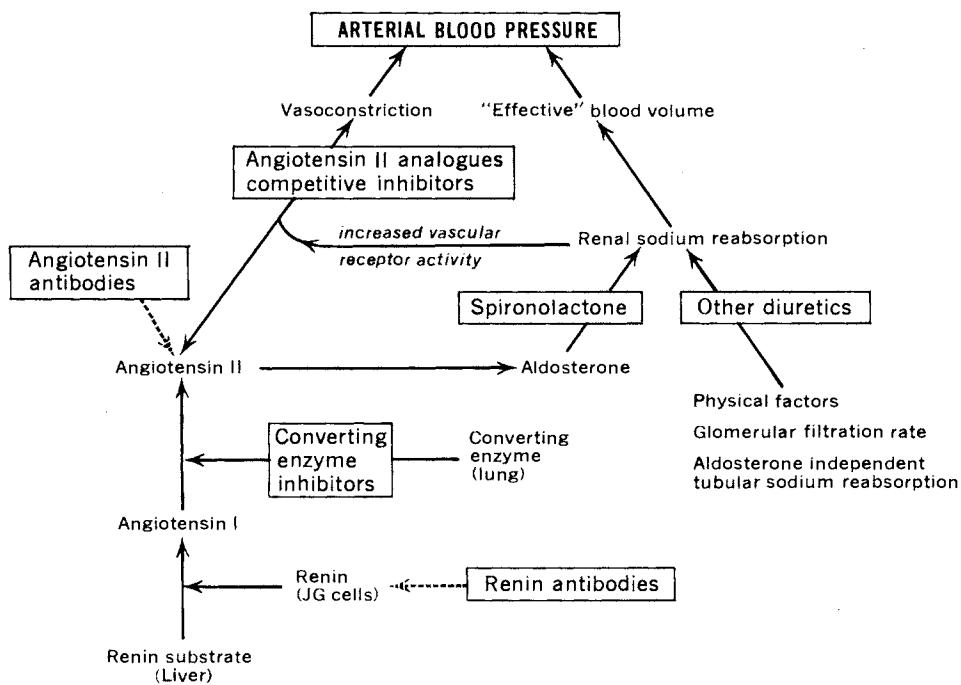


Figure 4. Synergism of the angiotensin II vasoconstrictor and the sodium-volume components in sustaining arterial blood pressure.

Points of action within the system of the various inhibitors and sodium-depleting agents are depicted in framed letters.

(Reproduced from *Prog. Cardiovasc. Dis.* 17 (1974) by permission.)

support but instead results in a parallel reduction of blood pressure" (59 refs.).

Gavras, H., Brunner, H. R., Laragh, J. H.: "Renin and aldosterone and the pathogenesis of hypertensive vascular damage." *Prog. Cardiovasc. Dis.* 17: 39-49 (1974).

J14,021/74

Largely on the basis of the evidence discussed by Brunner *et al.* (J16,270/74), the mechanisms of the two principal types of hypertension are depicted in Figure 5 (p. 794).

"Both forms induce arteriolar narrowing, impaired arteriolar wall and tissue perfusion, transudation, plasmatic vasculosis, pressure natriuresis, hemoconcentration, fibrin deposition, and, finally, fibrinoid necrosis. In the case of salt hypertension, vasoconstriction may not be present, but it is replaced by edema of the arteriolar wall. With this hypothesis, all vascular changes in chronic hy-

pertension can be explained in terms of an inappropriate interaction between a vasoconstrictor component (largely angiotensin) and a volume factor (determined by renal excretory capacity modulated by aldosterone)."

Varia. Dreifus, L. S., Watanabe, Y.: "Tension, drugs, and *premature systoles*." *Am. Heart J.* 70: 291-294 (1965).

F48,521/65

Nakamoto, K.: "Psychogenic paroxysmal cardiac arrhythmias. Contents of mental events, age and patterns of arrhythmias." *Jap. Circ. J.* 29: 700-717 (1965).

G36,402/65

Border, J. R., Tibbetts, J. C., Schenk, W. G. Jr.: "Hypoxic hyperventilation and acute respiratory failure in the severely stressed patient: massive pulmonary arteriovenous shunts?" *Surgery* 64: 710-719 (1968).

J22,741/68

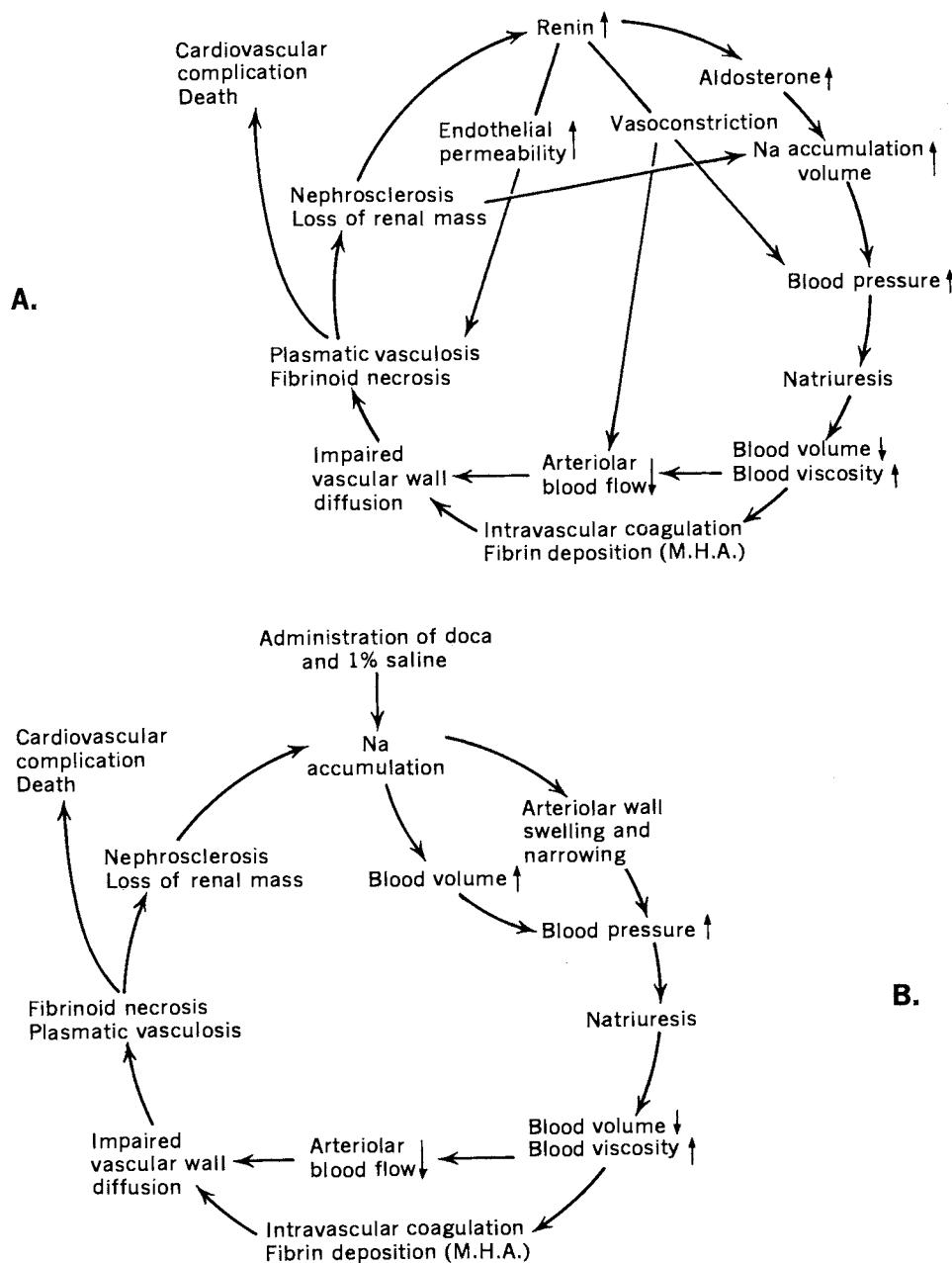


Figure 5. A, sequence of events in renin-dependent vascular injury. B, the sequence of events in salt-dependent vascular injury.

(Reproduced from *Prog. Cardiovasc. Dis.* 17 (1974) by permission.)

Experimental Cardiovascular Diseases

Generalities. Work on the role of *stress* in the production of experimental cardiovascular diseases has been reviewed extensively in my two-volume monograph, *Experimental Cardiovascular Diseases*. Hence, to avoid unnecessary duplications, I shall limit myself here to a brief mention of the most salient facts and the citation of a few key references.

In essence, it may be said that depending upon conditioning factors (particularly previous exposure to stress, age, genetic predisposition, the hormonal and nutritional status of the subject), stress may produce or inhibit the development of cardiovascular diseases, but it virtually always influences their course in some respect.

Most of the experimental work in this field has been done to establish the role of stress, or of hormones produced during stress, in **hypertension** with the associated renal and cardiovascular lesions. These include **arteriosclerosis** (of both the atheromatous and the purely calcifying type), **myocardial** necroses (caused either by vascular occlusion or by disturbances of cardiac metabolism) and thrombohemorrhagic phenomena.

In general, it may be said that malignant hypertension with **hyalinizing** cardiovascular and renal disease is most easily reproduced in rats by chronic stress on high sodium diets, especially after sensitization by uninephrectomy. Indeed, in unilaterally nephrectomized rats kept on high sodium diets, mineralocorticoids (DOC, aldosterone), STH, or MAD (which probably causes the adrenals to produce mineralocorticoids), easily induce such lesions by themselves, without exposure to stress.

Corticoids undoubtedly play a decisive role here and a mutual feedback mechanism exists between mineralocorticoids (particularly aldosterone) and the renal pressor system in that renin stimulates aldosterone production whereas aldosterone inhibits renin secretion. This interplay helps to maintain pressor homeostasis under ordinary conditions. However, if the feedback mechanism is defective and intense nephrosclerosis is produced, the blood pressure rises to a level where it further damages the kidney and a vicious circle develops. Possibly, some corticoids can induce nephrosclerosis and hypertension without raising renin production ("hyporeninemic hypotension"); thus, the rise in blood pressure is deprived of its self-inhibitory properties and becomes self-perpetuating and independent of renin.

Although this mechanism is far from being adequately proven by experimental evidence, it is obvious that the adrenal cortex plays a decisive role in the production of many types of hypertensive disease. Thus, in **adrenalectomized** rats kept on a fixed dose of glucocorticoids just sufficient to maintain life, neither stress, MAD nor STH can exert their usual hypertensive, vasotoxic and nephrosclerotic effects, even if the animals are maximally sensitized by uninephrectomy and a high sodium chloride intake. Yet in adrenalectomized rats, under similar conditions, exogenous mineralocorticoids retain their pressor vasotoxic and nephrotoxic actions. Therefore, it is postulated that stress, MAD and STH do not act directly upon the vascular system but through the intermediary of the adrenals in which they stimulate the synthesis of mineralocorticoids under certain conditions.

The so-called **adrenal regeneration hypertension (ARH)** has furnished us with another convenient tool for studying mineralocorticoid hypertension and proving that the production of excessive or abnormal adrenal corticoids may cause hypertensive disease. If one adrenal is removed and the other "demedullated" (an operation that also removes virtually the entire cortex except the glomerulosa), nephrosclerotic hypertension de-

velops with vascular lesions which are indistinguishable from those produced by DOC. Unilateral nephrectomy in rats on a high sodium chloride intake sensitizes for this effect, just as it does for the comparable actions of mineralocorticoids. There is much evidence supporting the view that in rats subjected to this operation, the regenerating adrenal cells of the subcortical layer produce an excessive amount of DOC and related steroids which have a high vasotoxic effect.

The pressor actions of catecholamines are transitory and hardly ever conducive to self-perpetuating nephrosclerotic hypertension. EP and NEP are effective even in the absence of the adrenals, but appear to potentiate the characteristic vasotoxicity of mineralocorticoids and hence probably play an important part in stress-induced hypertensive disease. Their increased secretion during stress may also raise the coagulability of blood and thereby predispose to stress-induced occlusive vascular thrombosis.

The *electrolyte steroid cardiopathies with necrosis (ESCN)* are produced in experimental animals, particularly in rats, by the conjoint administration of glucocorticoids and mineralocorticoids, or by steroids (for example, fluorocortisol) that exert both gluco- and mineralocorticoid actions, but only if this treatment is combined with a high sodium diet or with exposure to sudden stress. A great variety of stressors have proved effective in eliciting this manifestation after conditioning with corticoids and sodium. On the other hand, diets poor in sodium or rich in potassium and/or magnesium, as well as potassium-sparing agents (spironolactone, amiloride) protect against this type of cardiac lesion. Many of these experimental observations have found clinical application in the therapeutic use of low sodium, high potassium, or high magnesium diets, spironolactone and amiloride for cardiovascular disease.

It is also of interest that high fat diets are particularly effective in causing cardiac necroses in rats pretreated with appropriate corticoids and high sodium diets. In this respect, they may replace stressors.

Finally, it should be mentioned that in rats under identical conditions, acute exposure to *stress* (forced muscular exercise, restraint, traumatic injuries) *may produce or prevent cardiac necrosis*, depending upon circumstances. Gradual pretreatment with stressors, especially forced muscular exercise, can protect the fully-conditioned rat (essentially a "coronary candidate") against the induction of cardiac necrosis by a subsequent extremely severe stress.

These findings further suggest close relationships between the experimental cardiopathies and their clinical equivalents. They may explain the long-puzzling paradox that exercise is considered to be dangerous and also to be of prophylactic value in patients prone to cardiac infarction. Presumably, keeping fit through gradual comparatively mild exercise induces considerable resistance, whereas sudden extreme muscular effort may precipitate a cardiac accident, especially in persons used to sedentary life and unadapted to muscular effort.

It must be kept in mind, however, that unlike many patients who die from acute coronary accidents, the ESCN of the rat is not primarily due to coronary thrombosis, but to metabolic derangements in the cardiac muscle that predispose it to necrosis at times of increased demands for work. Only secondarily do thromboses tend to develop in necrotic areas of the heart, where the endothelium of the coronary vessels has lost its anticoagulant properties. In this connection, it is of particular interest that several investigators observed an inverse relationship between the incidence of detectable coronary thromboses and the rapidity with which a patient died after clinical manifestations of a heart attack. It has been deduced that probably sudden cardiac

death in man is often due primarily to *metabolic myocardial necrosis* and that the occlusive thrombus develops only secondarily in the dead myocardial region.

So-called "*fuchsinophilic degeneration*" frequently precedes myocardial necrosis in man (as indicated by histologic investigations in patients who died very suddenly after an accident) and in experimental animals during the ESCN.

After this extensive general survey, we need not discuss here the literature on each point separately. The reader is referred to my above-mentioned earlier monograph and to a few key references listed and abstracted under separate headings below.

Experimental Cardiovascular Diseases

(See also our earlier stress monographs, p. xiii)

Generalities. Green, D. M.: "Experimental hypertension." *Ann. Intern. Med.* **39**: 333-344 (1953). B87,911/53

Mishra, R. K.: "Studies on experimental magnesium deficiency in the albino rat. 8. The influence of stress on cardiac and renal lesions in rats on Mg-deficient diet." *Rev. Can. Biol.* **19**: 175-180 (1960).

E36,681/60

Various stressors precipitate the development of cardiac changes in rats on a magnesium-deficient diet.

Selye, H., Bajusz, E.: "A stress-kutatás újabb eredményei és a stress-elmélet szerepe a modern kórtani kutatómunkában. Záró közlemény. Kondicionáló tényezők az infarktoid cardiopathiák pathomechanizmusában" (Recent results of stress research, and the role of the stress theory in modern research on pathology. Final communication. Conditioning agents in the pathogenic mechanism of infarctoid cardiopathies). *Orv. Hetil.* **101**: 3-37 (1960) (Hungarian). C71,085/60

Review of experimental work on pluricausal cardiopathies and their treatment with potassium and magnesium salts (36 refs.).

Selye, H.: "Stress and cardiovascular disease." *J. Jap. Med. Assoc.* **45**: 871-876 (1961) (Japanese). D15,520/61

Review on the cardiovascular diseases of adaptation with special reference to the pluricausal cardiopathies.

Selye, H.: *The Pluricausal Cardiopathies*, p. 438. Springfield, Ill.: Charles C Thomas, 1961. C92,918/61

Extensive review of the literature concerning cardiopathies produced by the concurrent action of various potential pathogens, particularly diets, drugs and stressors.

Selye, H.: "Stress and heart damage.

Harmful and protective effects of stress." *Kardiol. Pol.* **4**: 177-186 (1961) (Polish).

C100,000/61

Production and prevention of experimental cardiopathies.

Selye, H.: "Stress and cardiac infarcts." *Klin. Med. (Mosk.)* **39** No. 11: 38-43 (1961) (Russian). C97,541/61

Prioreschi, P., Selye, H.: "A calcifying cardiopathy produced by stress and calcium acetate." *Br. J. Exp. Pathol.* **42**: 135-137 (1961). C90,111/61

In rats fed large amounts of calcium acetate, the stress of restraint greatly increases cardiovascular calcification.

Oka, M., Angrist, A.: "Experimental endocarditis." *Rev. Can. Biol.* **22**: 297-308 (1963). E21,313/63

"Experimental valvular lesions of identical nature were found following exposure of animals, particularly rats, to different forms of stress, including cold, high altitude, A-V shunts, parabiosis, etc. Adrenal hypertrophy was correlated with such valvular changes" (43 refs.).

Marino, A., Parise, A., Galdi, R.: "Protective effect of mebutamate in the experimental cardiopathy induced by strophanthin and psychological stress." *Arch. Int. Pharmacodyn. Ther.* **145**: 276-287 (1963).

E28,908/63

"Psychological stress exerts an evident and significant potentiation of strophanthin cardio-toxicity." Mebutamate has a protective action (67 refs.).

Marino, A., Bianchi, A., Giaquinto, S., Casola, L.: "Induzione e trattamento della cardiopatia sperimentale da stress psicologico e pitressina" (Induction and treatment of experimental cardiopathy by psychologic stress and pitressin). *Arch. Int. Pharmacodyn. Ther.* **141**: 377-395 (1963). D58,761/63

In guinea pigs, the cardiotoxicity of vasopressin is greatly increased by psychogenic

stress, as shown by an ischemic type of ECG. This can be combatted by treatment with a coronary vasodilator or psychotropic drugs (69 refs.).

Prioreschi, P.: "Protection of the myocardium by potassium." *Exp. Med. Surg.* **22**: 60-70 (1964). D57,154/64

In rats, oral potassium chloride protects against various experimental cardiopathies, including those elicited by stress, after suitable conditioning.

Bajusz, E., Jasmin, G., Mongeau, A.: "Dissociation by forced muscular exercise of the cardiotoxic from the myotoxic actions of plasmocid." *Rev. Can. Biol.* **23**: 29-36 (1964). F9,053/64

Forced muscular exercise, restraint, fasting or cold environmental temperatures counteract the cardiotoxic effects of plasmocid on the one hand, and enhance its myotoxic properties on the other so that the skeletal muscle becomes affected.

Campus, S., Pandolfo, G., Accatino, G., Rappelli, A.: "Effetto degli stimoli psichici isolati sulla pressione arteriosa ed il peso corporeo di ratti Sprague-Dawley" (Effect of isolated mental stimuli on arterial pressure and body weight in Sprague-Dawley rats). *Boll. Soc. Ital. Biol. Sper.* **41**: 1087-1089 (1965). J22,723/65

Marino, A., Jovino, R., Cotrufo, M.: "Preliminary research on the interference between psychological stress and experimental pharmacologic arteriopathies in the guinea pig." *Cazz. Int. Med. Chir.* **70**: 120-122 (1965). J23,770/65

Marino, A., Mazzeo, F., Mezza, F. di, Bracale, G.: "Arteropatia periferica da adrenalina + ergotamina + psicostress nella cavia" (Peripheral arteriopathies caused by adrenaline + ergotamine + psychologic stress in guinea pigs). *Arch. Int. Pharmacodyn. Ther.* **156**: 455-466 (1965). F49,371/65

Selye, H.: *Experimental Cardiovascular Diseases*, 2 vols., p. 1155. New York, Heidelberg and Berlin: Springer-Verlag, 1970.

G60,083/70

Extensive monograph surveying virtually the entire literature on experimental cardiovascular diseases produced by stressors, mineralocorticoids, MAD, ARH, and the ESCN.

Körge, P., Masso, R., Roosson, S.: "The effect of physical conditioning on cardiac

response to acute exertion." *Can. J. Physiol. Pharmacol.* **52**: 745-752 (1974).

H87,465/74

In rats, "an attempt was made to evaluate the possible role of Na-K-ATPase in the mechanism of depression of potassium transport against its electrochemical gradient after chronic physical overload. In comparison with normal response of the heart, both morphological and biochemical changes were diminished in both the trained and, to a smaller extent, the overtrained heart during acute extreme exertion. It is concluded that potassium accumulation in myocardial cells is an essential adaptive reaction to physical exertion and the extent of potassium uptake depends on the functional state of the heart."

Karen, P., Deyl, Z., Jelínek, J.: "Influence of age and treatment with sodium chloride and desoxycorticosterone acetate on collagenous stroma of compensatory growing kidneys in the rat." *Mech. Ageing Dev.* **3**: 157-163 (1974).

J17,680/74

Corbalan, R., Verrier, R., Lown, B.: "Psychologic stress and ventricular arrhythmias during myocardial infarction in the conscious dog." *Am. J. Cardiol.* **34**: 692-696 (1974).

H90,114/74

Ishii, Y., Homma, M., Yoshikawa, A.: "Effect of a dopamine β -hydroxylase inhibitor on tissue catecholamine levels in spontaneously hypertensive rats subjected to immobilization-cold stress." *Neuropharmacology* **14**: 155-157 (1975).

J22,214/75

"A single administration of FD-008, a new dopamine β -hydroxylase inhibitor, lowered norepinephrine levels in the heart, spleen and various brain regions of spontaneously hypertensive rats, which were subjected to immobilization-cold stress, but FD-008 did not affect norepinephrine in the adrenal medulla. The effect of FD-008 was much stronger in stressed than in non-stressed spontaneously hypertensive rats."

Hypertension, Arteriosclerosis. McCann, S. M., Rothbaler, A. B., Yeakel, E. H., Shenkin, H. A.: "Adrenalectomy and blood pressure of rats subjected to auditory stimulation." *Am. J. Physiol.* **155**: 128-131 (1948).

A51,784/48

In rats, prolonged auditory stimulation can produce hypertension that is favorably influenced by adrenalectomy. "It is suggested that the adrenal cortex mediated the elevation of blood pressure."

Sellers, E. A., You, R. W.: "Deposition of fat in coronary arteries after exposure to cold." *Br. Med. J.*, April 14, 1956, pp. 815-821. C14,591/56

In rats fed a high cholesterol diet with or without added choline, exposure to cold caused lipidosis of the coronary arteries, often associated with renal damage.

Myasnikov, A. L.: "Influence of some factors on development of experimental cholesterol atherosclerosis." *Circulation* **17**: 99-113 (1958). C68,103/58

In rabbits the development of cholesterol atherosclerosis can be delayed by such stressors as hypoxia or physical exercise. "These effects may be considered useful to some degree in preventing atherosclerosis in man as well."

Hudak, W. J., Buckley, J. P.: "Production of hypertensive rats by experimental stress." *J. Pharm. Sci.* **50**: 263-264 (1961).

D10,013/61

Rats maintained on 0.9 percent sodium chloride as a drinking solution were exposed to different types of stress (bright lights, noxious sounds, vibration), administered under varying conditions to prevent acclimation. Blood pressures rose to 150 mm. Hg after about twenty-five weeks. By itself, sodium chloride had no such effects. Earlier literature on stress-induced experimental hypertension is reviewed.

Khomulo, P. S.: "The importance of prolonged functional stress of the nervous system in the development of lipoidosis in the aorta and myocardial lesions in rabbits." *Biull. Éksp. Biol. Med.* **51** No. 5: 39-44 (1961) (English translation of Russian original). D50,066/61

"Lipoidosis of aorta with a thickening of the tunica intima of the coronary vessels and dystrophy of the cardiac muscle was seen to develop in prolonged functional stress of the nervous system (12-23 months) in rabbits which received food with or without cholesterol."

Sobel, H.: "Stress and emotions in problems bearing on experimental atherosclerosis." *Prog. Cardiovasc. Dis.* **4**: 500-525 (1962). G62,174/62

Review on the influence of stressors, particularly emotional arousal, upon the development of experimental atherosclerosis (177 refs.).

Katz, L. N., Pick, R.: "The role of endocrines, stress, and heredity on atherosclerosis." In: Hamilton, W. F. and Dow, P., *Handbook of Physiology. Section 2, Circulation*, pp. 1197-1213. Washington, D.C.: American Physiological Society, 1963.

E7,121/63

Handbook article on the role of hormones and stress in the pathogenesis of atherosclerosis, based mainly on animal experiments. It appears that environmental and in particular nervous factors can influence the vascular response to a potentially atherogenic diet. However, the authors clearly state that "it is much too early to extrapolate the findings and to make any major generalization."

Buckley, J. P., Kato, H., Kinnard, W. J., Aceto, M. D. G., Estevez, J. M.: "Effects of reserpine and chlorpromazine on rats subjected to experimental stress." *Psychopharmacologia* **6**: 87-95 (1964). G19,794/64

In rats, combined treatment with various stressors (sound, light, vibration, conditioned avoidance) elicited peak pressor responses after eleven weeks.

Leites, F. L.: "Affection of the coronary heart arteries in repeated stress states." *Patol. Fiziol. Éksp. Biol.* **8** No. 5: 27-31 (1964) (Russian). J25,188/64

"Morphological and histochemical methods were used to study changes in the coronary heart arteries in rats subjected to a repeated stress (provoked after Selye), as well as to a combination of stresses with food cholesterol loads. In a proportion of the animals it was already after a lapse of one month that there occurred lipoidosis of the coronary arteries, no such phenomenon being noted in controls. In pathogenesis of these changes a definite role is evidently played by reduction of the lipolytic enzyme activity in the walls of coronary arteries revealed in stress by histochemical methods."

Lempert, B. L.: "The effect of stress and of the combination of stress with cholesterol feeding on the β -lipoprotein content in the wall of the aorta in rats." *Probl. Endokrinol.* **II** No. 4: 74-77 (1965) (Russian).

F50,790/65

Dési, I., Csalay, L., Gát, T., Nikolits, I., Hajtman, B.: "EEG in experimental neurogenic hypertension (Evaluation with Fourier analysis)." *Activ. Nerv. Sup. (Praha)* **7**: 19-24 (1965). J23,488/65

In rats, hypertension was produced by

combined sound, light and electric stimulation and the associated EEG changes were registered.

Rosecrans, J. A., Watzman, N., Buckley, J. P.: "The production of hypertension in male albino rats subjected to experimental stress." *Biochem. Pharmacol.* **15**: 1707-1718 (1966). G42,049/66

In rats subjected "to a chronic variable stress program consisting of flashing lights, audiogenic stimulation, and oscillation," hypertension developed after several months. This was associated with an increase in catecholamine excretion that disappeared after several weeks, and a rise in plasma corticosterone that tended to persist. "These results suggest that the adrenal glands had become more efficient in the rate of synthesis and release of steroids after chronic exposure to the stressors."

Buckley, J. P., Vogen, E. E., Kinnard, W. J.: "Effects of pentobarbital, acetylsalicylic acid, and reserpine on blood pressure and survival of rats subjected to experimental stress." *J. Pharm. Sci.* **55**: 572-575 (1966). F67,051/66

Chronic exposure of rats to a variety of stressors (strong light, sound, electric shock) produces hypertension, which is not prevented by pentobarbital or acetylsalicylic acid but is diminished by reserpine. The ulcerogenic effect of stressors is aggravated by acetylsalicylic acid.

Fedoseev, A. N.: "Significance of the central nervous system stress in the development of experimental cholesterol atherosclerosis in dogs." *Patol. Fiziol. Éksp. Ter.* **11** No. 1-2: 35-38 (1967) (Russian).

J24,055/67

In dogs fed a high cholesterol diet, various psychogenic stressors intensified the development of atherosclerosis.

Shkhvatsabaia, I. K., Ananchenko, V. G.: "Mechanism of coronary thrombosis produced by neurogenic action on animals with experimental atherosclerosis." *Bull. Éksp. Biol. Med.* **63** No. 3: 28-31 (1967) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **63**: 242-244 (1967). J24,293/67

Friedman, M., Byers, S. O., Brown, A. E.: "Plasma lipid responses of rats and rabbits to an auditory stimulus." *Am. J. Physiol.* **212**: 1174-1178 (1967). F83,722/67

"Rats exposed to a continuous sound stimulus having an intensity of 102 db and an in-

termittent sound stimulus (200-cycle square wave with a duration of about 1 sec and having an intensity of 114 db) exhibited marked elevation and prolongation of clearing of postprandial plasma triglyceride for a period of approximately 21 days.... Cholesterol-fed rabbits exposed to similar sound stimulus for 10 weeks exhibited a higher blood cholesterol and more intense atherosclerosis than similarly fed control animals."

Dahl, L. K., Knudsen, K. D., Heine, M., Leitl, G.: "Hypertension and stress." *Nature* **219**: 735-736 (1968). H1,538/68

In a strain of rats genetically predisposed to hypertension, various stressors (electroshock, sound, light) did not cause significant increases in blood pressure. "Our findings do not support the popular concept that stress is a usual or common aetiological factor of hypertension."

Buckley, J. P., Parham, C., Smookler, H. H.: "Effects of reserpine on rats subjected to prolonged experimental stress." *Arch. Int. Pharmacodyn. Ther.* **172**: 292-300 (1968). F99,053/68

Reserpine prevented the hypertension which develops in rats exposed to diverse stressors.

Smookler, H. H., Buckley, J. P.: "Relationships between brain catecholamine synthesis, pituitary adrenal function and the production of hypertension during prolonged exposure to environmental stress." *Int. J. Neuropharmacol.* **8**: 33-41 (1969).

H22,172/69

In rats, experimental hypertension produced by a variety of stressors is beneficially influenced by α -MT.

Wexler, B. C., Saroff, J.: "Divergent responses of arteriosclerotic and non-arteriosclerotic rats to a catabolic dose of cortisone." *Acta Endocrinol. (Kbh.)* **61**: 509-524 (1969).

H15,114/69

Repeatedly bred rats tend to develop spontaneous arteriosclerosis. Injections of cortisone aggravate this effect. "It is believed that the increased activity of the hypothalamic-pituitary-adrenal axis in repeatedly bred rats conditions the arterial wall towards rearrangement of connective tissue ground substance and elements and the development of arteriosclerosis, i.e., a hormonal basis for the pathogenesis of this model of cardiovascular disease."

Grüner, M., Nitschkoff, S.: "Über die

Möglichkeiten der Ausarbeitung einer experimentellen neurotischen Hypertonie bei Hunden" (On the possibility of producing experimental neurotic hypertension in dogs). *Acta Biol. Med. Ger.* 24: 593-602 (1970).

J20,888/70

In dogs, chronic exposure to noise, electroshock or other aversive stimuli can produce a persistent hypertension.

Shimamoto, T., Kobayashi, M., Numano, F.: "Infiltration of γ -globulin, fibrinogen and β -lipoprotein into blood vessel wall by atherogenic stress visualized by immunofluorescence." *Proc. Jap. Acad.* 48: 336-341 (1972).

G98,558/72

"One shot treatment of rabbits with epinephrine or atherogenic substance induced an acute infiltration of γ -globulin, fibrinogen, and β -lipoprotein into the arterial wall with subendothelial stagnation, temporarily dammed by the internal elastic lamina. Gamma-globulin, fibrinogen, and β -lipoprotein are also visualized in chronic experimental atheromata. This model utilizes a physiological marker to study vascular permeability and suggests an important barrier function of the internal elastic lamina."

Rothfeld, B., Paré, W. P., Varady, A. Jr., Isom, K. E., Karmen, A.: "The effects of environmental stress on cholesterol synthesis and metabolism." *Biochem. Med.* 7: 292-298 (1973).

J2,491/73

In rats, the stressor effect of sound or electroshock caused cholesterol deposition in the aorta and liver with a rise in blood cholesterol.

Hecht, K., Poppei, M., Peschel, M., Trepotow, K., Moritz, V.: "Optimierungsaspekte in der zerebro-viszeralen Blutdruckregulation unter chronischem Einfluss kombinierter Stressoren" (Optimizing effects in cerebro-visceral blood pressure regulation following chronic exposure to combined stressors)." *Acta Biol. Med. Ger.* 31: 813-825 (1973).

J11,605/73

Observations on rats showed that "whereas chronic single presentation of stressors (learning, intermitting limitation of mobility) led to pronounced neurotically induced dysregulations of the blood pressure paralleling disturbances of the central nervous system and the carbohydrate metabolism, combination of the two stressors, or combination of one stressor with other environmental factors, produced an established compensatory effect." Presumably, treatment with a com-

bination of stressors need not entail summation of their effects in all respects (19 refs.).

Hauss, W. H.: "Tissue alterations due to experimental arteriosclerosis." In: Vogel, H. G., *Connective Tissue and Ageing* (Int. Congr. Ser. No. 264), pp. 23-33. Amsterdam: Excerpta Medica, 1973. J14,882/73

In rats the emotional stress produced by restraint elicits typical mesenchymal reactions in the blood vessel walls with increased ^{35}S -sulfate and ^3H -thymidine incorporation. Essentially similar changes occur after exposure to other stressors, and these are considered to be the first step in the arteriosclerotic process characteristic of aging. "The deformation of the structure of the arterial wall participates essentially in the development of lipidosis, fibrinosis, and cell necroses. Aggregation of thrombocytes and thrombosis in the arterial wall results from the frequent reduplication of intima cells."

Buckley, J. P.: "Biochemical and physiological effects of intermittent neurogenic stress." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 165-177. Bratislava: Slovak Academy of Sciences, 1973. E10,466/73

Various stressors (sound, light, vibration) chronically applied to rats caused hypertension with an increased NEP turnover in the CNS. Possibly, "the chronic phase of the response is associated with an action of angiotensin II on central receptors."

Baumann, H., Hecht, K.: "Quantitative evoked-potential-Analysen zur neurophysiologischen Charakterisierung von Fehlernprozessen in der experimentellen arteriellen Hypertonie-Pathogenese" (Quantitative evoked-potential analyses for neuro-physiologic characterization of miscontrolled learning processes in the pathogenesis of experimental hypertension). *Acta Biol. Med. Ger.* 30: 675-696 (1973).

J7,760/73

In rats, the nervous stress of learning conditioned reflexes led to arterial hypertension. Using electrodes implanted in various parts of the brain and evaluating the data by computer analysis, the authors found a general impairment of bioelectric information processing as nervous stress increased. "The experimental evidence of stepwise involvement of limbic brain structures due to the increasing learning stress gives reason to assume a differentiated function of this system in organism-environment adaptation."

Hecht, K., Poppei, M., Hecht, T., Bau-

mann, H., Treptow, K., Moritz, V., Choinowski, S., Michailow, M., Schlegel, T.: "A model designed to study the role of stressing environmental factors in the pathogenesis and primary prevention of experimental neurotically-induced hypertension." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 18-23. Baku, USSR, 1974 (Russian, with extensive English summary).

J17,526/74

Hallbäck, M., Folkow, B.: "Cardiovascular responses to acute mental 'stress' in spontaneously hypertensive rats." *Acta Physiol. Scand.* **90**: 684-698 (1974).

J13,405/74

Genetically hypertensive rats showed more pronounced cardiovascular responses to the stressor effect of sound than did normotensive controls or renal hypertensive rats of a normal strain. Hence the hyperreactivity is genetically conditioned.

Wexler, B. C.: "Adrenocortical changes associated with methylandrostenediol-induced hypertension and isoproterenol-induced myocardial infarction in arteriosclerotic versus nonarteriosclerotic rats." *Lab. Invest.* **30**: 251-259 (1974).

J12,177/74

Repeatedly bred rats had naturally occurring arteriosclerosis and mild hypertension. If treated with isoproterenol, their mortality rate was high, serum triglycerides and cholesterol were greatly elevated, and the repair of drug-induced cardiac necroses was impeded by the formation of aneurysms. It is concluded that "preexisting, chronic, severe hypertension plays a key role in the pathogenesis of left ventricular aneurysm formation during acute myocardial infarction and that severe hypertension combined with arteriosclerosis portends a poor prognosis toward survival" (42 refs.).

Friedman, R.: "The Effect of Punishment on the Blood Pressure of Rats with a Genetic Susceptibility to Experimental Hypertension," p. 78. Thesis, State University of New York at Stony Brook, 1974.

J22,102/74

Alexander, N.: "Psychosocial hypertension in members of a Wistar rat colony." *Proc. Soc. Exp. Biol. Med.* **146**: 163-169 (1974).

H87,183/74

Various social conditions (particularly aggregation and isolation) can cause hypertension in the rat.

Baumann, H., Urmantscheeva, T. G., Gurk, C., Martin, G., Wolter, F.: "Quantita-

tive evoked potential analyses in behavioural neurophysiology. A model of a stress-induced borderline hypertension in rhesus monkeys." *Acta Biol. Med. Ger.* **33**: 419-427 (1974).

J21,955/74

Friedman, R., Dahl, L. K.: "The effect of chronic conflict on the blood pressure of rats with a genetic susceptibility to experimental hypertension." *Psychosom. Med.* (In press).

J24,878/

Rats genetically susceptible to experimental hypertension were exposed to several aversive stimuli. "Despite weekly fluctuations, a pattern emerged wherein subjects exposed to an approach (food)-avoidance (shock) conflict usually exhibited the highest blood pressures followed closely by rats given the same amount of food and shock but independent of their behavior." Usually the blood pressures returned to normal after the stressful experience, but there was "some indication in a few rats that the 'stress-induced' elevations could be maintained for extended periods following removal of the stress."

Hyalinosis. Selye, H., Pentz, E. I.: "Pathogenetical correlations between periarteritis nodosa, renal hypertension and rheumatic lesions." *Can. Med. Assoc. J.* **49**: 264-272 (1943).

A59,789/43

First description of the technique for producing mineralocorticoid hypertension in uninephrectomized rats given one percent sodium chloride to drink. The rapidly developing high blood pressure is associated with "the hyalinosis syndrome," periarteritis nodosa, myocarditis and nephrosclerosis. Corresponding lesions in man may be "at least partly caused by an abnormal (probably excessive) adaptive response of the adrenal cortex and represent diseases of adaptation."

Selye, H.: "Hypertension as a disease of adaptation." *Rec. Prog. Horm. Res.* **3**: 343-361 (1948).

B1,433/48

Discussion of the role of stress in the development of hypertension with special reference to mineralocorticoids, sodium and Hypertensin (angiotensin).

Shorr, E.: "The American Journal of Medicine seminars on hypertension." *Am. J. Med.* **5**: 783-791 (1948).

B30,644/48

Review of experimental evidence on the humoral factors responsible for hypertension. Special emphasis is placed upon the probable

interrelations between mineralocorticoids, the renal pressor mechanism, VEM, and VDM.

Selye, H., Stone, H., Timiras, P. S., Schaffenburg, C.: "Influence of sodium chloride upon the actions of desoxycorticosterone acetate." *Am. Heart J.* **37**: 1009-1016 (1949).

B19,413/49

In rats kept on a sodium chloride-free diet, DOC fails to produce the usual fatal hypertensive cardiovascular disease. "From this, in conjunction with our previously published observations, it is concluded that sodium is essential for the renal, and, through the intermediation of the kidney, for the cardiovascular actions of desoxycorticosterone acetate."

Selye, H.: "Effect of desoxycorticosterone upon the toxic actions of somatotropic hormone." *Proc. Soc. Exp. Biol. Med.* **76**: 510-515 (1951).

B54,470/51

In uninephrectomized rats kept on a high sodium diet, STH produces results similar to the syndrome elicited by DOC: cardiac hypertrophy, myocarditis, hypertension, nephrosclerosis and polyuria. When STH and DOC are given simultaneously, all these actions are greatly increased, except for the hypertension which may be inhibited as a consequence of the pronounced edema and obvious physical deterioration. Even purified STH may stimulate the adrenal cortex or activate mineralocorticoids.

Salgado, E., Selye, H.: "The role of the thyroid in the production of cardiovascular and renal changes by methylandrostenediol." *J. Endocrinol.* **11**: 331-337 (1954).

B92,433/54

In rats sensitized by 1 percent sodium chloride and uninephrectomy, MAD causes accumulation of hyalin granules in adrenocortical cells, associated with nephrosclerosis, periarteritis nodosa, myocarditis and hypertension. These changes are prevented by adrenalectomy and presumably are due to the production of a DOC-like mineralocorticoid in the adrenals under the influence of MAD. Thyroidectomy diminishes the formation of these hyalin granules and dissociates the other actions of MAD so that nephrosclerosis, myocarditis and hypertension are largely inhibited, but polyuria, thymic involution and all the effects typical of androgens remain uninfluenced, while the severity of mesenteric periarteritis nodosa is aggravated. The reason for this dissociation remains to be explained.

Skelton, F. R.: "Experimental hypertensive vascular disease in the rat. A histopathologic study of the lesions produced by methylandrostenediol and desoxycorticosterone acetate." *Arch. Pathol.* **66**: 190-200 (1955) (26 refs.).

G61,768/55

Skelton, F. R.: "Effects of urea on the hypertension and vascular lesions produced in the rat by methylandrostenediol and desoxycorticosterone acetate." *Lab. Invest.* **6**: 266-274 (1957).

C36,541/57

Detailed description of factors influencing the development of vascular lesions in rats made hypertensive by uninephrectomy plus sodium chloride in combination with MAD or DOC. "These results suggest that the vascular lesions produced by these steroids are not the result of an elevated blood pressure per se, and the suggestion is made that the pathogenesis of these lesions may involve some metabolic action on the vessel wall."

Ingle, D.: "Current status of adrenocortical research." *Am. Sci.* **47**: 413-426 (1959).

D41,791/59

In rats, excessive sodium chloride intake can cause hypertension, and concurrent treatment with corticoids greatly accelerates its development. "This is the basis for my claim that the primary cause of pathology in the Selye experiments is the trouble the animal is having with electrolytes: the sodium-retaining steroids play a 'conditioning' role—to use Selye's word—when they are present."

Hall, C. E., Hall, O.: "Enhancement of somatotropic hormone-induced hypertensive cardiovascular disease by stress." *Am. J. Physiol.* **197**: 702-704 (1959).

C74,782/59

Skelton, F. R., Hyde, P. M.: "Plasma corticosterone levels and salt intake in experimental hypertension in the rat." *Am. J. Cardiol.* **8**: 700-704 (1961).

D13,276/61

In rats sensitized with uninephrectomy plus sodium chloride, severe hypertensive cardiovascular lesions can be produced by corticosterone at dose levels within the range attained during stress.

Accatino, G., Pandolfo, G., Rappelli, A., Campus, S.: "Effetto degli stimoli psichici associati a somministrazione di sale e DOCA sulla pressione arteriosa ed il peso corporeo di ratti Sprague-Dawley" (Effects of mental stimuli associated with administration of salt

and DOCA on arterial pressure and body weight in Sprague-Dawley rats). *Boll. Soc. Ital. Biol. Sper.* **41**: 1089-1092 (1965).

J22,724/65

Skelton, F. R., Brownie, A. C., Nickerson, P. A., Molteni, A., Gallant, S., Colby, H. D.: "Adrenal cortical dysfunction as a basis for experimental hypertensive disease." *Circ. Res.* **24** Supp. 1: I-35-I-57 (1969).

H13,163/69

In suitably conditioned rats a similar hypertensive cardiovascular disease was produced by adrenal regeneration, MAD, methyltestosterone, testosterone or metyrapone. "The development of all these forms of experimental hypertension was accompanied by inability of homogenized adrenal tissue or isolated mitochondria to 11 β -hydroxylate deoxycorticosterone to corticosterone readily, thereby allowing deoxycorticosterone to accumulate in the incubation media."

Selye, H.: *Experimental Cardiovascular Diseases*, 2 vols., p. 1155. New York, Heidelberg and Berlin: Springer-Verlag, 1970.

G60,083/70

Extensive monograph surveying virtually the entire literature on experimental cardiovascular diseases produced by stressors, mineralocorticoids, MAD, ARH, and the ESCN.

Stárka, L., Motlík, K.: "Suppression of adrenocortical steroid biosynthesis by methylandrostanediol in rats." *Acta. Univ. Carol. [Med.]* (Praha) **17**: 457-466 (1971).

H76,969/71

Review of the literature on the production of hypertensive cardiovascular disease by MAD. Personal observations with radio-carbon-marked steroids confirm that in the rat MAD depresses the synthesis of various corticoids but increases that of DOC. This process is associated with the formation of hyalin droplets and certain enzymatic derangements in the outer cortex; hence, MAD hypertension depends upon the presence of the adrenals.

Dusting, G. J., Rand, M. J.: "An anti-hypertensive action of propranolol in DOCA/salt-treated rats." *Clin. Exp. Pharmacol. Physiol.* **1**: 87-98 (1974).

J13,425/74

In rats made hypertensive by DOC plus sodium chloride, propranolol and guanethidine diminish the blood pressure. Various experiments suggest that the antihypertensive

effect of propranolol in this case is due not to adrenergic neurone blockade or to its pronounced specific depressant action, but to central impairment of sympathetic activity.

Svendsen, U. G.: "Thymus dependency of periorteritis nodosa in DOCA and salt treated mice." *Acta Pathol. Microbiol. Scand. [A]* **82**: 30-34 (1974).

J16,185/74

Severe periorteritis nodosa develops in the kidneys, with fewer lesions in the heart and pancreas, in unilaterally nephrectomized, hairless NMRI mice treated with DOCA plus sodium chloride, but not in littermates with congenital thymus aplasia.

Infarctoid Necroses. Selye, H.: *The Chemical Prevention of Cardiac Necroses*, p. 235. New York: Ronald Press, 1958.

C50,810/58

Detailed review of the experimental observations that led to the concept of "metabolic cardiac necroses," in which biochemical changes within the myocardium, rather than primary occlusion of the coronary arteries, are the causative factor. After they are suitably conditioned with various corticoids and high sodium diets, animals readily respond to stress with infarctoid myocardial necroses, which can be prevented by low sodium or high potassium diets. Magnesium and chloride ions also exert some protective effect, whereas dietary excessive saturated or unsaturated fatty acids facilitate the production of metabolic cardiac necroses in animals.

Selye, H.: "Wechselwirkungen zwischen Stress, Elektrolyten und Steroiden beim Entstehen verschiedener Kardiopathien und Myopathien" (Reciprocal actions between stress, electrolytes and steroids in the pathogenesis of various cardiopathies and myopathies). *Endokrinologie* **38**: 195-217 (1959).

C61,814/59

Relationships between stress, electrolytes and steroids in the pathogenesis of experimental cardiac diseases.

Selye, H.: *Elektrolyte, Stress und Herznekrose* (Electrolytes, stress and cardiac necroses), p. 228. Basel and Stuttgart: Benno Schwabe Verlag, 1960.

C88,872/60

German translation of *The Chemical Prevention of Cardiac Necroses*.

Bajusz, E.: "Unspecific systemic stress reactions and necrotizing cardiopathies." *Am.*

J. Phys. Med. **39**: 153-169 (1960) (53 refs.).
C60,936/60

Selye, H., Prioreschi, P., Jean, P.: "Production of cardiac necroses and nephrocalcinosis by stress in adrenalectomized rats." *Proc. Soc. Exp. Biol. Med.* **104**: 68-70 (1960).
C81,135/60

Various stressors such as cold, denervation and restraint elicited cardiac necroses, even in adrenalectomized rats, after conditioning with corticoids and sodium salts. "Apparently, these manifestations of stress are not mediated through increased secretion of adrenal hormones."

Selye, H., Prioreschi, P.: "Stress in the production of cardiac necrosis." *Tex. State J. Med.* **57**: 430-431 (1961). C92,220/61

Raab, W., Stark, E., Macmillan, W. H., Gige, W. R.: "Sympathogenic origin and antiadrenergic prevention of stress-induced myocardial lesions." *Am. J. Cardiol.* **8**: 203-211 (1961). D10,599/61

In the rat, various types of ESCN can be inhibited by antiadrenergic or ganglionic blocking agents. "It is concluded that the stress-induced severe myocardial structural lesions in hormone-preconditioned animals are directly attributable to the reflex liberation of potentially cardiotoxic adrenosympathogenic catecholamines which accompanies all stressful situations" (84 refs.).

Selye, H.: "Stress and cardiovascular disease." *World Wide Abstr. Gen. Med.* **4**: 8-13 (1961). C93,900/61

Review on the effect of stress upon the development of cardiovascular disease, particularly CHD. Special emphasis is placed upon the production of cardiac necrosis following humoral conditioning by sudden exposure to unaccustomed stress, and upon the fact that previous exposure to a stressor (for example, exercise) can protect the heart against this type of damage.

Selye, H.: *The Chemical Prevention of Cardiac Necroses*, p. 207. Moscow: MEDGIZ, 1961 (Russian). C88,871/61

Grasso, S.: "Stress e cardiopatie sperimentali" (Stress and experimental cardiopathies). *Mal. Cardiovasc.* **3**: 17-32 (1962). D5,316/62

Résumé of the experimental work on the production of cardiovascular diseases, particularly infarctoid necrosis, by stress, steroids and electrolytes.

Sobel, H., Mondon, C. E., Straus, R.: "Spontaneous and stress-induced myocardial infarction in aged atherosclerotic dogs." *Circ. Res.* **11**: 971-981 (1962). D46,380/62

In dogs on a high cholesterol plus thiouracil diet, exposure to various stressors produced myocardial infarction (24 refs.).

Bajusz, E.: "Nutritional factors in the pathogenesis of cardiac necroses. Part II." *Z. Ernährungswiss.* **3**: 1-26 (1962) (197 refs.). J24,572/62

Wasyluk, J.: "Selye's 'pseudo-infarction myocardial defect' (Clinical aspects)." *Kardiol. Pol.* **6**: 153-154 (1963) (Polish).

J24,382/63

Rigó, J., Szelényi, I.: "The role of magnesium in an alimentary cardiomyopathy complicated by disturbance of the nervous system." *Kisér. Orvostud.* **15**: 587-591 (1963) (Hungarian). G9,470/63

Selye, H.: "Stress and the pluricausal cardiopathies." In: James, T. N. and Keyes, J. W., *The Etiology of Myocardial Infarction*, pp. 139-151. Boston: Little, Brown, 1963. G46,793/63

Review of stress with special reference to the pluricausal cardiopathies produced experimentally in the rat.

Selye, H.: *The Chemical Prevention of Cardiac Necroses*, p. 200. Warszawa: Państwowy Zakład Wydawnictw Lekarskich, 1963 (Polish). D25,660/63

Akhmeteli, G. S.: "X-irradiation as a stress factor in the pathogenesis of myocardial necroses." *Patol. Fiziol. Éksp. Ter.* **8** No. 5: 24-27 (1964) (Russian).

J25,189/64

"For 12 days rats were subjected to a hormonal pretreatment with cortisone + Na₂HPO₄, or with cortisone + DOCA and Na₂HPO₄. Apart from this, rats of two groups were also exposed to x-irradiation (450 r.). The data obtained indicate that ionizing radiation may be attributed to stress factors, provoking myocardial necroses in rats pretreated through hormonal electrolyte action."

Andreichev, A. I.: "Myocardial changes in rats subjected to cortisone treatment and certain other conditions." *Fed. Proc.* **23** No. 2: T1095-T1098 (1964). Also in: *Kardiologija* **3** No. 5: 33-40 (1963) (Russian).

F23,718/64

Selye, H., Gabbiani, G.: "Fragen der Elektrolyte, des Stress und der Herznekrose" (Questions concerning electrolyte steroid cardiopathies). In: Kaufman, E. and Staemmler, M., *Lehrbuch der speziellen pathologischen Anatomie*, Vol. 1, Part 1, pp. 1-57. Berlin: Walter de Gruyter, 1967.

G11,108/67

Review of the literature on electrolyte steroid cardiopathies as influenced by stress, and on the protection provided by potassium and magnesium against infarctoid cardiopathies.

Veltri, C., Santagati, G., Sartori, S., Giraldi, M.: "Considerazioni sulla cardiopatia da corticosteroidi, sali e stress" (Considerations on cardiopathy due to corticosteroids, salts and stress). *Arch. De Vecchi Anat. Patol.* **49**: 459-466 (1967).

G59,114/67

In rats, combined treatment with strong stressors and corticoids produces infarctoid myocardial necroses, probably due to cardiac potassium depletion.

Raab, W.: "Myocardial metabolic vulnerability—key problem in pluricausal 'coronary' heart disease." *Cardiologia* **52**: 305-317 (1968).

G66,002/68

Review of the literature and particularly of the experiments with various forms of the ESCN led to the conclusion that "the traditional, one-sided view of 'coronary' degenerative heart disease as a purely vascular problem is currently replaced by a pluricausal concept. Coronary atherosclerosis constitutes an important predisposing element. However, attention is increasingly focused on cell vulnerability-determining derangements of myocardial metabolism which complicate and often decisively aggravate the cardiac pathogenicity of vascular lesions within the heart muscle itself." Major emphasis is laid upon the conditioning of the cardiac muscle by catecholamines and corticoids which predisposes the myocardium to necrosis following subsequent exposure to stress.

Selye, H., Somogyi, A., Savoie, L.: "Prevention of stress-induced cardiac necrosis by amiloride." *Angiologica* (Basel) **6**: 249-254 (1969).

G46,790/69

Solymoss, B., Varga, S., Classen, H. G., Selye, H.: "Stress und Herzinfarkt" (Stress and myocardial infarction). In: Heilmeyer, L. and Holtmeier, H. J., *Herzinfarkt und Schock*, pp. 28-34. Stuttgart: Georg Thieme Verlag, 1969.

G46,797/69

Brief résumé on the pluricausal cardiopathies (10 refs.).

Selye, H.: "The evolution of the stress concept. Stress and cardiovascular disease." *Am. J. Cardiol.* **26**: 289-299 (1970).

G60,009/70

Selye, H.: *Experimental Cardiovascular Diseases*, 2 vols., p. 1155. New York, Heidelberg and Berlin: Springer-Verlag, 1970.

G60,083/70

Extensive monograph surveying virtually the entire literature on experimental cardiovascular diseases produced by stressors, mineralocorticoids, MAD, ARH, and the ESCN.

Dimitriu, C. G., Karassi, A., Manu, P., Gavrilă, F.: "Stress și catecolamine în patologia cardiovasculară" (Stress and catecholamines in cardiovascular pathology). *Med. Interna* (Bucur.) **23**: 1155-1167 (1971) (Roumanian).

J2,821/71

Discussion of the ESCN as an experimental model of stress-induced cardiac necrosis.

Héroux, O.: "Physiological adjustments responsible for metabolic cold adaptation and possible deleterious consequences." *Rev. Can. Biol.* **33**: 209-222 (1974).

H97,110/74

Review of metabolic changes produced by cold in various mammals. Increased energy utilization may participate in stress-induced myocardial necroses.

Johansson, G., Jonsson, L., Lannek, N., Blomgren, L., Lindberg, P., Poupa, O.: "Severe stress-cardiopathy in pigs." *Am. Heart J.* **87**: 451-457 (1974).

H85,436/74

"In 23 healthy young pigs stress was produced by preventing escape behavior by pharmacologic restraint (Celocurin chloride)." All of them developed infarctoid myocardial necroses which were sometimes fatal.

Adrenal Regeneration Hypertension. Skelton, F. R., Guillebeau, J.: "The influence of age on the development of adrenal-regeneration hypertension." *Endocrinology* **59**: 201-212 (1956).

C22,147/56

The cardiovascular lesions characteristic of ARH are most evident in young rats, perhaps because STH secretion is particularly intense during growth.

Skelton, F. R.: "Production and inhibition of hypertensive disease in the rat by corticosterone." *Endocrinology* **62**: 365-368 (1958). C48,928/58

The hypertension produced in uninephrectomized, salt-treated rats by adrenal enucleation can be prevented by corticosterone, which interferes with adrenal regeneration.

Skelton, F. R.: "A study of the natural history of adrenal-regeneration hypertension." *Circ. Res.* **7**: 107-117 (1959) (21 refs.). C63,136/59

Skelton, F. R., Brownie, A. C.: "Adrenal-regeneration hypertension. An enigma." In: Bajusz, E. and Jasmin, G., *Methods and Achievements in Experimental Pathology. 2. Investigative Techniques*, pp. 257-284. Basel and New York: S Karger, 1967.

E7,223/67

In rats, ARH is associated with increased secretion of 18-OH-DOC and disturbances in NADPH generation. EM studies indicate gross mitochondrial anomalies during the early regenerative process. "Some association might therefore exist between this morphologic abnormality and the accumulation of abnormal quantities of DOC and 18-hydroxy-DOC" (89 refs.).

Skelton, F. R., Brownie, A. C.: "Studies on the pathogenesis of adrenal-regeneration and methylandrostanediol hypertension." In: Jasmin, G., *Endocrine Aspects of Disease Processes*, pp. 271-299. St. Louis, Mo.: Warren H Green, 1968.

E7,627/68

Detailed comparative review on the hypertensive vascular disease developing during adrenal regeneration following partial adrenalectomy or treatment with MAD in a rat sensitized by uninephrectomy and 1 percent sodium chloride. Special emphasis is laid upon EM and biochemical changes in the adrenal cortex, which suggest an interference with the 11 β -hydroxylation of DOC (60 refs.).

Selye, H.: *Experimental Cardiovascular Diseases*, 2 vols., p. 1155. New York, Heidelberg, Berlin: Springer-Verlag, 1970.

G60,083/70

Extensive monograph surveying virtually the entire literature on experimental cardiovascular diseases produced by stressors, mineralocorticoids, MAD, ARH, and the ESCN.

Hall, C. E., Hall, O.: "Adrenal regeneration hypertension." In: Onesti, G., Kim, K. E. et al., *Hypertension. Mechanisms and Management*, pp. 549-562. New York: Grune & Stratton, 1973. J11,591/73

A review of the present status of ARH leads to the yet unproven supposition that a modification in blood supply and other changes "so alter the availability of substrates, enzymes, co-factors, and the like, that the gland is unable to synthesize corticosterone and aldosterone optimally, with the result that a precursor of both, 11-deoxycorticosterone, is produced in excess, and in a continuous rather than rhythmic fashion" (77 refs.).

Gaunt, R., Melby, J. C., Dale, S. L., Grekin, R. J., Brown, R. D.: "Adrenal regeneration hypertension." Proc. 4th Int. Congr. Endocrinology, Washington, D. C., 1972. *Int. Congr. Ser. No. 273*, pp. 740-745 (1974).

J15,089/74

Brief but informative and up-to-date review on the hormonal changes during ARH in the rat.

Hall, C. E., Ayachi, S., Hall, O.: "Hypertensive vascular disease produced in rats by compression of the adrenal and its relationship to adrenal-regeneration hypertension." *Endocrinology* **94**: 355-362 (1974).

H86,268/74

In rats sensitized by uninephrectomy and sodium chloride, adrenal compression produces hypertensive vascular disease similar to that elicited by ARH. Technically, this new procedure is simpler.

Hall, C. E., Ayachi, S., Hall, O.: "Adrenal compression: effect of varied intensity on the resultant hypertensive response in rats." *Tex. Rep. Biol. Med.* **32**: 479-488 (1974).

J17,208/74

In uninephrectomized, sodium chloride-treated rats, even gentle compression of one adrenal (without extirpation or compression of the other) sufficed to produce hypertension and vascular disease. "The advantages of light compression over severe compression (or adrenal enucleation) include the greater simplicity of the procedure, prevention of adrenal atrophy, and better preservation of the medulla and of a relatively normal adrenocortical architecture." It remains to be seen whether here, as in ARH, increased secretion of mineralocorticoids is of pathogenic importance.

NEUROPSYCHIATRIC DISEASES

[See also Audiogenic Seizures, Gastrointestinal, Cardiovascular, and other potentially psychosomatic diseases]

Generalities

A large number of reviews and monographs in various languages attempt to summarize the psychosomatic and psychiatric consequences of maladjustment to stress. Special emphasis has been placed on the predisposing factors that determine why certain individuals respond with mental, others with somatic, manifestations when they are unable to adjust themselves to life situations. Although interpretations differ in detail, most investigators agree that derailments of the G.A.S. may be both the cause and the consequence of exposure to neurogenic stressors.

Because of many overlaps, it is notoriously difficult to classify mental diseases into sharply delimited categories, but to make the enormous literature on the subject as accessible as possible, we have arbitrarily subdivided pertinent data under the following headings:

- Psychosomatic Diseases
- Neuroses
- Schizophrenia and Related Psychoses
 - Generalities
 - Hormonal Changes
 - Nonhormonal Metabolic Changes
- Manic-depressive Disease (including mixed syndromes and those in which either manic excitement or depression predominate)
- Toxicomanias (including Alcoholism)
- Senile Psychosis
- Other Neuropsychiatric and Psychosomatic Diseases
- Experimental Neuroses (including Toxicomanias)

Generalities

(See also our earlier stress monographs, p. xiii)

Hoagland, H.: "Enzyme kinetics and the dynamics of behavior." *J. Comp. Physiol. Psychol.* **40**: 107-127 (1947). B4,974/47

An attempt to analyze the literature on enzyme kinetics in the brain and the dynamics of behavior in order to determine "why some persons become psychotic in the face of relatively unstressful social situations while others do not despite psychological stress" (42 refs.).

Malmo, R. B., Shagass, C.: "Physiologic study of symptom mechanisms in psychiatric

patients under stress." *Psychosom. Med.* **11**: 25-29 (1949). B47,046/49

Malmo, R. B.: "Experimental studies of mental patients under stress." In: Reymert, M. L., *Feelings and Emotions*, pp. 169-180. New York: McGraw-Hill, 1950.

E83,540/50

Malmo, R. B., Shagass, C., Davis, F. H.: "Specificity of bodily reactions under stress. A physiological study of somatic symptom mechanisms in psychiatric patients." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 231-261. Baltimore: Williams & Wilkins, 1950.

B51,906/50

Malmo, R. B., Shagass, C., Bélanger, D. J., Smith, A. A.: "Motor control in psychia-

tric patients under experimental stress." *J. Abnorm. Soc. Psychol.* **46**: 539-547 (1951).
B68,566/51

Benda, P.: "Le syndrome général d'adaptation. Ses applications cliniques et thérapeutiques en neuro-psychiatrie" (The general adaptation syndrome. Clinical and therapeutic applications in neuropsychiatry). *Encéphale* **40**: 228-284 (1951). B71,777/51

Extensive review of the G.A.S. with special reference to its application in psychiatry (104 refs.).

Malmo, R. B., Shagass, C., Davis, J. F.: "Electromyographic studies of muscular tension in psychiatric patients under stress." *J. Clin. Exp. Psychopathol.* **12**: 45-66 (1951). C90,082/51

Psychoneurotic and psychotic patients responded to various stressors (pain, discrimination, mirror drawing) with greater muscular tension (EMG) than did normal controls.

Loo, P., Breton, J.: "Idées de Selye et clinique psychiatrique" (Selye's ideas and psychiatric clinic). *Ann. Méd. Psychol.* **2**: 108-112 (1952). J25,471/52

Russell, R. W.: "Behaviour under stress." *Int. J. Psychoanal.* **34** Supp.: 1-12 (1953). D87,619/53

A lecture before the British Psycho-Analytical Society summarizing the G.A.S., with special emphasis upon behavioral changes induced by stress.

Cohn, J. B., Rubinstein, J.: "An experimental approach to psychological stress." *Am. J. Psychiatry* **111**: 276-282 (1954). D95,167/54

An attempt to furnish a basis for the interpretation of psychiatric illness in relation to the G.A.S.

Selye, H.: "Stress and psychiatry." *Am. J. Psychiatry* **113**: 423-427 (1956). C12,621/56

Whitehorn, J. C.: "Stress and emotional health." *Am. J. Psychiatry* **112**: 773-781 (1956). E68,251/56

Morozov, V. M.: "The stress concept and psychiatry." *Zh. Nevropatol. Psichiatr.* **57**: 657-661 (1957) (Russian). D2,827/57

Brief résumé on the role of stress in the pathogenesis of psychiatric illness.

Tanner, J. M. (ed.): *Stress and Psychiatric Disorder*, p. 151. Oxford: Basil Black-

well & Mott, 1960. C90,490/60

Second Oxford Conference of the Mental Health Research Fund, with contributions from many specialists on the psychologic and somatic aspects of the stress concept. The main subjects are: disorganization of behavior during stress in man and animals, physiologic responses to stressors, and prevention and treatment of psychiatric stress reactions.

Vickers, G.: "The concept of stress in relation to the disorganization of human behaviour." In: Tanner, J. M., *Stress and Psychiatric Disorder*, pp. 3-10. Oxford: Blackwell Scientific, 1960. C90,491/60

Tong, J. E., Murphy, I. C.: "A review of stress reactivity research in relation to psychopathology and psychopathic behaviour disorders." *J. Ment. Sci.* **106**: 1273-1295 (1960) (212 refs.). J10,963/60

Rogovin, M.: "Mental stress and mental disorders (from foreign literature)." *Zh. Nevropatol. Psichiatr.* **62**: 1731-1740 (1962) (Russian). J24,043/62

Langner, T. S., Michael, S. T.: *The Mid-Town Manhattan Study. Life Stress and Mental Health*, p. 517. London: The Free Press of Glencoe, Collier-MacMillan, 1963. E3,442/63

Extensive monograph on the role of psychogenic stress in the production of various mental disorders in the Manhattan area.

Michael, R. P., Gibbons, J. L.: "Interrelationships between the endocrine system and neuropsychiatry." *Int. Rev. Neurobiol.* **5**: 243-302 (1963). J10,431/63

Review on the participation of the endocrine system in normal and pathologic nervous activity, with a special section on stress and the adrenal cortex.

Cassidy, W. J.: "Psychiatric emergencies." *Henry Ford Hosp. Med. J.* **15**: 119-131 (1967). G49,025/67

Theoretical considerations lead to the assumption that a number of psychiatric emergencies (excitement, delirium, panic states, hysterical outbreaks, suicides) are consequences of exposure to stress.

Rahe, R. H., McKean, J. D. Jr., Arthur, R. J.: "A longitudinal study of life-change and illness patterns." *J. Psychosom. Res.* **10**: 355-366 (1967). D88,215/67

A close relationship was found between stress (as revealed by the LCU question-

naire) and the frequency of disease, especially psychiatric illness, among U.S. Navy personnel.

Beisser, A. R., Glasser, N.: "The precipitating stress leading to psychiatric hospitalization." *Compr. Psychiatry* **9**: 50-61 (1968). J22,596/68

Hudgens, R. W., Robins, E., Delong, W. B.: "The reporting of recent stress in the lives of psychiatric patients. A study of 80 hospitalized patients and 103 informants reporting the presence or absence of specified types of stress." *Br. J. Psychiatry* **117**: 635-643 (1970). G80,310/70

On the basis of statistical data, the authors "conclude that retrospective studies which purport to demonstrate a cause-effect relationship between stressful events and established non-organic psychiatric illness may be of dubious validity."

Cattell, R. B.: "Measurement of neuroticism and anxiety." In: Sahakian, W. S., *Psychopathology Today: Experimentation, Theory and Research*, pp. 173-181. Itasca, Ill.: F E Peacock, 1970. E10,330/70

The author examines the relationship between stress and psychologic changes as its cause or result. Anxiety appears when an individual evades reality and suffers internal conflicts, whereas "effort stress" occurs when he forcefully grapples with reality.

Kiev, A.: "Crisis intervention in industry." *J. Occup. Med.* **12**: 158-163 (1970). J11,373/70

A lecture reviewing the roles of social and psychologic stressors in precipitating psychiatric illness in predisposed persons.

Jaco, E. G.: "Mental illness in response to stress." In: Levine, S. and Scotch, N. A.: *Social Stress*, pp. 210-227. Chicago: Aldine, 1970. E10,715/70

Hocking, F. H.: "Stress and psychiatry." *Med. J. Aust.* **2**: 837-840 (1971). G87,773/71

Brief but stimulating lecture on stress as a factor in psychiatric illness.

Eisler, R. M., Polak, P. R.: "Social stress and psychiatric disorder." *J. Nerv. Ment. Dis.* **153**: 227-233 (1971). G87,329/71

In patients, various "situational or social stressors" can precipitate psychologic disorders, but the subject's predisposition will

determine whether the resulting derangement will be of a schizophrenic, depressive or other type.

Niederland, W. G.: "Introductory notes on the concept, definition, and range of psychic trauma." *Int. Psychiatr. Clin.* **8**: 1-9 (1971). J20,178/71

Berkman, P. L.: "Life stress and psychological well-being: a replication of Langner's analysis in the Midtown Manhattan study." *J. Health Soc. Behav.* **12**: 35-45 (1971). J20,538/71

As indicated by replies to an eight-item Index of Psychological Well-Being in Alameda County, California, a close association exists between stress factors in daily life and mental health, as rated by psychiatrists.

Brown, G. W., Birley, J. L.: "The reporting of recent stress in the lives of psychiatric patients." *Br. J. Psychiatry* **118**: 378-379 (1971). J20,737/71

Clinical experience shows that "external circumstances, such as an occurrence which may make adaptive demands upon the person, may also contribute to the development of mental disorder."

Smith, W. G.: "Critical life-events and prevention strategies in mental health." *Arch. Gen. Psychiatry* **25**: 103-109 (1971). J20,738/71

Myers, J. K., Lindenthal, J. J., Pepper, M. P.: "Life events and psychiatric impairment." *J. Nerv. Ment. Dis.* **152**: 149-157 (1971). J20,743/71

Myers, J. K., Lindenthal, J. J., Pepper, M. P., Ostrander, D. R.: "Life events and mental status: a longitudinal study." *J. Health. Soc. Behav.* **13**: 398-406 (1972). J19,658/72

Using a special questionnaire to appraise psychiatric derangements (insomnia, irritability, tension, and so on), the authors "found a substantial and positive relationship between changes in life events and changes in psychological impairment over a two-year period."

Aponte, J. F., Miller, F. T.: "Stress-related social events and psychological impairment." *J. Clin. Psychol.* **28**: 455-458 (1972). J19,676/72

Levi, L., Kagan, A.: "A synopsis of ecology and psychiatry: some theoretical psychosomatic considerations, review of some studies and discussion of preventive aspects."

Proc. 5th World Congr. of Psychiatry, Mexico, D. F., 1971, *Int. Congr. Ser. No. 274*, pp. 369-379 (1973). J16,708/73

Bugard, P.: *Stress, Fatigue et Dépression. (l'Homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue, and depression. Man and the aggression of daily life), Vol. 1, p. 294, Vol. 2, p. 302. Paris: Doin Edit., 1974. E10,487/74

Two-volume treatise on stress problems in daily life with a special chapter on fatigue and depression in relation to stress.

Adler, G.: "Acute psychosis." *N. Engl. J. Med.* **291**: 81-83 (1974). H87,634/74

Review of various acute psychotic episodes elicited by stressors in relatively healthy persons.

Paykel, E. S.: "Life stress and psychiatric disorder: applications of the clinical approach." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 135-149. New York,

London and Sydney: John Wiley & Sons, 1974. E10,786/74

Myers, J. K., Lindenthal, J. J., Pepper, M. P.: "Social class, life events, and psychiatric symptoms: a longitudinal study." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 191-205. New York, London and Sydney: John Wiley & Sons, 1974.

E10,790/74

Cohler, B. J., Grunbaum, H. U., Weiss, J. L., Gallant, D. H., Abernethy, V.: "Social relations, stress, and psychiatric hospitalization among mothers of young children." *Soc. Psychiatry* **9**: 7-12 (1974). J15,145/74

Hospitalization for psychiatric disturbances of mothers of young children is associated with psychogenic stress; it "is believed to be related both to impairment in a woman's performance of her role as housewife and mother, as well as to life stress experienced prior to hospitalization."

Psychosomatic Diseases

(See also Neuroses)

There can be no doubt that many psychosomatic derangements are due to stress and particularly to derailments of the G.A.S. A large number of maladies depend not so much upon the apparent pathogen, but upon the way we react to it. This idea was clearly expressed in the eighteenth century by C. H. Parry when he wrote: "It is much more important to know what sort of a patient has a disease, than what sort of a disease a patient has." Several statistical studies show that "clusters of illness" often occur during periods that are significantly stressful for people striving to adapt to conflicting and often threatening demands. Numerous books attempt to provide advice—both in medical and lay language—on how to deal with such situations.

It appears that many of the psychosomatic derangements can be predicted by questionnaires (for example, the SRE of Rahe and his coworkers). Among the most common somatic diseases frequently traced to a psychogenic stress situation are: allergies, asthma, skin disorders, gastrointestinal maladies, and derangements of the cardiovascular system (particularly hypertension and CHD). Even immune reactions can be influenced by psychogenic stress and in latent diabetics, ketoacidosis is occasionally precipitated by emotional stress.

The derangements in the CNS that can result from psychogenic stress are usually classified under neuroses and will be dealt with in more detail in the next section, but it might be mentioned here that in this category the most common complaints are migraine headaches, chronic fatigue and bruxism.

Many investigators have attempted to elucidate the mechanism of psychosomatic derangements, and if possible, cure them by psychoanalytic techniques.

Psychosomatic Diseases

(See also our earlier stress monographs, p. xiii)

Dunbar, F.: *Emotions and Bodily Changes*, p. 604. New York: Columbia University Press, 1947. B36,276/47

Survey of the literature produced between 1910 and 1945 on psychosomatic interrelations (2,400 refs.).

Weiss, E., English, O. S.: *Psychosomatic Medicine*, p. 803. Philadelphia and London: W B Saunders, 1949. B48,177/49

Extensive, though now somewhat outdated, textbook of psychosomatic medicine with a rich collection of historically interesting references.

Wolff, H. G., Wolf, S. G. Jr., Hare, C. C. (eds.): *Life Stress and Bodily Disease*, p. 1135. Baltimore: Williams & Wilkins, 1950. B51,891/50

Proceedings of the Association for Research in Nervous and Mental Diseases with papers on: mechanisms involved in reactions to stress; the problem of specificity; life stress; headaches; disorders of growth, development and metabolism; diseases of the eye, respiratory passages, gastrointestinal tract, locomotor apparatus, cardiovascular system, skin and genital organs.

Alexander, F.: *Psychosomatic Medicine*, p. 300. New York: W W Norton, 1950. B52,789/50

Simple textbook on psychosomatic medicine in relation to psychoanalysis and the G.A.S. (260 refs.).

Laborit, H.: *Réaction Organique à l'Aggression et Choc* (Organic reactions to stress and shock) (Preface by R. Leriche), p. 205. Paris: Masson, 1952. B71,290/52

General review on the relationship between the concepts of homeostatic mechanisms of Claude Bernard, Walter Cannon and J. Reilly. Detailed description of functional and structural changes in the nervous, hormonal and reticuloendothelial systems.

Harper, R.: "Allergy, and other stress-conditioned illness: a suggested association with obsolete autonomic defence reflexes." *Br. Med. J.* February 14, 1953, pp. 392-395. E98,761/53

Review on the role of stress in the precipitation of psychic disturbances, allergies and particularly asthma.

Altschule, M. D.: *Bodily Physiology in Mental and Emotional Disorders*, p. 288. New York: Grune & Stratton, 1953.

B79,943/53

Monograph on the somatic repercussions of mental disorders with a very brief section on stress and the hypothalamus-pituitary-adrenocortical system.

Margetts, E. L.: "Historical notes on psychosomatic medicine." In: Wittkower, E. D. and Cleghorn, R. A., *Recent Developments in Psychosomatic Medicine*, pp. 41-68. London: I Pitman & Sons, 1954. E89,578/54

A motto of C. H. Parry (1755-1822) was: "It is much more important to know what sort of a patient has a disease, than what sort of a disease a patient has." The history of ideas about correlations between man, body and cell is traced back to antiquity and followed through up to the publication of the first detailed monograph on stress (Selye, 1950).

Wolff, H. G.: "Stress, emotions and bodily disease." In: Galdston, I., *Medicine and Science. Lectures to the Laity*, No. XVI, p. 94. New York: International University Press, 1954. B94,724/54

Review on the role of stressors in the development of cutaneous, gastrointestinal, respiratory and mental disturbances.

Wolff, H. G.: "Stress and adaptive patterns resulting in tissue damage in man." *Med. Clin. N. Am.* May 1955, pp. 783-797. B28,531/55

Primarily psychologic analysis of psychosomatic diseases affecting various organs (16 refs.).

Lewinsohn, P. M.: "Some individual differences in physiological reactivity to stress." *J. Comp. Physiol. Psychol.* 49: 271-277 (1956). C39,686/56

Technical paper on physiologic reactivity to stress in patients with duodenal ulcer, essential hypertension or neuromuscular tension. Modified Cold Pressor Test and Failure Test were used.

Funkenstein, D. H., King, S. H., Drolette, M. E.: *Mastery of Stress*, p. 329. Cambridge, Mass.: Harvard University Press, 1957. C49,747/57

Observations on stress-producing situations and their prevention in man and experimental animals. Main emphasis is laid upon psychologic factors, but the somatic aspects of the G.A.S. are also considered.

Hinkle, L. E., Jr., Wolff, H. G.: "The nature of man's adaptation to his total environment and the relation of this to illness." *Arch. Intern. Med.* **99**: 442-460. (1957).

C32,709/57

Extensive statistical studies led to the conclusion that "clusters of illness often occurred during periods significantly stressful for the person, when he was striving to adapt to what were for him highly pertinent, conflicting, and often seriously threatening demands arising out of his relation to his total environmental constellation, as he perceived it."

Selye, H.: "Panorama general de la etiopatogenia de las enfermedades de adaptación" (A general view of the etiopathogenesis of the diseases of adaptation). *Acta Med. Psicol.* **1**: 11-20 (1958).

C52,444/58

Review lecture given to the second Psychological Congress of Latin America on the G.A.S. as a basis for the study of psychosomatic diseases of adaptation.

Reed, C. F., Alexander, I. E., Tomkins, S. S. (eds.): *Psychopathology. A Source Book*, p. 803. Cambridge, Mass.: Harvard University Press, 1958.

C57,851/58

An extensive anthology on various psychosomatic derangements, with several sections devoted to stress-induced diseases.

Schindler, J. A.: *How to Live 365 Days a Year*, p. 222. Englewood Cliffs, N.J.: Prentice-Hall, 1959.

C69,069/59

Recommendations on how to avoid psychosomatic illness, based primarily on the stress concept. Written exclusively for the lay reader.

Hambling, J. (ed.): *The Nature of Stress Disorder*, p. 298. Springfield, Ill.: Charles C Thomas, 1959.

E4,674/59

Proceedings of the Conference of the Society for Psychosomatic Research (Royal College of Physicians, London). Several experts discussed the G.A.S. on the basis of animal experiments and observations in man. Special sections deal with stress in aviation, skin disorders, gastrointestinal disease, industry, and the family setting, as well as genetic predisposition.

Rees, L.: "The role of stress in the aetiology of psychosomatic disorders." *Proc. R. Soc. Med.* **52**: 274-278 (1959).

C80,538/59

Review of psychosomatic diseases related to the G.A.S.

Selye, H.: "Some implications of the stress concept." In: Coleman, J. C., *Personality Dynamics and Effective Behavior*, pp. 486-492. Chicago: Scott, Foresman, 1960.

E24,124/60

Brief résumé on the stress factor in psychosomatic diseases, written in a semipopular style.

Wolff, H. G.: "Stressors as a cause of disease in man." In: Tanner, J. M., *Stress and Psychiatric Disorder*, pp. 17-31. Oxford: Blackwell Scientific, 1960.

C90,493/60

Kollar, E. J.: "Psychological stress: a re-evaluation." *J. Nerv. Ment. Dis.* **132**: 382-396 (1961).

D7,763/61

On the basis of the literature and personal observations, "the concept of stress has been extended to include inhibitory-conservative shifts as well as excitatory shifts in homeostasis. These shifts may be either adaptive or maladaptive. If the response is prolonged in duration or inappropriate to the stress, pathophysiological and tissue changes may result."

Menninger, K., Mayman, M., Pruyser, P.: *The Vital Balance, The Life Process in Mental Health and Illness*, p. 531. New York: Viking Press, 1963.

E6,393/63

Well-documented treatise with an extensive bibliography on psychosomatic medicine. Special emphasis is placed upon coping devices in everyday life, aggression, neurotic behavior, and the importance of a personal relationship between physician and patient.

Wolf, S.: "Life stress and patterns of disease." In: Lief, H. I., Lief, V. F. et al., *The Psychological Basis of Medical Practice*, pp. 109-114. New York, Evanston, Ill., and London: Hoeber Medical, 1963.

J8,207/63

Brief chapter on the pathogenesis of psychosomatic diseases, with special reference to the role of stress.

Graham, D. T., Stevenson, I.: "Disease as response to life stress. I. The nature of the evidence." In: Lief, H. I., Lief, V. F. et al., *The Psychological Basis of Medical Practice*, pp. 115-136. New York, Evanston, Ill., and London: Hoeber Medical, 1963.

J8,246/63

A review of the literature and personal observations led to the conclusion "that there is a considerable body of evidence that social stresses are etiologically important in many diseases."

Graham, D. T., Stevenson, I.: "Disease

as response to life stress. II. Obtaining the evidence clinically." In: Lief, H. I., Lief, V. F. et al., *The Psychological Basis of Medical Practice*, pp. 137-153. New York, Evans-ton, Ill., and London: Hoeber Medical, 1963.

J4,528/63

Brief chapter on the role of stress in psychosomatic disease.

Brady, J. V.: "Behavioral stress and physiological change: a comparative approach to the experimental analysis of some psychosomatic problems." *Trans. N.Y. Acad. Sci.* **26**: 483-496 (1964). F9,450/64

Müller, K. E.: *Einführung in die Allgemeine Psychologie* (Introduction to general psychology), p. 257. Stuttgart: Ferdinand Enke Verlag, 1965. E4,995/65

Textbook on psychology with a penetrating analysis of psychosomatic interrelations, especially with regard to the stress syndrome.

Corson, S. A.: "Neuroendocrine and behavioral response patterns to psychologic stress and the problem of the target tissue in cerebrovisceral pathology." *Ann. N.Y. Acad. Sci.* **125**: 890-918 (1966). G36,865/66

Review of the technical literature on the conditioning factors determining which particular target tissue will respond to physiologic or psychologic stressors.

Sternbach, R. A.: "Psychophysiological bases of psychosomatic phenomena." *Psychosomatics* **7**: 81-84 (1966). F65,665/66

Appley, M. H., Trumbull, R. (eds.): *Psychological Stress. Issues in Research*, p. 471. New York: Appleton-Century-Crofts, 1967. E10,048/67

Conference on psychologic stress attended by numerous specialists who presented papers on the technical aspects of the G.A.S. in relation to psychosomatic medicine.

Lacey, J. I.: "Somatic response patterning and stress: some revisions of activation theory." In: Appley, M. H. and Trumbull, R., *Psychological Stress. Issues in Research*, pp. 14-42. New York: Appleton-Century-Crofts, 1967. E10,408/67

Theoretical considerations on the interpretation of psychosomatic derangements.

De l'Émotion à la Lésion. Physiologie et Pathophysiologie des Corrélations Psychophysiques: Aspects Thérapeutiques (From emotion to lesion. Physiology and pathophysiology of psychophysiological correlations: therapeutic aspects), p. 165. Montreal: Hoffman-La Roche, 1968. E10,047/68

Extensive semipopular description of psychosomatic reactions, with a detailed discussion of the G.A.S.

Hubin, P.: "Fondements expérimentaux de la médecine psychosomatique. X. Hématologie" (Experimental basis of psychosomatic medicine. X. Hematology). *Rev. Méd. Liège* **23**: 706-711 (1968). J21,399/68

Wolf, S., Goodell, H. (eds.): *Harold G. Wolff's Stress and Disease*, p. 277. Springfield, Ill.: Charles C Thomas, 1968.

E120/68

A revised and updated edition of Harold G. Wolff's *Stress and Disease*. Emphasis is placed on protective adaptive reactions which can play a decisive role in man's resistance to the common stressors of modern life. Special sections are devoted to "stress interviews" and to the part played by stress in headache and migraine and in respiratory, cardiovascular and digestive diseases in relation to social adjustment and a healthy philosophy of life.

Shanon, J.: "Stress and conflict as criteria for the classification of psychosomatic skin disorders." *Arch. Belg. Dermatol. Syphiligr.* **25**: 429-437 (1969). J2,894/69

Psychosomatic skin disorders are common among survivors of Nazi concentration camps. Stress and conflict are of pathogenic importance in such cases.

Christian, P.: "Berufsunfähigkeit aus psychosomatischer und psychoneurotischer Ursache in der Lebensmitte und der zweiten Lebenshälfte" (Occupational disability from psychosomatic and psychoneurotic causes in the middle and in the second half of life). *Z. Psychosom. Med. Psychoanal.* **15**: 282-287 (1969). J9,207/69

Cassel, J.: "Physical illness in response to stress." In: Levine, S. and Scotch, N. A., *Social Stress*, pp. 189-209. Chicago: Aldine, 1970. J12,699/70

Bruschi, W. C.: "La psicofarmacología y el síndrome de adaptación general de Hans Selye" (Psychopharmacology and Hans Selye's general adaptation syndrome). *3rd Congr. Int. Acad. Med. Psicosomática*, pp. 1-14. Buenos Aires, 1970. Also in: *Psychosomatics* **11**: 513-516 (1970). G72,989/70

Brief outline of the role of stress in psychosomatic medicine and psychopharmacology.

Sahakian, W. S.: "Psychosomatic and stress disorders." In: Sahakian, W. S., *Psy-*

chopathology Today: Experimentation, Theory and Research, pp. 191-196. Itasca, Ill.: F E Peacock, 1970. E10,331/70

The role of the G.A.S. in psychosomatic disease is reviewed.

Silverman, S.: *Psychologic Cues in Forecasting Physical Illness*, p. 403. New York: Appleton-Century-Crofts, 1970.

E10,672/70

Monograph on psychosomatic diseases, particularly stress-induced derangements, based largely on psychoanalytic investigations. The more of the following characteristics that appear together in a person, the greater the probability of the occurrence of somatic disease: "(1) exposure to critical psychologic stress inadequately compensated for by other environmental factors of a favorable nature; (2) some degree of physical dysfunction (ranging up to major illness) as part of a general style of adaptation to psychologic stress in the past, with previously sensitized body areas representing potential current target organs; (3) evidence of increasing instability and regressive shifts in psychologic equilibrium; (4) blocking of affects from adequate emotional expression or insufficient awareness of their significance if they are being so discharged; (5) presence of denial as a prominent psychologic defense; (6) existence of a high degree of ego-superego tensions despite lessening psychologic manifestations of their presence; (7) build-up of unmodified aggressiveness which is internalized; (8) a persisting increase in awareness of physical sensations and perceptions compared with previous levels; (9) recurrent dreams (and parapraxia) whose latent content contains prominent physical references especially to some form of dysfunction; (10) verbal references to somatic identification with an emotionally significant object, reinforced by actual occurrence of similar or related organ dysfunction in that person."

Kagan, A.: "Epidemiology and society, stress and disease." In: Levi, L., *Society, Stress and Disease. 1. The Psychosocial Environment and Psychosomatic Diseases*, pp. 36-48. London, New York and Toronto: Oxford University Press, 1971. E9,303/71

Lazarus, R. S.: "The concepts of stress and disease." In: Levi, L., *Society, Stress and Disease. 1. The Psychosocial Environment and Psychosomatic Diseases*, pp. 53-58. London, New York and Toronto: Oxford University Press, 1971. E9,305/71

Rioch, D. M.: "Transition states as stress." In: Levi, L., *Society, Stress and Disease. 1. The Psychosocial Environment and Psychosomatic Diseases*, pp. 85-90. London, New York and Toronto: Oxford University Press, 1971. E9,307/71

Lazarus, R. S., Averill, J. R., Opton, E. M. Jr.: "Towards a cognitive theory of emotion." In: Levi, L., *Society, Stress and Disease. 1. The Psychosocial Environment and Psychosomatic Diseases*, pp. 190-205. London, New York and Toronto: Oxford University Press, 1971. E9,312/71

Mason, J. W.: "A re-evaluation of the concept of 'nonspecificity' in stress theory." *J. Psychiatr. Res.* 8: 323-333 (1971).

G86,484/71

Brief but excellent analysis of the evidence allegedly contradicting Selye's definition of stress. Mason states that stress "may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole."

Thurlow, H. J.: "Illness in relation to life situation and sick-role tendency." *J. Psychosom. Res.* 15: 73-88 (1971). J14,015/71

Life stress, as determined by the SRE of Rahe and Holmes in 165 industrial employees, showed a definite correlation with "sick-role tendency." However, "the most effective predictor of the number of future illness episodes was the number of past illness episodes and the most effective predictor of future absenteeism was past absenteeism" (23 refs.).

Brock, J. F.: "Nature, nurture, and stress in health and disease." *Lancet* April 1, 1972, pp. 701-704. J19,861/72

Birley, J. L. T.: "Stress and disease." *J. Psychosom. Res.* 16: 235-240 (1972). G92,488/72

Barlow, W.: *The Alexander Principle*. London: Gollancz, 1973. E10,659/73

Detailed account of the principles of F. M. Alexander who, during the late nineteenth century, developed a therapeutic system based on the theory that many somatic and mental diseases are essentially caused by poor posture. Often, astonishing therapeutic results have been obtained merely by educating patients to use their musculature more efficiently.

Vincent, M. O.: "Help stamp out psychia-

- trists." *Can. Family Physician* 19: 69-71 (1973). H66,479/73
- Brief review on psychosomatic disease in relation to the G.A.S.
- Moss, G. E.: *Illness, Immunity, and Social Interaction. The Dynamics of Biosocial Resonation*, p. 281. New York, London, Sydney and Toronto: John Wiley & Sons, 1973. E10,030/73
- Effect of social interactions upon the development of illness and immunity.
- Schwab, J. J., Fennell, E. B., Warheit, G. J.: "The epidemiology of psychosomatic disorders." *Psychosomatics* 15: 88-93 (1974). H87,387/74
- Review on the principal stress-induced psychosomatic disorders.
- Suematsu, H., Kurokawa, N., Tamai, H., Ikemi, Y.: "Changes of serum growth hormone in psychosomatic disorders." *Psychother. Psychosom.* 24: 161-164 (1974). J16,922/74
- Rahe, R. H.: "The pathway between subjects' recent life changes and their near-future illness reports: representative results and methodological issues." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 73-86. New York, London and Sydney: John Wiley & Sons, 1974. E10,782/74
- Mechanic, D.: "Discussion of research programs on relations between stressful life events and episodes of physical illness." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 87-97. New York, London and Sydney: John Wiley & Sons, 1974. E10,783/74
- Kellam, S. G.: "Stressful life events and illness: a research area in need of conceptual development." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 207-214. New York, London and Sydney: John Wiley & Sons, 1974. E10,791/74
- Krauss, B.: "Zur Interpretation und Werteung somatischer Beschwerden älterer Menschen" (Interpretation and diagnosis of somatic disturbances in the aged). *Internist (Berlin)* 15: 254-257 (1974). H87,928/74
- Review on psychosomatic disturbances produced by stress in the aged.
- Gunderson, E. K. E., Rahe, R. H. (eds.): *Life Stress and Illness*, p. 264. Springfield, Ill.: Charles C Thomas, 1974. E10,677/74
- Review on a symposium held by NATO in 1972 at which fifteen comparatively independent papers were presented on stress in relation to psychosomatic medicine.
- Gunderson, E. K. E.: "Introduction." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 3-7. Springfield, Ill.: Charles C Thomas, 1974. E10,678/74
- Introduction to a symposium on stress and psychosomatic medicine.
- Selye, H.: "Stress and the general adaptation syndrome (G.A.S.)." In: Sahakian, W. S., *Readings on Introductory Psychology* (In press). G70,496/
- Review on the G.A.S., especially in relation to psychosomatic disease.

Neuroses

There is a great tendency to explain neurotic behavior on the basis of maladjustment to the stress of life. However, unequivocal objective evidence of deranged ACTH or corticoid secretion has not been consistently observed in psychoneurotic subjects.

Anxiety, autism (especially in children), various types of war neuroses, stuttering, motor disturbances, head or backaches and anorexia nervosa are often regarded as typical neurotic traits that can be traced to stress, but—as previously mentioned—it is virtually impossible to classify these diseases with precision, and almost any psychosomatic derangement may be looked upon as neurotic.

Neuroses

(See also our earlier stress monographs, p. xiii)

Simmel, E.: "War neuroses." In: Lorand, S., *Psychoanalysis Today*, pp. 227-248. New York: International University Press, 1944.

E85,797/44

A psychologic study of stress-induced war neuroses.

Jones, M.: "Physiological and psychological responses to stress in *neurotic* patients." *J. Ment. Sci.* **94**: 392-427 (1948) (43 refs.).

B41,022/48

Marcussen, R. M.: "Vascular headache experimentally induced by presentation of pertinent life experiences: modification of the course of vascular headache by alterations of situations and reactions." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 609-614. Baltimore: Williams & Wilkins, 1950.

B51,931/50

"It was possible to induce typical vascular headache in individuals subject to migraine during periods of accumulating tension and fatigue by introducing pertinent stress-producing situations." This was most readily accomplished by interfering with the subject's relentless pursuit of self-established goals.

Holmes, T. H., Wolff, H. G.: "Life situations, emotions and backache. In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 750-772. Baltimore: Williams & Wilkins, 1950.

B51,943/50

Increased generalized skeletal muscle hyperfunction and electric activity were a common response in patients exposed to a threatening life situation engendering conflict, anxiety, and other strong emotions. This response "was often provocative of pain in the back, neck and extremities."

Malmo, R. B., Shagass, C., Heslam, R. M.: "Blood pressure response to repeated brief stress in *psychoneurosis*: a study of adaptation." *Can. J. Psychol.* **5**: 167-179 (1951).

B68,568/51

Shands, H. C., Bartter, F. C.: "A statistical analysis of the 'ACTH test': changes in the eosinophil count in normal and in psychoneurotic subjects." *J. Clin. Endocrinol. Metab.* **12**: 178-183 (1952).

B66,982/52

The eosinopenia produced by a standard dose of ACTH is the same in *psychoneurotics* as in normal controls.

Malmo, R. B., Shagass, C.: "Studies of

blood pressure in psychiatric patients under stress." *Psychosom. Med.* **14**: 82-93 (1952).

C90,083/52

During stress, the rise in systolic blood pressure was greater in *psychoneurotics* than in controls.

Stenbäck, A.: "Headache and life stress. A psychosomatic study of headache." *Acta Psychiatr. Scand. [Suppl.]* **92**: 1-143 (1954).

B95,701/54

Monograph on stress-induced *headache*, with special reference to the G.A.S. (100 refs.).

Malmo, R. B., Smith, A. A.: "Forehead tension and motor irregularities in *psychoneurotic* patients under stress." *J. Pers.* **23**: 391-406 (1955).

C8,586/55

Ostfeld, A. M., Wolff, H. G.: "Arterenol (norepinephrine) and vascular headache of the migraine type." *Arch. Neurol. Psychiatry* **74**: 131-136 (1955).

J13,196/55

Migraine *headache*—a common manifestation of stress in certain individuals—can be promptly terminated by NEP, a pure vasoconstrictor. These findings represent "further evidence that the genesis of this pain is vasodilatation, granting that local tissue changes do lower the pain threshold so as to make vascular distention more painful."

Malmo, R. B.: "Experimental approach to symptom mechanisms in psychiatric patients." Symposium on Experimental Psychology, Montreal, November, 1955. *Psychiatr. Res. Rep. APA* **7**: 33-49 (1957).

C46,637/57

Discussion of the reticular systems, which have been called nonspecific projection systems, in connection with arousal, anxiety and especially stressors. "Under 'stress', *psychoneurotic* patients appeared to show a higher level of physiological reaction than controls, and that level of reaction seemed particularly high in patients suffering mainly from pathological anxiety" (32 refs.).

Sloane, R. B., Saffran, M., Cleghorn, R. A.: "Autonomic and adrenal responsiveness in psychiatric patients. Effect of methacholine and corticotropin." *Arch. Neurol. Psychiatry* **79**: 549-553 (1958).

C52,524/58

In anxious psychiatric patients, methacholine induces little eosinopenia but a definite lowering in corticoid excretion. *Psychoneurotic* subjects show a marked hypersecretion of ACTH, while schizophrenics exhibit

no evidence of significant changes in corticoid production (18 refs.).

Anthony, E. J.: "Effects of training under stress in children." In: Tanner, J. M., *Stress and Psychiatric Disorder*, pp. 34-46. Oxford: Blackwell Scientific, 1960. C90,494/60

Both stimulus deprivation and overstimulation may act as stressors in children and cause disorganization of their behavior. The author examines "some of the alleged stresses entailed in the transformation of an *autistic*, egocentric, pleasure-driven infant into a socially-conforming, considerate, and reality-orientated adult."

Curtis, G. C., Cleghorn, R. A., Sourkes, T. L.: "The relationship between affect and the excretion of adrenaline, noradrenaline, and 17-hydroxycorticosteroids." *J. Psychosom. Res.* 4: 176-184 (1960). C92,119/60

"In affective states of depression noradrenaline is excreted preferentially in comparison with adrenaline and corticoids, while corticoids are excreted preferentially in states of anxiety." These data "tend to suggest that affective states of differing quality are not non-specific in Selye's sense if one relates them to the balance between hormones rather than to a single hormone. This interpretation must remain tentative until confirmed by further study and until the problems of metabolism and renal clearance of these hormones are clarified."

Kusuma, M.: "Studies on the function of pituitary adrenocortical and autonomic nervous system in neurosis." *J. Jap. Soc. Intern. Med.* 52: 65 (1963). J11,872/63

In *neurotic* patients the plasma 17-OHCS level is increased.

Ryan, R. E.: "Tension headache." *Lancet* 84: 349-352 (1964). J25,142/64

Mackay, J.: "Migraine as a stress disorder." *Nurs. Times* 61: 84-86 (1965).

J24,459/65

Overview of the causes of migraine *headache*, with special emphasis on the way a nurse can help the patient to overcome it.

Robbins, S. D.: "Relation between insecurity and onset of *stuttering*." *Cereb. Palsy Rev.* 26: 7-14 (1965). J24,610/65

Howarth, E.: "Headache, personality, and stress." *Br. J. Psychiatry* 111: 1193-1197 (1965). G36,010/65

"Some type of environmental stress factor was found in 54 per cent of patients, and

those patients whose *headache* occurred in association with stress had a much better prognosis than those with personality disorder."

Müller-Hegemann, D.: "Untersuchungen zur Frage der Ätiopathogenese der Neurosen" (On the problem of the etiopathogenesis of neuroses). *Psychiatr. Neurol. Med. Psychol.* 17: 125-131 (1965). J23,879/65

In the development of *neuroses* "for the female patients the chief etiological factors were familial and erotic-sexual stresses, while for men the etiological factors were primarily found to be occupational or professional stresses."

Martin, M. J.: "Tension headache, a psychiatric study." *Headache* 6: 47-54 (1966). J23,051/66

Grinker, R. R.: "The psychosomatic aspects of anxiety." In: Spielberger, C. D., *Anxiety and Behavior*, pp. 129-142. New York and London: Academic Press, 1966.

E10,534/66

Review on the role of *anxiety* in psychosomatic disease.

Levi, L.: "Emotions and sympathoadrenomedullary activity." Proc. 4th World Congr. of Psychiatry, Madrid. *Int. Congr. Ser. No. 150*, pp. 2394-2398 (1966).

G62,229/66

In patients who suffered from intractable *stuttering* since childhood, the stress of having to speak in public greatly increased EP excretion.

Smith, B. H.: "Low back pain." *N.Y. State J. Med.* 67: 2449-2453 (1967).

J22,506/67

Low back pain may be due to lesions in the spinal column and also frequently to psychogenic stress.

Anthony, M., Hinterberger, H., Lance, J. W.: "Plasma serotonin in *migraine* and stress." *Arch. Neurol.* 16: 544-552 (1967). G46,944/67

Leanderson, R., Levi, L.: "A new approach to the experimental study of *stuttering* and stress." *Acta Otolaryngol.* (Stockh.) Supp. 224: 311-316 (1967). G47,174/67

Edgren, B., Leanderson, R., Levi, L.: "A research programme on *stuttering* and stress." *Acta Otolaryngol.* (Stockh.) Supp. 263: 113-118 (1970). G75,883/70

Grim, P. F.: "Relaxation therapies and neurosis: a central fatigue interpretation." *Psychosomatics* **13**: 363-370 (1972).

J15,998/72

General review of the relationship between stress, *neurosis* and *fatigue* (56 refs.).

Horowitz, M. J.: "Phase oriented treatment of stress response syndromes." *Am. J. Psychother.* **27**: 506-515 (1973).

J17,978/73

In concentration camp survivors, psychologic "stress response syndromes" may persist for decades. Their characteristics are classified and treatment schedules recommended. Even viewing "stress films" may induce persistent, *intrusive* and *repetitive thoughts* in normal subjects (23 refs.).

Steen, R. E.: "Stress disorders in childhood. Second of 3 parts." *J. Ir. Med. Assoc.* **66**: 78-84 (1973).

J19,613/73

Steen, R. E.: "Third of 3 parts." *J. Ir. Med. Assoc.* **66**: 101-107 (1973).

J19,614/73

Review on stress diseases in childhood with special emphasis on various types of neurosis. A group of functional nervous disorders in childhood with a cyclic tendency is described as the "*periodic syndrome*." It is often associated with *asthma*, *migraine headache*, *vomiting*, *diarrhea* or *fever*. Both a hereditary predisposition and a stress-induced trigger mechanism appear to be involved.

Henryk-Gutt, R., Rees, W. L.: "Psychological aspects of *migraine*." *J. Psychosom. Res.* **17**: 141-153 (1973).

J21,556/73

Rees, W. L.: "Personality and psycho-dynamic mechanisms in *migraine*." *Psychother. Psychosom.* **23**: 111-122 (1974).

J21,033/74

Studies on *migraine headaches* suggest that "among the precipitating factors are emotional reactions, changes in life situation; various psychosocial stresses, periods of overactivity and 'let down' periods. In addition to the operation of the above psychological factors, which constitute a psychosomatic sequence of events, there are also mood changes which may accompany an attack of *migraine* associated with alterations in energy, concentration, and ability to work."

Hoskins, L. M.: "Vascular and tension headaches." *Am. J. Nurs.* **74**: 846-851 (1974).

J21,630/74

Rozhdestvenskaia, G. G.: "Role of psychic trauma in the development of *stuttering* and

characteristics of the neurotic reactions during these states." *Zh. Nevropatol. Psichiatr.* **74** No. 4: 569-574 (1974) (Russian).

J21,265/74

Harper, J., Williams, S.: "Early environmental stress and infantile autism." *Med. J. Aust.* **1**: 341-346 (1974).

J12,191/74

Autistic children are particularly sensitive to various psychologic stressors; indeed, stress during early infancy may be a contributing factor to the development of autism.

Steger, E., Windhorst, C., Wilhelm, K.: "Kopfschmerzen als Folge von Erkrankungen und Funktionsstörungen im Kausystem" (Headache as a consequence of diseases and dysfunctions of the masticatory system). *Med. Klin.* **69**: 1044-1047 (1974).

H87,829/74

Review on *headache* as a consequence of dysfunction in the masticatory system, particularly malocclusion. *Bruxism* is frequently the manifestation of psychogenic stress (26 refs.).

Mecklenburg, R. S., Loriaux, D. L., Thompson, R. H., Andersen, A. E., Lipsett, M. B.: "Hypothalamic dysfunction in patients with *anorexia nervosa*." *Medicine* (Baltimore) **53**: 147-159 (1974).

J12,039/74

Clinical "observations suggest that psychic stress may have an adverse effect on the hypothalamus." In many cases, hypothalamic dysfunction appears to be an important factor in *anorexia nervosa* (98 refs.).

Tinbergen, N.: "Ethology and stress diseases." *Science* **185**: 20-27 (1974).

H87,100/74

Autism appears to be due predominantly to environmental factors, mainly behavior towards a child. The parents of autistic children are often under stress and "at least a large proportion of autists are victims of some kind of environmental stress, whose basic trouble is of an emotional nature." Hence, treatment should be based primarily upon restoration of emotional security. In this Nobel lecture the author points out that more than half a century ago and without any medical training, F. M. Alexander developed a technique for correcting various somatic and mental disorders by improvement of body posture and avoidance of faulty use of our neuromuscular system. "Misuse, with all its psychosomatic, or rather somatopsy-

chic, consequences must therefore be considered a result of modern living conditions of a culturally determined stress." There is considerable evidence that arthritis, respiratory troubles, asthma, hypertension, gastrointestinal disorders, various gynecologic derangements, sexual failures, migraine and depression (all diseases not caused by identifiable pathogens), as well as suicide, are often actually due to stress. These diseases can be corrected by proper ethologic counselling. "It is stress in the widest sense, the inadequacy of our adjustability, that will become perhaps the most important disruptive influence in our society."

Frankel, R. J., Jenkins, J. S.: "Hypothalamic-pituitary function in anorexia nervosa."

Acta Endocrinol. (Kbh.) 78: 209-221
(1975).
H96,571/75

Description of hormonal derangements in *anorexia nervosa*. The sulfation factor is deficient, and through a negative feedback, it could be responsible for the enhanced STH secretion.

Parantainen, J.: "Prolactin, levodopa, and migraine." *Lancet* February 22, 1975, p. 467.
H99,280/75

"Factors that deplete noradrenaline stores from nerve-endings (reserpine, tyramine, phenylethylamine, and stress) may elicit *migrainous attacks* in sensitive subjects, and in severe headache crisis, catecholamine depletion may be a secondary component of stress."

Schizophrenia and Related Psychoses

Generalities. Several studies indicate that stressful life situations can precipitate schizophrenia in genetically predisposed individuals. It has also been stated that the prognosis is better in subjects with a history of stress shortly before the onset of the illness. It is not clear why stress can precipitate either schizophrenia or manic-depressive states in predisposed individuals, but presumably this depends upon differences in endogenous and exogenous conditioning factors.

Schizophrenic patients appear to exhibit heightened activity during rest, but are less subject than normals to arousal by interpersonal stress situations. This has been ascribed to the fact that schizophrenics are less responsive to stressors because they are already under continuous stress as a consequence of their disease. Some investigators speak of a "hierarchy of stressors" and believe that schizophrenics tend to experience life-threatening stressors constantly and hence practically disregard current events.

→**Hormonal Changes.** The earliest investigations of a possible relationship between schizophrenia and the G.A.S. led to the conclusion that unlike normal subjects, schizophrenics fail to react to various stressors with the usual lymphocytopenia and increase in corticoid output, sometimes exhibiting even inverse responses. They also fail to show the normal circadian variations in adrenocortical activity. Some schizophrenics are allegedly resistant even to adrenal stimulation by ACTH injections. Since these patients are regarded as having been "broken as a result of the stresses of daily life, this basic failure of a fundamental stress-response mechanism is especially interesting." Subsequent investigations confirmed that psychotics do not react to stressful psychologic disturbances with the usual lymphocytopenia (or even hyperglycemia), but they are capable of normal responses to such stressors as EP, insulin or electroshock. However, other investigators maintained that schizophrenics are unable to respond even to physical stressors (EP, insulin) with the usual hematologic and biochemical reaction pattern and hence concluded that they suffer from a disturbance of the pituitary-adrenocortical mechanism itself.

The existence of such an inherent deficiency has not been uniformly confirmed; in

any event, it has been questioned whether the postulated adrenocortical deficiency is a primary trait rather than the consequence of metabolic disturbances induced by the psychosis.

In surveying the innumerable publications on this subject, it is difficult to draw any meaningful conclusions because most authors failed to differentiate between acute and chronic schizophrenia or even more or less closely related, yet manifestly different, psychiatric derangements. Furthermore, the techniques used for the determination of hormones were quite dissimilar and often not clearly specified. However, in surveying the pertinent data, the impression is gained that there is often some disturbance of adrenocortical function in schizophrenics, although this is rarely very prominent and is far too inconstant to be regarded as an essential link in the pathogenesis of the disease.

More recently, considerable attention was given to the fact that in psychotics the corticoid feedback mechanism appears to be defective, since dexamethasone only partially depresses their plasma cortisol levels. According to another study, dexamethasone eliminates significant circadian variations of the plasma corticoid but not of the FFA levels in schizophrenic and depressive patients. However, when administered for several weeks, it does lower cortisol, corticosterone and FFA concentrations.

Some investigators maintain that thyroid function is also disturbed in schizophrenics, but the evidence for this is still scanty.

→**Nonhormonal Metabolic Changes.** Several researchers have claimed that the plasma FFA and glucose concentrations in schizophrenics, though normal under resting conditions, fail to respond to insulin and other stressors as they do in controls.

Earlier claims of a derangement in hippuric acid excretion in catatonic schizophrenics apparently have never been verified.

Schizophrenia and Related Psychoses

(See also our earlier stress monographs, p. xiii)

Generalities. Malmo, R. B., Shagass, C.: "Behavioral and physiologic changes under stress after operations on the frontal lobes." *Arch. Neurol. Psychiatry* **63**: 113-124 (1950). B47,040/50

In schizophrenics the stress response following painful stimulation by means of the Hardy-Wolff thermal stimulator is diminished, as indicated by muscular tension, heart rate and GSR. These findings parallel the clinical observation of diminished pathologic anxiety.

Waldman, M.: "Personality factors and performance under stress in schizophrenics" (abstracted). *Am. Psychol.* **6**: 314 (1951). G85,801/51

Williams, M.: "Psychophysiological responsiveness to psychological stress in early

chronic schizophrenic reactions." *Psychosom. Med.* **15**: 456-462 (1953). J6,662/53

Early chronic schizophrenics show a heightened physiologic activity during rest and psychogenic stress, but they exhibit "less arousal in personal and interpersonal stress situations."

Delay, J., Lainé, B., Azima, H., Puech, J.: "Contribution à l'étude de l'homéostasie dans la schizophrénie et les autres psychoses. (Etude comparative des courbes de rétablissement de quelques éléments minéraux sanguins, du PH, et de la réserve alcaline avant et après stress)" (Contribution to the study of homeostasis in schizophrenia and other psychoses. [Comparative study on the recovery curves of certain blood minerals, of pH, and alkaline reserve, before and after stress]). *Encéphale* **42**: 385-406 (1953). J6,312/53

Review on the response of schizophrenics to stress (particularly electroshock), with

special reference to blood electrolyte and pH changes (54 refs.).

Binswanger, H., Meier, L.: "Psychiatrisch-klinische Untersuchungen zur Selyeschen Adaptationslehre. 2. Mitteilung" (Psychiatric-clinical studies of Selye's theory on adaptation. Second report). *Schweiz. Med. Wochenschr.* **83**: 25-30 (1953). J25,778/53

Study on the response of schizophrenics to therapy.

Fischer, R.: "Schizophrenie: ein regressiver Adaptationsprozess" (Schizophrenia: a regressive adaptation process). *Monatsschr. Psychiatr. Neurol.* **126**: 315-333 (1953).

B90,110/53

Attention is called to the many similarities in the metabolic changes characteristic of the G.A.S. and of schizophrenia.

Fischer, R.: "Schizophrenia: a regressive process of adaptation." *J. Nerv. Ment. Dis.* **119**: 492-497 (1954). B99,768/54

"Certain stages of the schizophrenic process seem to correspond with certain stages of the general adaptation syndrome."

Georgi, F., Rieder, H. P., Weber, R.: "Remarks on Fischer's article, 'Stress and the toxicity of schizophrenic serum.'" *Science* **120**: 504-506 (1954). B97,938/54

Fischer, R., Agnew, N.: "A hierarchy of stressors." *J. Ment. Sci.* **101**: 383-386 (1955). C7,812/55

Schizophrenic patients may be less responsive to stressors because they are already under stress. "The concept of a hierarchy of stressors is introduced. Such a concept explains the different adaptive answers elicited if an organism is threatened (1) by a life stressor of primary importance or (2) by 'alarming' stimuli directed toward less basic urges and needs. Stressors of primary importance may establish new adaptive responses, while stressors perceived as less important are practically disregarded if the organism is already under stress of similar importance and magnitude."

Tucker, W. I.: "Progesterone treatment in postpartum schizo-affective reactions." *J. Neuropsychiatry* **3**: 150-153 (1962).

G78,689/62

In postpartum women with schizo-affective derangements, progesterone therapy is sometimes useful.

Popoff, F. E.: "A numerical index for outpatient schizophrenics: its relation to stress

concepts." *Hawaii Med. J.* **25**: 323-327 (1966) J22,346/66

Discussion of the relationships between schizophrenia and the alarm reaction of the G.A.S.

Bernstein, A. S.: "Electrodermal base level, tonic arousal, and adaptation in chronic schizophrenics." *J. Abnorm. Psychol.* **72**: 221-232 (1967). J24,053/67

Steinberg, H. R., Durell, J.: "A stressful social situation as a precipitant of schizophrenic symptoms: an epidemiological study." *Br. J. Psychiatry* **114**: 1097-1105 (1968). G60,671/68

Statistical studies on military personnel suggest that stressful social situations can precipitate schizophrenia in predisposed individuals.

Guggenheim, F. G., Pollin, W., Stabenau, J. R., Mosher, L. R.: "Prevalence of physical illness in parents of identical twins discordant for schizophrenia." *Psychosom. Med.* **31**: 288-299 (1969) (36 refs.). J22,419/69

Laury, G., Meerloo, J. A. M.: "Adaptive disability: some precipitating factors in schizophrenic decompensation." *Psychiatr. Q.* **43**: 319-330 (1969). J22,111/69

Gaskin, L. Z., Minsker, E. I., Orlovskaia, D. D., Faivishevskii, V. A.: "The central mechanisms of the stress effect of schizophrenic patient serum." *Zh. Nevropatol. Psichiatr.* **70**: 576-581 (1970) (Russian). J21,600/70

Birley, J. L. T., Brown, G. W.: "Crises and life changes preceding the onset or relapse of acute schizophrenia: clinical aspects." In: Cancro, R., *Annual Review of the Schizophrenic Syndrome*, 1971, Vol. 1, pp. 293-304. New York: Brunner/Mazel, 1971. Also in: *Br. J. Psychiatry* **116**: 327-333 (1970). J16,330/71

Review of the evidence suggesting that stress can precipitate schizophrenia or manic-depressive states in genetically predisposed individuals.

Wallis, G. G.: "Stress as a predictor in schizophrenia." *Br. J. Psychiatry* **120**: 375-384 (1972). G91,718/72

A review of the literature and personal observations suggest that "in schizophrenia the outcome is better in cases where there is a history of stress shortly before the onset of the illness."

Rubin, L. S., Barry, T. J.: "The effect of the cold pressor test on pupillary reactivity of schizophrenics in remission." *Biol. Psychiatry* **5**: 181-197 (1972). J19,380/72

"All actively psychotic as well as remitted patients showed distinct, discrete varieties of disorganized, unintegrated autonomic responses to stress and during homeostatic recovery."

Jacobs, S.: "Stress and the schizophrenias." *Brit. Med. J.* June 17, 1972, p. 712.

J20,193/72

Under certain conditions, there exists an inverse ratio between severe stress and the favorable outcome of schizophrenias. This may be due to the fact that, generally speaking, the more 'reactive' the mental illness, the better its prognosis.

Payk, T. R.: "Beitrag zur Frage der Auslösung einer akuten Schizophrenie durch psychische Erschütterungen" (Induction of acute schizophrenia by psychic shock). *Schweiz. Arch. Neurol. Neurochir. Psychiatr.* **111**: 131-141 (1972) (52 refs.).

J19,889/72

Beck, J. C., Worthen, K.: "Precipitating stress, crisis theory, and hospitalization in schizophrenia and depression." *Arch. Gen. Psychiatry* **26**: 123-129 (1972).

J20,203/72

"Stress and the schizophrenias." *Brit. Med. J.* June 3, 1972, p. 550. H56,453/72

In patients with already established schizophrenias, exposure to stress actually ameliorates the prognosis.

Leff, J. P., Hirsch, S. R., Gaind, R., Rohde, P. D., Stevens, B. C.: "Life events and maintenance therapy in schizophrenic relapse." *Br. J. Psychiatry* **123**: 659-660 (1973). J21,581/73

Wray, S. R.: "Interaction of stress and psychotomimetic drug-action: possible implication for psychosis." *Psychopharmacologia* **30**: 263-268 (1973). J4,950/73

From experiments on rats concerning the effect of avoidance responses to electroshock upon the psychotomimetic drug cyclazocine, it is concluded that "environmental stress can play a crucial role in the genesis and underlying mechanism of schizophrenia."

Clancy, J., Crowe, R., Winokur, G., Morrison, J.: "The Iowa 500: precipitating factors in schizophrenia and primary affective disorder." *Compr. Psychiatry* **14**: 197-202 (1973). J20,519/73

Pollin, W.: "The pathogenesis of schizophrenia: possible relationships between genetic, biochemical, and experimental factors." In: Cancro, R., *Annual Review of the Schizophrenic Syndrome, 1973*, Vol. 3, pp. 38-57. New York: Brunner/Mazel, 1974. Also in: *Arch. Gen. Psychiatry* **27**: 29-37 (1972). J16,331/74

In genetically predisposed individuals, stress may act as an eliciting factor for the development of schizophrenia (36 refs.).

Brown, G. W.: "Life-events and the onset of depressive and schizophrenic conditions." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 164-188. Springfield, Ill.: Charles C Thomas, 1974.

E10,689/74

Discussion on the use of the SRE questionnaire in predicting the development of schizophrenia or depression (25 refs.).

Dewolfe, A. S., Youkilis, H. D.: "Stress and the word associations of process and reactive schizophrenics." *J. Clin. Psychol.* **30**: 151-153 (1974). J12,011/74

Snyder, S. H.: *Madness and the Brain*, p. 295. New York, St. Louis and San Francisco: McGraw-Hill, 1974. E10,648/74

Monograph on the mechanisms of mental illness, with special reference to schizophrenia. The so-called "acute schizophrenics" often appear fairly well adjusted until they suddenly deteriorate as a result of some stressful life event. "Acute schizophrenia does not seem to run in families. Perhaps it is some sort of reaction to extreme stress, which could conceivably afflict almost anyone exposed to an overwhelmingly traumatic situation. For example, it is well known that many soldiers, otherwise normal, become psychotic in the battlefield, but recover rapidly when removed from the battlefield and do not become mentally ill thereafter."

Jacobs, S. C., Prusoff, B. A., Paykel, E. S.: "Recent life events in schizophrenia and depression." *Psychol. Med.* **4**: 444-453 (1974). J21,683/74

Serban, G., Woloshin, G. W.: "Relationship between pre- and postmorbid psychological stress in schizophrenics." *Psychol. Rep.* **35**: 507-517 (1974). J20,522/74

Using the SSFIPD as a basis for measurement, a statistical study on several hundred schizophrenics demonstrated that they "encountered more problems in their youth, adolescence and their adult years compared

to the normals. Also, both chronic and acute schizophrenics showed a high degree of continuity between earlier and later types of difficulties."

Serban, G.: "Parental stress in the development of schizophrenic offspring." *Compr. Psychiatry* **16**: 23-36 (1975). J20,419/75

Using the SSFIPD on a large patient population, the author envisions "schizophrenia as a manifestational entity with possible multiple etiologies where one could identify a genetic etiology separately from the environmental one, the interaction between them producing the most stressful form of all."

Serban, G.: "Stress in schizophrenics and normals." *Br. J. Psychiatry* **126**: 397-407 (1975). J20,523/75

Using the SSFIPD in schizophrenics, the author found that "chronics experienced maximum stress, acutes an intermediate amount, while normals evidenced a minimum level of stress in their daily life. The highest stressors for acutes and chronics were interpersonal relationships and social performance.... The classical concept of low stress in chronics and favorable prognosis in the presence of precipitating factors were not supported by the present data."

→ACTH and Corticoids. Pincus, G., Elmadjian, F.: "The lymphocyte response to heat stress in normal and psychotic subjects." *J. Clin. Endocrinol.* **6**: 295-300 (1946). B1,243/46

Normal men exposed to temperatures of 40.5 to 44.0°C at 85 to 95 percent relative humidity exhibited marked "stress lymphocytopenia" which was attributed to increased corticoid secretion. "With the short-time stress employed here it is entirely likely that we are dealing with the first stage of the adaptation syndrome which involves adrenocortical hypersecretion as the result of the pituitary stimulation." By contrast, twenty out of twenty-one psychotic (mostly schizophrenic) subjects exhibited a rise in blood lymphocytes after heat exposure.

Hoagland, H., Elmadjian, F., Pincus, G.: "Stressful psychomotor performance and adrenal cortical function as indicated by the lymphocyte response." *J. Clin. Endocrinol.* **6**: 301-311 (1946). B1,244/46

The stress of operating the Hoagland-Werthessen pursuit meter causes marked lymphopenia and an increased 17-KS output

in normal subjects, but only irregular results in schizophrenics.

Pincus, G.: "Studies of the role of the adrenal cortex in the stress of human subjects." *Rec. Prog. Horm. Res.* **1**: 123-145 (1947). 98,426/47

Excellent review on the biochemical changes characteristic of the G.A.S. in man, with special reference to 17-KS excretion and blood counts under the influence of circadian variations, the stresses of daily life, operation of a Hoagland-Werthessen pursuit meter, flying and heat. The response of schizophrenics is abnormal in many respects, and the question is raised whether adrenal malfunction may play a pathogenic role in mental disease (20 refs.).

Hoagland, H.: "The human adrenal cortex in relation to stressful activities." *J. Aviat. Med.* **18**: 450-464 (1947). B4,975/47

Endocrine and metabolic studies revealed profound disturbances of adrenal cortical function in schizophrenic patients exposed to stress. This failure is particularly interesting "since psychotics are persons who have broken under the stresses of daily life and have developed bizarre and socially inadequate behavior patterns to cope with their environment." The author states that "in about half of our psychotic patients, we have found that the adrenal cortex simply does not respond to injections of purified pituitary adrenocorticotrophin."

Hoagland, H.: "Scientific capital and the dividends of applied science." *Dis. Nerv. Syst.* **8**: 3-8 (1947). J7,400/47

Popularized description of deranged adrenocortical hormone production in psychotic and psychoneurotic patients. Although their total twenty-four-hour output of corticoids is essentially normal, the pattern of metabolic excretion is deranged. "Since a characteristic of mental patients is that they have broken as a result of the stresses of life this basic failure of a fundamental stress response mechanism is especially interesting."

Pincus, G., Hoagland, H., Freeman, H., Elmadjian, F.: "Adrenal function in mental disease." *Rec. Prog. Horm. Res.* **4**: 291-322 (1949). B41,235/49

General review on the role of the adrenal in schizophrenia from which it is concluded that in some respects "the schizophrenic subject may be likened somewhat to an organism in the stage of resistance of the adaptation syndrome. He is capable of little or no

further reaction to an alarm. His adrenal cortex is performing to the limit of which it is capable. Our data generally conform to this notion except again for the ability for lymphocyte (and eosinophile) response and the necessity to explain the low neutral reducing lipide output which contrasts with the relatively high 17-ketosteroid excretion."

Parsons, E. H., Gildea, E. F., Ronzoni, E., Hulbert, S. Z.: "Comparative lymphocytic and biochemical responses of patients with schizophrenia and affective disorders to electroshock, insulin shock, and epinephrine." *Am. J. Psychiatry* **105**: 573-580 (1949).

B45,571/49

In psychotic (mainly schizophrenic) patients the blood lymphocyte response to EP, insulin and electroshock is essentially normal. However, the psychotics do not respond to apparently stressful psychologic disturbances with the usual lymphocytopenia and hyperglycemia.

Pincus, G.: "Adrenal cortex function in stress." *Ann. N. Y. Acad. Sci.* **50**: 635-645 (1949).

B37,780/49

General review on changes in adrenocortical function during stress and psychiatric illness. Special emphasis is placed upon blood sugar, lymphocytes, corticoids and 17-KS.

Pincus, G., Hoagland, H., Freeman, H., Elmadjian, F., Romanoff, L. P.: "A study of pituitary-adrenocortical function in normal and psychotic men." *Psychosom. Med.* **11**: 74-101 (1949).

B41,883/49

Extensive review on adrenocortical activity in psychotics with special reference to the G.A.S. These patients respond normally with the classic indicators of corticoid excess when treated with adrenocortical extracts, but the endogenous activation of the adrenal cortex by ACTH is deficient. "Evidence is thus provided of a species of hypoadrenalinism in the psychotic subjects" (44 refs.).

Friedlander, J. H., Perrault, R., Turner, W. J., Gottfried, S. P.: "Adrenocortical response to physiologic stress in schizophrenia." *Psychosom. Med.* **12**: 86-88 (1950).

B65,978/50

In schizophrenic patients the response to stressors (EP, insulin) was rather inconsistent when blood counts, serum ascorbic acid, uric acid excretion, and plasma corticoids were employed as indicators. There appeared to be some derangement in adrenocortical function during schizophrenia, but its nature could not be clearly characterized.

Hoagland, H., Callaway, E., Elmadjian, F., Pincus, G.: "Adrenal cortical responsiveness of psychotic patients in relation to electroshock." *Psychosom. Med.* **12**: 73-77 (1950).

B49,303/50

Pincus, G., Hoagland, H.: "Adrenal cortical responses to stress in normal men and in those with personality disorders. Part I. Some stress responses in normal and psychotic subjects." *Am. J. Psychiatry* **106**: 641-650 (1950).

B51,602/50

Pincus, G., Hoagland, H.: "Part II. Analysis of the pituitary-adrenal mechanism in man." *Am. J. Psychiatry* **106**: 651-659 (1950).

B51,603/50

Normal and schizophrenic men were subjected to psychogenic stressors (target ball frustration test, operation of a pursuit meter), after which the following indices of stress were determined: urinary sodium, potassium, uric acid, 17-KS and neutral reducing lipids (corticoids), as well as circulating lymphocytes and eosinophils. There was "a highly significant failure of normal adrenal stress responses in the schizophrenic population." The adrenal response to ACTH was likewise diminished and could not be corrected by high protein diets or vitamins. By contrast, psychoneurotics responded normally to ACTH. These findings are regarded as important in interpreting the pathogenesis of schizophrenia (35 refs.).

Cleghorn, R. A., Graham, B. F.: "Studies of adrenal cortical activity in psychoneurotic subjects." *Am. J. Psychiatry* **106**: 668-672 (1950).

B56,026/50

In schizophrenic and psychoneurotic patients, adrenocortical activity (as revealed by various indices) appears to be proportional to anxiety and tension.

Faurbye, A., Vestergaard, P., Kobbernagel, F., Nielsen, A.: "Adrenal cortical function in chronic schizophrenia (Stress, adrenaline-test, ACTH-test)." *Acta Endocrinol. (Kbh.)* **8**: 215-246 (1951).

B63,996/51

As indicated by various stress tests (EP or fever vaccine injections), "there is a slight relative adrenal cortex insufficiency in chronic schizophrenia, but it is uncertain whether this insufficiency is an original constitutional trait which facilitates the manifestation of schizophrenia, or whether it arises simultaneously with the disease as the result of a provoking stress, secondary to the psychosis caused by inactivity, or as part of

a complex metabolic disturbance which is the cause of the psychosis or accompanies it."

Stein, M., Ronzoni, E., Gildea, E. F.: "Physiological responses to heat stress and ACTH of normal and schizophrenic subjects." *Am. J. Psychiatry* **108**: 450-455 (1951). B27,764/51

In schizophrenics the blood eosinophils and lymphocytes, as well as the uric acid/creatinine ratios, showed no obvious anomalies, either under basal conditions or after exposure to "heat stress." The reactions to ACTH were also normal.

Pechstein, H.: "Reaction to stress in schizophrenia." *Psychiatr. Q.* **26**: 425-432 (1952). B84,622/52

Schizophrenics show a normal eosinopenia after operative stressors such as lobotomy. "The immediate rise, followed by a sharp drop, in eosinophils, suggestive of a marked output of 11 and 11,17-corticosteroids, is identical to the usual shock and counter-shock phase of the alarm reaction in the adaptation syndrome as described by Selye. Therefore, any alteration possibly present in the schizophrenic's adaptation reaction is not one which would interfere with the immediate response to acute stress situations."

Lehmann, H. E.: "Stress dynamics in psychiatric perspective." *Psychiatry* **15**: 387-393 (1952). B76,849/52

Review on the relationship between the G.A.S. and various psychiatric diseases, with special reference to the role of corticoids.

Altschule, M. D.: *Bodily Physiology in Mental and Emotional Disorders*, p. 288. New York: Grune & Stratton, 1953.

B79,943/53

Monograph on the somatic repercussions of mental disorders, with a very brief section on stress and the hypothalamus-pituitary-adrenocortical system.

Hoagland, H., Pincus, G., Elmadjian, F., Romanoff, L., Freeman, H., Hope, J., Ballan, J., Berkeley, A., Carlo, J.: "Study of adrenocortical physiology in normal and schizophrenic men." *Arch. Neurol. Psychiatry* **69**: 470-485 (1953). B88,375/53

Stevenson, J. A. F., Metcalfe, E. V., Hobbs, G. E.: "Eosinophile response in schizophrenic patients." *Arch. Neurol. Psychiatry* **70**: 802-812 (1953). C3,534/53

Lingjaerde, O.: "Beiträge zur somatolo-

gischen Schizophrenieforschung. Bedeutung des Kohlenhydratdefizits" (Somatologic studies in schizophrenia. Importance of carbohydrate deficits). *Arch. Psychiatr. Z. Neurol.* **191**: 114-133 (1953). B90,122/53

Metabolic investigations, particularly on urinary steroids and the eosinopenic response to stressors, lead to the conclusion that "acute schizophrenia in its active phase must be regarded as an expression of disturbed homeostasis, an alarm reaction with its efforts for readaptation in the form of the 'chronic inactive defect schizophrenia' that is a disease of adaptation in Selye's sense."

Hoagland, H.: "Panel discussion of evidences for the nonpsychogenic origins of psychoses. I. Some considerations of the role of the adrenal cortex in the origin of the psychoses." *J. Nerv. Ment. Dis.* **119**: 75-76 (1954). B95,212/54

Patzig, B., Schmitz, W. P.: "Besteht bei schizophrenen Psychosen eine besondere Aktivität im Hypophysen-Nebennierenrinden-System im Sinne eines Dauer-Stress? (Ergebnisse von Uropepsin-Untersuchungen)" (Is there special activity in the pituitary-adrenocortical system of schizophrenics, in the sense of permanent stress? [Results of uropepsin studies]). *Nervenarzt*, **25**: 104-111 (1954). D82,296/54

Freeman, H., Pincus, G., Elmadjian, F., Romanoff, L. P.: "Adrenal responsivity in aged psychotic patients." *Geriatrics* **10**: 72-77 (1955). C4,830/55

Young and old schizophrenics show essentially similar anomalies in their response to ACTH.

Bliss, E. L., Migeon, C. J., Branch, C. H., Samuels, L. T.: "Adrenocortical function in schizophrenia." *Am. J. Psychiatry* **112**: 358-365 (1955). C12,236/55

The adrenocortical and pituitary-adrenocortical reactivity of chronic schizophrenic and normal subjects was equivalent after treatment with ACTH, bacterial pyrogen or insulin (46 refs.).

Hoagland, H., Pincus, G.: "Adrenocortical responsivity to stress and ACTH." *Am. J. Psychiatry* **112**: 748 (1956). D93,394/56

Freeman, S., Steed, W. D., Hoegemeier, H. W., Wheeler, J. X., Savage, L. W., Wadeson, R. W.: "Plasma corticoids in psychiatric illness." *J. Clin. Exp. Psychopathol.* **17**: 263-275 (1956). J11,375/56

In patients with acute mental illness (mostly schizophrenics) the cortisol fraction of plasma corticoids was usually subnormal. "The plasma corticoid response to ACTH infusion was less than that observed in healthy subjects. The plasma corticoid elevation in response to cortisone ingestion was less than normal in 11 of 15 patients tested. The diurnal variation in the concentration of plasma corticoids differed in the patient and control groups. Plasma corticoid data obtained on these patients provide direct evidence of altered adrenocortical function in patients with acute mental illness."

Board, F., Persky, H., Hamburg, D. A.: "Psychological stress and endocrine functions. Blood levels of adrenocortical and thyroid hormones in acutely disturbed patients." *Psychosom. Med.* **18**: 324-333 (1956).

C20,942/56

Gunne, L.-M., Gemzell, C. A.: "Adrenocortical and thyroid function in periodic catatonia." *Acta Psychiatr. Scand.* **31**: 357-378 (1956).

C29,993/56

Tui, C., Riley, E., Columbus, P., Orr, A.: "17-Hydroxycorticosteroid levels in the peripheral blood of schizophrenic patients. A preliminary study." *J. Clin. Exp. Psychopathol.* **17**: 276-282 (1956).

J11,386/56

Smith, F. L., Simon, A., Lingoes, J. C.: "Excretion of urinary corticoids in mental patients." *J. Nerv. Ment. Dis.* **124**: 381-387 (1956).

C58,591/56

The variability of corticoid excretion in both acute and chronic schizophrenics is greater than normal but can be reduced by electroshock treatment.

Lamson, E. T., Elmadjian, F., Hope, J. M., Pincus, G., Jorjorian, D.: "Aldosterone excretion of normal, schizophrenic and psychoneurotic subjects." *J. Clin. Endocrinol. Metab.* **16**: 954 (1956).

C14,904/56

In schizophrenics, aldosterone excretion is somewhat diminished on the average, but individual variations are very great. Insulin shock treatment causes a rise in aldosterone elimination.

Eiduson, S., Brill, N. Q., Crumpton, E.: "Adrenocortical activity in psychiatric disorders." *Arch. Gen. Psychiatry* **5**: 227-233 (1961).

E56,433/61

Chronic schizophrenics tend to react with a decreased corticoid response to various external stressors but not to ACTH. Apparently, their adrenal reactivity is normal, but

they do not perceive usually stressful experiences as such, especially when they are withdrawn (19 refs.).

Yamashita, I., Shinohara, S., Nakazawa, A., Yoshimura, Y., Ito, K., Takasugi, K.: "Endocrinological study of atypical psychoses." *Folia Psychiatr. Neurol. Jap.* **16**: 293-299 (1962).

D69,731/62

Hatotani, N., Ishida, C., Yura, R., Maeda, M., Kato, Y., Nomura, J., Wakao, T., Takekoshi, A., Yoshimoto, S., Yoshimoto, K., Hiramoto, K.: "Psycho-physiological studies of atypical psychoses—endocrinological aspect of periodic psychoses." *Folia Psychiatr. Neurol. Jap.* **16**: 248-292 (1962).

D69,729/62

Urinary hormone determinations in various atypical psychoses revealed disturbances of "hepato-cerebral homeostasis." This may lead to what has been called the "endocrine psychosyndrome" (65 refs.).

Suwa, N., Yamashita, I., Owada, H., Shinohara, S., Nakazawa, A.: "Psychic state and adrenocortical function: a psychophysiological study of emotion." *J. Nerv. Ment. Dis.* **134**: 268-276 (1962).

D23,490/62

In psychoneurotics, fluctuations in blood eosinophils, urinary 17-OHCS, and uropepsin were usually synchronous with changes in emotional state. In schizophrenics and manic-depressives, these parameters varied considerably (32 refs.).

Kobayashi, J.: "Endocrine studies on the urinary 17-ketosteroids and 17-hydroxycorticosteroids in schizophrenia. II. Values in schizophrenics." *J. Okayama Med. Ass.* **74**: 8-9, 659-678 (1962) (Japanese).

G14,818/62

Pekkarinen, A., Rinne, U., Saarimaa, H., Sourander, C.: "The determination of the pituitary corticotrophin reserve by a two-day metyrapone (Metopirone) test in psychiatric patients." *Acta Physiol. Scand.* **59** Supp. 213: 122-123 (1963).

E30,222/63

Poirier, L. J., Richer, C. L., Berthiaume, M., Gravel, G., Beaulnes, R., Martel, P.: "Adrenocortical and autonomic reactivity in schizophrenia." *Arch. Gen. Psychiatry* **8**: 605-613 (1963).

D67,989/63

Hodges, J. R., Jones, M., Elithorn, A., Bridges, P.: "Effect of electroconvulsive therapy on plasma cortisol-levels." *Nature* **204**: 754-756 (1964).

F26,097/64

Lingjaerde, P. S.: "Plasma hydrocortisone

in mental diseases." *Br. J. Psychiatry* **110**: 423-432 (1964). G12,998/64

Cardon, P. V. Jr., Mueller, P. S.: "Effects of norepinephrine on the blood pressure, glucose, and free fatty acids of normal and schizophrenic men, with reference to heart rate and to indices of physical fitness and of thyroid and adrenal cortical function." *J. Psychiatr. Res.* **2**: 11-23 (1964).

G10,031/64

Farstad, M., Skaug, O. E.: "Blood glucose (BG), plasma free fatty acids (FFA) and 17-hydroxycorticosteroids (17-OHCS) during insulin stress in psychiatric patients." *Scand. J. Clin. Lab. Invest.* **17** Supp. 86: 140 (1965). F63,855/65

Psychiatric patients (not otherwise identified) show an abnormal adrenal reactivity to "insulin stress."

Cortez, P. E., Durazo, Q. F., Guillén, M. A.: "Endocrine changes observed in patients treated with psychotropic drugs." *Int. Congr. Ser. No. 99*, E177. Amsterdam: Excerpta Medica, 1965. F55,354/65

Brief abstract on the effect of various psychotropic drugs upon urinary corticoids and the serum content of protein-bound iodine, estrogens and electrolytes. [The abstract does not lend itself to critical evaluation (H.S.).]

Meng, H. C., Kaley, J. S.: "Effects of multiple infusions of a fat emulsion on blood coagulation, liver function and urinary excretion of steroids in schizophrenic patients." *Am. J. Clin. Nutr.* **16**: 156-164 (1965).

G24,032/65

Farstad, M., Skaug, O. E.: "Interrelationship between blood sugar, plasma free fatty acids and plasma 17-hydroxycorticosteroids in mental patients before and after insulin administration." *Scand. J. Clin. Lab. Invest.* **18**: 657-665 (1966). F76,544/66

Blood sugar, FFA and 17-OHCS determinations in schizophrenics "suggested that the prolonged insulin-induced hypoglycemia in mental patients may be due to reduced insulin antagonism, resulting from diminished insulin-stimulated adrenal activity."

Stokes, P. E.: "Pituitary suppression in psychiatric patients" (abstracted). *Program 48th Meeting Endocr. Soc.*, No. 150, Chicago, 1966. F66,648/66

In tests of psychiatric patients, plasma cortisol levels were not suppressed by dexamethasone in twelve cases; in three cases, suppression was incomplete.

Sachar, E. J., Harmatz, J., Bergen, H., Cohler, J.: "Corticosteroid responses to milieu therapy of chronic schizophrenics" *Arch. Gen. Psychiatry* **15**: 310-319 (1966). G41,432/66

Matsumoto, K., Berlet, H. H., Bull, C., Himwich, H. E.: "Excretion of 17-hydroxycorticosteroids and 17-ketosteroids in relation to schizophrenic symptoms." *J. Psychiatr. Res.* **4**: 1-12 (1966). G42,035/66

In schizophrenics the mean urinary excretion of 17-KS and 17-OHCS was above normal, especially in withdrawn catatonic patients showing signs of intense anxiety and tension (29 refs.).

Kistler, C. R., Besch, N. F., Sickle, G. R., van, McCluer, R. H., Morris, H., Jackson, D. B.: "Epinephrine and insulin effects. II. ACTH and cortisol." *Arch. Gen. Psychiatry* **14**: 287-290 (1966). G37,554/66

In psychotics (not otherwise characterized), EP and insulin did not increase plasma ACTH levels. EP caused no significant rise in plasma cortisol either, whereas insulin hypoglycemia was effective in this respect in both normal and psychotic subjects.

Coppen, A., Julian, T., Fry, D. E., Marks, V.: "Body build and urinary steroid excretion in mental illness." *Br. J. Psychiatry* **113**: 269-275 (1967). G45,109/67

Elithorn, A., Bridges, P. K., Hodges, J. R., Jones, M. T.: "Adrenocortical responsiveness during courses of electro-convulsive therapy." *Br. J. Psychiatry* **115**: 575-580 (1969). G65,995/69

In patients with schizophrenia the plasma cortisol rise after electroconvulsive therapy is essentially normal, but in depressives it is often decreased.

Ellman, G. L., Blacker, K. H.: "Diurnal patterns of 17-hydroxy-corticosteroid excretion in psychiatric illness." *Dis. Nerv. Syst.* **30**: 683-688 (1969). G71,182/69

Yamashita, I., Moroji, T., Yamazaki, K., Kato, H., Sakashita, A., Onodera, I., Ito, K., Okada, F., Saito, Y., Tamakoshi, M., Suwa, N.: "Neuroendocrinological studies in mental disorders and psychotropic drugs. Part I. On the circadian rhythm of the plasma adrenocortical hormone in mental patients and methamphetamine- and chlorpromazine-

treated animals." *Folia Psychiatr. Neurol. Jap.* **23**: 143-158 (1969). G72,651/69

Patients in an acute stage of schizophrenia showed marked disturbances in the circadian rhythm of plasma 17-OHCS. This was not so after recovery, nor in patients with depression, except in very severe cases. Some changes in circadian rhythm were noted occasionally in cases of general paresis and in epileptics.

Sachar, E. J., Kanter, S. S., Buie, D., Engle, R., Mehlman, R.: "Psychoendocrinology of ego disintegration." *Am. J. Psychiatry* **126**: 1067-1078 (1970). J11,480/70

In acute ego disorganization which initiated a schizophrenic episode, "corticosteroid excretion during this phase reached levels 250 percent of subsequent recovery values, far exceeding the elevations seen in normals under stress."

Franzén, G.: "Serum cortisol in chronic schizophrenia. A study of the adrenocortical response to intravenously administered insulin and ACTH." *Acta Psychiatr. Scand.* **47**: 82-91 (1971). G85,242/71

Franzén, G.: "Serum cortisol in chronic schizophrenia. Changes in the response to intravenously administered insulin and ACTH on withdrawal of drugs." *Acta Psychiatr. Scand.* **47**: 150-162 (1971). G86,662/71

Franzén, G.: "The effect of intravenously administered synthetic lysine-vasopressin (L.V.P.) on serum cortisol in chronic schizophrenic patients." *J. Psychosom. Res.* **15**: 361-365 (1971). G85,725/71

The reduced reactivity of the pituitary-adrenal system in schizophrenia reported earlier was not confirmed when lysine-vasopressin was used as a stressor.

Franzén, G.: "Serum cortisol in chronic schizophrenia. A study of the diurnal rhythm in relation to psychiatric mental status." *J. Psychosom. Res.* **15**: 367-373 (1971). G85,726/71

Franzén, G.: "Serum Cortisol in Chronic Schizophrenia and its Relation to Psychiatric Mental Status," p. 40. Thesis, University of Lund, Sweden. 1971. G86,702/71

Doctoral thesis reviewing the effects of diurnal variations, insulin, ACTH, lysine-vasopressin and psychogenic stress upon the serum cortisol of schizophrenics (about 55 refs.).

Franzén, G.: "Serum cortisol in chronic

schizophrenia. Changes in the diurnal rhythm and psychiatric mental status on withdrawal of drugs." *Psychiatr. Clin. (Basel)* **4**: 237-246 (1971). G86,703/71

Franzén, G.: "Plasma free fatty acids, serum cortisol and circulatory response to insulin in acute schizophrenic men." *Psychiatr. Clin. (Basel)* **5**: 201-208 (1972). G92,339/72

The plasma FFA elevations caused by insulin were increased in schizophrenics, but there was no clear parallelism between these results and plasma cortisol. Schizophrenics showed a positive correlation between FFA and blood glucose values in response to insulin whereas normal subjects exhibited a negative correlation, suggesting defective homeostasis in schizophrenia.

Saldanha, V. F., Havard, C. W. H., Bird, R., Gardner, R.: "The effect of chlorpromazine on pituitary function." *Clin. Endocrinol. (Oxf.)* **1**: 173-180 (1972). H56,815/72

In schizophrenics the circadian plasma corticoid level remained normal following treatment with chlorpromazine. The rise in plasma corticoids after insulin hypoglycemia or ACTH was only insignificantly diminished, and chlorpromazine caused no significant drop in plasma STH.

Silbergeld, S., Noble, E. P.: "Corticosteroids in psychiatric patients: subacute and diurnal effects on free fatty acid and catecholamine metabolism." *J. Psychiatr. Res.* **10**: 59-71 (1973). J4,364/73

In a group of psychotics (including depressives, schizophrenics and anxiety-types), "dexamethasone achieved a significant lowering in mean plasma levels of cortisol, corticosterone and FFA after treatment for one, 22, and 15 days, respectively. Significant differences were not obtained in NE excretion between the two experimental groups, but significant increases in mean daily urinary NE/E ratios were obtained after treatment for 7, 14, 24 and 28 days. Diurnal results from the final 24-hr periods (days 28 and 29) suggest that dexamethasone significantly lowered the mean plasma level of cortisol throughout the day. However, the mean levels of corticosterone and FFA were significantly reduced at the 7 a.m. interval only. Dexamethasone did eliminate significant diurnal variation in the mean levels of these corticosteroids, but did not do so for FFA" (45 refs.).

Carroll, B. J.: "Limbic system-adrenal cortex regulation in depression and schizophrenia." *Psychosom. Med.* (In press).

J20,864/

In depressed patients, unlike in schizophrenics, the free cortisol excretion and the cortisol content of the CSF are high and do not respond to dexamethasone suppression. Thus, "a psychoendocrine distinction can be made between primary depressive illness and secondary depressive symptomatology, and psychological defense breakdown is not related to these neuroendocrine observations."

→**Catecholamines.** Funkenstein, D. H.: "The interrelationship of acute emergency reactions during stress and affective disorder." *Am. J. Psychiatry* **112**: 930-932 (1956).

C16,888/56

Purely speculative outline of a theory which postulates that "angry paranoid patients, who show a deeper level of regression than depressed patients, have a physiological pattern (norepinephrine) characteristic of an earlier period in life than the physiological pattern shown by depressed patients (epinephrine)."

Sachar, E. J., Mason, J. W., Kolmer, H. S. Jr., Artiss, K. L.: "Psychoendocrine aspects of acute schizophrenic reactions." *Psychosom. Med.* **25**: 510-537 (1963). E35,406/63

"Corticosteroids and epinephrine excretion may not be influenced by the type of psychological defenses employed by the patient in protecting himself from anxiety and depression, but rather by the effectiveness of the defenses, whether they be psychotic or neurotic."

Lovegrove, T. D., Metcalfe, E. V., Hobbs, G. E., Stevenson, J. A. F.: "The urinary excretion of adrenaline, noradrenaline, and 17-hydroxycorticosteroids in mental illness." *Can. Psychiatr. Assoc. J.* **10**: 170-179 (1965). G35,322/65

Catecholamine and 17-OHCS determinations were made in normals, acute and chronic schizophrenics, nonschizophrenic psychotics, psychoneurotics, and a miscellaneous group composed primarily of patients with personality disorders. "Although no significant differences in hormone excretion were observed among the groups studied, other than increased excretion of free corticoids in the acute schizophrenics, the longitudinal studies in several groups suggest significant correlations may occur between changes in clinical condition and/or emotional state and

the excretion of some of the hormones measured."

Shiotsuka, R. N., Reinberg, A., Ungar, F., Sonstroem, R., Sothern, R. B., Nelson, W., Kahane, Z., Vestergaard, P. B., Esser, A. H., Fröberg, J., Levi, L., Kline, N. S., Halberg, F.: "Circadian variation of norepinephrine ratio (NER) in health, sleep deprivation and schizophrenia." *Physiologist* **14**: 230 (1971).

H41,969/71

Snyder, S. H.: "Catecholamines as mediators of drug effects in schizophrenia." In: Schmitt, F. O. and Worden, F. G., *The Neurosciences. Third Study Program*, pp. 721-732. Cambridge, Mass. and London: MIT Press, 1974.

J17,227/74

Ban, T. A.: "Pharmacotherapy of schizophrenia: facts, speculations, hypotheses and theories." *Psychosomatics* **15**: 178-187 (1974).

H96,180/74

Review of the literature and personal observations on biochemical changes, for and against "the view that schizophrenia is the outcome of stress induced anxiety and a failure of metabolizing the increased amount of catecholamines which results in highly toxic, mescaline-like compounds."

→**Other Hormones.** Nuremberg, T., Brambilla, F.: "Aspetti endocrini della schizofrenia" (Endocrinological aspects of schizophrenia). *Folia Endocrinol.* (Roma) **17**: 312-337 (1964). F45,785/64

Review and personal observations on 17-KS, 17-OHCS, and sex hormone excretion in schizophrenia (136 refs.).

Libow, L. S., Durell, J.: "Clinical studies on the relationship between psychosis and the regulation of thyroid gland activity. I. Periodic psychosis with coupled change in thyroid function. Report of a case." *Psychosom. Med.* **27**: 369-376 (1965) (31 refs.). G31,899/65

Dewhurst, K. E., Kabir, D. J. el. Exley, D., Harris, G. W., Mandelbrote, B. M.: "Blood-levels of thyrotrophic hormone, protein-bound iodine, and cortisol in schizophrenia and affective states." *Lancet* November 30, 1968, pp. 1160-1162. H4,563/68

Soulairac, A., Schaub, C., Franchimont, P.: "Action de la chlorpromazine sur le fonctionnement de l'appareil hypothalamo-hypophysaire chez l'homme" (Effects of chlorpromazine on hypothalamo-hypophyseal

function in man). *Thérapie* 25: 1083-1088 (1970). G80,745/70

In normal subjects, cholinergic stimulation causes a parallel increase in serum STH and plasma cortisol, with a peak after twenty to thirty minutes. In patients treated with chlorpromazine, these responses are dissociated: the STH increase is normal, but corticotropin stimulation is inhibited.

Brambilla, F., Guerrini, A., Raggi, F., Ricciardi, F.: "Psychoendocrine investigation in schizophrenia: relationship between pituitary-gonadal function and behavior." *Dis. Nerv. Syst.* 35: 362-367 (1974).

J15,213/74

Matthysse, S.: "Schizophrenia: relationships to dopamine transmission, motor control, and feature extraction." In: Schmitt, F. O. and Worden, F. G., *The Neurosciences*.

• *Third Study Program*, pp. 733-737. Cambridge, Mass. and London: MIT Press, 1974.

J17,228/74

Swanson, D. W., Hanson, N. P., Rosenbaum, A. H., Swenson, W. M.: "Correlation of psychiatric factors and pituitary responsiveness: a negative report." *J. Nerv. Ment. Dis.* 158: 100-103 (1974).

J10,817/74

In both normal and schizophrenic patients, electroshock often caused a rapid increase in plasma FSH and LH, but this was inconstant and apparently not influenced by the mental disease.

→**Nonhormonal Metabolic Changes.** Persky, H., Gamm, S. R., Grinker, R. R.: "Correlation between fluctuation of free anxiety and quantity of hippuric acid excretion." *Psychosom. Med.* 14: 34-40 (1952).

B54,166/52

In patients with manifest anxiety and in individuals exposed to the mild stressors of daily life, hippuric acid excretion increases, but in catatonic schizophrenics it is subnormal.

Osmond, H., Smythies, J.: "Schizophrenia: a new approach." *J. Ment. Sci.* 98: 309-315 (1952). J19,372/52

"The close clinical connections between schizophrenia, anxiety states and stress have been known for a long time, and the process involved may be that, in certain people, when the adrenals are overworked," methylation becomes disturbed and highly toxic substances are produced. Additional evidence in support of this view is presented.

Mueller, P. S.: "Plasma free fatty acid response to insulin in schizophrenia." *Arch. Gen. Psychiatry* 7: 140-146 (1962).

J11,260/62

Mueller, P. S.: "Plasma free fatty acid concentrations (FFA) in chronic schizophrenia before and after insulin stimulation." *J. Psychiatr. Res.* 1: 106-115 (1963).

E37,699/63

Although initial plasma FFA concentrations were identical in normal and schizophrenic subjects, insulin caused a fall in the FFA levels of normals, while in schizophrenics the levels either showed no change or in some cases rose.

Orlovskaia, D. D., Gaskin, L. Z., Davydova, I. B., Minsker, E. I.: "Some characteristics of the biologic (stress) effect of the serum of patients with various forms of schizophrenia." *Zh. Nevropatol. Psichiatr.* 64: 1396-1407 (1964) (Russian).

E76,816/64

The serum of certain schizophrenics produces definite G.A.S.-like symptoms when injected into rabbits.

Sickle, G. R. van, McCluer, R. H., Kistler, C. R., Besch, N. F.: "Epinephrine and insulin effects. I. Glucose and plasma free fatty acid." *Arch. Gen. Psychiatry* 14: 284-286 (1966).

G37,553/66

Schizophrenics differ from normal people in both their FFA and glucose response to insulin.

Orlovskaia, D. D., Gaskin, L. Z., Minsker, E. I.: "Biological action of blood serum of schizophrenic patients in relation to stress." *Nature* 217: 473-475 (1968). F93,892/68

Pfeiffer, C. C., Iliev, V., Nichols, R. E., Sugerman, A. A.: "The serum urate level reflects degree of stress." *J. Clin. Pharmacol.* 9: 384-392 (1969).

H18,436/69

"The level of serum urate may reflect the degree of stress in the schizophrenic since serum urate usually decreases with antipsychotic therapy."

Polis, B. D., Polis, E., Cani, J. de, Schwarz, H. P., Dreisbach, L.: "Effect of physical and psychic stress on phosphatidyl glycerol and related phospholipids." *Biochem. Med.* 2: 286-312 (1969).

G65,013/69

In rats exposed to ionizing radiation or "acceleration stress," the plasma concentration of phosphatidylglycerol was consistently increased. "Extension of the studies to humans stressed by acceleration to grayout,

sleep deprivation, schizophrenia, combat, etc., revealed that all stresses were accompanied by significant increments in plasma phosphatidyl glycerol." In rats, hypophysectomy prevented the increase in phosphatidyl-

glycerol induced by acceleration stress, but a rise in the brain level of this compound was observed even in the absence of the pituitary.

Manic-depressive Disease

It is especially noteworthy that the first episode of depression or mania is often precipitated by environmental stressors.

In general, the corticoid and catecholamine levels of plasma and urine are reported to be high in manic-depressive patients, particularly during acute exacerbations of the disease, and return toward normal under the influence of treatment with appropriate psychotropic drugs. Allegedly, excretion of 17-KGS is significantly correlated with the clinical symptomatology of depressive patients.

Most investigators concur that urinary 17-OHCS excretion increases, particularly during exacerbations of both the manic and depressive phases. This finding would agree with the view that the hormonal changes are secondary to the stress created by the disease and are not factors of pathogenic significance. However, certain observations on patients with Cushing's syndrome or those treated with ACTH and glucocorticoids "support the possibility of a primary brain state alteration which results in both a depressive affect associated with loss of ego-defense strength and in stimulation of the hypothalamic-pituitary-adrenal axis."

Some investigators especially point out that the changes in plasma 11-OHCS connected with depressive or manic illness are surprisingly mild, considering the mental anguish felt by many of these patients. It has even been claimed that in about 30 percent of depressives, the corticoid levels are lower before than after recovery, because the abnormal mental mechanisms in this disease "reduce the inner experience of stress." Only in stages of acute psychotic turmoil, associated with disruption of ego defenses, did the corticoid levels rise. Patients in stages of organized chronic or stable depression showed no evidence of adrenocortical hyperactivity. However, the relevant literature, though extremely voluminous, is most contradictory, and many investigators claim to have found consistently elevated plasma and/or urinary corticoid levels during depression.

The circadian rhythm of corticoid production has also been claimed to be altered in some depressed patients.

Dexamethasone diminishes the plasma cortisol level in manic-depressives, whereas treatment with lithium carbonate usually (but not always) raises it, perhaps because it produces a "general stress reaction."

In one extensive study, depressives showed elevated plasma and urinary corticoid levels with a disturbed circadian rhythm and resistance to dexamethasone suppression of corticoid production. All these changes disappeared after successful treatment of the depression.

On the other hand, in some carefully conducted clinical studies, the midnight dexamethasone suppression test was ineffective in depressives. It was concluded that "resistance to dexamethasone suppression correlated with the clinical rating of the severity of depression while recovery from depression was associated with the return of normal responsiveness to dexamethasone."

In depressives, the plasma cortisol increase following insulin hypoglycemia is significantly impaired before treatment, particularly among those resistant to dexamethasone suppression.

It appears that those depressives whose corticoid secretion can readily be suppressed by dexamethasone also respond well to antidepressant drug therapy, in contrast to subjects who do not respond with suppression of 11-OHCS secretion after dexamethasone administration.

Curiously, agitation was significantly greater in depressives whose plasma cortisol levels were not suppressed by dexamethasone. However, even in this respect the literature is contradictory; some investigators claim that dexamethasone suppression of corticoid secretion is not altered either in bipolar or in unipolar depressives, and that the circadian variations are likewise normal.

Special attention has been called to the fact that many patients suffering from Cushing's disease and from depression share the following disturbances: (1) abnormal circadian cortisol rhythms, (2) impaired cortisol suppression by dexamethasone, (3) impaired cortisol response to hypoglycemia and (4) elevated cortisol secretion rates. According to these investigations, successful lithium treatment of the depression also reverses the hypothalamo-pituitary-adrenal disturbances. The high unbound plasma cortisol levels are likewise uninfluenced by dexamethasone in both Cushing's disease and depression. It appears that men with unipolar depression have a significantly lower cortisol-binding capacity than normals.

In depressives considered to be suicidal risks, a high percentage of those with elevated plasma cortisol levels subsequently did commit suicide. Hence a high plasma cortisol level may reflect vulnerability to suicide and may perhaps even be causative. (For additional data, cf. Suicide under Neuropsychologic Stimuli.)

Among other biochemical changes possibly related to depression, the literature contains data on 5-HT and related compounds, such as EP, NEP, dopamine, VMA, IAA, kynurenine, metanephrine, normetanephrine, tryptophan pyrolase, plasma FFA, 5-HIAA and so on.

Allegedly, a small group of depressed patients failed to secrete STH adequately after an insulin tolerance test.

Manic-depressive Disease

(See also our earlier stress monographs, p. xiii)

Generalities. Oken, D., Grinker, R. R., Heath, H. A., Sabshin, M., Schwartz, N.: "Stress response in a group of chronic psychiatric patients." *Arch. Gen. Psychiatry* **3**: 451-466 (1960). D1,428/60

Študent, V.: "Blood pressure changes under experimental stress in aggressive and anxious-depressive patients." *Activ. Nerv. Sup. (Praha)* **7**: 200-201 (1965).

J23,491/65

Hudgens, R. W., Morrison, J. R., Barchha, R. G.: "Life events and onset of primary

affective disorders. A study of 40 hospitalized patients and 40 controls." *Arch. Gen. Psychiatry* **16**: 134-145 (1967). J22,688/67

"The data suggest that when mania or depression began soon after stressful life events in this group of patients, the temporal relationship between stress and the onset of illness might have been a chance occurrence."

Ostow, M.: "The consequences of ambivalence." *Psychosomatics* **9**: 255-260 (1968). H3,750/68

Anecdotal description of similarities between ambivalence, particularly melancholia, and the signs characteristic of the G.A.S. (no refs.).

Gallemore, J. L. Jr., Wilson, W. P.: "Pre-

cipitating factors in affective disorders." *South. Med. J.* **64**: 1248-1252 (1971).

J19,078/71

Stress is often the precipitating factor in the development of depression.

Tamerin, J. S., Scavetta, J. F.: "Iatrogenic depression. A case of misguided paternalism." *J.A.M.A.* **219**: 375-376 (1972).

J20,197/72

Certain types of depression arise because of misguided overprotection. For some patients, the protected job is, paradoxically, the most distressful, because they develop a depression if they are made to feel useless.

Benton, R. F.: "The structure of the depressive response to stress." *Am. J. Psychiatry* **128**: 1212-1218 (1972).

J20,204/72

Beck, J. C., Worthen, K.: "Precipitating stress, crisis theory, and hospitalization in schizophrenia and depression." *Arch. Gen. Psychiatry* **26**: 123-129 (1972).

J20,203/72

Braceland, F. J.: "Stresses that cause depression in middle life." *Geriatrics* **27** No. 2: 45-56 (1972).

J20,344/72

Cadoret, R. J., Winokur, G., Dorzab, J., Baker, M.: "Depressive disease: life events and onset of illness." *Arch. Gen. Psychiatry* **26**: 133-136 (1972).

J20,751/72

"Patients whose depressive illness started before age 40 had a significantly higher incidence of real or threatened personal losses than did later-onset depressives."

Bunney, W. E. Jr., Murphy, D. L., Goodwin, F. K., Borge, G. F.: "The 'switch process' in manic-depressive illness. I. A systematic study of sequential behavioral changes." *Arch. Gen. Psychiatry* **27**: 295-302 (1972).

G99,007/72

The first episode of depression or mania is often precipitated by environmental stressors.

Thomson, K. C., Hendrie, H. C.: "Environmental stress in primary depressive illness." *Arch. Gen. Psychiatry* **26**: 130-132 (1972).

G88,405/72

Davies, B., Carroll, B. J., Mowbray, R. M.: *Depressive Illness. Some Research Studies*, Sect. 1-5, p. 354. Springfield, Ill.: Charles C Thomas, 1972.

E10,502/72

A monograph in which six experts discuss the hypothalamus-pituitary-adrenal axis and

other humoral mechanisms in relation to depressive illness (several hundred refs.).

Kreitman, N., Chowdhury, N.: "Distress behaviour: a study of selected Samaritan clients and parasuicides ('attempted suicide' patients). Part I: General aspects." *Br. J. Psychiatry* **123**: 1-8 (1973).

J19,559/73

Fabrega, H. Jr.: "Problems implicit in the cultural and social study of depression." *Psychosom. Med.* **36**: 377-398 (1974).

J19,287/74

Jacobs, S. C., Prusoff, B. A., Paykel, E. S.: "Recent life events in schizophrenia and depression." *Psychol. Med.* **4**: 444-453 (1974).

J21,683/74

Hudgens, R. W.: "Personal catastrophe and depression: a consideration of the subject with respect to medically ill adolescents, and a requiem for retrospective life-event studies." In: Dohrenwend, B. S. and Dohrenwend, B. P., *Stressful Life Events: Their Nature and Effects*, pp. 119-154. New York, London and Sydney: John Wiley & Sons, 1974.

E10,785/74

Brenner, C., Ritvo, S., Kahana, R. J., Levin, S., Sachar, E. J.: "The concept and phenomenology of depression, with special reference to the aged. Discussion." *J. Geriatr. Psychiatry* **7**: 78-83 (1974).

J20,922/74

Brierley, H., Jamieson, R.: "Anomalous stress reactions in patients suffering from depression and anxiety." *J. Neurol. Neurosurg. Psychiatry* **37**: 455-462 (1974).

J13,469/74

The forearm muscle blood flow changes caused by the stressor effect of noise revealed that "depressive patients show something akin to a freeze response to stress, while patients with anxiety states show an arousal response."

Flach, F. F.: *The Secret Strength of Depression*, p. 288. Philadelphia and New York: J B Lippincott, 1974.

E10,695/74

Monograph describing depression as a social psychologic defense reaction against stressful life situations.

Paykel, E. S.: "Recent life events and clinical depression." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 134-163. Springfield, Ill.: Charles C Thomas, 1974.

E10,688/74

Discussion of the predictive value of the

SRE questionnaire in the development of depression.

Brown, G. W.: "Life-events and the onset of depressive and schizophrenic conditions." In: Gunderson, E. K. E. and Rahe, R. H., *Life Stress and Illness*, pp. 164-188. Springfield, Ill.: Charles C Thomas, 1974.

E10,689/74

Discussion of the SRE questionnaire as a predictor of the development of schizophrenia or depression (25 refs.).

→**ACTH and Corticoids.** Rizzo, N. D., Fox, H. M., Laidlaw, J. C., Thorn, G. W.: "Concurrent observations of behavior changes and of adrenocortical variations in a cyclothymic patient during a period of 12 months." *Ann. Intern. Med.* **41**: 798-815 (1954). J5,880/54

Bryson, R. W., Martin, D. F.: "17-Ketosteroid excretion in a case of manic-depressive psychosis." *Lancet* August 21, 1954, pp. 365-367. B97,130/54

Sloane, R. B., Saffran, M., Cleghorn, R. A.: "Steroid response to A.C.T.H. and the effect of ataractic drugs." In: Reiss, M., *Psychoenocrinology* (2nd Int. Congr. Psychiat., Zürich, September, 1957), pp. 198-204. New York and London: Grune & Stratton, 1958. D13,352/58

Chlorpromazine reduces the increase in urinary 17-OHCS following intravenous ACTH in depressive and mixed psychoneurotic patients.

Gibbons, J. L., McHugh, P. R.: "Plasma cortisol in depressive illness." *J. Psychiatr. Res.* **1**: 162-171 (1963). E37,690/63

In depressed patients, elevated blood cortisol levels were found before treatment, but these declined upon recovery after treatment with antidepressants.

Brambilla, F., Nuremberg, T.: "Adrenal cortex function of cyclotimic patients in depressive phase." *Dis. Nerv. Syst.* **24**: 727-731 (1963). E35,424/63

A high percentage of depressive patients "show androgen and cortisone secretion of the low-normal limits. The ACTH test, negative in one third of the cases, is dissociated in half of the patients, with a good response in the cortisonic series and absent response with the androgens" (45 refs.).

Pryce, I. G.: "The relationship between 17-hydroxycorticosteroid excretion and glu-

cose utilization in depressions." *Br. J. Psychiatry* **110**: 90-94 (1964). G13,357/64

Kurland, H. D.: "Urinary steroids in neurotic- and manic-depression." *Proc. Soc. Exp. Biol. Med.* **115**: 723-725 (1964).

F6,686/64

In male neurotic- and manic-depressive patients, urinary 17-KGS excretion was elevated, but that of 17-KS and 17-OHCS was not.

Gibbons, J. L.: "Cortisol secretion rate in depressive illness." *Arch. Gen. Psychiatry* **10**: 572-575 (1964). G14,359/64

In depressed patients, elevated cortisol secretion rates were characteristic, and relief of depression coincided with a decrease in these values.

Kurland, H. D.: "Steroid excretion in depressive disorders." *Arch. Gen. Psychiatry* **10**: 554-560 (1964). G18,931/64

"The excretion of 17-KGS for the total group of ten patients was significantly correlated with the clinical depressive symptomatology. Significant increases in the relative amounts of urinary 17-KGS, 17-KS, and 17-OHCS accompanied the intensification of clinical symptoms. However, only the 17-KGS were excreted in greater absolute quantities than would be expected from comparable groups of normal control subjects. The diurnal variation in the excretion of all these compounds revealed that the highest rate occurred during the early morning hours and then progressively decreased throughout the day and night."

Martinis, C. de, Doglio, R., Fonzo, D., Gandiglio, G.: "Studi sui rapporti tra sistema nervoso centrale ed attivita' corticosurrenale. I. La funzione corticosurrenalica nelle psicosi maniaco-depressive" (Study on the relationship between the central nervous system and adrenocortical activity. I. Adrenocortical function in manic-depressive psychoses). *Folia Endocrinol. (Roma)* **18**: 157-180 (1965). F50,445/65

In seven manic-depressive patients, plasma cortisol, 17-OHCS, 17-KS and urinary creatinine excretion (both under normal conditions and after ACTH, dexamethasone, or metyrapone treatment) were found to differ from the norm, suggesting some derangements of the pituitary-adrenal stress mechanism (140 refs.). [The results were too complex to be meaningfully summarized here (H.S.).]

Anderson, W. McC., Dawson, J.: "The variability of plasma 17-hydroxycorticosteroids—levels in affective illness and schizophrenia." *J. Psychosom. Res.* **9**: 237-248 (1965). G36,220/65

The plasma 17-OHCS levels of disturbed depressives tended to be higher than those of schizophrenics but showed great variations in all cases (23 refs.).

Bunney, W. E. Jr., Mason, J. W., Roatch, J. F., Hamburg, D. A.: "A psychoendocrine study of severe psychotic depressive crises." *Am. J. Psychiatry* **122**: 72-80 (1965).

G31,018/65

Correlation of behavioral changes and 17-OHCS excretion in depressive crises which were usually preceded by increased environmental stress or breakdown of ego defenses.

Bunney, W. E. Jr., Hartmann, E. L., Mason, J. W.: "Study of a patient with 48-hour manic-depressive cycles. Part II. Strong positive correlation between endocrine factors and manic defense patterns." *Arch. Gen. Psychiatry* **12**: 619-625 (1965).

G29,865/65

"Psychiatrists have suggested in the past that mania is a defense against the distress or pain of depression. Our findings are consistent with those of other investigators and may offer an interesting biochemical confirmation of this psychological theory." At times of intense mania, 17-OHCS levels were low and during immobile depressed days they were high.

Bunney, W. E. Jr., Mason, J. W., Hamburg, D. A.: "Correlations between behavioral variables and urinary 17-hydroxycorticosteroids in depressed patients." *Psychosom. Med.* **27**: 299-308 (1965).

G31,895/65

"The data suggest that patients in a group with high 17-OHCS levels were often more involved in the struggle with their illness, regarded their thoughts as ego alien, and tended to have ineffective defenses, while many of those severely depressed patients who showed low 17-OHCS levels tended to employ extensive denial of their illness."

Bridges, P. K., Jones, M. T.: "The diurnal rhythm of plasma cortisol concentration in depression." *Br. J. Psychiatry* **112**: 1257-1261 (1966). G43,296/66

Gibbons, J. L., Fahy, T. J.: "Effect of dexamethasone on plasma corticosteroids in depressive illness." *Neuroendocrinology* **1**: 358-363 (1966). G44,210/66

Three hours after intramuscular injection of dexamethasone in patients with endogenous depression, plasma 11-OHCS levels fell approximately as in normal subjects. "It is concluded that the feedback control of pituitary-adrenal function is intact in depressive illness."

Schwartz, M., Mandell, A. J., Green, R., Ferman, R.: "Mood, motility and 17-hydroxycorticoid excretion; a polyvariable case study." *Br. J. Psychiatry* **112**: 149-156 (1966). G37,319/66

In manic-depressives, urinary 17-OHCS excretion tends to increase during both the manic and the depressive phases, perhaps as a consequence of "non-specific 'discomfort' and motility."

McClure, D. J.: "The diurnal variation of plasma cortisol levels in depression." *J. Psychosom. Res.* **10**: 189-195 (1966).

G41,115/66

McClure, D. J.: "The effects of antidepressant medication on the diurnal plasma cortisol levels in depressed patients." *J. Psychosom. Res.* **10**: 197-202 (1966).

G41,116/66

Rubin, R. T., Mandell, A. J.: "Adrenal cortical activity in pathological emotional states: a review." *Am. J. Psychiatry* **123**: 387-400 (1966). G41,185/66

"A review of the psychoendocrine research on this subject indicates that heightened activity of the adrenal cortex occurs concomitantly with depressive reactions of various types and in certain phases of acute schizophrenic reactions. The psychological variable that appears to correlate most closely with increased adrenal cortical secretion is loss of 'ego defense strength,' that is, absence of denial, awareness of illness and suffering, anxiety, and depressive affect.... The behavioral observations and biochemical methodologies used in the studies reviewed are discussed. Data from psychiatric observations on patients with Cushing's syndrome and patients treated with ACTH and exogenous glucocorticoids support the possibility of a primary brain state alteration which results in both the depressive affect associated with loss of ego defense strength and in stimulation of the hypothalamic-pituitary-adrenal axis" (107 refs.).

Doig, R. J., Mummery, R. V., Wills, M. R., Elkes, A.: "Plasma cortisol levels in depression." *Br. J. Psychiatry* **112**: 1263-1267 (1966). G43,297/66

In hospitalized depressed patients, the mean 06:00 level of plasma cortisol was significantly above normal.

"Amines and depression." *Br. Med. J.* February 25, 1967, pp. 448-449.

F77,991/67

Letter to the editor evaluating the literature on the possible role of 5-HT, dopamine and catecholamines in depression, as related to stress and cortisol.

Brooksbank, B. W. L., Coppen, A.: "Plasma 11-hydroxycorticosteroids in affective disorders." *Br. J. Psychiatry* **113**: 395-404 (1967).

G45,651/67

"The changes in 11-OHCS are not intimately connected with a depressive or manic illness, and indeed the levels found in plasma are surprisingly normal when one considers the mental anguish felt by many of these patients. The analysis of the data suggests that 'reactive and mixed' states of depression paradoxically seem to show even less reaction as far as their morning plasma 11-OHCS are concerned, but that before and after recovery they show rather higher levels than normal. The evening plasma 11-OHCS levels seem to correlate better with the clinical state."

"Corticosteroids in depressions." *J.A.M.A.* **202**: 904 (1967).

F91,218/67

Letter to the editor. In about 30 percent of depressives, corticoid levels were lower before than after recovery. In such patients, mental mechanisms apparently "reduce the inner experience of stress." On the other hand, "those patients in stages of acute psychotic turmoil (associated with disruption of ego defenses and arousal of disintegrative anxiety) did indeed have very high corticosteroid levels, but patients in stages of organized (chronic or stable) psychosis did not."

Rubin, R. T.: "Adrenal cortical activity changes in manic-depressive illness. Influence on intermediary metabolism of tryptophan." *Arch. Gen. Psychiatry* **17**: 671-679 (1967).

G53,082/67

Urinary 17-OHCS excretion tends to increase during depression and to decrease during mania. But this is inconstant, and "the urine kynurene data suggest an increased metabolism of tryptophan via the kynurene pathway during depression and support the hypothesis of hydrocortisone induction of tryptophan pyrolase during depression" (33 refs.).

Sachar, E. J., MacKenzie, J. M., Binstock, W. A., Mack, J. E.: "Corticosteroid responses to psychotherapy of depressions. I. Elevations during confrontation of loss." *Arch. Gen. Psychiatry* **16**: 461-470 (1967). G46,637/67

Green, R.: "Morning and afternoon plasma 17-hydroxycorticosteroid levels during affective psychosis." *Int. J. Neuropsychiatry* **3**: 133-137 (1967). H9,064/67

Clower, C. G. Jr., Migeon, C. J.: "Psychoendocrine aspects of depression and ECT." *Johns Hopkins Med. J.* **121**: 227-233 (1967). G51,371/67

In depressive patients, 17-OHCS excretion tended to be elevated and to drop after successful electroconvulsive therapy (21 refs.).

Sachar, E. J.: "Corticosteroids in depressive illness. I. A reevaluation of control issues and the literature." *Arch. Gen. Psychiatry* **17**: 544-553 (1967). G51,423/67

Sachar, E. J.: "II. A longitudinal psychoendocrine study." *Arch. Gen. Psychiatry* **17**: 554-567 (1967). G51,424/67

In depressed patients the 17-OHCS excretion did not correlate well with the severity or course of the illness, but did drop slightly after recovery. The findings are somewhat at variance with the literature, but many authors failed to consider such interfering factors as the stress of admission to hospital and the tests performed (28 refs.).

Knapp, M. S., Keane, P. M., Wright, J. G.: "Circadian rhythm of plasma 11-hydroxycorticosteroids in depressive illness, congestive heart failure, and Cushing's syndrome." *Br. Med. J.* April 1, 1967, pp. 27-30. F81,858/67

Hullin, R. P., Bailey, A. D., McDonald, R., Dransfield, G. A., Milne, H. B.: "Variations in 11-hydroxycorticosteroids in depression and manic-depressive psychosis." *Br. J. Psychiatry* **113**: 593-600 (1967). G47,390/67

The plasma 11-OHCS levels were higher in depressed patients before, during, and after electroconvulsive therapy than in normal controls. There was a significant decrease in the levels of these corticoids after successful electroconvulsive therapy.

Mason, J. W.: "A review of psychoendocrine research on the pituitary adrenal cortical system." *Psychosom. Med.* **30**: 576-607 (1968). H29,040/68

Excellent review on the effect of psychologic stimuli and psychiatric disease upon the pituitary-adrenocortical axis. "Elevation of 17-OHCS levels is not related to a highly specific affective state, but rather appears to reflect a relatively undifferentiated state of emotional arousal or involvement, perhaps in anticipation of activity or coping. The elements of novelty, uncertainty, or unpredictability are particularly potent influences in eliciting 17-OHCS elevations" (222 refs.).

Sachar, E. J., MacKenzie, J. M., Binstock, W. A., Mack, J. E.: "Corticosteroid responses to the psychotherapy of reactive depressions. II. Further clinical and physiological implications." *Psychosom. Med.* **30**: 23-44 (1968).

G54,793/68

Platman, S. R., Fieve, R. R.: "Lithium carbonate and plasma cortisol response in the affective disorders." *Arch. Gen. Psychiatry* **18**: 591-594 (1968). G57,186/68

Newly admitted manic-depressives show increased levels of plasma cortisol, but these fall after recovery as well as upon treatment with dexamethasone. Lithium carbonate usually raises plasma cortisol in psychotics despite their clinical improvement, perhaps because it produces a "general stress reaction."

Butler, P. W. P., Besser, G. M.: "Pituitary-adrenal function in severe depressive illness." *Lancet* June 8, 1968, pp. 1234-1236.

F99,079/68

Depressives showed elevated plasma and urinary corticoid levels, disturbed circadian rhythm, and resistance to dexamethasone suppression of corticoid production. These changes disappeared after successful treatment of the depression.

Rimón, R., Salonen, S., Pekkarinen, A.: "Antidepressive medication and diurnal variation of plasma 17-OHCS levels in depression." *J. Psychosom. Res.* **12**: 289-295 (1968). G63,267/68

Fullerton, D. T., Wenzel, F. J., Lohrenz, F. N., Fahs, H.: "Circadian rhythm of adrenal cortical activity in depression. I. A comparison of depressed patients with normal subjects." *Arch. Gen. Psychiatry* **19**: 674-681 (1968). G62,923/68

In depressed patients, serum and urinary 17-OHCS levels were above normal throughout the day, but the nadir was reached three hours earlier than in controls.

Fullerton, D. T., Wenzel, F. J., Lohrenz,

F. N., Fahs, H.: "Circadian rhythm of adrenal cortical activity in depression." *Arch. Gen. Psychiatry* **19**: 682-688 (1968).

G62,924/68

Carroll, B. J., Martin, F. I. R., Davies, B.: "Resistance to suppression by dexamethasone of plasma 11-O.H.C.S. levels in severe depressive illness." *Br. Med. J.* August 3, 1968, pp. 285-287. H2,689/68

In many depressives, the midnight dexamethasone suppression test is ineffective. "Resistance to dexamethasone suppression correlated with the clinical rating of the severity of depression, while recovery from depression was associated with return of normal responsiveness to dexamethasone."

Rubin, R. T., Young, W. M., Clark, B. R.: "17-hydroxycorticosteroid and vanillylmandelic acid excretion in a rapidly cycling manic-depressive." *Psychosom. Med.* **30**: 162-171 (1968). G63,129/68

Lohrenz, F. N., Fullerton, D. T., Fahs, H., Wenzel, F. J.: "Adrenocortical function in depressive states—Study of circadian variation in plasma and urinary steroids." *Int. J. Neuropsychiatry* **4**: 21-25 (1968). F93,488/68

The circadian rhythm of corticoid production is altered in some depressed patients.

Jakobson, T., Blumenthal, M., Hagman, H., Heikkinen, E.: "The diurnal variation of urinary and plasma 17-hydroxy-corticosteroid (17-OHCS) levels and the plasma 17-OHCS response to lysine-8-vasopressin in depressive patients." *J. Psychosom. Res.* **13**: 363-375 (1969) (50 refs.). G71,764/69

Sclare, A. B., Grant, J. K.: "Plasma 11-hydroxycorticosteroid concentration in depressive illness." *J. Endocrinol.* **43**: 677-678 (1969). H11,671/69

The diurnal variations in 11-OHCS excretion are significantly increased in depressives. "Patients with endogenous depression had a significantly higher plasma 11-OHCS level in the evening than those with reactive depression. Although plasma 11-OHCS changes are present in depressive illness, they are comparatively mild. They probably represent a nonspecific response to stress."

Baer, L., Durell, J., Bunney, W. E., Levy, B. S., Cardon, P. V.: "Sodium-22 retention and 17-hydroxycorticosteroid excretion in affective disorders: a preliminary report." *J. Psychiatr. Res.* **6**: 289-297 (1969).

G66,564/69

"In depression, sodium is retained to a greater extent than in less depressed, recovered and/or hypomanic states. This was correlated with increased 17-OHCS excretion in the depressed state" (16 refs.).

Carroll, B. J.: "Hypothalamic-pituitary function in depressive illness: insensitivity to hypoglycaemia." *Br. Med. J.* July 5, 1969, pp. 27-28. H13,765/69

In depressive patients the plasma cortisol increase following insulin hypoglycemia is significantly impaired before treatment, particularly among those resistant to dexamethasone suppression.

Gibbons, J. L.: "Corticosteroid metabolism in depressive illness." *Psychiatr. Neurol. Neurochir.* 72: 195-199 (1969).

H31,970/69

Sachar, E. J., Hellman, L., Fukushima, D. K., Gallagher, T. F.: "Cortisol production in depressive illness. A clinical and biochemical clarification." *Arch. Gen. Psychiatry* 23: 289-298 (1970). G78,352/70

"Adrenocortical activity in depressed patients is primarily related to dimensions of emotional arousal and psychotic disorganization rather than to depressive illness per se.... Measurements of cortisol production can help greatly in interpreting data gathered from other stress-sensitive biological systems in depressed patients" (23 refs.).

Sachar, E. J., Hellman, L., Kream, J., Fukushima, D. K., Gallagher, T. F.: "Effect of lithium-carbonate therapy on adrenocortical activity." *Arch. Gen. Psychiatry* 22: 304-307 (1970). G73,841/70

In patients with manic-depressive illness, no significant changes in plasma cortisol were noted after lithium therapy.

Mueller, P. S., Davis, J. M., Bunney, W. E. Jr., Weil-Malherbe, H., Cardon, P. V. Jr.: "Plasma free fatty acids concentration in depressive illness." *Arch. Gen. Psychiatry* 22: 216-221 (1970). G73,045/70

In fasted hospitalized depressives, morning plasma FFA levels were increased in comparison with those of normals or schizophrenics. "The averages of the ratings of depression, anxiety, and psychotic behavior correlated with average FFA concentrations. Somatic complaints, physical activity, and food intake were not significantly related to average FFA concentrations. Average urinary 17-OHCS excretion was not significantly related to the above average ratings of clinical distress."

Sharma, S. D., Shah, P. B., Acharya, P. T.: "Urinary 17-hydroxycorticosteroids levels and urine electrolytes in depression." *Dis. Nerv. Syst.* 31: 343-347 (1970).

G76,432/70

Urinary 17-OHCS levels were lower in patients with endogenous depression than in those with neurotic depression (16 refs.).

Krieger, G.: "Biochemical predictors of suicide." *Dis. Nerv. Syst.* 31: 478-482 (1970).

H47,537/70

In psychiatric patients considered to be suicidal risks, a high percentage of those with increased plasma cortisol levels subsequently committed suicide. "The elevated plasma cortisol may reflect the vulnerability to suicide and be causative" (17 refs.).

Carroll, B. J., Davies, B.: "Clinical associations of 11-hydroxycorticosteroid suppression and non-suppression in severe depressive illnesses." *Br. Med. J.* March 28, 1970, pp. 789-791.

H24,181/70

In some depressives, dexamethasone failed to exert its usual suppressive effect upon plasma cortisol. Curiously, "agitation was significantly greater in the patients whose corticosteroid levels were not suppressed by dexamethasone and adverse childhood experiences [were greater] in those whose levels were suppressed."

Shopsin, B., Gershon, S.: "Plasma cortisol response to dexamethasone suppression in depressed and control patients." *Arch. Gen. Psychiatry* 24: 320-326 (1971).

G83,553/71

"Plasma cortisol response to dexamethasone was normal in both bipolar and unipolar depressives, reactive depressives and schizophrenics. As a group, schizophrenics showed significantly higher morning cortisol values than the depressed population." The findings are discussed in connection with the possible role of stress in the pathogenesis of mental disorders (47 refs.).

Stančáková, A., Stančák, A.: "Die Ausscheidung der Cortisol-Metaboliten bei Kranken mit endogener Depression mit Berücksichtigung der Tagesschwankung der Steroidmetaboliten" (Diurnal excretion of cortisol metabolites in patients suffering from endogenous depression). *J. Steroid Biochem.* 2: 121-131 (1971).

G91,053/71

In depressives the urinary excretion of corticoids and their metabolites is diminished, particularly in the cortisone fraction. This decrease is aggravated by treatment with

thioridazine. Noteworthy changes in normal circadian variations were not observed (35 refs.).

Sclare, A. B., Grant, J. K.: "Urinary steroids in depressive illness." *Scott. Med. J.* **16**: 224-227 (1971). G93,955/71

The urinary 17-OHCS and 17-KS output of depressives shows no pronounced deviation from the norm, and hence "measurements of urinary excretion of corticosteroids in affective disorders constitute a limited source of information."

Platman, S. R., Hilton, J. G., Koss, M. C., Kelly, W. G.: "Production of cortisol in patients with manic-depressive psychosis treated with lithium carbonate." *Dis. Nerv. Syst.* **32**: 542-544 (1971). G86,455/71

Lithium carbonate increased both the secretory rate and the plasma concentration of cortisol in manic-depressives but not in normal controls.

Coppen, A., Brooksbank, B. W. L., Noguera, R., Wilson, D. A.: "Cortisol in the cerebrospinal fluid of patients suffering from affective disorders." *J. Neurol. Neurosurg. Psychiatry* **34**: 432-435 (1971).

G90,735/71

The cortisol concentration showed no significant differences among patients with depression or those with mania.

Carpenter, W. T. Jr., Bunney, W. E. Jr.: "Diurnal rhythm of cortisol in mania." *Arch. Gen. Psychiatry* **25**: 270-273 (1971).

H62,035/71

Carroll, B. J.: "Studies with hypothalamic-pituitary-adrenal stimulation tests in depression." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Section 2, pp. 149-201. Springfield, Ill.: Charles C Thomas, 1972. E10,501/72

Extensive studies on the mechanism responsible for the malfunction of the hypothalamus-pituitary-adrenocortical axis in depressed patients (several hundred refs.).

McLeod, W. R.: "Poor response to antidepressants and dexamethasone nonsuppression." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Section 2, pp. 202-206. Springfield, Ill.: Charles C Thomas, 1972. E10,506/72

In depressed patients, dexamethasone does not adequately suppress the secretion of 11-OHCS. Most of those depressives whose corticoid secretion can be readily suppressed by dexamethasone also respond well to anti-

depressant drug therapy, unlike those who do not respond to dexamethasone by suppression of 11-OHCS secretion.

Sclare, A. B., Grant, J. K.: "The Synacthen test in depressive illness." *Scott. Med. J.* **17**: 7-8 (1972). G89,102/72

In depressives the plasma 11-OHCS rise after ACTH (tetracosactrin) is essentially normal, although the pretreatment level is comparatively high.

Dunner, D. L., Goodwin, F. K., Gershon, E. S., Murphy, D. L., Bunny, W. E., Jr.: "Excretion of 17-OHCS in unipolar and bipolar depressed patients." *Arch. Gen. Psychiatry* **26**: 360-363 (1972) (27 refs.).

G90,675/72

Carroll, B. J.: "Control of plasma cortisol levels in depression: studies with the dexamethasone suppression test." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Section 2, pp. 87-148. Springfield, Ill.: Charles C Thomas, 1972. E10,505/72

Detailed studies on the dexamethasone resistance of the pituitary-adrenocortical system in depressed patients.

Carroll, B. J.: "Plasma cortisol levels in depression." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Section 2, pp. 69-86. Springfield, Ill.: Charles C Thomas, 1972. E10,504/72

In untreated depressed patients the circadian variations of plasma cortisol were significantly elevated but fell after treatment. Clinical features and rating scales indicated that among depressives "biologic factors" rather than anxiety were responsible for the high plasma cortisol levels.

Sachar, E. J., Hellman, L., Fukushima, D. K., Gallagher, T. F.: "Cortisol production in mania." *Arch. Gen. Psychiatry* **26**: 137-139 (1972). G88,406/72

In unanxious hypomanic patients, cortisol production rates (isotope dilution analysis) were within the normal range and did not change following successful treatment of the clinical manifestations with lithium carbonate.

Carroll, B. J.: "The hypothalamic-pituitary-adrenal axis: functions, control mechanisms and methods of study." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Section 2, pp. 23-68. Springfield, Ill.: Charles C Thomas, 1972.

E10,503/72

The human adrenal cortex does not secrete corticoids continuously but only in discrete pulsatile episodes which appear to vary largely and to be programmed by the CNS. During endogenous depression, psychogenic stress fails to exert its normal effect upon the adrenal cortex, and the hypothalamus-pituitary-adrenal axis appears to be disturbed in a manner different from that in such psychiatric illnesses as anxiety states or schizophrenia. The hypothalamus-pituitary-adrenal feedback mechanism is analyzed in detail, including the role of the amygdala, hippocampus, midbrain and pons.

Stančáková, A., Žurindová, Z., Stančák, A.: "Der Einfluss von ACTH und Metopiron auf die Ausscheidung der Cortisol-Metaboliten bei endogener Depression im Verlauf der Thioridazin-Verabreichung" (The influence of ACTH and metopirone on the excretion of cortisol metabolites in endogenous depression during Thioridazine treatment). *Endokrinologie* **60**: 205-217 (1972). H63,651/72

"Before ACTH and Metopirone administration the depressive group already exhibited decreased values of free corticosteroids and tetrahydrogenated derivatives, extractable with chloroform. This decrease, which was found to occur predominantly in the fractions comprising cortisone, cortisol, 11-desoxycortisol, tetrahydrocortisol, allo-tetrahydrocortisol and tetrahydrocortisone, continued in the depressive patients also during ACTH administration." Excretion of cortisol metabolites during metyrapone administration was nearly normal in depressives, but the dose of the drug was probably too low. Thioridazine, like other phenothiazines, inhibited adrenocortical activity (24 refs.).

Sachar, E. J., Hellman, L., Roffwarg, H. P., Halpern, F. S., Fukushima, D. K., Gallagher, T. F.: "Disrupted 24 hour patterns of cortisol secretion in psychotic depression." *Arch. Gen. Psychiatry* **28**: 19-24 (1973). H76,340/73

Carroll, B. J.: "Hypothalamic-pituitary-adrenal (HPA) function and depression." *Int. Soc. of Psychoneuroendocrinology Ann. Meeting*, p. 4. Berkeley, Cal., 1973.

J7,393/73

Brief summary of an oral presentation on the participation of the hypothalamus-pituitary-adrenocortical system in depression. There is reason to believe that this system may sometimes be etiologically related to depression and, under other circumstances, to

euphoria. Many patients suffering from Cushing's disease and from depression share the following disturbances: "(1) abnormal diurnal rhythm of cortisol levels, (2) impaired suppression of cortisol in response to dexamethasone, (3) impaired cortisol response to hypoglycemia, and (4) elevated cortisol secretion rate." Successful treatment of depression (for example, by lithium) also reverses these anomalies in the hypothalamus-pituitary-adrenal system. Some depressed patients have unusually high free cortisol plasma levels. Also, as in Cushing's disease, dexamethasone causes little or no diminution of the high unbound plasma cortisol levels.

King, D. J.: "Plasma cortisol-binding capacity in mental illness." *Psychol. Med.* **3**: 53-65 (1973). J763/73

In a group of patients with various psychiatric ailments, plasma cortisol-binding capacity (CBC) was determined. "Men with unipolar depressive illnesses had significantly lower CBC values than men with bipolar illnesses and male controls. No other significant differences in CBC values were found and it was concluded that elevated total plasma cortisol levels in affective disorder were probably associated with increased levels of unbound cortisol."

Bugard, P.: *Stress, Fatigue et Dépression. (l'Homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue, and depression. Man and the aggression of daily life), Vol. 1, p. 294, Vol. 2, p. 302. Paris: Doin Edit., 1974. E10,487/74

Two-volume monograph on stress, fatigue and depression with a special chapter on psychiatric and psychologic problems of daily life.

Lukash, N. A., Siletskii, O. Y.: "Glucocorticoid function of the adrenals during emotional stress." *Zh. Nevropatol. Psichiatr.* **73** No. 12: 1833-1837 (1973) (Russian). Engl. trans.: *Sov. Neurol. Psychiatry* **7** No. 3: 82-90 (1974). J19,500/74

Carroll, B. J.: "Limbic system-adrenal cortex regulation in depression and schizophrenia." *Psychosom. Med.* (In press).

J20,864/

In depressed patients, unlike in schizophrenics, the free cortisol excretion and the cortisol content of the CSF are high and do not respond to dexamethasone suppression. Thus, "a psychoendocrine distinction can be made between primary depressive illness and

secondary depressive symptomatology, and psychological defense breakdown is not related to these neuroendocrine observations."

→**Other Hormones.** Funkenstein, D. H., Greenblatt, M., Solomon, H. C.: "Nor-epinephrine-like substances in psychotic and psychoneurotic patients." *Am. J. Psychiatry* **108**: 652-662 (1952). B97,013/52

"The great majority of the cases interpreted as showing excessive secretion of an *epinephrine-like substance* were diagnosed as manic-depressive or involutional psychosis; whereas the majority of the cases interpreted as showing excessive secretion of a *norepinephrine-like substance* were diagnosed schizophrenia. The response to electric shock followed the autonomic type rather than diagnostic category, as the majority of the schizophrenic patients who showed evidence interpreted as indicating excessive secretion of an epinephrine-like substance responded to electric shock therapy."

Board, F., Wadeson, R., Persky, H.: "Depressive affect and endocrine function. Blood levels of adrenal cortex and thyroid hormones in patients suffering from depressive reactions." *Arch. Neurol. Psychiatry* **78**: 612-620 (1957). J12,053/57

In depressed patients the mean blood cortisol levels are elevated, especially during periods of severe emotional distress. *PBI* levels also tend to be elevated but not significantly.

Coppen, A.: "The biochemistry of affective disorders." *Br. J. Psychiatry* **113**: 1237-1264 (1967). G51,286/67

Review on *catecholamine*, indole derivative, and electrolyte changes occurring in various affective disorders which may be of pathogenic importance, and which may be responsible for the effectiveness of psychotropic drugs (187 refs.).

Schildkraut, J. J., Davis, J. M., Klerman, G. L.: "Biochemistry of depressions." In: Efron, D. H., *Psychopharmacology. A Review of Progress, 1957-1967*, pp. 625-648. Washington, D.C.: U.S. Department of Health, Education, and Welfare, 1968.

E7,976/68

A review on *catecholamines* and *5-HT* in depression, with special reference to their possible participation in the therapeutic effect of antidepressants (over 300 refs.).

Rubin, R. T.: "Multiple biochemical cor-

relates of manic-depressive illness." *J. Psychosom. Res.* **12**: 171-180 (1968).

G63,713/68

"VMA excretion was higher during mania and correlated with level of physical activity. Kynurene excretion was lower during depression, possibly on the basis of heightened metabolism of kynurene during depression. IAA excretion was increased during depression, although variations in daily levels during all phases were considerable" (18 refs.).

Perez-Reyes, M.: "Differences in the capacity of the sympathetic and endocrine systems of depressed patients to react to a physiological stress." *Pharmakopsychiatrie* **2**: 245-251 (1969). G72,888/69

"In response to insulin-induced hypoglycemia, neurotic depressed patients, who had higher GSR inhibition and sleep threshold values mobilized more 17-OHCS in the plasma and *epinephrine*, *norepinephrine*, *metanephrine*, *normetanephrine* and *VMA* in the urine than normal control subjects. Psychotic depressed patients reacted adversely."

Curzon, G.: "A relationship between brain serotonin and adrenocortical secretion and its possible significance in endogenous depression." *Pharmakopsychiatrie* **2**: 234-244 (1969). G72,887/69

In depression, there are disturbances in *5-HT* metabolism and corticoid production. Experiments on rats suggest "that these disturbances may be metabolically related through the enzyme tryptophan pyrolase, synthesis of which depends upon adrenal activity" (78 refs.).

Sachar, E. J., Finkelstein, J., Hellman, L.: "Growth hormone responses in depressive illness. I. Response to insulin tolerance test." *Arch. Gen. Psychiatry* **25**: 263-269 (1971). G85,910/71

Among thirteen hospitalized depressed patients, five failed to secrete *STH* adequately after an insulin tolerance test. In contrast, all of twenty-three nondepressed age-matched subjects had adequate *STH* responses (32 refs.).

McLeod, W. R., McLeod, M. F.: "Indoleamines and the cerebrospinal fluid." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Section 3, pp. 209-225. Springfield, Ill.: Charles C Thomas, 1972. E10,507/72

Depressed subjects have subnormal *5-HIAA* levels in the CSF, but patients suf-

fering from other psychiatric disorders do not. A positive correlation exists between the 5-HIAA values of the CSF and the plasma 11-OHCS concentrations in depressed patients both before and after the dexamethasone suppression test.

Carroll, B. J.: "Relations between serotonin and hypothalamic-pituitary-adrenal function in depression." *Int. Symp. on 5-Hydroxytryptamine and Other Indolealkylamines in Brain*, p. 11. St. Margherita (Cagliari), Italy, 1973. J7,399/73

Preliminary evidence suggesting that the high plasma free cortisol level and its relative resistance to dexamethasone suppression, characteristic of depressed patients, may in some way be related to derangements in 5-HT metabolism.

Messiha, F. S., Savage, C., Turek, I., Hanlon, T. E.: "A psychopharmacological study of catecholamines in affective disorders." *J. Nerv. Ment. Dis.* **158**: 338-347 (1974). J12,820/74

In the majority of manic patients, dopamine excretion was increased at the height of the manic phase and returned to normal following successful lithium treatment.

Matussek, N., Ackenheil, M., Athen, D., Beckmann, H., Benkert, O., Dittmer, T., Hippius, H., Loosen, P., Rüther, E., Scheller, M.: "Catecholamine metabolism under sleep deprivation therapy of improved and not improved depressed patients." *Pharmakopsychiatrie* **7**: 108-114 (1974). J12,520/74

Sleep deprivation is often but not invariably effective as a transitory treatment in certain types of depressed patients. NEP and VMA elimination is increased in those with definite improvement, but not in the others.

Shopsin, B., Wilk, S., Sathananthan, G.,

Gershon, S., Davis, K.: "Catecholamines and affective disorders revised: a critical assessment." *J. Nerv. Ment. Dis.* **158**: 369-383 (1974). J12,823/74

A review of the literature on the possible role played by *catecholamines* in the pathogenesis of affective diseases shows that most pertinent views were based on relationships between the clinical effects of reserpine, MAO inhibitors, tricyclic antidepressants, L-dopa, α -MT, physostigmine and so on, and their pharmacologic actions upon adrenergic and cholinergic mechanisms. No definite conclusion is reached, but it appears unlikely that catecholamines alone might explain the development of affective disorders.

Schildkraut, J. J.: "Biogenic amines and affective disorders." *Annu. Rev. Med.* **25**: 333-348 (1974). J12,641/74

Review of the literature and personal observations indicate that "different subgroups of patients with depressive disorders may exhibit different specific abnormalities in the metabolism of norepinephrine or other biogenic amines," particularly dopamine and 5-HT. The relationship between stress and metabolic changes in these substances is considered, but is not regarded as of proven significance (119 refs.).

→**Metabolites.** Rubin, R. T., Clark, B. R.: "Tryptophan pyrolase induction in patients with manic depression." *Science* **165**: 1146-1147 (1969). H16,528/69

Hafner, R. J.: "Physiological changes with stress in depression and obsessional neurosis." *J. Psychosom. Res.* **18**: 175-179 (1974). J15,135/74

Comparative studies on the salivary flow and sodium/potassium ratio in the saliva of depressed and obsessional subjects.

Toxicomanias (including Alcoholism)

[See also Experimental Neuroses (including Toxicomanias)]

Various toxicomanias, including alcoholism, have been ascribed to stress, particularly the distress of being unable to cope with life situations, which engenders the desire to replace stark reality with the pleasant sensations and fictitious world offered by drugs.

The most common among these defense mechanisms is the craving for alcohol, for which treatment with glucocorticoids has been recommended but with very little practical success.

It has been claimed that certain people are genetically predisposed to alcoholism, that this is associated with evidence of hypocorticoidism and hypoglycemia, and, further, that chronic alcoholics go "through the stages of alarm reaction, resistance, and eventually exhaustion," but there is little tangible evidence with which to support such a view. Chronic alcoholics show a diminished excretion of certain corticoid metabolites after surgical trauma, but this appears to be a consequence of impaired steroid metabolism rather than of defective corticoid secretion.

About twelve hours after acute alcohol withdrawal, the 09:00 plasma cortisol level was above normal and then fell upon ingestion of moderate amounts of alcohol, instead of rising as it did in healthy controls.

In methadone-treated heroin addicts, the pituitary corticoid feedback (metyrapone) and stress (insulin hypoglycemia) mechanisms appear to function normally, but the circadian periodicity of corticoid production is often deranged. Heroin addicts not on methadone display a normal corticoid response to insulin and a normal fasting blood sugar level. However, their hyperglycemic reaction to oral glucose is delayed.

On the whole, it can be said that although stress may be involved in the motivation for toxicomanias, there is little evidence of a consistent and severe derangement in the hormonal responses to stressors that could be ascribed to drug addiction.

Toxicomanias (including Alcoholism)

(See also our earlier stress monographs, p. xiii)

Tintera, J. W., Lovell, H. W.: "Endocrine treatment of alcoholism." *Geriatrics* **4**: 274-280 (1949). B41,221/49

Alcoholism is viewed as a disease of adaptation, and a combined hormonal (mainly adrenocortical extract) and dietary treatment is recommended, mostly on speculative grounds.

Izikowitz, S., Mårtens, S., Dahlbom, L.: "On the cortisone treatment of alcoholism." *Acta Psychiatr. Scand.* [Supp.] **80**: 175-180 (1952). B53,935/52

Jellinek, E. M., Isbell, H., Lundquist, G., Tiebout, H. M., Duchêne, H., Mardones, J., MacLeod, L. D.: "The 'craving' for alcohol. A symposium by members of the WHO expert committees on mental health and on alcohol." *Q. J. Stud. Alcohol* **16**: 34-66 (1955). B56,097/55

Review on the effect of stress and corticoids upon alcohol craving in experimental animals and man.

Hershenson, D. B.: "Stress-induced use of alcohol by problem drinkers as a function of their sense of identity." *Q. J. Stud. Alcohol* **26**: 213-222 (1965). J22,989/65

Mendelson, J. H., Stein, S.: "Serum cortisol levels in alcoholic and nonalcoholic sub-

jects during experimentally induced ethanol intoxication." *Psychosom. Med.* **28**: 616-626 (1966).

G40,648/66

Tintera, J. W.: "Stabilizing homeostasis in the recovered alcoholic through endocrine therapy: evaluation of the hypoglycemia factor." *J. Am. Geriatr. Soc.* **14**: 126-150 (1966).

F62,090/66

People genetically predisposed to alcoholism have evidence of hypocorticoidism and hypoglycemia. "By the continued use of alcohol the organism as a whole goes through the stages of alarm reaction, resistance, and eventually exhaustion." [The data do not lend themselves to statistical evaluation (H.S.).]

Margraf, H. W., Moyer, C. A., Ashford, L. E., Lavalle, L. W.: "Adrenocortical function in alcoholics." *J. Surg. Res.* **7**: 55-62 (1967).

F98,222/67

Chronic alcoholics show a diminished excretion of certain corticoid metabolites after surgical trauma, but this is due to impaired steroid metabolism rather than to defective corticoid secretion by the adrenals.

Glickman, L., Blumenfield, M.: "Psychological determinants of 'LSD reactions.'" *J. Nerv. Ment. Dis.* **145**: 79-83 (1967).

J22,634/67

Myers, R. D., Holman, R. B.: "Failure of stress of electric shock to increase ethanol

intake in rats." *Q. J. Stud. Alcohol* **28**: 132-137 (1967). G45,967/67

The contradictory literature on the effect of stress upon ethanol consumption in animals is reviewed. In the present experiments, intermittent electric shocks failed to influence the voluntary ethanol intake of rats. "The use of unavoidable electric shock to the footpads does not seem to constitute a reliable method whereby volitional ethanol consumption increases in the selection-avoidance situation." However, other stressors may be effective.

Krengel, B.: "The effect of chronic alcoholism on ketosteroid and hydroxycorticoid excretion." *S. Afr. Med. J.* **42**: 83-84 (1968). G54,270/68

Merry, J., Marks, V.: "Plasma-hydrocortisone response to ethanol in chronic alcoholics." *Lancet* May 3, 1969, pp. 921-923 (18 refs.). H11,812/69

Steer, P., Marnell, R., Werk, E. E. Jr.: "Clinical alcohol hypoglycemia and isolated adrenocorticotrophic hormone deficiency." *Ann. Intern. Med.* **71**: 343-348 (1969) (34 refs.). G68,780/69

Cushman, P. Jr., Bordier, B., Hilton, J. G.: "Hypothalamic-pituitary-adrenal axis in methadone-treated heroin addicts." *J. Clin. Endocrinol. Metab.* **30**: 24-29 (1970). H20,853/70

"Although interference with the hypothalamic pituitary nycthemeral periodicity may occur in methadone-treated heroin addicts, their feedback (metyrapone) and stress (insulin hypoglycemia) mechanisms regulating hypothalamic-pituitary axis function appeared to operate normally." Heroin addicts not on methadone displayed an essentially normal corticoid metabolism and response to insulin (28 refs.).

Whitlock, F. A.: "The syndrome of barbiturate dependence." *Med. J. Aust.* **2**: 391-396 (1970). J22,715/70

Barbiturate addiction depends upon a combination of many factors, but among these, stressful experiences are predominant.

Bell, D. S.: "The precipitants of amphetamine addiction." *Br. J. Psychiatry* **119**: 171-177 (1971). J21,812/71

Mendelson, J. H., Ogata, M., Mello, N. K.: "Adrenal function and alcoholism. I. Serum cortisol." *Psychosom. Med.* **33**: 145-157 (1971). G83,763/71

In chronic alcoholics, ethanol increases serum cortisol levels.

Cushman, P. Jr.: "Growth hormone in narcotic addiction." *J. Clin. Endocrinol. Metab.* **35**: 352-358 (1972). H58,973/72

Merry, J., Marks, V.: "The effect of alcohol, barbiturate, and diazepam on hypothalamic/pituitary/adrenal function in chronic alcoholics." *Lancet* November 11, 1972, pp. 990-991. H61,781/72

"In acutely withdrawn alcoholics the 9 A.M. plasma-'cortisol' level was higher than normal after about 12 hours without alcohol and fell after the ingestion of moderate amounts of alcohol, instead of rising as it did in normal healthy patients. In acutely withdrawn alcoholics, amylobarbitone, like alcohol, caused a significant fall in plasma-'cortisol' levels between 9 A.M. and midday, whereas diazepam, in sufficient amounts to allay anxiety and produce subjective improvement, or placebo had no significant effect on the plasma-'cortisol' level."

Sattes, H.: "Psychische Spannungszustände und Sucht" (Mental stress and drug addiction). *Med. Klin.* **67**: 60-64 (1972).

J20,198/72

Abuse of hashish is found almost exclusively among juveniles and very young adults. It is the seeming harmlessness of many preparations that encourages this type of drug addiction, particularly among those unable to master the psychogenic stressors of daily life (31 refs.).

Allman, L. R.: "Group drinking during stress: effects on alcohol intake and group process." *Int. J. Addict.* **8**: 475-488 (1973).

J7,425/73

Reed, J. L., Ghodse, A. H.: "Oral glucose tolerance and hormonal response in heroin-dependent males." *Br. Med. J.* June 9, 1973, pp. 582-585. H72,290/73

The fasting blood sugar of heroin addicts was normal, but their hyperglycemic response to oral glucose was delayed. They had high resting insulin levels and a delayed peak after oral glucose. Their STH response was also abnormal.

Klempel, K.: "Über die Nebennierenrinden- und Schilddrüsen-Aktivität von Alkoholikern und Polytoxikomanen" (Function of the adrenal cortex and thyroid in alcoholics and "polytrop" toxicomaniacs). *Nervenarzt* **44**: 268-272 (1973). J3,906/73

In both alcoholics and "polytrop" toxicomaniacs, 17-OHCS elimination is increased (61 refs.).

Litman, G. K.: "Stress, affect and craving in alcoholics. The single case as a research strategy." *Q. J. Stud. Alcohol* **35**: 131-146 (1974). *J13,260/74*

Khantzian, E. J., Mack, J. E., Schatzberg, A. F.: "Heroin use as an attempt to cope: clinical observations." *Am. J. Psychiatry* **131**: 160-164 (1974). *J21,511/74*

The authors attempt to demonstrate that the addict's use of opiates "represents a unique and characteristic way of dealing with a range of human problems involving emotional pain, stress, and dysphoria."

Miller, P. M., Hersen, M., Eisler, R. M., Hilsman, G.: "Effects of social stress on operant drinking of alcoholics and social drinkers." *Behav. Res. Ther.* **12**: 67-72 (1974). *J20,847/74*

Various techniques of testing the voluntary intake of alcohol, comparing alcoholics and social drinkers. "Alcoholics significantly increased their operant responding to obtain alcohol following stress conditions while social drinkers did not."

Wessels, C. H.: "Psychologische Motive des Drogenmissbrauches" (Psychologic motives of drug abuse). *Med. Klin.* **69**: 1015-1026 (1974). *H87,827/74*

General review on motivation in drug

abuse, with special reference to psychologic and social stressors (44 refs.).

"Alcoholics may perceive life in different fashion." *J.A.M.A.* **229**: 630-631 (1974). *H88,692/74*

Report on a congress in which statistical studies were interpreted as indicating that alcoholics "are under constant stress because of misperceptions about the effect of life changes." They rated "various events that most people consider very stressful, such as divorce, separation, death of a spouse, or loss of a job, as requiring less life change than is, in fact, needed. However, events that most people do not perceive as very stressful—vacations, Christmas, or changes in eating and sleeping habits—were rated as higher stress items."

Takki, S., Tammisto, T.: "The effect of operative stress on plasma catecholamine levels in chronic alcoholics." *Acta Anaesthesiol. Scand.* **18**: 127-132 (1974). *J15,791/74*

In chronic alcoholics, tolerance to anesthetics is reflected in an increased sympathetic activity during "operative stress."

Glass, G. B. J., Pitchumoni, C. S., Kawashima, K.: "Gastric injury from acute and chronic alcohol use: its potentiation by stress" (abstracted). *Clin. Res.* **22**: 558A (1974). *H90,434/74*

In mice, "acute ethanol excess and stress are more important than underlying gastritis in causing mucosal injury and bleeding."

Senile Psychosis

In senile psychotic women, the plasma corticoid and eosinophil responses to the stressor effect of blindfolding for thirty minutes were excessive, but their reaction to ACTH remained normal. It was concluded that senile psychosis "might have its cause in a dysfunction of either the pituitary or the hypothalamus or both."

However, there is no clearcut evidence that senile psychosis is directly related to stress, other than the data (discussed under Theories) suggesting that aging in general is largely the consequence of the cumulative effect of the stressors to which an individual is exposed during a lifetime.

Senile Psychosis

(See also our earlier stress monographs, p. xiii)

Kral, V. A., Grad, B.: "Adrenal cortical stress effects in senility." *Can. Psychiatr. Assoc. J.* **5**: 8-18 (1960). *C87,139/60*

Studies on electrolyte and eosinophil changes in young and old people, as well as in patients with senile dementia (28 refs.).

Kral, V. A.: "Stress and mental disorders of the senium." *Med. Serv. J. Can.* **18**: 363-370 (1962). *D25,424/62*

Review of the author's work suggesting that "the lowered stress resistance of the aged may be one of the determining factors of, at least, some of the mental disorders encountered in the aged. On the other hand, stress endured in the past may play a role in the aetiology of the psychoses of the senium." However, "the mental disorders of the senium per se may be so stressful to the aging organism as to accelerate senescent decline or even precipitate death."

Kral, V. A., Grad, B., Cramer-Azima, F., Russell, L.: "Biologic, psychologic and sociologic studies in normal aged persons and patients with senile psychosis." *J. Am. Geriatr. Soc.* **12**: 21-37 (1964). F329/64

In elderly normal individuals and in senile psychotics, thirty minutes of blindfolding was used as a stressor procedure, and various determinations were made before and after this test. "Plasma corticoid levels were significantly higher in senile psychotic women than in all other persons in the study. The salivary sodium/potassium ratio was significantly higher in the patients with senile psychosis, whether male or female, than in normal elderly persons, but there was no statistically significant difference in the circulating eosinophil counts between the two main groups. However, the pattern of the eosinophilic response to blindfolding showed a statistically significant change in the senile psychotic patients but not in the normal subjects."

Grad, B., Kral, V. A., Payne, R. C., Berenson, J.: "Adrenal cortical function in the psychoses of later life." *Laval Méd.* **37**: 126-134 (1966). G37,699/66

There were no significant differences in plasma cortisol and corticosterone levels between male or female normal and senile psychotic patients. However, normal men had significantly higher urinary corticoid excretions than psychotic subjects. This difference was less obvious in women.

Kral, V. A., Grad, B., Payne, R. C., Berenson, J.: "The effect of ACTH on the plasma and urinary corticoids in normal elderly persons and in patients with senile psychosis." *Am. J. Psychiatry* **123**: 1260-1269 (1967). G45,322/67

In patients with senile psychosis, the rise in plasma cortisol and corticosterone levels following exposure to physical and psychologic stressors was excessive, but their response to ACTH remained within normal limits. This "might have its cause in a dysfunction of either the pituitary or the hypothalamus or both."

Grad, B., Kral, V. A.: "The delayed effect of ACTH administration on the plasma corticoid level of normal elderly persons and patients with chronic brain syndrome." *J. Am. Geriatr. Soc.* **17**: 15-24 (1969).

H6,490/69

"Patients with senile or arteriosclerotic brain syndrome are more reactive to stress than are normal aged subjects—their adrenal cortices are more reactive" to ACTH.

Kral, V. A.: "Stress and senile psychosis." Proc. 5th World Congr. of Psychiatry, Mexico, D.F. 1971. *Int. Congr. Ser.* No. 274, pp. 331-337 (1973). J17,514/73

Resistance to stress decreases with age. Hormonal studies indicate "firstly, that there is a decline in adrenocortical function with aging; and secondly, that patients suffering from organic psychoses of the senium, particularly senile dementia, show a tendency to a delayed adrenocortical overactivity, to ACTH stimulation as well as in stressful situations. It would appear, therefore, that cerebral pathology modified the function of the adrenal cortex."

Müller, H. F., Grad, B.: "Clinical-psychological, electroencephalographic, and adrenocortical relationships in elderly psychiatric patients." *J. Gerontol.* **29**: 28-38 (1974).

J9,661/74

Other Neuropsychiatric and Psychosomatic Diseases

Various neuropsychiatric derangements that are often regarded as neurotic have been discussed previously in the section on Neuroses. Among these are *headache*, *backache*, *bruxism* and *autism*.

It is also well known that *Parkinson's disease* is aggravated by psychogenic stressors, and that *epileptic attacks* can be provoked in predisposed individuals by a variety of stressors, particularly lack of sleep, emotional arousal and intellectual overexertion.

Stress may also play a role in *retrograde amnesia, insomnia, multiple sclerosis, susto, Huntington's disease* and so on.

The association of *mongoloid idiocy* (Down's syndrome) with a dysfunction of the hypothalamus-pituitary system has not yet been established, but appears to be probable. This disease, being congenital, has been discussed under Prenatal Stress Conducive to Malformations or Stillbirths.

Other Neuropsychiatric and Psychosomatic Diseases

(See also our earlier stress monographs, p. xiii)

Schwab, R. S., Prichard, J. S.: "Situational stresses and extrapyramidal disease in different personalities." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 48-60. Baltimore: Williams & Wilkins, 1950. B51,894/50

There appears to be a relationship between stress and *Parkinson's disease*, since its manifestations are aggravated by psychogenic stressors (12 refs.).

Barucci, M.: "Su le possibili correlazioni tra epilessia e sindrome generale di adattamento" (Possible correlations between epilepsy and general adaptation syndrome). *Folia Endocrinol. (Roma)* 8: 1027-1053 (1955). C15,159/55

There are close relationships between the G.A.S. and *epilepsy*, since epileptic fits can be caused by or act as the cause of stress.

Persky, H., Grinker, R. R., Hamburg, D. A., Sabshin, M. A., Korchin, S. J., Basowitz, H., Chevalier, J. A.: "Adrenal cortical function in anxious human subjects. Plasma level and urinary excretion of hydrocortisone." *Arch. Neurol. Psychiatry* 76: 549-558 (1956). C25,458/56

In *anxious* patients, plasma cortisol and urinary corticoid excretion were increased, but stress interviews failed to cause further rises.

Marcus, J.: "The interrelations of myasthenia gravis and psychic stress: presentation of a case." *Isr. Med. J.* 21: 178-184 (1962). D54,093/62

Patients with *myasthenia gravis* are particularly sensitive to the effects of psychic stressors.

Weiner, H.: "Subcortical substrate of autonomic and psychological stress." *Percept. Mot. Skills* 17: 259-262 (1963).

J23,591/63

Discussion of stress and *Parkinson's disease*.

Yeager, C. L., Gianascol, A. J.: "Psychological stress and *petit mal* variant, a telemeter study." *Am. J. Psychiatry* 119: 996-997 (1963). J23,460/63

Tenen, S. S.: "Retrograde amnesia from electroconvulsive shock in a one-trial appetitive learning task." *Science* 148: 1248-1250 (1965). J22,825/65

Schwab, R. S., Zieper, I.: "Effects of mood, motivation, stress and alertness on the performance in *Parkinson's disease*." *Psychiat. Neurol. (Basel)* 150: 345-357 (1965). G40,007/65

"Akinesia paradoxica is defined as a complete loss of akinesia and disability of *Parkinson's disease* under emergency, extraordinary stimulation such as a house afire, but it lasts only a minute or two, and the patient is then back to his previous degree of disability."

Chorover, S. L., Schiller, P. H.: "Reexamination of prolonged retrograde amnesia in one-trial learning." *J. Comp. Physiol. Psychol.* 61: 34-41 (1966). J22,883/66

Electroconvulsive shock may cause prolonged *retrograde amnesia*.

Marsden, C. D., Owen, D. A. L.: "Mechanisms underlying emotional variation in parkinsonian tremor." *Neurology (Minneap.)* 17: 711-715 (1967). G48,499/67

Observations suggesting that "the effect of emotional and mental stress on *parkinsonian tremor* is mediated by release of endogenous adrenaline and by direct influence of the prefrontal cortex on brainstem reticular formation" (14 refs.).

Antonovsky, A., Kats, R.: "The life crisis history as a tool in epidemiological research." *J. Health Soc. Behav.* 8: 15-21 (1967). J23,004/67

Epidemiologic studies in Israel using a newly-developed questionnaire suggest some relationship between *multiple sclerosis* and

stress "within the framework of a multi-factor theory of etiology."

O'Neill, C. W.: "Sex differences in the incidence of susto in two Zapotec Pueblos: an analysis of the relationships between sex role expectations and a folk illness." *Ethnology* 7: 95-105 (1968). J19,563/68

Susto is a name given to an illness common in various parts of Latin America and also known as *espanto*, *miedo*, *pasmo* and *desasombro*. It has somewhat different characteristics in various locations, but in general, "the susto sufferer is listless, depressed, and timid, usually exhibiting a loss of interest in his customary affairs, and frequently complaining of poor appetite and loss of strength. In sleep, the patient is restless, often complaining of troublesome dreams or other manifestations of sleep disturbance. One of the more consistently encountered folk beliefs is that the asustado (sufferer from susto) has lost his soul to a malignant spirit and that the patient's cure rests upon the recovery of the soul through specific treatments or rites performed by a curing specialist." The condition is more common among women than among men. In the author's opinion, "susto represents an important culturally and socially sanctioned mechanism of escape and rehabilitation for persons suffering from intra-culturally induced stress resulting from failure in sex-role performance. The ethnographic evidence encountered in the two villages indicated that women stand the greater likelihood of experiencing role stress both because their sex roles are more narrowly defined than are those for men and because fewer outlets of escape from stress are open to them in this culture."

Baekeland, F., Koulack, D., Lasky, R.: "Effects of a stressful presleep experience on electroencephalograph-recorded sleep." *Psychophysiology* 4: 436-443 (1968).

J22,711/68

Goldblatt, D.: "Seizure disorder in gerbils" (abstracted). *Neurology* (Minneapolis) 18: 303-304 (1968). J22,710/68

In genetically predisposed gerbils, stressors (electroshock, photic or auditory stimulation) can precipitate seizures which greatly resemble *epilepsy* in man.

"Stress, multiple sclerosis, and corticosteroids." *Lancet* March 7, 1970, pp. 508-509.

H21,827/70

Review of the literature, suggesting a relationship between stress and relapses of *multiple sclerosis*.

Mei-Tal, V., Meyerowitz, S., Engel, G. L.: "The role of psychological process in a somatic disorder: *multiple sclerosis*. 1. The emotional setting of illness onset and exacerbation." *Psychosom. Med.* 32: 67-86 (1970). J21,701/70

Semenov, S. F., Kamenskaia, V. M.: "A clinico-electroencephalographic study of the effect of emotional stress on the convulsive predisposition of *epileptic* patients." *Zh. Nevropatol. Psichiatr.* 72: 227-233 (1972) (Russian). J20,572/72

Korenyi, C., Whittier, J. R., Conchado, D.: "Stress in Huntington's disease (chorea)." *Dis. Nerv. Syst.* 33: 339-344 (1972). G91,806/72

"The review of the literature revealed that 38 publications out of 205 (18.5%) listed the presence of stress in the anamnesis of 48 patients which either triggered the onset or aggravated the disease." It is suggested that protection against stress could have a prophylactic and therapeutic value in *Huntington's disease* (41 refs.).

Arbona, N. J., Patterson, S. M., Cape, C. A.: "Endogenous ACTH induced remission in myasthenia gravis." *Bull. Los Angeles Neurol. Soc.* 38: 183-187 (1973).

J7,111/73

In *myasthenia gravis*, remissions occur "following infections, anticholinesterase medication withdrawal or other stressful conditions." This effect may be due to stress-induced ACTH discharge.

Friis, M. L., Lund, M.: "Stress convulsions." *Arch. Neurol.* 31: 155-159 (1974).

J16,341/74

"Stress convulsions are defined as *epileptic* attacks in persons who have not previously had unprovoked epileptic attacks, and who, during the period immediately prior to the attack, have been exposed to 'stressing' exogenous influences such as lack of sleep, emotional stress, or somatic or intellectual overexertion" (34 refs.).

Bock, J. E.: "The hypothalamic-pituitary-gonadal and adrenal cortical function in adult women with *Down's syndrome*." *Acta Obstet. Gynecol. Scand.* 53: 69-72 (1974).

J13,366/74

Experimental Neuroses (including Toxicomanias)

In continuation of Pavlov's classic experiments, a great deal of work has been done on the induction of neuroses by stressful conditioned reflexes.

In neurotic goats, the presence of the mother, regardless of her behavior towards her offspring, had an ameliorating effect on the nervous responses of the young to environmental stress.

Liddell, in his classic experiments on sheep and goats, used ten-second conditioned signals separated by constant time-intervals. When the interval between all signals was two minutes, a type of experimental neurosis resulted which was characterized by tonic immobility taking the form of severe muscular rigidity in a particular posture. This suggests a distorted startle pattern. Treatment with the cortical extracts available at the time these experiments were performed allegedly resulted in some improvement.

The literature on the effect of stress upon ethanol consumption in animals is contradictory. In one carefully-conducted series of experiments, intermittent electric shocks failed to affect voluntary ethanol intake in rats that exhibited their normal aversion to alcohol. However, the behavioral stress of cued, random unavoidable shock and non-cued unavoidable shock is quite different; an increase in volitional ethanol consumption occurs only following interference with a learned avoidance response.

"Isolation stress" increases the voluntary consumption of alcohol by rats that have free access to drinking water. On the other hand, intermittent electric shocks failed to influence voluntary alcohol intake in this species.

Experimental Neuroses (including Toxicomanias)

(See also our earlier stress monographs, p. xiii)

Liddell, H.: "Some specific factors that modify tolerance for environmental stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 155-171. Baltimore: Williams & Wilkins, 1950.

B51,903/50

Résumé of the author's extensive investigations concerning the experimental induction of neurosis by stressful conditioned-reflex techniques. In neurotic goats, "the presence of the mother, regardless of her behavior toward her offspring, had an ameliorating effect on the young animal subjected to environmental stress."

Liddell, H. S.: "Experimental induction of psychoneuroses by conditioned reflex with stress." In: *The Biology of Mental Health and Disease*, pp. 498-507. New York: P B Hoeber, 1952.

B87,746/52

Liddell, H. S.: "Effect of corticosteroids in experimental psychoneurosis." In: *The Biol-*

ogy of Mental Health and Disease, pp. 591-594. New York: P B Hoeber, 1952.

B68,669/52

Review on the effect of corticoids upon experimentally induced psychoneurosis in sheep, with a general outline of the relationship between these psychic disturbances and Pavlov's conditioned reflexes, Cannon's emergency theory, and Selye's G.A.S. The technique used "in the sheep or goat was to employ ten-second conditioned signals separated by constant time intervals. When the interval between all signals was two minutes a type of 'experimental neurosis' resulted which we have characterized as tonic immobility. At the signal the animal reacts with pronounced muscular rigidity, lifting the stiffly extended forelimb from the shoulder instead of flexing it freely in anticipation of the electric shock as the normal animal does. This neurotic pattern suggests a frozen and distorted startle pattern." Treatment with the cortical extracts available at the time of the first experiment revealed improvement, whereas EP (usually present as a contaminant) appeared to aggravate this effect. [The paper was followed by an invited discussion

in which Selye summarized the pertinent aspects of his G.A.S. concept (H.S.).]

Eränkö, O., Muittari, A.: "Effects of experimental neurosis on the thyroid and adrenal glands of the rat." *Acta Endocrinol.* (Kbh.) **26**: 109-116 (1957). C40,371/57

In rats that developed a neurosis owing to the frustration of conditioned reflexes, the resulting adrenal and thyroid hypertrophy was ascribed to the G.A.S.

Casey, A.: "The effect of stress on the consumption of alcohol and reserpine." *Q. J. Stud. Alcohol* **21**: 208-216 (1960).

G91,496/60

Electroshock increases voluntary ethanol consumption in the rat.

Korn, S. J.: "The relationship between individual differences in the responsivity of rats to stress and intake of alcohol." *Q. J. Stud. Alcohol* **21**: 605-617 (1960).

D432/60

Rats "more responsive to stress may select alcohol solutions as a learned adaptive response. The alcohol may function to attenuate the effects of stress."

Myers, R. D.: "Effects of meprobamate on alcohol preference and on the stress of response extinction in rats." *Psychol. Rep.* **8**: 385-392 (1961).

J12,455/61

Havlíček, V.: "Experimental neurosis and Selye's adaptation syndrome." *Activ. Nerv. Sup.* (Praha) **4**: 322-330 (1962) (Czech).

G57,692/62

Leikola, A.: "Influence of stress on alcohol intoxication in rats." *Q. J. Stud. Alcohol* **23**: 369-375 (1962).

D38,054/62

Rats stressed by swimming exhibited an accelerated clearance of orally-administered ethanol. Upon intraperitoneal treatment, they showed the same alcohol concentrations in blood as unstressed animals. "The stressed rats, however, were less intoxicated than the unstressed animals with corresponding blood alcohol levels." Possibly, adrenal hormones released during stress may be responsible for this increased tolerance.

Clay, M. L.: "Conditions affecting voluntary alcohol consumption in rats." *Q. J. Stud. Alcohol* **25**: 36-55 (1964) (28 refs.).

G13,871/64

Rodgers, D. A., Thiessen, D. D.: "Effects of population density on adrenal size, behavioral arousal, and alcohol preference of

inbred mice." *Q. J. Stud. Alcohol* **25**: 240-247 (1964). G19,626/64

Kamano, D. K., Arp, D. J.: "Chlordiazepoxide (Librium) consumption under stress conditions in rats." *Int. J. Neuropsychiatry* **1**: 189-192 (1965). F41,678/65

In rats that had a free choice between water and a dilute chlordiazepoxide solution, the stress of electroshock unexpectedly decreased preferential consumption of the tranquilizer.

Powell, B. J., Kamano, D. K., Martin, L. K.: "Multiple factors affecting volitional consumption of alcohol in the Abrams Wistar rat." *Q. J. Stud. Alcohol* **27**: 7-15 (1966).

J23,052/66

Increased volitional alcohol consumption was observed in female rats, while the reverse occurred in males, upon exposure to stressors (11 refs.).

Myers, R. D., Holman, R. B.: "Failure of stress of electric shock to increase ethanol intake in rats." *Q. J. Stud. Alcohol* **28**: 132-137 (1967). G45,967/67

The contradictory literature on the effect of stress upon ethanol consumption in animals is reviewed. In the present experiments, intermittent electric shocks failed to influence the voluntary ethanol intake of rats. "The use of unavoidable electric shock to the footpads does not seem to constitute a reliable method whereby volitional ethanol consumption increases in the selection-avoidance situation." However, other stressors may be effective.

Soulairac, A., Steenkiste, J. van, Steenkiste, J. N. van: "Influence d'un stress sur le comportement de soif hydrique et alcoolique du rat London Black" (Effect of stress on alcohol and water consumption in London Black rats). *J. Physiol. (Paris)* **59** Supp.: 296-297 (1967). G47,904/67

Cicero, T. J., Myers, R. D., Black, W. C.: "Increase in volitional ethanol consumption following interference with a learned avoidance response." *Physiol. Behav.* **3**: 657-660 (1968). H28,222/68

Discriminated shock avoidance tasks increased the voluntary ethanol intake of rats when unavoidable random shock signals were simultaneously delivered. During control shock avoidance periods, or when noncued unavoidable shocks were delivered, the animals exhibited their normal aversion to etha-

nol. The behavioral stress of cued random unavoidable shock and noncued unavoidable shock must be clearly distinguished in this respect. "For the first time a relationship has been established in animals between a so-called psychological stressor and the volitional selection of ethanol" (14 refs.).

Gowdey, C. W., Klaase, J.: "Voluntary alcohol consumption and avoidance learning by rats. Lack of correlation." *Q. J. Stud. Alcohol* **30**: 336-344 (1969). G66,874/69

Wright, J. M. von, Pekanmäki, L., Malin, S.: "Effects of conflict and stress on alcohol intake in rats." *Q. J. Stud. Alcohol* **32**: 420-433 (1971). G84,239/71

In rats repeatedly exposed to the stressor effect of electroshocks, voluntary alcohol consumption may increase although drinking water is also available ad libitum.

Opsahl, C. A., Hatton, G. I.: "Volitional ethanol increases during acquisition and extinction of avoidance responding." *Physiol. Behav.* **8**: 87-93 (1972). G90,591/72

"In a discriminated shock avoidance situation, rats offered a choice between water and ethanol increased their ethanol consumption significantly during acquisition of the avoidance response and when random unavoidable shock signaled by a warning light was simultaneously delivered." However, the thymus and adrenal weights did not change significantly, and plasma corticosterone levels were only minimally elevated. Literature concerning increased voluntary ethanol consumption in stressed animals is quoted (15 refs.).

Holmes, P. W., Smith, B. L.: "Ethanol consumption by pigeons under stress." *Q. J. Stud. Alcohol* **34**: 764-768 (1973).

J21,557/73

Pigeons chronically exposed to repeated electroshocks voluntarily drank solutions of 1 to 4 percent ethanol in preference to water.

Anisman, H., Waller, T. G.: "Effects of inescapable shock and shock-produced conflict on self selection of alcohol in rats." *Pharmacol. Biochem. Behav.* **2**: 27-33 (1974).

J21,237/74

The stressor effect of inescapable shock increased self selection of alcohol.

Hill, S. V., Goldstein, R.: "Effect of p-chlorophenylalanine and stress on alcohol consumption by rats." *Q. J. Stud. Alcohol* **35**: 34-41 (1974).

J13,259/74

PCPA caused a marked depletion of brain 5-HT and reduced volitional alcohol intake in the rat. Under certain conditions this effect could be inhibited by stressors (for example, electroshock). Indeed, there is no evidence that under ordinary conditions PCPA induces avoidance of alcohol (20 refs.).

Parker, L. F., Radow, B. L.: "Isolation stress and volitional ethanol consumption in the rat." *Physiol. Behav.* **12**: 1-3 (1974).

J9,601/74

Isolation increases the voluntary consumption of ethanol by rats who have the alternative of drinking water. This change is ascribed to "isolation stress."

OTHER DISEASES OF ADAPTATION

Diabetes Mellitus

There can be no doubt that predisposition to diabetes is a genetically-inherited trait. However, in predisposed individuals, exposure to severe stressors can precipitate its development while in cases of mild, controlled diabetes, stress undoubtedly aggravates the condition and may provoke an increase in blood ketones and considerable fluctuations in blood sugar, which increase requirements for insulin or oral antidiabetic drugs. In this respect not only physical but also psychogenic stressors may act as precipitating agents.

Stress produces polyuria in both normal and diabetic persons; however, in the latter, this may be accompanied by a massive loss of glucose and electrolytes, which contributes to the development of dehydration and coma. The theory is advanced that in diabetes an appropriate, normal adaptive response to starvation (associated with

stress) may assume pathogenic importance. In any event, several investigators concluded that "diabetes mellitus is a disorder of adaptation, and that persons showing this disorder react to various life stresses with a physiological response which is appropriate to starvation, but ineffective in dealing with the stresses to which they have been exposed."

Another group of investigators found that in patients undergoing surgery the glucose tolerance curves assume a diabetic pattern. They came to essentially the same conclusion: "the hyperglycemia occurring after hemorrhage and after tissue injury is presumably a purposeful metabolic alarm reaction tending to maintain an adequate supply of fuel to the brain and peripheral nerves during stress conditions," but in predisposed individuals it may precipitate diabetes.

In rats, steroid diabetes caused by cortisone overdosage is ameliorated by carcinoma transplants, surgery, toxicants and other stressors, although these stimulate endogenous glucocorticoid secretion and hence would be expected to induce an inverse response. Here the situation is probably quite different from that which exists in patients hereditarily predisposed to diabetes. Catecholamines inhibit insulin release by stimulation of pancreatic alpha receptors and raise it by stimulation of beta receptors. Hence, the insulin component in diabetes depends upon complex conditioning factors that determine whether one or the other of these effects will predominate. Activation of the sympathetic nervous system inhibits glucose-induced insulin secretion, but this effect is balanced by simultaneous stimulation of beta receptors. Intense stress may result in metabolic changes similar to those of diabetes and a poor insulin response to glucose challenge.

Diabetes Mellitus

(See also our earlier stress monographs, p. xiii)

Hinkle, L. E. Jr., Conger, G. B., Wolf, S.: "Studies on diabetes mellitus: the relation of stressful life situations to the concentration of ketone bodies in the blood of diabetic and non-diabetic humans." *J. Clin. Invest.* **29**: 754-769 (1950). B49,214/50

Various interpersonal stress situations interpreted as threats may produce an increase in blood ketones and fluctuations in blood sugar in both diabetic and nondiabetic persons. When relative emotional security is achieved the blood chemical changes subside, even without extra insulin or other therapeutic measures. These disturbances are ascribed to stimulation of the pituitary-adrenocortical axis and illustrate how psychogenic stress can unmask a latent disease tendency. The literature on stress and diabetes is discussed in detail (63 refs.).

Hinkle, L. E. Jr., Wolf, S.: "Studies in diabetes mellitus: changes in glucose, ketone, and water metabolism during stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life*

Stress and Bodily Disease, pp. 338-389. Baltimore: Williams & Wilkins, 1950.

B51,913/50

During stress, polyuria may occur in both diabetic and nondiabetic persons. However, in the latter a massive loss of glucose and electrolytes contributes to the development of dehydration and coma. "The life history of one diabetic person was presented; and a brief formulation of a possible meaning of diabetes mellitus as the inappropriate use of a normal adaptive mechanism to starvation because of early conditioning, and perhaps of constitutional predisposition, has been suggested" (76 refs.).

Hinkle, L. E. Jr., Edwards, C. J., Wolf, S.: "Studies in diabetes mellitus. II. The occurrence of a diuresis in diabetic persons exposed to stressful life situations, with experimental observations on its relation to the concentration of glucose in blood and urine." *J. Clin. Invest.* **30**: 818-837 (1951).

B61,253/51

"In persons with diabetes mellitus, exposure to stressful life situations may lead to a diuresis. This diuresis is characterized by a 200-500% increase in the rate of water ex-

cretion, accompanied by a rise in the excretion of chlorides and ketone bodies.... When stress diuresis occurs in diabetic persons who are glycosuric, the rate of glucose excretion rises in parallel with the rate of water excretion, and there is no major change in the glucose concentration of the urine" (34 refs.).

Hinkle, L. E. Jr., Evans, F. M., Wolf, S.: "Studies in diabetes mellitus. III. Life history of three persons with labile diabetes, and relation of significant experiences in their lives to the onset and course of the disease." *Psychosom. Med.* 13: 160-183 (1951). J5,386/51

Studies indicate that "diabetes mellitus is a disorder of adaptation, and that persons showing this disorder react to various life stresses with a physiologic response which is appropriate to starvation, but inappropriate to the deprivations which they have suffered."

Hinkle, L. E. Jr., Evans, F. M., Wolf, S.: "Studies in diabetes mellitus. IV. Life history of three persons with relatively mild, stable diabetes, and relation of significant experiences in their lives to the onset and course of the disease." *Psychosom. Med.* 13: 184-202 (1951). B37,226/51

Often the onset of diabetes occurs at times of "significant life stress." The findings reported here "are consistent with the hypothesis that diabetes mellitus is a disorder of adaptation, and that persons showing this disorder react to various life stresses with a physiological response which is appropriate to starvation, but ineffective in dealing with the stresses to which they have been exposed."

Hinkle, L. E. Jr., Wolf, S.: "The effects of stressful life situations on the concentration of blood glucose in diabetic and non-diabetic humans." *Diabetes* 1: 383-392 (1952). B75,041/52

In healthy people, stressful life experiences usually cause a fall in the postabsorptive blood glucose concentration, often to definitely hypoglycemic levels, and a rise in circulating ketone bodies. In diabetics, definite ketoacidosis sometimes ensues in association with hyperglycemia (26 refs.).

Hinkle, L. E. Jr., Wolf, S.: "Importance of life stress in course and management of diabetes mellitus." *J.A.M.A.* 148: 513-520 (1952). B66,606/52

"Study of the life histories and daily experiences of persons with diabetes indicates

that many of the apparently spontaneous fluctuations in the syndrome are the results of life stress."

Hinkle, L. E. Jr., Wolf, S.: "A summary of experimental evidence relating life stress to diabetes mellitus." *J. Mt. Sinai Hosp.* 19: 537-570 (1952). B81,801/52

In diabetics, various life stress situations can aggravate hyperglycemia and cause ketosis much more readily than in normals. Apparently, "life experiences are of great importance in the onset and course of the disease" (61 refs.).

Frank, E.: "Über die Anwendung der psychosomatischen Betrachtungs- und Forschungsweise auf Diabetes-Probleme" (Application of psychosomatic concepts to diabetes problems). *Acta Neurolog. (Wien)* 9: 286-299 (1954). J25,478/54

Peck, F. B., Peck, F. B. Jr.: "Tautologous diabetic coma—a behavior syndrome. Multiple unnecessary episodes of diabetic coma." *Diabetes* 5: 44-48 (1956). C25,191/56

A syndrome characterized by extremely frequent diabetic coma is ascribed to stressful situations.

Ellenberg, M.: "Diabetic neuropathy following stress situations." *Am. J. Med. Sci.* 238: 418-426 (1959). C75,972/59

Jenson, R. L.: "Diabetes in flying personnel." *Aerosp. Med.* 32: 1127-1134 (1961). D16,277/61

Stress associated with flying, especially combat missions, may lead to aggravation of preexistent diabetes.

Ingle, D. J., Ingle, D. J.: "The effect of some stressors on symptoms of cortisone overdosage." *J. Okla. State Med. Assoc.* 54: 113-117 (1961). D91,762/61

In rats, steroid diabetes is ameliorated by carcinoma transplants, surgery, toxic drugs and various other stressors, although these stimulate glucocorticoid production and hence could be expected to induce an inverse response.

Sukiennik, S.: "The influence of states of mental tension on diabetes mellitus." *Dapim Refuim* 21: 97-104 (1962) (Hebrew).

J22,341/62

Slawson, P. F., Flynn, W. R., Kollar, E. J.: "Psychological factors associated with the onset of diabetes mellitus." *J.A.M.A.* 185: 166-170 (1963). E22,193/63

"Psychological stress may trigger the ini-

tial metabolic imbalance in predisposed individuals" (22 refs.).

Bruni, B.: "Anamnesi psicologica del diabete. Sui rapporti tra alterazioni psicoemotive e inizio del diabete" (Psychologic history of the diabetic. On the relation between psychomotor alterations and the beginning of diabetes). *Minerva Med.* **54**: 3516-3524 (1963). E36,698/63

Discussion of the pathogenic importance of "acute emotional stress" in diabetes, with special reference to its legal implications.

Danowski, T. S.: "Emotional stress as a cause of diabetes mellitus." *Diabetes* **12**: 183-184 (1963). J10,797/63

It remains uncertain whether emotional stress can produce diabetes in a totally normal individual, but there is no doubt "that stress intensifies known preexistent diabetes mellitus, brings to clinical recognition previously unrecognized actual diabetes, and may convert prediabetes to actual diabetes."

Larcan, A.: "Stress et diabète" (Stress and diabetes). *Agressologie* **7**: 447-458 (1966).

F75,116/66

Meticulous collection of literature on the aggravation of preexistent, and the production of previously undetected diabetes by a variety of stressors. This may have legal implications in constituting a basis for awarding compensation (over 100 refs.).

Clayer, J. R., Dumbrill, M. N.: "Diabetes mellitus and mental illness." *Med. J. Aust.* **1**: 901-904 (1967). G47,271/67

Although the literature clearly indicates that emotional stress can elicit diabetes in previously nonsymptomatic individuals, and the incidence of diabetes in South Australian mental hospitals was found to be high, it was low in other psychiatric services. "This would mean that observations based on the incidence of diabetes amongst mental hospital patients alone are biased. We do not believe that the 'abnormal mental frailty of the diabetic' has yet been proved."

Vandenbergh, R. L., Sussman, K. E., Vaughan, G. D.: "Effects of combined physical-anticipatory stress on carbohydrate-lipid metabolism in patients with diabetes mellitus." *Psychosomatics* **8**: 16-19 (1967). F77,327/67

Felix, H.: "Etude critique du diabète sucré émotionnel" (Critical study of emotional diabetes mellitus). *Diabète (Le Raincy)* **15**: 41-49 (1967). F95,827/67

Psychogenic stressors play an indisputable etiologic role in the pathogenesis of juvenile diabetes in predisposed individuals.

Tsukushi, S.: "Stress and diabetes mellitus, with special reference to surgical tissue." *Jap. J. Clin. Med.* **26**: 640-644 (1968). J24,638/68

Tauber, J. B.: "Diabetes in an occupational group." *J. Occup. Med.* **10**: 65-66 (1968). J15,861/68

The incidence of diabetes mellitus in truck drivers was about ten times the national average. [In view of the small number of cases examined, confirmation on a larger scale will be necessary (H.S.).]

Baker, L., Barcay, A., Kaye, R., Hague, N.: "Beta adrenergic blockade and juvenile diabetes: acute studies and long-term therapeutic trial. Evidence for the role of catecholamines in mediating diabetic decompensation following emotional arousal." *J. Pediatr.* **75**: 19-29 (1969) (25 refs.). G67,253/69

Schrub, J.-C., Dubuisson, M.: "Diabète et traumatisme" (Diabetes and injury). *Cah. Méd.* **12**: 285-294 (1971) (88 refs.). J20,896/71

Jordan, H. W., Kalish, M. D.: "Diabetic acidosis and emotional stress. A case report." *J. Natl. Med. Assoc.* **63**: 256-258 (1971). J20,759/71

Diabetic acidosis can be elicited by emotional stress.

Ivanova, I. I., Lapshina, V. F.: "Stress in rats with alloxan diabetes." *Biull. Èksp. Biol. Med.* **74** No. 10: 25-28 (1972) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **74**: 1247-1249 (1972). J21,622/72

In alloxan diabetic rats, unlike in controls, stress does not diminish but actually increases the corticosterone concentration in the adrenals. "Secretion of the hormone into the blood in response to stress is not reduced in diabetic animals."

Koski, M. L., Kumento, A.: "Repeated episodes of ketoacidosis as psychosomatic reactions in juvenile diabetes: A case report." *Duodecim* **88**: 1450-1453 (1972). H77,980/72

Review on psychosomatic reactions in juvenile diabetics, with a case history of a girl who showed severe episodes of ketoacidosis precipitated by emotional stress.

Casey, J. H.: "Modern concepts in the management of surgical diabetic patients." *Anaesth. Intensive Care* 1: 144-149 (1972). H78,671/72

The stress of surgery and anesthesia aggravates preexisting diabetes, and the necessary prophylactic procedures are described.

Porte, D. Jr., Robertson, R. P.: "Control of insulin secretion by catecholamines, stress, and the sympathetic nervous system." *Fed. Proc.* 32: 1792-1796 (1973).

H71,915/73

Catecholamines inhibit insulin release by stimulation of pancreatic α -receptors and enhance it by stimulation of β -receptors. "Activation of the sympathetic nervous system causes inhibition of glucose-stimulated insulin secretion via the α -receptor but insulin output is maintained, probably via simultaneous β -receptor stimulation.... Pathological stress states may induce a metabolic state similar to diabetes with hyperglycemia and poor insulin responses to glucose challenge" (68 refs.).

Scheibe, O.: "Chirurgische Aspekte des Kohlenhydrat-Stoffwechsels" (Surgical aspects of carbohydrate metabolism). *Chirurg.* 44: 394-400 (1973).

J7,720/73

In hereditarily predisposed patients, juvenile diabetes is usually elicited by stress situations, whereas among older people adiposity is a more common causative factor.

Geiger, A., Barta, L., Hubay, M.: "Diabetes and mental state." *Acta Paediatr. Acad. Sci. Hung.* 14: 119-124 (1973).

J8,578/73

From "psychological investigation of 58 diabetic children and adolescents it has been concluded that emotional components, via their effect exerted upon neurohormonal functions, together with other factors, may play a role in the time of onset of diabetes." The observations agree with the concept that predisposition to diabetes is an inherited trait whose development may be precipitated by stress (17 refs.).

Arnold, L. C.: "Diabetes and trauma." *Med. Trial Tech. Q.* 20: 89-98 (1973).

J23,506/73

Arguments for and against the concept that diabetes can be produced or aggravated by stress.

Grant, I., Kyle, G. C., Teichman, A., Mendels, J.: "Recent life events and diabetes in

adults." *Psychosom. Med.* 36: 121-128 (1974). J18,918/74

On the basis of a clinical study, it is suggested that a relationship exists between life events, particularly undesirable ones, and aggravation of a genetically-determined diabetic condition (19 refs.).

Maidorn, K., Wächter, B., Kühling, P., Klein, W., Raschke, G., Rocker, L.: "Vergleichende Spiroergometrie bei Diabetikern und Nichtdiabetikern" (Comparative spiroergometry in diabetics and non-diabetics). *Diagnostik* 7: 761-765 (1974).

J19,100/74

Koch, M. F., Molnar, G. D.: "Psychiatric aspects of patients with unstable diabetes mellitus." *Psychosom. Med.* 36: 57-68 (1974). J9,818/74

Review of the literature on the precipitation of diabetes by stress, particularly emotional arousal. However, the present study on comparatively small groups of patients revealed no "relationship between the onset of the diabetes and coexisting emotional stress" (16 refs.).

Tashima, C. K., Fillhart, M., Cunanan, A.: "Jet lag ketoacidosis." *J.A.M.A.* 227: 328 (1974).

H80,686/74

In a patient with diabetic ketoacidosis, severe complications arose during air travel from Chicago to Hawaii owing to "the confusion of a time difference of five hours in addition to other factors such as the stress of a wedding ceremony, inactivity, and additional meals on board an aircraft."

Bruhn, J. G.: "Psychosocial influences in diabetes mellitus." *Postgrad. Med.* 56: 113-118 (1974). J14,704/74

Review on the association of ketosis and coma with life changes and other stressors in diabetic patients (23 refs.).

Unger, R. H.: "Alpha- and beta-cell interrelationships in health and disease." *Metabolism* 23: 581-593 (1974). H86,900/74

"An inappropriately low concentration of insulin and/or high level of glucagon relative to fuel availability is observed in genetic diabetes, and in a variety of stressful illnesses such as severe infection, trauma, burns, fetal distress, and other conditions, all of which are characterized by a negative nitrogen balance" (88 refs.).

Äärimaa, M., Slätis, P., Haapaniemi, L., Jeglinsky, B.: "Glucose tolerance and in-

sulin response during and after elective skeletal surgery." *Ann. Surg.* **179**: 926-929 (1974). J13,288/74

In patients undergoing surgery the glucose tolerance curves assumed a diabetic pattern. Insulin secretion was suppressed on the day of operation but rose above pre-

operative values in the postoperative period. "The hyperglycemia occurring after hemorrhage and after tissue injury is presumably a purposeful metabolic alarm reaction tending to maintain an adequate supply of fuel to the brain and peripheral nerves during stress conditions."

Hypoglycemia and Hyperinsulinism

Whether true hyperinsulinism can occur as a consequence of stress remains to be proven. However, a great deal has been written about a type of "pernicious fatigue" present especially on arising with a recurrence in the afternoon. This is often accompanied by overactivity of the parasympathetic system, with periods of dizziness, weakness, headaches and a general feeling of misery and anxiety. The glucose tolerance curves are usually flat.

Without any convincing reason, the syndrome has often been ascribed to hypoglycemia, and led to the organization of the Hypoglycemia Foundation in the U.S.A. Pernicious fatigue is especially common among neurotic patients, and is often treated (without much justification) by adrenocortical extracts rather than by pure natural or synthetic corticoids.

Hypoglycemia and Hyperinsulinism

(See also our earlier stress monographs, p. xiii)

Rennie, T. A. C., Howard, J. E.: "Hypoglycemia and tension-depression." *Psychosom. Med.* **4**: 273-282 (1942). B19,676/42

Description of a syndrome designated "functional hypoglycemia" which can occur in a predisposed patient "when any one of the many factors of [the] normal homeostatic mechanism [of blood sugar] is interfered with." It is especially common among patients with a variety of neuropsychiatric disturbances and appears to be the result of these, since it disappears when the latter are successfully treated. This syndrome is often difficult to distinguish from adrenocortical deficiency or hyperinsulinism.

Portis, S. A.: "Life situations, emotions and hyperinsulinism." *J.A.M.A.* **142**: 1281-1286 (1950). B51,914/50

Extensive review of the literature and personal observations suggesting that "life situations and emotions may produce a symptom complex resulting in fatigue. There is experimental and clinical evidence

to show that hyperinsulinism is a possible mechanism."

Raichle, M. E., King, W. H.: "Functional hypoglycemia: a potential cause of unconsciousness in flight." *Aerosp. Med.* **43**: 76-78 (1972). J20,017/72

In a student pilot, functional hypoglycemia with unconsciousness developed during acceleration a few hours after a high carbohydrate meal.

Kaye, P. L.: "'Pernicious' fatigue. Identification, pathogenesis, and treatment." *Behav. Neuropsychiatry* **5**: 24-29 (1974).

H88,050/74

Description of a type of "pernicious fatigue" which has a clearly diurnal cycle: present on arising, then relieved; recurring in the afternoon and again relieved in the evening. One of the manifestations of this syndrome is an overactivity of the autonomic particularly the vagal system, with periods of dizziness, weakness, headaches and a general feeling of misery and anxiety. Frequently there are flat glucose tolerance curves among these patients, but this is regarded as a symptom, not a cause, of the malady. Atropine is recommended to relieve the manifes-

tations. The syndrome of pernicious fatigue has often been ascribed to a low blood sugar level, and there is an organization called the Hypoglycemia Foundation (claiming a five hundred-physician membership)

which, according to the author, makes claims and has methods of treatment that are entirely unjustified. "The syndrome is best conceived as a common physiologic reaction to stress" (10 case reports, 7 refs.).

Thyroid Diseases

Emotional stress often precedes the appearance of hyperthyroidism and probably often plays an important part in eliciting this disease.

Allegedly, increased cortisol production during stress could predispose both to Graves' disease and Hashimoto's thyroiditis, for it is hypothesized that these conditions are due primarily to inherited defects in immune surveillance, permitting specific thyroid-directed clones of thymus-dependent lymphocytes to survive.

Thyroid Diseases

(See also our earlier stress monographs, p. xiii)

Lidz, T.: "Emotional factors in the etiology of hyperthyroidism. The report of a preliminary survey." *Psychosom. Med.* **11**: 2-8 (1949).

B52,737/49

Review of the literature and personal observations suggest that emotional disturbances frequently precede the onset of hyperthyroidism, and appear to be causally related to it.

Lidz, T., Whitehorn, J. C.: "Life situations, emotions and Graves' disease." In: Wolff, H. G., Wolf, S. G. Jr. *et al.*, *Life Stress and Bodily Disease*, pp. 445-450. Baltimore: Williams & Wilkins, 1950.

B51,919/50

Clinical data suggest that "emotional stresses of considerable severity precede the onset of hyperthyroidism in over 90 per cent of the cases." Many illustrative case reports are presented.

Mandelbrote, B. M., Wittkower, E. D.: "Emotional factors in Graves' disease." *Psychosom. Med.* **17**: 109-123 (1955).

C4,825/55

Csepel, K. B.: "Über die den endokrinen Exophthalmus begünstigenden Faktoren" (Factors promoting the development of endocrine exophthalmus). *Acta Chir. Acad. Sci. Hung.* **1**: 451-463 (1960).

J25,382/60

Alexander, F., Flagg, G. W., Foster, S., Clemens, T., Blahd, W.: "Experimental

studies of emotional stress: I. Hyperthyroidism." *Psychosom. Med.* **23**: 104-114 (1961).

D2,647/61

Brown, L. B., Hetzel, B. S.: "Stress, personality and thyroid disease." *J. Psychosom. Res.* **7**: 223-228 (1963) (28 refs.).

E37,640/63

Schäfer, H., Voss, C., Henschel, H. J., Hartmann, N.: "Jodtyrosin-Dejodasen im Stoffwechsel der Schilddrüsen-Hormone" (Iodo-tyrosine deiodases in the metabolism of thyroid hormones). *Hoppe Seylers Z. Physiol. Chem.* **341**: 268-283 (1965).

J24,473/65

In wild rabbits, experimentally-induced fright causes characteristic changes in the iodo-tyrosine deiodase content of various tissues which may be involved in the mechanism of stress-induced hyperthyroidism in animals and man (37 refs.).

Flagg, G. W., Clemens, T. L., Michael, E. A., Alexander, F., Wark, J.: "A psychophysiological investigation of hyperthyroidism." *Psychosom. Med.* **27**: 497-507 (1965).

G35,677/65

Bourquin, M.: "Psychosomatische Aspekte der Hyperthyreose" (Psychosomatic aspects of hyperthyroidism). *Schweiz. Med. Wochenschr.* **97**: 603-611 (1967).

H1,071/67

Neurogenic stress may precipitate hyperthyroidism in man.

Hamburg, D. A., Lunde, D. T.: "Relation of behavioral, genetic, and neuroendocrine factors to thyroid function." In: Spuhler, J.

N., *Genetic Diversity and Human Behavior*, pp. 135-170. Chicago: Aldine, 1967.

J16,064/67

L'Épée, P., Lazarini, H. J., Doignon, J., Malaplate, M.: "Contribution à l'étude de la maladie de Basedow traumatique" (Contribution to the study of traumatic Basedow's disease). *Med. Leg. Domm. Corpor.* (Paris) **3**: 102-104 (1970). H45,440/70

Various types of physical or mental trauma can induce the appearance of hyperthyroidism.

Sprung, M.: "Postemotional dysthyreosis." *Vojnosanit Pregl.* **28**: 468-471 (1971) (Polish). J24,626/71

Ashkar, F. S., Miller, R., Jacobi, G., Naya, J. N.: "Increased incidence of hyperthyroidism in the Cuban population of greater Miami." *J. Fla. Med. Assoc.* **59**: 42-43 (1972). H65,669/72

Forteza, M. E.: "Precipitating factors in hyperthyroidism." *Geriatrics* **28** No. 2: 123-126 (1973). G99,542/73

"Stress often precedes the onset of hyperthyroidism. A study of 116 patients shows that stresses vary by age groups."

Volpé, R., Farid, N. R., Westarp, C. von, Row, V. V.: "The pathogenesis of Graves' disease and Hashimoto's thyroiditis." *Clin. Endocrinol. (Oxf.)* **3**: 239-261 (1974). H88,160/74

Review of the literature on the role of stress in precipitating hyperthyroidism. The increased cortisol production during stress which results in a suppression of immune reactions could affect both Graves' disease and Hashimoto's thyroiditis, according to a hypothesis that these syndromes "are due primarily to inherited defects in immune surveillance, permitting specific thyroid-directed clones of thymus-dependent (T) lymphocytes (arising at random throughout life, normally through mutation) to survive, interact with their previously normal complementary antigen (presumably on the thyroid cell membrane) and establish a cell-mediated immune (CMI) reaction. This contact would presumably cause the specific clone of sensitized T-lymphocytes to replicate and expand. In addition, these T-lymphocytes appear to direct (and cooperate with) groups of bursa-equivalent (B) lymphocytes which in turn produce humoral immunoglobulins. In the case of Graves' disease, the important immunoglobulins would appear to be the

IgG thyroid stimulators, i.e. long acting thyroid stimulator" and related factors.

Hadden, D. R., McDevitt, D. G.: "Environmental stress and thyrotoxicosis. Absence of association." *Lancet* September 7, 1974, pp. 577-578. H91,773/74

During the three years preceding and the three years following the beginning of unrest in Northern Ireland, no statistically significant change in the incidence of thyrotoxicosis was noted, "which supports the concept that environmental stress is not important in the pathogenesis of this disease."

Susser, M.: "Environmental stress and thyrotoxicosis." *Lancet* October 19, 1974, p. 951. H93,960/74

Redding, R. A., Pereira, C.: "Thyroid function in respiratory distress syndrome (RDS) of the newborn." *Pediatrics* **54**: 423-428 (1974). J17,458/74

In premature babies with respiratory distress syndrome the mean total serum thyroxine level is usually subnormal. "An association between lung immaturity and fetal thyroid function is postulated."

Newmark, S. R., Himathongkam, T., Shane, J. M.: "Hyperthyroid crisis." *J.A.M.A.* **230**: 592-593 (1974). H94,368/74

Thyrotoxic storm often arises in predisposed patients during "surgical stress" or "stressful" medical illness" such as uncontrolled diabetes, trauma or infection.

Hoffenberg, R.: "Aetiology of hyperthyroidism-II." *Br. Med. J.* August 24, 1974, pp. 508-510. H94,297/74

In predisposed individuals, stressors may precipitate the onset of hyperthyroidism. However, several statistical studies are cited showing that this is not always the case (146 refs.).

Carter, J. N., Eastman, C. J., Corcoran, J. M., Lazarus, L.: "Effect of severe, chronic illness on thyroid function." *Lancet* October 26, 1974, pp. 971-974. H94,571/74

In patients with severe chronic, non-thyroidal illnesses, the mean total serum T₃ levels are reduced to the hypothyroid range, apparently as a result of decreased conversion of T₄ to T₃. Depressed production of TTH-RF secondary to stress or under-nutrition may also contribute by reducing thyroidal hormone output. [The apparently contrary observations on hyperthyroidism precipitated by stress are not discussed (H.S.).]

Cushing's Disease

Since Cushing's disease may be due to a derangement in the hypothalamic CRF-regulating mechanism, research has been done to determine whether this malady is caused by an upward setting of the ACTH feedback control mechanism. However, this could not be demonstrated. On the other hand, the diurnal rhythm of ACTH production is disturbed in Cushing's disease and dexamethasone suppressibility of ACTH secretion is inhibited, just as it is in severe depression.

Cushing's Disease

(See also our earlier stress monographs, p. xiii)

Besser, G. M.: "Response to stress." *Br. Med. J.* October 17, 1970, p. 176.

H31,436/70

Cushing's disease may be due to a defect in the hypothalamic mechanism controlling the secretion of CRF, and hence of ACTH and corticoids, rather than to a primary lesion within the pituitary. "It is unlikely that Cushing's disease is caused by an upward resetting of the feedback control mechanism resulting from the impaired stress response, as suggested by Professor Shuster. Such a mechanism could not account for either the absence of the nyctohemeral rhythm of ACTH secretion found in Cushing's disease, or the very high basal levels of plasma ACTH after adrenalectomy. On the other hand, loss of nyctohemeral rhythmicity and dexamethasone suppressibility of ACTH se-

cretion with high basal plasma corticosteroid levels may also be a feature of untreated severe depression, producing a biochemical picture indistinguishable from that found in Cushing's disease, yet we find that stress responsiveness in these patients is unimpaired." In any event, many patients with Cushing's disease show an unusually low ACTH discharge during stress (insulin hypoglycemia).

Werder, K. von, Smilo, R. P., Hane, S., Forsham, P. H.: "Pituitary response to stress in Cushing's disease." *Acta Endocrinol. (Kh.)* **67**: 127-140 (1971). H40,513/71

"The similarity in response to stress in (acutely) dexamethasone-suppressed normal subjects and those with Cushing's disease is striking. It suggests that feedback inhibition of increased ACTH secretion, rather than an intrinsic hypothalamic defect, may be the critical factor in the poor steroid response to a variety of stresses in Cushing's disease."

Immunity, Allergy and Infections

Data on Hashimoto's thyroiditis have just been cited. Publications on various cutaneous allergies, tumorigenesis in relation to immune reactions, asthma and rheumatic diseases will also be listed in special chapters, because of their importance and frequent association with maladaptation to stressful life events.

Suffice it to point out here that glucocorticoids, whose secretion is increased during stress, inhibit immunologic and allergic reactions in general; but often, psychogenic stress may precipitate attacks of *urticaria*, *hay fever*, *atopic dermatitis*, *lupus erythematosus* and various other autoimmune diseases. In children, antismallpox vaccination can cause hyperlipemia, cholesterolemia and other manifestations allegedly characteristic of the G.A.S. The mechanism through which stress can precipitate pathogenic immune reactions is not clearly understood, but it may be related to its effect upon the thymicolymphatic apparatus.

Furthermore, the anamnestic reaction in rats previously immunized (for example with paratyphoid) is elicited by stress, presumably owing to a lysis of plasmocytes in the involuting lymph nodes that liberate agglutinins. Interestingly, in allergic

subjects, though not in healthy controls, a sauna bath fails to raise the urinary excretion of 17-OHCS.

Numerous observations have shown beyond doubt that psychogenic stressors can precipitate *asthmatic* attacks in predisposed individuals. There is also some evidence of a deranged adrenal reactivity to stress in asthmatic patients, and both corticoids and catecholamines can relieve asthmatic attacks. However, there is no convincing evidence to show that asthma can be provoked by nonpsychogenic stimuli, even in predisposed patients, and hence the importance of a truly nonspecific element in its pathogenesis remains to be determined.

The concept that stress may play an important part in the pathogenesis of *rheumatic diseases*, and particularly in rheumatoid arthritis, was first suggested by animal experiments indicating that inflammatory lesions (including arthritis produced by periarticular injection of formaldehyde in the rat) are more readily caused after adrenalectomy than in intact controls. It was also noted that mineralocorticoids (DOC, aldosterone) facilitate whereas glucocorticoids (cortisone, cortisol) inhibit the development of such inflammatory lesions. This antagonistic interaction between what we named glucocorticoids (anti-inflammatory corticoids) and mineralocorticoids (proinflammatory corticoids) was later found to apply also to various other animal models of inflammation. These included certain types of experimental polyarthritis, which resembled the clinical syndrome of rheumatoid arthritis more closely than the initially used "topical irritation arthritis," produced by the injection of irritants (formalin, carrageenin).

However, the first unequivocal proof of a close relationship between rheumatoid arthritis in man and the adrenal cortex was given in 1949 when Hench and his co-workers demonstrated that cortisone can also cause a dramatic remission in patients suffering from this disease. Yet, despite many efforts, a true deficiency in glucocorticoids could not be demonstrated in rheumatoid arthritis with any regularity. Thus it has come to be regarded as a "pluricausal disease," whose development depends upon the interplay among several factors. One of these is probably an immunologic derangement that elicits inflammatory defense reactions; however, the latter are largely controlled by high blood levels of glucocorticoids. In other words, the immunologic pathogen creates a state of relative glucocorticoid deficiency in that it requires more than the normal amount of these hormones to control its tendency to produce excessive inflammation.

This complex problem is far from being solved, since some stressors (including excessive muscular exertion, cold, humidity, traumatic injuries, environmental toxicants) can provoke attacks of rheumatic or rheumatoid arthritis, while others (through their stimulation of glucocorticoid production) can elicit a beneficial, "nonspecific therapeutic action," as do exogenous glucocorticoids.

This whole topic has been discussed with particular care in our earlier stress monographs (p. xiii). In these, the interested reader will also find additional data on STH, which exerts a strong proinflammatory action, at least in animal experiments.

Through the increased production of glucocorticoids, stress predisposes both experimental animals and man to a variety of *infections*. This has been shown particularly for tuberculosis, whose development, like that of other infectious diseases, is also greatly accelerated by exogenous glucocorticoids.

On the other hand, infections often act as potent stressors and stimulate adrenocortical functions.

Immunity, Allergy and Infections

(See also our earlier stress monographs, p. xiii)

Holmes, T. H., Treuting, T., Wolff, H. G.: "Life situations, emotions and nasal disease: evidence on summative effects exhibited in patients with 'hay-fever'." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 545-565. Baltimore: Williams & Wilkins, 1950. B51,926/50

In patients with hay fever, one of the important "etiological factors is a life setting engendering conflict and anxiety."

Funkenstein, D. H.: "Psychophysiologic relationship of asthma and urticaria to mental illness." *Psychosom. Med.* **12**: 377-385 (1950). B64,759/50

Studies on psychotic patients suggest that both asthma and urticaria attacks are closely related to psychogenic stress.

Harper, R.: "Allergy, and other stress-conditioned illness: a suggested association with obsolete autonomic defence reflexes." *Br. Med. J.* February 14, 1953, pp. 392-395. E98,761/53

Review on the role of stress in the precipitation of psychic disturbances, allergies and particularly asthma.

Crede, R. H., Carman, C. T., Whaley, R. D., Schumacher, I. C.: "Dissimilar allergic disease in identical twins. A study of psychosomatic aspects." *Calif. Med.* **78**: 25-28 (1953). A15,205/53

"Emotional stress is accompanied by physiologic changes which facilitate increased reactions to antigenic agents that in normal circumstances would not cause clinical disease."

Goldman, A., Breckler, I. A., Stern, E., Robison, R.: "Stress in pulmonary tuberculosis. I. Thorn test and circulating eosinophils in surgical patients." *Dis. Chest* **24**: 608-618 (1953). C129/53

Clarke, E. R. Jr., Zahn, D. W., Holmes, T. H.: "The relationship of stress, adrenocortical function, and tuberculosis." *Am. Rev. Tuberc.* **69**: 351-369 (1954). B98,325/54

In patients, 17-KS excretion (used as an indicator of corticoid production) is usually reduced in extensive exudative tuberculosis, and is increased if the lesions are fibrotic and limited. Emotional conflict and threatening life situations cause a rise, but the interpretation of these results is difficult in view of

the nonspecificity of urinary 17-KS as an index of adrenocortical or testicular function. The extensive literature on steroid excretion and tuberculosis is reviewed (55 refs.).

Bottiglioni, E., Sturani, P. L.: "Stress da formaldeide e tubercolosi sperimentale. Nota I. Aspetti istologici del granuloma cutaneo" (Formaldehyde stress and experimental tuberculosis. Note I. Histologic aspects of cutaneous granuloma). *Arch. Patol. Clin. Med.* **32**: 134-145 (1955). C11,773/55

Bottiglioni, E., Sturani, P. L.: "Nota II. Modificazioni della sostanza fondamentale del connettivo nella cute, nel granuloma specifico e nel rene" (Note II. Changes of the ground substance in the connective tissue of the skin, of specific granuloma, and of the kidney). *Arch. Patol. Clin. Med.* **32**: 210-219 (1955). C11,774/55

Bottiglioni, E., Sturani, P. L.: "Nota III. Sulle localizzazioni metastatiche nei filtri ematici" (Note III. On the metastatic localization of hematic filters). *Arch. Patol. Clin. Med.* **32**: 220-227 (1955). C11,775/55

Bottiglioni, E., Sturani, P. L.: "Nota IV. Aspetti istopatologici e funzionali del corticosurrene" (Note IV. Histopathologic and functional aspects of the adrenal cortex). *Arch. Patol. Clin. Med.* **32**: 297-304 (1955). C13,096/55

Bottiglioni, E., Sturani, P. L.: "Nota VI. Sull'esistenza di una correlazione endocrinoinfettiva e sui meccanismi che la determinano" (Note VI. On the existence of an endocrine-infection correlation and the mechanisms determining it). *Arch. Patol. Clin. Med.* **32**: 316-329 (1955). C13,095/55

Review of the literature and personal observations concerning the relationship of the G.A.S. to tuberculosis (several hundred references).

Wolf, S.: "Life stress and allergy." *Am. J. Med.* **20**: 919-928 (1956). C19,679/56

Review of the literature and personal observations suggest strong evidence of a relationship between life stress and allergy. In "highly reactive subjects any appropriate stimulus, be it irritant, allergen or emotional challenge, might produce a disturbance great enough to be recognizable and symptomatic" (37 refs.).

Mate, J.: "Importance of stress and bacil-

lary excretion in the epidemiology of dysentery." *Orv. Hetil.* **102**: 2161-2169 (1961).

J24,366/61

Fukui, S.: "The influence of stress upon the excretion of adrenocortical hormone in pulmonary tuberculosis. I. The influence of hemoptysis." *Kekkaku* **37**: 99-102 (1962) (Japanese). J23,477/62

Stress plays an important role in the pathogenesis of pulmonary tuberculosis.

Muir, E.: "Lepra reaction and the general adaptation syndrome." *Leprosy Rev.* **33**: 240-251 (1962). D37,052/62

General review of leprosy in relation to the G.A.S.

Holmes, T. H.: "Infectious disease and stress with special reference to tuberculosis." In: Lief, H. I., Lief, V. F. et al., *The Psychological Basis of Medical Practice*, pp. 155-162. New York, Evanston, Ill., and London: Hoeber Medical Division, 1963. J8,247/63

A review of the literature and statistical studies indicate that social stressors play a major role in the development of various infectious diseases, particularly tuberculosis, in man. Furthermore, "the fact that alterations in 17-ketosteroid excretion parallel changes in the course of tuberculosis suggests that endogenous adrenocortical hormones influence resistance to tuberculosis."

Solomon, G. F., Moos, R. H.: "Emotions, immunity, and disease. A speculative theoretical integration." *Arch. Gen. Psychiatry* **11**: 657-674 (1964). F13,008/64

"The paper attempts a speculative theoretical integration of the relation of stress, emotion, immunological dysfunction (especially autoimmunity), and physical and mental disease" (125 refs.).

Juszkiewicz, T., Stefaniak, B., Madejski, Z., Karczewski, W.: "Corticosteroidal stress and Newcastle disease virus infection." *Acta Microbiol. Pol.* **15**: 35-51 (1966).

J23,961/66

Rees, W. L.: "Interrelationships of physical and psychological factors in asthma and allergy." *St. Barth. Hosp. J.* **70**: 350-354 (1966). G41,062/66

Under certain circumstances, "allergic states may be regarded as reactions to stress.... In asthma and allied disorders, as well as in many other diseases, the integrating concept of stress adaptation and homoeostasis is a valuable dynamic concept

which makes us consider the interaction and interplay of many forces rather than one single specific cause. The understanding of these mechanisms not only increases the physician's ability to control and treat disease, but opens up possibilities of applying more effective preventive measures."

Gorizontov, P. D.: "Infection and corticosteroid hormones." *Klin. Med. (Mosk.)* **44** No. 6: 5-12 (1966) (Russian).

G43,190/66

Discussion of the relationships between infection and the G.A.S., with major emphasis on the one hand upon microbes and their toxins as stressors, and on the other upon stress hormones as modifiers of infectious disease.

Radenbach, K. L.: "Tuberkulose, Nebennierenrindenfunktion und endokrine Störungen" (Tuberculosis, adrenal cortex function and endocrine disturbances). *Med. Welt* No. 15: 941-948 (1967). F82,347/67

Adrenocortical function may be increased or decreased in certain phases of tuberculosis in man. These changes may be related to the G.A.S., although their role is not yet known.

Goldstein, G., Mackay, I. R.: "The thymus in systemic lupus erythematosus: a quantitative histopathological analysis and comparison with stress involution." *Br. Med. J.* May 20, 1967, pp. 475-478. F81,223/67

In man, stress involution reduced the cortex of the thymus and caused the appearance of epithelial cell aggregates in the medulla with cystic Hassall's corpuscles. In lupus erythematosus, there was complete cortical atrophy due to lymphocyte depletion and disorganization of the medulla, which was largely occupied by epithelial cell aggregates and cystic Hassall's bodies. The number of plasma cells increased, and germinal centres were present in two cases. "Our interpretation is that the thymus in systemic lupus erythematosus is a target organ. There is histological evidence of extreme stress involution and of an autoimmune reaction which could augment changes usually associated with stress involution."

Zardini, V., Plastino, G.: "Contributo allo studio della fisiopatologia delle vaccinazioni. Comportamento della glicemia, lipemia e colesterinemia sotto stimolo vaccinico anti-vaioloso" (Contribution to the study of the physiopathology of vaccinations. Behavior of glycemia, lipemia, and cholesterololemia following the stimulus of an antismallpox

vaccination). *Minerva Pediatr.* **20**: 907-910 (1968). G59,176/68

In children, antismallpox vaccination caused hypoglycemia, hyperlipemia and an initial fall followed by an increase in cholesterol. These changes presumably reflect the development of a G.A.S.

Sundberg, M., Kotovirta, M.-L., Pesola, E.-L.: "Effect of the Finnish sauna-bath on the urinary excretion of 17-OH-corticosteroids and blood eosinophil count in allergic and healthy persons." *Acta Allergol.* (Kh.) **23**: 232-239 (1968). G61,502/68

Urinary 17-OHCS excretion was essentially the same in allergic and normal individuals. "During the sauna day and 24 hours after the sauna bath the healthy subjects showed a statistically significant increase in the excretion of 17-OHCS. This kind of reaction was not found in the allergics and the difference between allergics and healthy subjects was also significant." The weak response of allergics was attributed to decreased reactivity to stressors. The eosinophil count was not consistently affected by the sauna.

Solomon, G. F.: "Emotions, stress, the central nervous system, and immunity." *Ann. N.Y. Acad. Sci.* **164**: 335-343 (1969).

H19,302/69

A speculative evaluation of the literature suggests that "stress and emotional distress may influence the function of the immunologic system. Thus, environmental and psychologic factors might in some circumstances be implicated in the pathogenesis of cancer, the resistance to which growing evidence finds immunologic in nature, as well as of infections and of autoimmune diseases, which seem to have an association with states of relative immunologic incompetence."

Rasmussen, A. F. Jr.: "Emotions and immunity." *Ann. N.Y. Acad. Sci.* **164**: 458-462 (1969). H19,304/69

Review of the literature and personal observations on the effect of stress upon immune mechanisms, including those against tumorigenic viruses, and the possible participation of interferon in these phenomena (22 refs.).

Shanon, J.: "Delayed psychosomatic skin disorders in survivors of concentration camps." *Br. J. Dermatol.* **83**: 536-542 (1970). J10,417/70

"The mechanism of the delayed reaction has been discussed in terms of stress and conflict and their interaction."

Zdrodovskii, P. F., Gurvich, G. A.: *Physiologic Basis and Regulation of Immune Reactions*, p. 88. Moskva: Meditsina, 1972 (Russian). E9,933/72

Monograph on the regulation of immunologic mechanisms. The G.A.S. is intimately involved in the first anamnestic reactions. For example, in rats previously immunized with paratyphoid, the G.A.S. (produced by cold) first leads to a "passive anamnestic reaction" in which the preformed agglutinins are liberated owing to lysis of plasmocytes in the involuting lymph nodes. Later, during the stage of resistance, there is an "active anamnestic reaction," ascribed to increased synthesis, under the influence of anabolic hormone production, which follows the initial glucocorticoid discharge. Several other experiments are cited in support of the concept that the G.A.S., through the effect of adaptive hormones upon antibody formation, represents an important aspect of immunologic defense even in the adult organism. On the other hand, it has previously been well demonstrated that immunologic challenge can act as a stressor provoking the manifestations of the G.A.S.

Cazzullo, C. L., Altamura, A. C., Giordano, P. L., Pazzaglia, P.: "La corteccia surrenalica nella encefalomielite sperimentale allergica (Studio istologico nel coniglio. Con particolare riguardo allistochemica dei lipidi)" (The adrenal cortex in experimental allergic encephalomyelitis [Histologic study in rabbits. With special reference to the histochemistry of lipids]). *Morgagni Riv. Morfol. Clin.* **4** Suppl.: 1-14 (1973). H96,298/73

Asthma

(See also our earlier stress monographs, p. xiii)

McDermott, N. T., Cobb, S.: "A psychiatric survey of fifty cases of bronchial asthma." *Psychosom. Med.* **1**: 203-244 (1939). B26,613/39

In thirty-seven out of fifty cases of asthma, attacks were precipitated by emotional stimuli (22 refs.). [Stress is not specifically mentioned (H.S.).]

Stevenson, I.: "Variations in the secretion of bronchial mucus during periods of life stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp.

596-601. Baltimore: Williams & Wilkins, 1950.
B51,929/50

Emotional stressors may greatly stimulate bronchial mucus secretion in man. "In a patient with bronchiectasis the secretion of bronchial mucus was found to increase during periods of life stress, sometimes to as much as six to eight times the usual amount. In a patient with bronchial asthma, during an interview, increased bronchial secretion was observed to be associated with feelings of anxiety and resentment evoked by discussions of stressful life situations."

Funkenstein, D. H.: "Psychophysiologic relationship of asthma and urticaria to mental illness." *Psychosom. Med.* **12**: 377-385 (1950).
B64,759/50

Studies on psychotic patients suggest that both asthma and urticaria attacks are closely related to psychogenic stress.

Boulanger, J. B.: "Exploration du psychisme de l'astmatique. Essai de médecine psychosomatique" (Exploration of the psyche of asthmatics. A test of psychosomatic medicine). *Un. Méd. Can.* **81**: 1041-1063 (1952).
J11,571/52

Discussion of the literature with many personally observed cases of a relationship between asthma and stress.

Funkenstein, D. H.: "The relationship of experimentally produced asthmatic attacks to certain acute life stresses." *J. Allergy* **24**: 11-17 (1953).
B90,074/53

Mecholyl precipitates asthma only in asthmatic patients; it did so in eight asthmatics only during nonstressful situations and not under real-life stress-inducing conditions. This resistance may be due to the discharge of catecholamines during stress. It is difficult to reconcile these findings, however, with the repeatedly observed asthma-inducing action of real stress situations. [Possibly, the end result depends upon whether the asthma-provoking effect of stress or the contrary action of catecholamine discharge predominates (H.S.).]

Dekker, E., Groen, J.: "Reproducible psychogenic attacks of asthma. A laboratory study." *J. Psychosom. Res.* **1**: 58-67 (1956).
J25,125/56

Murce, A.: "Elementos hormonais e 'stress' na asma brônquica" (Hormonal factors and "stress" in bronchial asthma). *Hospital* **66**: 601-609 (1964) (Portuguese).
J23,727/64

Hodek, B., Škretová, K., Škreta, M.: "Über psychische Einflüsse beim Entstehen des Bronchialasthmas" (On psychic factors in the development of bronchial asthma). *Allergie Asthma* **11**: 197-202 (1965).
J23,032/65

Hale, R.: "Observations concerning the effects of emotional stress on asthma." *Ann. Allergy* **24**: 183-184 (1966).
J22,888/66

Markham, T. N.: "Asthma and occupational stress." *J. Occup. Med.* **9**: 315-317 (1967).
E70,859/67

Weiss, J. H.: "Birth order and asthma in children." *J. Psychosom. Res.* **12**: 137-140 (1968).
J22,404/68

Selesnick, S. T., Malmstrom, E. J., Younger, J., Lederman, A. R.: "Induced somatic reactions in asthmatic adults. (Their reduction by use of a psychotropic drug)." *Dis. Nerv. Syst.* **30**: 385-391 (1969).
J24,776/69

Jacobs, M. A., Spilken, A. Z., Norman, M. M., Anderson, L. S.: "Life stress and respiratory illness." *Psychosom. Med.* **32**: 233-242 (1970) (20 refs.).
G75,826/70

Kourilsky, R., Hugelin, A.: "Preuves physiologiques de l'importance des émotions dans l'asthme" (Physiologic tests of the importance of the emotions in asthma). *J. Fr. Méd. Chir. Thor.* **25**: 245-251 (1971).
J21,293/71

Mathé, A. A., Knapp, P. H.: "Emotional and adrenal reactions to stress in bronchial asthma." *Psychosom. Med.* **33**: 323-340 (1971).
G85,739/71

When compared with normal controls, asthmatics had subnormal urinary EP values during stress (solving arithmetic problems, viewing distressing films) as well as during control periods. Initial NEP and VMA excretion rates were normal. Both urinary NEP and plasma cortisol rises were normal during stress in asthmatics. "These findings argue against a global sympathetic nervous system or adrenal cortical defect, and are consistent with the hypothesis of a specific hypothalamicadrenal medullary defect in bronchial asthma. Respiratory indices (unlike heart rate and blood pressure) differentiated between the groups: asthmatics had lower airway conductance and respiratory rate and an opposite direction of change in these indices under stress. Psychologically, asthmatic Ss exhibited a marked field indepen-

dence and, although as emotionally aroused by stressors as were controls, gave evidence of inhibition of aggressive impulses" (75 refs.).

Sly, R. M., Joseph, F., Johnson, C. M.: "Effect of exercise upon plasma cortisol and airway obstruction in asthmatic children." *Ann. Allergy* **31**: 371-374 (1973).

J5,042/73

In asthmatic children, treadmill exercise causes decreases in peak expiratory flow rate, but plasma cortisol concentrations are essentially the same as in controls. The literature shows that asthmatic children have normal resting plasma corticoid levels, although increases are observed during exacerbations of asthma, presumably because of the consequent stress. In any event, cortisol often dramatically relieves asthmatic symptoms, and some relation between the disease and the adrenal cortex must be assumed although its nature is difficult to formulate precisely (25 refs.).

Miklich, D. R., Rewey, H. H., Weiss, J. H., Kolton, S.: "A preliminary investigation of psychophysiological responses to stress among different subgroups of asthmatic children." *J. Psychosom. Res.* **17**: 1-8 (1973).

G98,343/73

Asthmatic attacks are often precipitated by stress. When asthmatic boys were criticized for their performance in solving arithmetic problems, the resulting stress caused respiratory difficulties. Some pertinent literature is reviewed (13 refs.).

Steen, R. E.: "Stress disorders in childhood. Second of 3 parts." *J. Ir. Med. Assoc.* **66**: 78-84 (1973).

J19,613/73

Steen, R. E.: "Stress disorders in childhood. Third of 3 parts." *J. Ir. Med. Assoc.* **66**: 101-107 (1973).

J19,614/73

Review on stress diseases in childhood with special emphasis on various types of neurosis. A group of functional nervous disorders in childhood with a cyclic tendency is described as the "periodic syndrome." It is often associated with asthma, migraine headache, vomiting, diarrhea or fever. Both a hereditary predisposition and a stress-induced trigger mechanism appear to be involved.

Kinsman, R. A., Spector, S. L., Shucard, D. W., Luparello, T. J.: "Observations on patterns of subjective symptomatology of acute asthma." *Psychosom. Med.* **36**: 129-143 (1974).

J19,038/74

Jack, D.: "V. Selective drug treatments for bronchial asthma." *Can. Med. Assoc. J.* **110**: 436-441 (1974). H81,897/74

Clinical evidence suggests that selective β -adrenergic stimulants and glucocorticoids assure particularly favorable results in asthmatic patients.

Sherman, N. A., Smith, R. S., Middleton, E. Jr.: "Comparison of immunoglobulin formation in vitro by leukocytes of normal donors and steroid- and nonsteroid-treated asthmatic patients." *J. Allergy Clin. Immunol.* **54**: 77-85 (1974) (31 refs.).

J15,236/74

Coffey, R. G., Middleton, E. Jr.: "Effects of glucocorticosteroids on the urinary excretion of cyclic AMP and electrolytes by asthmatic children." *J. Allergy Clin. Immunol.* **54**: 41-53 (1974).

J14,089/74

Methylprednisolone relieves asthmatic attacks in children and raises the otherwise low cAMP excretion. "Restoration of beta adrenergic responsiveness by the steroid is suggested as a possible explanation for the increased cAMP excretion and the duration of the effects" (37 refs.).

König, P., Jaffe, P., Godfrey, S.: "Effect of corticosteroids on exercise-induced asthma." *J. Allergy Clin. Immunol.* **54**: 14-19 (1974).

J14,087/74

Only in some patients examined were prednisolone and other glucocorticoids beneficial in exercise-induced asthma (11 refs.).

Salk, L., Grellong, B. A., Straus, W., Dietrich, J.: "Perinatal complications in the history of asthmatic children." *Am. J. Dis. Child.* **127**: 30-33 (1974).

J18,287/74

Perinatal complications may predispose children to asthma, which later becomes manifest under conditions of stress.

Friedman, M., Frears, J.: "Hypothalamic-pituitary-adrenal function and growth in asthmatic children on long-term betamethasone valerate aerosol." *Postgrad. Med. J.* **50** Supp. 4: 33-37 (1974).

J17,967/74

Rheumatic Diseases

(See also our earlier stress monographs, p. xiii)

Thorn, G. W., Bayles, T. B., Massell, B. F., Forshaw, P. H., Hill, S. R. Jr., Smith, S., Warren, J. E.: "Studies on the relation of pituitary-adrenal function to rheumatic

disease." *N. Engl. J. Med.* **241**: 529-537 (1949). B30,384/49

In patients with rheumatoid arthritis, adrenocortical function is usually normal although subject to wide variations which show no clear correlation with the severity of the clinical manifestations. Still, the effectiveness of ACTH and cortisone therapy suggests some adrenal factor in the evolution of rheumatic diseases (26 refs.).

Hellman, L.: "The relation of life stress to arthritis." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 412-417. Baltimore: Williams & Wilkins, 1950. B51,916/50

Clinical observations suggest that "in the relation of physical or psychic stress to arthritis, the central nervous system appears, from available evidence, to act as a regulator of pituitary-adrenal function. Stress increases pituitary-adrenal activity and arthritis may occur in the subsequent phase of decreased adrenal activity in the presence of another unknown factor. However, beneficial effects in arthritis are produced by stress during the phase of increased adrenal cortical function."

Uehlinger, E., Akert, K., Pirozynski, W.: "Nebennierenrindenhormone und Gelenke" (Hormones of the adrenal cortex and the joints). *Bull. Schweiz. Akad. Med. Wiss.* **6**: 157-170 (1950). B53,765/50

Confirmation of the observation that overdosage with DOC can produce polyarthritis in the rat.

Selye, H.: "Rheumatic diseases as diseases of adaptation." *Br. Med. J.* June 10, 1950, pp. 1362-1363. B52,703/50

The Heberden Oration on the relationship between stress and rheumatic diseases.

Fassbender, H. G.: "Rheumatismus, allergisch-hyperergische Entzündung und Nebenniere" (Rheumatism, allergic-hyperergic inflammation, and the adrenals). *Virchows Arch. [Pathol. Anat.]* **321**: 275-282 (1952). G44,239/52

Although the production of rheumatic-like lesions in DOC-treated rats has been confirmed, allergy is probably also involved. "Rheumatism in man is not an 'adaptation disease' in the sense of Selye, although the adrenal hormones undoubtedly play a role in regulating the associated mesenchymal reactions and inflammation."

McLaughlin, J. T., Zabarenko, R. N., Diana, P. B., Quinn, B.: "Emotional reac-

tions of rheumatoid arthritics to ACTH." *Psychosom. Med.* **15**: 187-199 (1953). B86,816/53

"There was an apparently significant relationship between changes in stress levels and clinical response to ACTH."

Solomon, C., Cohn, T. D., Feldman, F.: "Intravenous typhoid vaccine therapy in rheumatic diseases: a correlative study of the stress phenomenon and the clinical results." *Am. Practit.* **5**: 769-775 (1954).

B99,056/54

Rheumatism is considered to be a disease of adaptation, and the beneficiary results of intravenous typhoid vaccine therapy are ascribed to stimulation of ACTH production (20 refs.).

Kelley, V. C., Ely, R. S., Done, A. K., Ainger, L. E.: "Studies of 17-hydroxycorticosteroids. VI. Circulating concentrations in patients with rheumatic fever." *Am. J. Med.* **18**: 20-26 (1955).

E53,694/55

In patients with acute rheumatic fever, plasma 17-OHCS concentrations are elevated, whereas the opposite is true in inactive rheumatic fever and Sydenham's chorea (50 refs.).

Ward, L. E., Wu, C., Hench, P. S., Mason, H. L., Slocumb, C. H., Polley, H. F., Mayne, J. G.: "Plasma 17-hydroxycorticosteroids in patients with certain rheumatic diseases and in normal persons." *Proc. Mayo Clin.* **33**: 611-626 (1958) (44 refs.).

J13,142/58

Studer, A., Reber, K.: *Rheumatismus als Problem der Experimentellen Medizin* (Rheumatism. A problem of experimental medicine), p. 138. Darmstadt: D Steinkopff-Verlag, 1959.

D87,724/59

Monograph on various experimental models of rheumatic and related diseases in animals, particularly those produced by mineralocorticoids in the rat (560 refs.).

Kodicek, E.: "Rheumatoid-like joint lesions in guinea-pigs with chronic partial vitamin C deficiency." *Proc. Nutr. Soc.* **19**: xxxiii (1960).

D7,279/60

Arthritis developed frequently in vitamin C-deficient guinea pigs, and not as a result of scorbutic hemorrhages. These lesions were aggravated by DOC and prevented by cortisone. "It is suggested that the joint lesions are due to an indirect effect of deficiency" acting as a stress factor.

Selye, H., Bajusz, E.: "Stress and rheu-

matic diseases." In: Hollander, J. L., *Arthritis and Allied Conditions*, pp. 607-620. Philadelphia: Lea & Febiger, 6th ed., 1960.

C71,400/60

Review based mainly on experimental observations indicating that although DOC and STH by themselves do not produce polyarthritis regularly in laboratory animals, they do condition for its development (for example, under the influence of lathyrogens, or parenteral administration of Murphy rat lymphosarcoma exudate, which is now known to contain PPLOs).

Hubault, A.: "La situation physiopathologique de la polyarthrite rhumatoïde. (Polyarthrite chronique évolutive)" (The physiopathologic aspect of rheumatoid polyarthritis. [Chronic evolutive polyarthritis]). *Presse Méd.* **69** No. 38: 1649-1651; No. 39: 1683-1685; No. 41: 1749-1752 (1961).

D11,760/61

Extensive review of clinical and experimental findings lead to the conclusion that "despite the critical remarks raised against it, the pituitary adrenocortical theory remains an etiologic concept worthy of further investigation."

Cantilo, E.: "Rheumatism and the endocrine glands. Current status of Selye's doctrine." *Dia Med.* **34**: 2117-2120 (1962).

J24,314/62

Taller, A.: "Über die Therapie der Arthropathien mit besonderer Berücksichtigung der Plenosolkuren" (The therapy of arthropathies with special reference to plenosol treatment). *Med. Welt* No. 35: 1747-1749 (1963). E34,911/63

Various arthropathies ascribed to stress respond well to plenosol homeopathic treatment. [The alleged success rate is not impressive (H.S.).]

Taube, H.: "Rheumatismus. Wissen und Praxis" (Rheumatism. Knowledge and practice). *Berl. Med.* **15**: 252-258 (1964).

F12,174/64

Review on the relationship between rheumatism and the pituitary-adrenocortical axis, emphasizing that immunologic mechanisms probably also play a pathogenic role.

Prick, J. J. G., Loo, K. J. M. van de: *The Psychosomatic Approach to Primary Chronic Rheumatoid Arthritis*, p. 365. Assen: Van Gorcum & Comp. N.V., 1964.

E4,624/64

Monograph on psychosomatic factors in

rheumatoid arthritis, which is interpreted as a disease of adaptation dependent upon derailment of the G.A.S.

Mozziconacci, P., Binoux, M., Girard, F.: "Étude de l'activité corticotrope et du cortisol plasmatiques chez l'enfant au cours du rhumatisme articulaire aigu et de maladies infectieuses avant l'institution du traitement" (Study of plasma corticotropin and cortisol activities in children during acute articular rheumatism and infectious diseases, before treatment). *Ann. Pediatr.* **41**: 1623-1629 (1965). G30,566/65

In rheumatic children, plasma ACTH determinations indicated hypofunctioning of the pituitary-adrenal axis which appeared to be greater than that caused by infections of comparable severity. These observations are discussed in relation to the pathogenesis of rheumatic diseases (27 refs.).

Raestrup, O.: "Gelenkrheumatismus als Unfallfolge? Versicherungsmedizinische Beurteilung in der privaten Unfall- und Haftpflichtversicherung" (Can rheumatic fever result from an accident? Insurance-medical assessment in the field of private accident and liability insurance). *Münch. Med. Wochenschr.* **108**: 265-269 (1966).

F61,978/66

Clinical observations suggest that not only streptococcal and other infections but also various stressors (including excessive muscular exhaustion, cold, humidity, traumatic injuries, environmental toxicants) can be followed by characteristic manifestations of rheumatic diseases, and the latter "must undoubtedly be regarded as typical diseases of adaptation" (56 refs.).

Moos, R. H., Solomon, G. F.: "Social and personal factors in rheumatoid arthritis: pathogenic considerations." *Clin. Med.* **73**: 19-23 (1966). G40,451/66

Review of clinical observations suggesting that psychologic stressors (anger, anxiety, depression) "appear to play a role in the onset and course of rheumatoid arthritis, a disease with autoimmune features, a possible mechanism linking psychologic and physiologic events being the effect of stress-responsive adrenal cortical hormones on the immunologic system" (38 refs.).

Selye, H., Bajusz, E.: "Stress and rheumatic disease." In: Comroe, B. I., *Arthritis and Allied Conditions*, pp. 618-630. Philadelphia: Lea & Febiger, 7th ed., 1966.

G11,141/66

Compilation of the literature on the relationship between stress and collagen diseases, particularly rheumatism. Special attention is called to the effect of corticoids and STH upon the development of the most varied types of inflammation, osteolathyrism and calciphylaxis. Even when stress is not the primary pathogenic factor, it can play a decisive role by conditioning to disease susceptibility (for example, through adaptive hormones) (32 refs.).

Weintraub, A.: "Beitrag zur Psychosomatik der progredient chronischen Polyarthritiden" (Psychosomatic studies on progressive chronic polyarthritis). *Ther. Umsch.* **24**: 368-372 (1967).

G72,998/67

Review of clinical and experimental data suggesting that rheumatic diseases are due partly to stress and corticoids but also to immunologic predisposing factors. The psychosomatic origin of certain rheumatic disorders definitely indicates that they are essentially "diseases of adaptation."

Sanders, H. J.: "Arthritis and drugs. The ongoing quest to reveal its causes. Part II." *Ind. Med. Surg.* **38**: 290-308 (1969).

G69,544/69

Emotional stress frequently aggravates rheumatoid arthritis in man. Sensitivity to climatic changes may also depend upon the latter's stressor effect.

Hendrie, H. C., Paraskevas, F., Baragar, F. D., Adamson, J. D.: "Stress, immunoglobulin levels and early polyarthritis." *J. Psychosom. Res.* **15**: 337-342 (1971).

G85,722/71

After a review of the literature on the role of psychologic factors in the development of rheumatoid arthritis, the authors report personal observations indicating that questionnaire responses from patients with early polyarthritis revealed no particularly high psychologic stress ratings prior to the dis-

ease. "However, polyarthritic patients with elevated immunoglobulin levels, tended also to have increased life change scores." Hence, it is suggested that "psychological stress does act as a precipitant for rheumatoid arthritis in at least some patients and that its mode of action is via immunological processes."

Meyerowitz, S.: "The continuing investigation of psychosocial variables in rheumatoid arthritis." *Mod. Trends Rheum.* **2**: 92-105 (1971).

J20,491/71

Heisel, J. S.: "Life changes as etiologic factors in juvenile rheumatoid arthritis." *J. Psychosom. Res.* **16**: 411-420 (1972).

J19,671/72

Children who develop juvenile rheumatoid arthritis or Still's disease "tend to have recently experienced a cluster of changes in their world, higher in amount and intensity than the average child." Several life change questionnaires have been worked out for different age groups.

Crown, J. M., Crown, S.: "The relationship between personality and the presence of rheumatoid factor in early rheumatoid disease." *Scand. J. Rheum.* **2**: 123-126 (1973).

H78,166/73

Personality studies suggest that "from the complex of environmental factors relevant to the aetiology or onset of Rheumatoid Disease, there may be a sub-group of seronegative patients, especially female patients, for whom psychological stress factors are relevant."

Rimon, R.: "Rheumatoid factor and aggression dynamics in female patients with rheumatoid arthritis." *Scand. J. Rheum.* **2**: 119-122 (1973).

H78,165/73

"The possibility of two kinds of life stress and aggression dynamics profiles correlating with the presence or absence of rheumatoid factor is discussed."

Tumors

A number of investigators speculated about the possibility that stress can influence tumorigenesis. There can be no doubt about the fact that chronic local irritation of certain tissue areas by prolonged treatment with a topical stressor can result in neoplasia at the site of injury. For example, it has definitely been shown that local neoplasia can be produced by prolonged irritation of the lip by a pipe stem, of the cervix by a pessary, of the skin by solar radiation or of the connective tissue wall of a granuloma pouch in experimental animals by croton oil.

Considerably less evidence supports the assumption that systemic stress can influence tumorigenesis. Undoubtedly, the glucocorticoids secreted upon exposure to stressors do exert a moderate carcinolytic effect, and of course the stress-induced changes in the immunologic system may also influence resistance to neoplasia.

Stress caused by avoidance learning of high frequency sound had no significant effect upon the development of malignant tumors induced in mice by polyoma virus. On the other hand, in rats, restraint definitely increased susceptibility to the tumorigenic action of murine sarcoma virus.

In rats, psychogenic stress allegedly inhibits the growth of most transplanted and chemically-induced tumors, a change that allegedly may be "characteristic of the stage of resistance of the G.A.S."

Conversely, any type of tumor may produce stress manifestations, although the claim that adrenal enlargement in tumor-bearing rats is not prevented by hypophysectomy requires confirmation.

Tumors

(See also our earlier stress monographs, p. xiii, and cf Tumors under Morphologic Manifestations)

Rashkis, H. A.: "Systemic stress as an inhibitor of experimental tumors in Swiss mice." *Science* 116: 169-171 (1952).

B72,776/52

Stephenson, J. H., Grace, W. J.: "Life stress and cancer of the cervix." *Psychosom. Med.* 16: 287-294 (1954). J21,392/54

In women with cancer of the cervix, certain types of personality maladjustment are especially common.

Ayre, J. E.: "Cervical cancer: chronic inflammation, stress and adaptation factors." *Acta Un. Int. Cancr.* 12: 20-27 (1956).

J25,135/56

Since chronic inflammation allegedly often precedes cervical cancer, "an hypothesis is introduced suggesting that Selye's stress and adaptation syndrome may fit into the complex picture of cervical carcinogenesis. The leukorrhea of chronic cervicitis, the presence of an estrogen in cervical mucus, and hypoxia resulting from the fibrotic changes of chronic inflammation are presented as 'links' in a 'chain reaction'" of carcinogenesis (25 refs.).

Krasnoff, A.: "Problems in the study of stress and tumor developments." *Meeting American Psychol. Assoc.*, 1958.

J23,791/58

Stern, J. A., Winokur, G., Graham, D. T., Lefton, R.: "Effect of enforced activity

stress on the development of experimental papillomas in mice." *J. Natl. Cancer Inst.* 23: 1013-1018 (1959). D87,860/59

In mice, "the experimental stress of enforced activity was shown to be related to a significant enhancement of papilloma development and death rate. Stress initiated concurrently with application of the carcinogen exerted a more profound effect than was observed in prestressed animals" (12 refs.).

Pendergrass, E. P.: "Host resistance and other intangibles in the treatment of cancer." *Am. J. Roentgenol.* 85: 891-896 (1961).

J23,261/61

Review of the role of the G.A.S. in the pathogenesis of cancer.

Baltrusch, H.-J.F.: "Leukämien und andere maligne Erkrankungen des haemopoetischen, lymphatischen und reticuloendothelialen Systems in psycho-somatischer Sicht. Teil II" (Leukemias and other malignant diseases of the hematopoietic, lymphatic and reticuloendothelial systems from a psychosomatic viewpoint. II). *Z. Psychosom. Med.* 8: 12-23 (1962). J23,395/62

Discussion of the role of the G.A.S. in various malignancies of the hematopoietic system.

Rasmussen, A. F., Hildemann, W. H., Sellers, M.: "Malignancy of polyoma virus infection in mice in relation to stress." *J. Natl. Cancer Inst.* 30: 101-112 (1963). D57,134/63

Stress caused by avoidance learning or high frequency sound had no significant effect upon the development of malignant tumors in mice infected with polyoma virus.

Anderson, M. R.: "Variations in the rate of induction of chemical carcinogenesis according to differing psychological states in rats." *Nature* **204**: 55-56 (1964).

F22,448/64

Ader, R., Friedman, S. B.: "Differential early experiences and susceptibility to transplanted tumor in the rat." *J. Comp. Physiol. Psychol.* **59**: 361-364 (1965). G32,592/65

"Stress in experimental carcinogenesis." *Lancet* January 2, 1965, pp. 38-39 (12 refs.). J22,872/65

Paiva, A. P. L. F. de: *Teoria Unitária da Implantacão e Evolução do Tumor Primitivo do Homem. Hipótese TU-K₁₁ do Dismetabolismo Endócrino-Celular* (A unifying theory of implantation and evolution of the primary tumor in man. Hypothesis TU-K₁₁ of endocrinocellular dysmetabolism), p. 43. Coimbra: Tip. da Atlântida, 1966 (Portuguese). G46,105/66

Monograph attempting to establish some relationship between neoplasia and the G.A.S. on purely speculative grounds (no refs.).

Iaremenko, K. V., Moskalik, K. G.: "The combined action of some stress effects and eleutherococcus extract on inoculation of tumor cells injected intravenously." *Vopr. Onkol.* **13** No. 9: 65-69 (1967) (Russian). H4,112/67

In mice inoculated with Ehrlich tumor cells intravenously, intermittent cooling or injection of ACTH enhanced the take of neoplastic cells, but this effect could be eliminated by administering the eleutherococcus extract.

Milcu, S. M., Zimel, H., Petrea, I., Măcrieanu, A.: "Influența stressului (electric și audiogen) asupra dezvoltării carcinosarcomului Walker 256 la șobolani" (Influence of stress [electric and audiogenic] on the development of Walker 256 carcinosarcoma in rats). *Stud. Cercet. Endocrinol.* **19**: 131-137 (1968) (Roumanian). H7,035/68

Sutton, P. R. N.: "Prognosis of carcinoma of the lip or tongue in relation to mental stress: speculation on an anomalous finding." *Med. J. Aust.* **2**: 312-313 (1968).

J21,994/68

Solomon, G. F.: "Emotions, stress, the central nervous system, and immunity." *Ann. N.Y. Acad. Sci.* **164**: 335-343 (1969).

H19,302/69

A speculative evaluation of the literature

suggests that "stress and emotional distress may influence the function of the immunologic system. Thus, environmental and psychologic factors might in some circumstances be implicated in the pathogenesis of cancer, the resistance to which growing evidence finds immunologic in nature, as well as of infections and of autoimmune diseases, which seem to have an association with states of relative immunologic incompetence."

Greene, W. A., Swisher, S. N.: "Psychological and somatic variables associated with the development and course of monozygotic twins discordant for leukemia." *Ann. N.Y. Acad. Sci.* **164**: 394-408 (1969).

J21,914/69

"In each twin pair, the symptoms of leukemia developed in a setting of major psychological stress."

Margolin, S.: "Integration and evaluation of current psychophysiological approaches to cancer. Panel discussion 1: the neuroendocrinologic approach." *Ann. N.Y. Acad. Sci.* **164**: 611-619 (1969).

H19,313/69

A discussion on the relationships between stress and neoplasia.

Kissen, D. M., Rao, L. G. S.: "The nervous system, hormones, and cancer. Steroid excretion patterns and personality in lung cancer." *Ann. N.Y. Acad. Sci.* **164**: 476-482 (1969).

H19,307/69

Dechambre, R.-P., Gosse, C.: "Influence d'un 'stress' d'isolement sur l'évolution des tumeurs ascitiques greffées de la souris. Rôle des surrénales" (Influence of isolation stress on the development of transplanted ascites tumors in mice. Role of the adrenals). *C.R. Acad. Sci. (Paris)* **272**: 2720-2722 (1971).

J21,153/71

In mice, the stress of isolation can produce adrenal enlargement and an increase in the speed of development of transplanted ascites tumors.

Arasa, F.: "Psique y cáncer" (Psyche and cancer). *Folia Humanist.* (Barcelona) **9**: 501-509 (1971). Also in: *Folia Clin. Int.* (Barcelona) **21**: 431-437 (1971).

G84,153/71

Speculations concerning the possible role of mental stress in the pathogenesis of cancer.

Abeatici, S., Terracini, B.: "Studio sull'interferenza dello stress (centrifugazioni ripetute) con la cancerogenesi sottocutanea nei topi" (A study of stress [repeated centrifu-

gations] interference with subcutaneous carcinogenesis in mice). *Tumori* **57**: 353-356 (1971). G88,661/71

In Swiss mice, methylcholanthrene-induced tumorigenesis was not influenced by the stressor effect of repeated centrifugation (10 refs.).

Graham, S., Snell, L. M., Graham, J. B., Ford, L.: "Social trauma in the epidemiology of cancer of the cervix." *J. Chron. Dis.* **24**: 711-725 (1971). J20,331/71

Contrary to some data in the earlier literature, the incidence of cervical cancer was not dependent upon social stressors, in a group of 447 women of various backgrounds.

Snell, L., Graham, S.: "Social trauma as related to cancer of the breast." *Br. J. Cancer* **25**: 721-734 (1971). J20,189/71

There is no evidence that psychosocial or somatic stressors play an important role in the pathogenesis of breast cancer.

Truhaut, R., Dechambre, R. P.: "Modalités de l'induction chez la souris de tumeurs pulmonaires par le benzo-(α)-pyrène; influence de la dose d'hydrocarbure aromatique et de facteurs écologiques" (Methods of induction in mice of pulmonary tumors with benzo-(α)-pyrene; influence of the dose of aromatic hydrocarbon and of ecologic factors). *C.R. Acad. Sci. (Paris)* **274**: 2263-2267 (1972). J20,220/72

Benzopyrene produces pulmonary tumors more rapidly in isolated mice than in those kept in groups of ten.

Gala, R. R., Loginsky, S. J.: "Correlation between serum prolactin levels and incidence of mammary tumors induced by 7,12-dimethylbenz[α]anthracene in the rat." *J. Natl. Cancer Inst.* **51**: 593-597 (1973).

J5,797/73

Rats that secrete large amounts of LTH after ether stress fail to develop mammary tumors under the influence of 7,12-dimethylbenz[α]anthracene.

Amkraut, A. A., Solomon, G. F., Kasper, P., Purdue, A.: "Stress and hormonal intervention in the graft-versus-host response." *Adv. Exp. Med. Biol.* **29**: 667-674 (1973).

J24,477/73

The authors quote literature which indicates that stress generally suppresses immune reaction. They then add, "We have shown such suppressive effect on antibody formation and have also reported stress-induced increases in tumor size, which are

probably a consequence of immunosuppression."

Hinton, J.: "Bearing cancer." *Br. J. Med. Psychol.* **46**: 105-113 (1973). J19,558/73

Analysis of the psychogenic stress associated with the early stages of recognition of cancer, and methods for coping with this situation.

Smith, A. E., Kenyon, D. H.: "A unifying concept of carcinogenesis and its therapeutic implications." *Oncology* **27**: 459-479 (1973). J6,692/73

Review of the literature suggests that "cancer cells are an attempt of portions of the body to recover from chronic injury, and are an overcompensation to the stress.... The greatly increased reproductive activity of the cancer cell can be seen as a localized attempt to heal stress-induced cellular disease."

Cole, W. H.: "The mechanisms of spread of cancer." *Surg. Gynecol. Obstet.* **137**: 853-871 (1973). H77,359/73

Review of the literature indicating that various stressors enhance tumor metastasis in experimental animals (125 refs.).

Seifter, E., Rettura, G., Zisblatt, M., Levenson, S. M., Levine, N., Davidson, A., Seifter, J.: "Enhancement of tumor development in physically-stressed mice inoculated with an oncogenic virus." *Experientia* **29**: 1379-1382 (1973). H80,975/73

In mice, restraint by a partial body cast produced the typical manifestations of systemic stress and at the same time increased susceptibility to the tumorigenic action of murine sarcoma virus. In the immobilized animals, "there appeared to be a smaller number of small lymphocytes due to stress and a proliferation of epithelioid elements. Hassal bodies were also involved in agreement with earlier findings of Selye. If stress or cortisone treatment results in impaired function of these structures, then the endocrine function of the thymus gland as well as its role in providing circulating cells would be disturbed." In any event, the response of the thymus during stress is assumed to increase susceptibility to the virus through interference with immune reactions.

Spackman, D., Riley, V.: "Increased corticosterone, a factor in LDH-virus induced alterations of immunological responses in mice" (abstracted). *Proc. Am. Assoc. Cancer Res.* **15**: 143 (1974). H83,767/74

In mice, LDH-virus increases blood corti-

costerone levels and causes thymus involution with lymphocytopenia, that is, a stress reaction. It is possible that LDH-virus modifies neoplastic diseases by inhibiting immune responses through its stressor effect.

Coombs, R. R. H., Castro, J. E., Sellwood, R. A.: "Adrenal hyperplasia in rats with Walker carcinosarcoma 256." *Br. J. Surg.* **61**: 136-140 (1974). H85,492/74

The adrenal enlargement of tumor-bearing rats was not prevented by hypophysectomy. Adrenalectomy inhibited tumor growth.

Howard, R. J., Simmons, R. L.: "Acquired immunologic deficiencies after trauma and surgical procedures." *Surg. Gynecol. Obstet.* **139**: 771-782 (1974). H95,043/74

In man, "surgical trauma is associated with a number of temporary deficits in the immune system which might conceivably lead to increased susceptibility to infection or tumor spread" (109 refs.).

Arasa, F.: "La problemática del cáncer vista por un médico humanista" (Problems of cancer as seen by a humanistic physician). *Folia Clin. Int.* (Barcelona) **24**: 547-557 (1974). H90,549/74

Largely theoretical considerations concerning the possible carcinogenic effect of systemic stress.

Ray, P., Pradhan, S. N.: "Brief communication: Growth of transplanted and induced tumors in rats under a schedule of punished behavior." *J. Natl. Cancer Inst.* **52**: 575-577 (1974). J11,064/74

In rats, psychogenic stress inhibits the growth of both transplanted and chemically induced tumors. This effect may be "characteristic of the stage of resistance of the G.A.S."

Pradhan, S. N., Ray, P.: "Effects of stress on growth of transplanted and 7,12-dimethylbenz [α] anthracene-induced tumors and their modification by psychotropic drugs." *J. Natl. Cancer Inst.* **53**: 1241-1245 (1974). J24,475/74

Various stressors (restraint, sound, electroshock) increased the growth of transplanted or induced tumors in rats, concomitant with an increase in adrenal and a decrease in splenic weight. Chlorpromazine abolished this protective action.

Tromp, S. W.: "The possible effect of meteorological stress on cancer and its importance for psychosomatic cancer research." *Experientia* **30**: 1474-1478 (1974). H98,793/74

Personal observations and a review of the literature allegedly "confirm the effect of meteorological stresses (in particular thermal stresses) on thermoregulatory processes and cancer development. The similarity in physiological processes during meteorological and psychological stresses may facilitate the studies on the influence of psychosomatic factors on cancer."

Riscalla, L. M.: *Consciousness. An Added Dimension in the Treatment of Cancer.* Manuscript (1975) (71 refs.). J19,683/75

Pancreatitis

Pancreatitis and even pancreatic necrosis have been noted in animals and man after exposure to various stressors. The most common clinical form of the latter is the well-known "postoperative pancreatitis." This condition may result from a particularly acute breakdown of pancreatic acinar tissue during the alarm reaction, which liberates proteolytic enzymes.

Pancreatitis

(See also our earlier stress monographs, p. xiii)

Kaplan, M. H.: "Acute and chronic relapsing pancreatitis. The clinical implications of their acceptance as diseases of adaptation." *Am. J. Gastroenterol.* **25**: 234-252 (1956). C19,305/56

"Pancreatitis is a disease of adaptation."

Duguid, H., Simpson, R. G., Stowers, J. M.: "Accidental hypothermia." *Lancet* December 2, 1961, pp. 1213-1219.

D15,581/61

Pancreatic necrosis and pancreatitis often occur in combination with other manifestations of the alarm reaction in elderly patients

with the syndrome of "accidental hypothermia."

Singh, L. M., Okukubo, F., James, P. M., Salmon, J., Howard, J. M.: "Further studies on postoperative pancreatitis." *Arch. Surg.* **90**: 43-49 (1965). G23,137/65

Review on postoperative pancreatitis, with special emphasis upon the diagnostic value of serum enzymes (12 refs.).

Clercx, L., Dupont, J. M.: "Les pancréatites aigües postopératoires" (Acute postop-

erative pancreatitis). *Acta Chir. Belg. Suppl.* **1**: 217-290 (1967). G47,873/67

Monograph on postoperative pancreatitis emphasizing its possible relationship to acute stress (326 refs.).

Sibilly, A., Boutelier, P.: "Les complications digestives du stress" (The digestive complications of stress). *J. Chir. (Paris)* **108**: 117-134 (1974). J17,165/74

Brief review on stress-induced pancreatitis and gastroduodenal ulcers in man (no refs.).

Renal Diseases

The circulatory disturbances characteristic of the "shock kidney," and particularly the so-called "Trueta-Shunt," which tend to develop during very acute, severe stress, are typical of an intense alarm reaction.

A "heat stress nephropathy" tends to develop during intense physical exercise in hot climates, but its degree of nonspecificity has not yet been established.

Renal Diseases

(See also our earlier stress monographs, p. xiii)

Burkland, C. E.: "Causal factors in urolithiasis (role of possible interrelationship of stress, metabolism, and occupation)." *Stanf. Med. Bull.* **12**: 134-139 (1954).

C5,884/54

Clinical observations suggest that stress may be involved in the pathogenesis of urolithiasis.

Erak, P., Skrivaneli, N.: "Sur la pathogénie neuro-endocrinienne de la néphrose lipoïdique" (Neuroendocrine pathogenesis of lipid nephrosis). *Arch. Fr. Pédiatr.* **12**: 515-523 (1955). C21,077/55

Lipid nephrosis in man is presumably a disease of adaptation.

Marshall, V. F., Schnittman, M., Davalos, A., Butterick, A.: "Cystolithiasis in rats as influenced by hyaluronidase, sex, and stress." *J. Urol.* **73**: 677-680 (1955). C25,482/55

Cohen, A. L., Gelblung, I., Goijman, I.: "Hematuria and rash after exercise and emotion." *Arch. Argent. Pediatr.* **56**: 67-68 (1961). J24,321/61

Martin-Vivaldi, J.: "Stress and diseases of the urinary apparatus." *Arch. Exp. Urol.* **16**: 254-263 (1963). J24,365/63

Sarre, H., Gessler, U.: "Zur Pathogenese der Schockniere" (The pathogenesis of shock kidney). *Med. Klin.* **58**: 2125-2130 (1963). E37,703/63

Review on the "shock kidney" with special reference to intrarenal circulatory disturbances, particularly the "Trueta-Shunt," and their significance in human pathology (15 refs.).

Sharma, V. N., Gupta, D. P., Barar, F. S. K., Godhwani, J. L.: "The pattern of renal changes following stress; an experimental study in rats." *Ind. J. Med. Res.* **54**: 1108-1114 (1966). F77,432/66

In rats, various stressors can produce interstitial nephritis.

Selye, H., Pahk, U. S., Somogyi, A.: "Prevention of renal necrosis by stress." *J.A.M.A.* **201**: 1026-1029 (1967). G46,701/67

Obstruction of the renal hilus for two hours with a clip causes selective necrosis affecting only the medulla of the rat kidney. "Exposure to systemic stress (restraint, spinal-cord transection) and treatment with certain drugs (chlorpromazine hydrochloride, cyproheptadine hydrochloride) offer virtually complete protection against the macroscopic and histologic manifestations of the ischemic renal necrosis thus produced."

Knochel, J. P., Dotin, L. N., Hamburger,

R. J.: "Heat stress, exercise and muscle injury: effects on urate metabolism and renal function." *Ann. Intern. Med.* **81**: 321-328 (1974).
J16,296/74

Description of the "heat stress nephropathy" that develops during intense physical training in hot climates.

Gynecologic Diseases

It has been claimed that stress plays a role in the pathogenesis of premenstrual tension and pelvic congestion that may cause pain in women.

As we said in the section on Morphology, certain irregularities of menstruation, and even prolonged amenorrhea and cessation of lactation, are also common manifestations of stress.

Gynecologic Diseases

(See also our earlier stress monographs, p. xiii)

Taylor, H. C. Jr.: "Life situations, emotions and gynecologic pain associated with congestion." In: Wolff, H. G., Wolf, S. G. Jr *et al.*, *Life Stress and Bodily Disease*, pp. 1051-1056. Baltimore: Williams & Wilkins, 1950.

B51,959/50

Description of "a gynecologic syndrome developing in response to life stress. A very brief review of a series of 105 typical, but severe, cases of this disorder will serve to illustrate some of the more striking clinical characteristics of 'pelvic congestion'."

Bickers, W.: "Premenstrual tension and its relationship to water metabolism." *Am. J. Obstet. Gynecol.* **64**: 587-590 (1952).

J12,253/52

Clinical observations suggesting that stress may play a role in the pathogenesis of premenstrual tension.

Fanelli, A., Lauro, V., Giornelli, C.: "Stress and the genital sphere: experimental findings." *Arch. Ostet. Ginekol.* **68**: 483-491 (1963) (Italian).
J23,763/63

Schmidt, A. L. C.: "Een oestrogeeneffect als behorend bij het stress-syndroom" (An estrogen effect associated with the stress syndrome). *Ned. T. Geneesk.* **107**: 834-840 (1963) (Dutch).
D66,050/63

Igarashi, M., Tohma, K., Ozawa, M., Hosaka, H., Matsumoto, S.: "Pathogenesis of psychogenic amenorrhea and anovulation." *Int. J. Fertil.* **10**: 311-319 (1965).
F54,882/65

In women with amenorrhea or anovulation following psychogenic stress, hypersecretion of ACTH coincided with low elimination of FSH, 17-KS and 17-OHCS. "Selye proposed a hypothesis called the 'shift theory' that stress increases ACTH secretion from the pituitary at the sacrifice of gonadotropin secretion. His hypothesis was not based on assay of gonadotropin, but only on finding of ovarian atrophy in rats under stress. Therefore our results seem to give the first actual supportive evidence to Selye's hypothesis."

Gotsiridze, O. A.: "Obstetric-gynaecological aspects of the concept of stress." *Nauch. Issled. Inst. Akush. Ginek.* **12**: 343-351 (1965) (Russian).
G38,595/65

Brief summary of the literature on the applications of the stress concept to obstetrics and gynecology.

Bibileishvili, Z. A.: "Some data on experimental analysis of the genesis of late toxemia of pregnancy." *Akush. Ginekol.* **46** No. 9: 28-31 (1970) (Russian).
J22,376/70

In pregnant rabbits, various stressors produce arterial hypertension and acidosis which is compared to pregnancy toxicooses.

Fries, H., Nillius, S. J.: "Psychological factors, psychiatric illness and amenorrhoea after oral contraceptive treatment." *Acta Psychiatr. Scand.* **49**: 653-668 (1973).
J10,395/73

"Stressful life events in connection with the onset of amenorrhoea were experienced by 36% of the women (41% if travels abroad were included) and significantly correlated to low solidity and high neuroticism scores."

Oral, Dental Diseases

Most of the work on the oral manifestations of stress is concerned with dentistry, and the majority of investigators agree that in both man and experimental animals, chronic intense stress increases the incidence of dental caries. Stress has also been reported to predispose to the development of sometimes necrotizing ulcerative gingivitis and chronic periodontitis.

Bruxism is a particularly characteristic dental manifestation of stress. According to one author, the first description of bruxism must be ascribed to St. Matthew in his warning: "And there shall be a weeping and gnashing of teeth." Several investigators have expressed the opinion that bruxism is an atavistic remnant of the biting instinct. It has been said that "on, or related to, the occasion when man is under stress, he will sharpen his teeth. To prepare for an emergency he grinds his teeth together—innately and unconsciously." Whatever its anthropologic origin, bruxism—though very common and on the border of what might be called a normal response—has been regarded as a neurotic stress-induced trait. Furthermore, the associated "stress-induced muscle activity is a contributory factor in the etiology of mandibular dysfunction." It can be assessed objectively by the EMG.

Among other oral diseases that have been attributed to stress are dental asymmetry, herpes labialis and changes in saliva secretion.

Oral, Dental Diseases

(See also our earlier stress monographs, p. xiii)

Manhold, J. H., Manhold, V. W.: "A preliminary report on the study of the relationship of psychosomatics to oral conditions. Relationship of personality to dental caries." *Science* **110**: 585-586 (1949). B23,160/49

Moulton, R., Ewen, S., Thieman, W.: "Emotional factors in periodontal disease." *Oral Surg.* **5**: 833-860 (1952).

J21,692/52

Necrotizing gingivitis and chronic periodontitis appear to be closely associated with stressful life situations (28 refs.).

Ratcliff, P. A.: "The relationship of the general adaptation syndrome to the periodontal tissues in the rat." *J. Periodontol.* **27**: 40-43 (1956). C13,362/56

Goldberg, H., Ambinder, W. J., Cooper, L., Abrams, A. L.: "Emotional status of patients with acute gingivitis." *N.Y. State Dent. J.* **22**: 308-318 (1956). J21,493/56

Miller, S. C., Thaller, J. L., Soberman, A.: "The use of the Minnesota Multiphasic Personality Inventory as a diagnostic aid in periodontal disease. A preliminary report." *J. Periodontol.* **27**: 44-46 (1956).

J21,492/56

Bernier, J. L.: "The role of organ systems and age in periodontal disease." *J. Periodontol.* **30**: 247-253 (1958). J24,113/58

Steinman, R. R.: "The effect of stress upon the incidence of caries." *J. S. Calif. Dent. Assoc.* **28**: 367 (1960). J24,627/60

Steinman, R. R., Brussett, M., Tartaryn, P.: "Comparison of caries incidence in exercised and immobilized rats." *J. Dent. Res.* **40**: 218 (1961). J21,694/61

In rats given a cariogenic diet, immobilization increased the incidence of dental caries.

Davis, C. H., Jenkins, C. D.: "Mental stress and oral diseases." *J. Dent. Res.* **41**: 1045-1049 (1962). J23,327/62

Review of the literature and personal observations on the relationship between oral disease and the G.A.S.

John, R.: "Stress and the dental organ: a review of the literature." *J. West. Soc. Periodontol.* **10**: 22 (1962). J24,349/62

Giddon, D. B., Goldhaber, P., Dunning, J. M.: "Prevalence of reported cases of acute necrotizing ulcerative gingivitis in a university population." *J. Periodontol.* **34**: 366-371 (1963). J21,495/63

In a university population, the prevalence of necrotizing ulcerative gingivitis "appeared

to have some relation to situational factors such as academic examinations or vacation periods."

Dyce, J. M., Dow, J. A.: "Further studies of the stress factor in dentistry." *Dent. Practit. Dent. Rec.* **15**: 326-331 (1965).
J23,132/65

Detailed discussion of the G.A.S. in dentistry.

Sutton, P. R. N.: "The early onset of acute dental caries in adults following mental stress." *N.Y. State Dent. J.* **31**: 450-456 (1965).
J23,171/65

"Acute dental crown caries follows the onset of a period of severe mental stress."

Every, R. G.: "The teeth as weapons. Their influence on behavior." *Lancet* March 27, 1965, pp. 685-688.
F36,762/65

"On, or related to, the occasion when man is under stress, he will sharpen his teeth. To prepare for an emergency he grinds his teeth together—innately and unconsciously."

Molin, C., Levi, L.: "A psycho-odontologic investigation of patients with bruxism." *Acta Odont. Scand.* **24**: 373-391 (1966).
G41,393/66

Bruxism is associated with neurotic traits and may be regarded as a stress-induced disease.

Sutton, P. R. N.: "Stress and dental caries." *Adv. Oral Biol.* **2**: 101-148 (1966) (about 300 refs.).
J22,683/66

Giddon, D. B.: "Psychophysiology of the oral cavity." *J. Dent. Res.* **45** Supp. 6: 1627-1636 (1966).
J22,585/66

O'Leary, T. J., Rudd, K. D., Nabers, C. L., Stumpf, A. J. Jr.: "The effect of a 'tube-type' diet and stress-inducing conditions on tooth mobility." *J. Periodontol.* **38**: 222-226 (1967).
J22,687/67

"Stress-inducing conditions apparently can induce bruxing in susceptible individuals, thus increasing tooth mobility. Tooth mobility values return to pre-experimental levels when the conditions are removed."

Reyna, L. J., Mascio, A. di, Berezin, N.: "Psychological stress and experimental caries." *Psychosomatics* **8**: 138-140 (1967).
F85,046/67

In rats, psychogenic stressors (electroshock, sound) can increase the incidence of dental caries.

Feldman, H.: "Caries susceptibility, anx-

iety and stress." *J. Am. Soc. Psychosom. Dent. Med.* **15**: 28-32 (1968).
J22,705/68

Giddon, D. B., Clark, R. E., Varni, J. G.: "Apparent digital vasomotor hypotonicity in the remission stage of acute necrotizing ulcerative gingivitis." *J. Dent. Res.* **48**: 431-438 (1969).
J21,497/69

Various stressors can predispose patients to necrotizing ulcerative gingivitis, presumably as a consequence of vasomotor hypotonicity.

Thilander, B., Thilander, H.: "Catecholamine excretion in children in connection with various types of dental treatment." *Acta Odontol. Scand.* **27**: 199-203 (1969).
J22,575/69

Shannon, I. L., Kilgore, W. G., O'Leary, T. J.: "Stress as a predisposing factor in necrotizing ulcerative gingivitis." *J. Periodontol.* **40**: 240-242 (1969).
J22,713/69

Yemm, R.: "Temporomandibular dysfunction and masseter muscle response to experimental stress." *Br. Dent. J.* **127**: 508-510 (1969).
J21,803/69

Bailit, H. L., Workman, P. L., Niswander, J. D., MacLean, C. J.: "Dental asymmetry as an indicator of genetic and environmental conditions in human populations." *Hum. Biol.* **42**: 626-638 (1970).
J20,565/70

Dental asymmetry may occur in various human populations as a consequence of genetic or environmental stress factors. "Genetic stress may result from inbreeding due to the finite size of the population or to a mating pattern involving consanguinity. This can lead to a reduction in population fitness because of the exposure of deleterious recessive genes in a homozygous state or, more importantly, because of a breakdown in the coadaptation of the genetic system. Indications of inbreeding stress are provided by estimates of the inbreeding coefficient, the effective population size, the amount of gene flow into the population, or by a comparison of the genetic variance of different quantitative characters with that observed in large random mating populations. Another genetic stress may result from a drastic diminution in population size, leaving too little genetic variation to adapt to a changing or extremely heterogeneous environment."

Regenbaum, G.: "Psychogenic aspects of periodontal disease. Case history." *N.Y. State Dent. J.* **36**: 609-612 (1970).
J23,981/70

Stress appears to play an important part in the pathogenesis of periodontal disease.

Schönberger, A., Waldmann, W.: "Der Einfluss von Zahnektaktion und Lokalanästhesie auf Pulsfrequenz, Blutdruck und Plasmahydroxykortikoidspiegel des Menschen" (The effect of tooth extraction and local anesthesia on human pulse frequency, blood pressure and plasma corticoid level). *Dtsch. Zahn Mund Kieferheilkd.* **54:** 241-248 (1970). J21,808/70

Eichenbaum, I. W., Dunn, N. A.: "Projective drawings by children under repeated dental stress." *J. Dent. Child.* **38:** 164-173 (1971). J20,828/71

Yemm, R.: "Comparison of the activity of left and right masseter muscles of normal individuals and patients with mandibular dysfunction during experimental stress." *J. Dent. Res.* **50:** 1320-1323 (1971).

J19,856/71

In patients under psychogenic stress, EMGs showed similar patterns on left and right masseter muscles, despite tenderness in only one of them. It is suggested that "stress-induced muscle activity is a contributory factor in the etiology of mandibular dysfunction."

Sutton, P. R. N.: "Mental stress and dental caries." *Stomatologia (Athinai)* **28:** 173-187 (1971) (Greek). J23,289/71

Wasik, A.: "The role of stress in oral diseases." *Czas. Stomatol.* **24:** 901-904 (1971) (Polish). J23,288/71

Review of the literature on the relationship between the G.A.S. and various oral diseases.

Graber, G.: "Psychisch motivierte Parafunktionen auf Grund von Aggressionen und Myoarthropathien des Kauorgans" (Psychic motivation of parafunctions caused by aggression and myoarthropathy of the masticatory apparatus). *Schweiz. Monatsschr. Zahnheilkd.* **81:** 713-718 (1971). J20,542/71

Manhold, J. H., Doyle, J. L., Weisinger, E. H.: "Effects of social stress on oral and other bodily tissues. II. Results offering substance to a hypothesis for the mechanism of formation of periodontal pathology." *J. Periodontol.* **42:** 109-111 (1971). J20,761/71

Observations on rats suggest that social

stress can be a cause of periodontal disease (20 refs.).

Lefer, L.: "Psychic stress and the oral cavity." *Postgrad. Med.* **49:** 171-175 (1971). G81,047/71

Discussion of the oral manifestations of stress, with special reference to the temporomandibular pain-dysfunction syndrome, bruxism, clenching of the teeth, salivation, etc. The author quotes a statement of St. Matthew: "And there shall be a weeping and gnashing of teeth."

Whittaker, D. K., Wilson, T. R.: "The effect of age and strain differences on the incidence of restraint-induced oral and gastric ulcers in three strains of rats." *J. Dent. Res.* **51:** 619-625 (1972). J19,863/72

In different strains of rats, the stress of restraint may cause predominantly gastric or oral ulcers. The clinical literature suggesting that ulcerative gingivitis, chronic periodontitis and herpes labialis may also be related to stress in man is reviewed.

Evaskus, D. S., Laskin, D. M.: "A biochemical measure of stress in patients with myofascial pain-dysfunction syndrome." *J. Dent. Res.* **51:** 1464-1466 (1972).

J20,142/72

Solberg, W. K., Flint, R. T., Brantner, J. P.: "Temporomandibular joint pain and dysfunction: a clinical study of emotional and occlusal components." *J. Prosthet. Dent.* **28:** 412-422 (1972). J20,138/72

Olkiniuora, M.: "A psychosomatic study of bruxism with emphasis on mental strain and familiar predisposition factors." *Proc. Finn. Dent. Soc. Toim.* **68:** 110-123 (1972).

J19,858/72

Review and personal observations on the role of stress in the pathogenesis of bruxism.

Kulmer, S.: "Dental occlusion and stress." *Österr. Z. Stomatol.* **69:** 466-471 (1972). J24,358/72

Grieder, A.: "Psychologic aspects of prosthodontics." *J. Prosthet. Dent.* **30:** 736-744 (1973). J21,626/73

Katcher, A. H., Brightman, V., Luborsky, L., Ship, I.: "Prediction of the incidence of recurrent herpes labialis and systemic illness from psychological measurements." *J. Dent. Res.* **52:** 49-58 (1973). J19,865/73

Recurrent herpes labialis in man may be the result of stress (23 refs.).

Feldman, H.: "Salivary buffer capacity, pH and stress." *J. Am. Soc. Psychosom. Dent. Med.* **21**: 25-30 (1974).

J23,989/74

The buffer capacity of human saliva is significantly decreased during stress and this

may play a role in the development of dental caries.

Siegel, M. I., Doyle, W. J.: "The differential effects of prenatal and postnatal audio-genic stress on fluctuating dental asymmetry." *J. Exp. Zool.* **191**: 211-214 (1975).

J24,770/75

Ocular Diseases

In our earlier descriptions of the stress syndrome, we noted that in certain animal species it is associated with transient clouding of the cornea. This has subsequently been confirmed in various species and is referred to in Japan as "Komi's nonspecific corneal reaction."

In rabbits, allegedly, various stressors may also elicit experimental herpetic keratitis, at least under certain predisposing conditions.

Some observations suggest that in predisposed patients stress can produce ophthalmic zoster, foveomacular retinitis, uveitis, glaucoma, chorioretinitis and allegedly in young children, even strabismus and amblyopia.

Ocular Diseases

(See also our earlier stress monographs, p. xiii)

Cholst, M.: "The alarm reaction in relation to scotometry." *Arch. Ophthalmol.* **43**: 580-581 (1950).

D25,049/50

Prewitt, L. H.: "Retinal detachment possibly due to stress, parasympathetonia and non-adaptation syndromes. Report of a case." *Ann. Allergy* **13**: 690-694 (1955).

J25,094/55

Campbell, D. A.: "Ophthalmic stress." *Trans. Ophthalmol. Soc. U.K.* **79**: 511-517 (1959).

E51,405/59

Ikeda, I.: "The stress and changes of the cornea." *Folia Ophthal. Jap.* **12**: 639-650 (1961).

E84,262/61

Stress causes corneal opacity (Komi's non-specific corneal reaction) in the rabbit. Furthermore, "various stressors, such as electro-shock, moist heat, gravity shock, enucleatio bulbi without anesthesia, are found to favour the incidence of experimental herpetic keratitis in rabbits, to shorten its latent period, to make worse its clinical course and to delay its natural healing."

Fukunaga, K.: "On stress worsening in a case of pigmentary degeneration of the

retina." *J. Clin. Ophthalmol. (Tokyo)* **16**: 1145-1149 (1962).

J24,337/62

Ragnetti, E.: "Ricerche sull'azione esercitata da uno stimolo acustico sul tono endoculare di soggetti normali e glaucomatosi" (Research on the action of an acoustic stimulus on intraocular tonus of normal and glaucomatous subjects). *Minerva Oftalmol.* **5**: 105-113 (1963).

J23,875/63

Ikeda, I., Maeda, I.: "Retinal detachment surgery and stress." *Folia Ophthalmol. Jap.* **17**: 613-621 (1966).

J24,343/66

Holm-Pedersen, E.: "Traumatic ophthalmic zoster." *Acta Ophthalmol. (Kbh.)* **47**: 591-595 (1969).

J22,286/69

Review of the literature and personal observations on stress-induced ophthalmic zoster.

Ford, C. V.: "Foveomacular retinitis: the relationship to stress." *Milit. Med.* **135**: 756-759 (1970).

J21,201/70

Foveomacular retinitis is often seen following exposure to traumatic injuries and other stressors.

Nail, R. L.: "Foveomacular retinitis." *Milit. Med.* **136**: 575-577 (1971).

J19,712/71

Studies in the U.S. Armed Forces suggest that foveomacular retinitis is a stress-dependent disease.

Beckwitt, M. L.: "Stress and strabismus." *Isr. Ann. Psychiatry* **9**: 11-29 (1971).

J20,544/71

In predisposed children, strabismus and amblyopia may be precipitated by stress.

Sen, D. K.: "Endogenous uveitis in relation to stress. A clinical study." *Eye, Ear, Nose, Throat Mon.* **50**: 56-59 (1971).

J20,541/71

Cohen, S. I., Hajioff, J.: "Life events and the onset of acute closed angle glaucoma." *J. Psychosom. Res.* **16**: 335-341 (1972).

J19,892/72

A review of the literature and the authors'

personal observations support the impression that emotional stress plays a part in the etiology of acute closed-angle glaucoma.

Miki, T., Sunada, I., Higaki, T.: "Studies on chorioretinitis induced in rabbits by stress (repeated administration of epinephrine)." *Acta Soc. Ophthalmol. Jap.* **76**: 1037-1045 (1972) (Japanese). J19,656/72

"The nonspecific ocular reaction, based on the General Adaptation Syndrome theory of Selye, was first described by Komi and Ikeda et al. in 1954. It was reported that nonspecific choroidal reaction due to stress is quite similar to central serous retinopathy of the human eye." Further studies along these lines confirmed that, in rabbits, repeated injections of EP can cause chorioretinitis.

Skin Diseases

The changes in galvanic skin resistance have repeatedly been mentioned as characteristic cutaneous responses to stress, but these cannot be considered as pathologic conditions.

Emotional stressors may elicit urticaria, exudative skin disease, "prickly heat" (miliaria rubra), Quincke's edema, psoriasis, a variety of so-called stress dermatoses, lichen sclerosus and allegedly even acne and vitiligo, contact dermatitis and eczema.

Skin Diseases

(See also our earlier stress monographs, p. xiii)

Grant, R. T., Pearson, R. S. B., Comeau, W. J.: "Observations on *urticaria* provoked by emotion, by exercise and by warming the body." *Clin. Sci.* **2**: 253-272 (1935-36).

D83,741/35-36

Funkenstein, D. H.: "Psychophysiologic relationship of asthma and urticaria to mental illness." *Psychosom. Med.* **12**: 377-385 (1950). B64,759/50

Studies on psychotic patients suggest that both asthma and *urticaria* attacks are closely related to psychogenic stress.

Graham, D. T.: "The pathogenesis of hives: experimental study of life situations, emotions, and cutaneous vascular reactions." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 987-1009. Baltimore: Williams & Wilkins, 1950.

B51,955/50

Review of the literature and numerous personal observations on the pathogenic role of psychogenic stressors in the production of *urticaria*. "Traumatic life situations responsible for attacks were almost exclusively those in which the patient developed resentment because he saw himself as the victim of unjust treatment which he could do nothing about."

Kepecs, J. G., Robin, M.: "Life situations, emotions, and atopic dermatitis." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 1010-1015. Baltimore: Williams & Wilkins, 1950. B51,956/50

Clinical observations which "indicate a significant relationship between weeping and rises in blister fluid level, were made on several patients with *exudative skin disease*, and also on several individuals without skin disease. The patients with normal skins revealed the same rises with weeping as did the dermatological cases."

Ladell, W. S. S.: "Changes in sweating

- after *prickly heat.*" *Br. Med. J.* June 16, 1951, pp. 1358-1360. B63,039/51
- "To adopt Selye's (1950) terminology, Type II exhaustion might be called, as a working hypothesis, a 'disease of adaptation.'"
- Arnold, H. L. Jr.: "Stress dermatoses. Suggested integration of the allergic-psychogenic dermatoses." *Arch. Derm. Syph.* **67**: 566-574 (1953). B88,307/53
- "It is suggested that it is true of these 'stress dermatoses,' as Osler, in 1900, said of the diseases of the 'erythema group,' that (1) 'similarity of lesions may result from a variety of causes,' and (2) 'unity of cause may be associated with a variety of lesions.' It is further suggested that many of these dermatoses, which have been attributed to either allergic reactions or emotional tension, or both, may with profit be regarded as being variants of the stress response of Selye. Whether the wide variations in the response are due (1) to qualitative variations in the effect of the stressor agent, or (2) effects of the actual or apparent etiologic agent independent of its stressor effect, or (3) latent innate tendencies or individual predilections of the patient, or any two, or all three, or other as yet unknown factors, remains to be elucidated."
- Wittkower, E. D.: "Studies of the personality of patients suffering from urticaria." *Psychosom. Med.* **15**: 116-126 (1953). J17,501/53
- Several case reports support the concept that *urticaria* and *Quincke's edema* can be elicited in predisposed individuals by stressful life events.
- Reiss, F.: "Psoriasis and stress." *Dermatologica* **113**: 71-78 (1956) (13 refs.). J25,134/56
- Poole, W. L.: "Chronic urticaria as a manifestation of the stress syndrome." *South. Med. J.* **53**: 1048-1052 (1960). J23,323/60
- Clinical observations suggest "that chronic *urticaria* may be explained in some patients in terms of Selye's adaptation theory."
- Reinhold, M.: "Relationship of stress to the development of symptoms in *alopecia areata* and *chronic urticaria.*" *Br. Med. J.* March 19, 1960, pp. 846-849. C83,292/60
- Cohen, A. L., Gelblung, I., Goijman, I.: "Hematuria and rash after exercise and emotion." *Arch. Argent. Pediatr.* **56**: 67-68 (1961). J24,321/61
- Seville, R. H.: "*Dermatomyositis* and *lichen sclerosus et atrophicus.*" *Br. J. Dermatol.* **76**: 151 (1964). J23,219/64
- Noojin, R. O.: "How stress and strain may affect the skin." *Med. Rec.* (Houston) **57**: 389-391 (1964). J24,374/64
- Loewenthal, L. J. A., Hins, S. C.: "The aetiology of miliaria." *S. Afr. Med. J.* **38**: 613-615 (1964). J24,124/64
- Miliaria rubra or "prickly heat" is a dermatosis common in the gold mines of South Africa, and is regarded as a disease of adaptation due to stress.
- MacDonald, A. C.: "Measurement in angioneurotic oedema." *J. Psychosom. Res.* **8**: 207-211 (1964). G24,079/64
- Quincke's edema* often develops as a consequence of stress.
- Knight, J. A.: "Psychodynamics of the allergic eczemas." *Ann. Allergy* **25**: 392-396 (1967). J23,358/67
- Glen, A. I. M., Halliburton, I. M., MacDonald, A. C.: "The effect of stress and of mild dehydration on renal solute output in angioneurotic and periodic oedema." *J. Psychosom. Res.* **13**: 61-66 (1969). H23,756/69
- Stressful life events may precipitate both angioneurotic (*Quincke*) and periodic *edema*.
- Kraus, S. J.: "Stress, acne and skin surface free fatty acids." *Psychosom. Med.* **32**: 503-508 (1970). G78,820/70
- In students, emotional stress exacerbates *acne* and increases skin surface FFA.
- Brassai, Z., Hadnagy, C., Horváth, E., Nagy, L.: "Data regarding the problem of physical allergies." *Allergie Asthma* **16**: 68-74 (1970). J20,724/70
- Statistical studies on *urticaria* produced by various stressors.
- Fischer, H.: "Vitiligo als Verfolgungs-schaden" (Vitiligo as sequelae of persecution). *Berufsdermatosen* **19**: 317-324 (1971). J21,408/71
- Baughman, R., Sobel, R.: "Psoriasis, stress, and strain." *Arch. Dermatol.* **103**: 599-605 (1971). J21,154/71
- Mettrop, P. J. G., Visser, P.: "Influence on the induction and elicitation of contact-

dermatitis in guinea pigs." *Psychophysiology* **8**: 45-53 (1971). J21,219/71

Experimental observations suggest that the "stress preceding the first contact directly influences the sensitization on the second contact...."

Sanborn, D. E., Sanborn, C. J., Cimbalic, P., Niswander, G. D.: "Suicide and stress-related *dermatoses*." *Dis. Nerv. Syst.* **33**: 391-394 (1972). J21,824/72

Brown, D. G.: "Stress as a precipitant of eczema." *J. Psychosom. Res.* **16**: 321-327 (1972). G92,625/72

The literature on possible relationships between stress and *eczema* is analyzed. Although stress may be an eliciting factor, the importance of its role remains questionable.

Teshima, H., Inoue, S., Ago, Y., Ikemi, Y.: "Plasminic activity and emotional stress." *Psychother. Psychosom.* **23**: 218-228 (1974). J16,685/74

Angioneurotic or *Quincke's edema* often develops immediately after psychogenic stress. This may be related to increased plasmin activity, which occurs in animals following various stressors or EP.

Cormane, R. H.: "A molecular explanation of stress dermatitis." *Psychother. Psychosom.* **23**: 188-196 (1974). J16,682/74

In contact *dermatitis*, deposition mecha-

nisms of immune complexes are "hastened by release of vasoactive amines and hormones due to psychological reasons, stress, or trauma. As a consequence of the forementioned sequence of events, it is understandable that release of sympathomimetic amines and hormones along with the presence of antigen may perpetuate or even worsen cell-mediated immunity."

Hoede, N., Morschies, B., Holzmann, H.: "Psoriasis- eine Allgemeinerkrankung" (*Psoriasis*, a dermatosis seen very often). *Internist* (Berlin) **15**: 186-191 (1974). J19,094/74

Holzmann, H., Hoede, N., Krapp, R.: "Gutachterliche Probleme bei der Beurteilung der Psoriasis" (Problems of expert opinion in the assessment of psoriasis). *Z. Hautkr.* **49**: 493-496 (1974). J20,840/74

Psoriasis may occur as a disease of adaptation during the post-concentration camp survivor syndrome. The medical and legal implications of this observation are discussed.

Klein, R. F., Gonan, J. Y., Smith, C. M.: "Psychogenic *purpura* in a man." *Psychosom. Med.* **37**: 41-49 (1975). J23,313/75

Robertson, I. M., Jordan, J. M., Whitlock, F. A.: "Emotions and skin (II)—the conditioning of scratch responses in cases of *lichen simplex*." *Br. J. Dermatol.* **92**: 407-412 (1975). J23,633/75

Gastrointestinal Diseases

Peptic ulcers and ulcerative colitis were discussed at the very beginning of the chapter on the Diseases of Adaptation, since they are the most common gastrointestinal manifestations of stress, but some investigators believe that "idiopathic celiac disease" is also due largely to psychogenic stress situations.

There is much less evidence to support the view that appendicitis can be produced by stress in man, but in rats various very acute stressors, particularly intravenous injections of histamine, tend to cause necrotizing inflammation of the cecum in the region that allegedly corresponds to the appendix (a true appendix does not exist in rats).

Nutritional Diseases (including Kwashiorkor)

Any nutritional disease causes stress, and starvation (partial or complete) is among the most commonly-used experimental stressors. The subject has been discussed at greater length in the section on agents capable of evoking the stress re-

spose. Here, we should like to mention only a few observations which suggest that, stress plays a special role at least in some nutritional deficiencies.

Studies performed in India suggested that a failure of the adrenal cortex to respond adequately to malnutrition may cause a breakdown of adaptation, resulting in the characteristic biochemical and clinical picture of kwashiorkor and marasmus, which are considered to be different facets of the same disease. Here, the growth retardation and catabolism are regarded as useful adaptations to the stress of protein-caloric malnutrition. The plasma level of somatomedine is greatly diminished in various types of malnutrition, especially in kwashiorkor.

Stress also appears to participate in the pathogenesis of vitamin C deficiency. In his classic *Treatise of the Scurvy*, Lind stated, "cold, damp, fatigue, and hard work precipitated scurvy."

Nutritional Diseases (including Kwashiorkor)

(See also our earlier stress monographs, p. xiii)

Lind, J.: *A Treatise of the Scurvy*. Edinburgh, 1753. J13,727/1753

In this classic treatise the author states that "cold, damp, fatigue and hard work precipitated scurvy."

Jaya Rao, K. S.: "Evolution of kwashiorkor and marasmus." *Lancet* April 20, 1974, pp. 709-711. H85,623/74

Studies on kwashiorkor and marasmus in India show that the two are only different facets of the same disease. "It is suggested that marasmus, characterised by severe growth retardation but remarkably well-preserved metabolic processes, represents a state of good adaptation to the stress of protein-caloric malnutrition. The response of the adrenal cortex may be crucial for this adaptation, a normal increase in plasma-cortisol helping in adequate mobilisation of muscle

protein and in maintenance of metabolic integrity. The failure of the adrenal cortex to respond adequately may represent the crucial step in dysadaptation or breakdown of adaptation, resulting in the characteristic biochemical and clinical picture of kwashiorkor" (25 refs.).

Job, J. C., Rappaport, R.: "Somatomédines et croissance" (Somatomedines and growth). *Arch. Fr. Pédiatr.* 31: 333-338 (1974). J12,952/74

The plasma level of somatomedine is greatly diminished in various types of malnutrition, especially in protein deficiencies causing kwashiorkor.

Beitins, I. Z., Kowarski, A., Migeon, C. J., Graham, G. G.: "Adrenal function in normal infants and in marasmus and kwashiorkor. Cortisol secretion, diurnal variation of plasma cortisol, and urinary excretion of 17-hydroxycorticoids, free corticoids, and cortisol." *J. Pediatr.* 86: 302-308 (1975). J21,352/75

Ménière's Disease

In patients with Ménière's disease, attacks may occur at times of stress. Curiously, the usual increase in urinary catecholamine excretion is not observed in patients with unilateral labyrinthine dysfunction.

Ménière's Disease

(See also our earlier stress monographs, p. xiii)

Gejrot, T., Fluur, E., Levi, L.: "Sympathoadrenomedullary activity during experiment-

ally provoked mental stress in patients with labyrinthine defects." *Acta Otolaryngol. (Stockh.) Supp.* 224: 260-261 (1967). G53,263/67

"In the normal subjects, experimentally induced emotional stress was accompanied by

a significantly increased excretion of urinary catecholamines. This was not the case in the patients with unilateral labyrinthine dysfunction."

Suurala, U., Gelhar, K.: "Further studies on the relationship between Ménière, psychosomatic constitution and stress." *Acta Otolaryngol.* (Stockh.) **70**: 142-147 (1970).

J20,530/70

Williamson, D. G., Gifford, F.: "Psychosomatic aspects of Ménière's disease." *Acta Otolaryngol.* (Stockh.) **72**: 118-120 (1971).

J17,102/71

Patients predisposed to Ménière's disease "showed attacks of vertigo and later tinnitus and deafness that could definitely be related to a life stress situation."

Fluur, E.: "Long-term postoperative results following selective section of the vestibular nerve in Ménière's disease." *Acta Otolaryngol.* (Stockh.) **74**: 425-429 (1972).

J17,880/72

In patients with Ménière's disease, stress may accentuate the symptoms.

Pulec, J. L.: "Symposium on Ménière's disease. I. Ménière's disease: results of a two and one-half-year study of etiology, natural history and results of treatment." *Laryngoscope* **82**: 1703-1715 (1972). J17,103/72

"Patients already suffering from a vertiginous problem will sometimes have an exaggeration of symptoms during periods of stress. Two causes seem likely: 1) stress and fatigue tend to reduce the effectiveness of the vestibular efferent system and its suppressing effect upon a malfunctioning labyrinth. When suppression is reduced the existing abnormal labyrinthine stimulation becomes evident; and 2) Ménière's patients whose etiology is allergic or metabolic and who are on the borderline of control may have inadequate adrenocortical output during these periods of stress with the subsequent exaggeration of symptoms."

Varia

Since increased corticoid production has been demonstrated in virtually every pathologic condition of any importance, a certain relationship between stress and the most dissimilar diseases has been suspected. It would serve no purpose to discuss all the relevant publications in detail here. (Malformations were dealt with in Chapter II, p. 382.) However, among the publications cited in the abstract section, the reader will find data on the possible role played by stress in *status asthmaticus*, *coronary infarct*, *bronchopneumonia*, *carcinoma of the pancreas*, *pneumococcal meningitis*, *congestive cardiac failure*, *diabetic ketosis*, *adrenocortical necrosis*, *various forms of tuberculosis*, *skin diseases*, *inguinal hernia*, *Milkman's syndrome*, *thymus hyperplasia*, *myasthenia gravis*, *cystathioninuria*, *hepatic porphyrias*, *chronic rhinitis*. Many of these diseases have already been discussed at great length in the previous pages, but relevant papers are quoted here if they report maladies in conjunction with other allegedly stress-induced derangements.

Varia

(See also our earlier stress monographs, p. xiii)

Ehrich, W. E., Seifter, J.: "Role played by the salivary glands in the 'alarm reaction.'" *Arch. Pathol.* **45**: 239-245 (1948).

B31,789/48

Various stressors produce focal necroses in experimental animals. "It is possible that the alarm reaction plays a role in the causation of *parotitis* following operation. It is not un-

likely that at least in some cases this sialadenitis is merely another part phenomenon or sequel of this reaction."

Cope, C. L., Boysen, X., McCrae, S.: "Some observations on endogenous cortisone excretion in man." *Br. Med. J.* September 29, 1951, pp. 762-767. B64,531/51

Urinary corticoid excretion (assayed by eosinopenia in adrenalectomized mice) is increased in a variety of diseases (*status asthmaticus*, *coronary infarct*, *bronchopneu-*

monia, carcinoma of the pancreas, pneumococcal meningitis, congestive cardiac failure, diabetic ketosis), as well as in late pregnancy.

Bachrach, W. H., Smith, J. L., Halsted, J. A.: "Spasm of the choledochal sphincter accompanying sudden stress." *Gastroenterology* **22**: 604-606 (1952). B90,156/52

Lawrence, J. H., Berlin, N. I.: "Relative polycythemia—the polycythemia of stress." *Yale J. Biol. Med.* **24**: 498-505 (1952).

B74,019/52

Patients under intense psychogenic stress may develop *polycythemia*.

Grace, W. J.: "Life stress and *regional enteritis*." *Gastroenterology* **23**: 542-553 (1953).

C7,649/53

Wolf, S.: "Reactions in the nasal mucosae. Relation of life stress to chronic *rhinitis* and 'sinus' headache." *Arch. Otolaryngol.* **59**: 461-475 (1954).

J25,507/54

Moore, S. F. Jr., Simpson, J. W.: "The emotional component in *Trichomonas vaginitis*." *Am. J. Obstet. Gynecol.* **68**: 974-980 (1954).

J25,353/54

"Symptomatic infestations with *Trichomonas vaginitis* occur only in patients suffering from a significant degree of psychobiologic stress."

Champeau, M., Pineau, P., Tzanck, R.: "Iléus intestinal d'origine psychique après intervention pour obstacle mécanique" (Intestinal *ileus* of psychic origin after intervention for mechanical obstacle). *Arch. Mal. Appar. Dig.* **44**: 1168-1174 (1955).

J25,118/55

Caveness, W. F.: "Emotional and psychological factors in *epilepsy*. General clinical and neurological considerations." *Am. J. Psychiatry* **112**: 190-193 (1955).

J25,168/55

"Emotional stress may act as a precipitant to individual seizures."

Rawlins, A. G.: "Corticotropin and cortisone in *otolaryngology*." *J.A.M.A.* **157**: 500-502 (1955).

C1,570/55

Mattioli-Foggia, C.: "Stress e miopatia lipo-fibro-calcarea" (Stress and *lipo-fibro-calcareous myopathy*). *Riv. Patol. Nerv. Ment.* **81**: 337-350 (1960).

C93,915/60

Tedeschi, L. G., Peabody, C. N.: "Cortical necrosis of the adrenal gland." *Arch. Pathol.* **73**: 18-23 (1962).

D16,081/62

In three cases of acute colonic surgery as-

sociated with *adrenal cortical necrosis*, "death was precipitated by the development of a bacterial infection. The role of the endocrine hyperfunction brought about by stress as well as the epinephrine-endotoxin reaction phenomenon are discussed as an explanation for the adrenal cortical damage" (42 refs.).

Roy, B. B., Chatterjee, P.: "Milkman's syndrome. A disease of adaptation." *Calcutta Med. J.* **61**: 113-117 (1964).

G25,751/64

In two patients, *Milkman's syndrome* was interpreted as a disease of adaptation since it was associated with considerable periodic increases in blood corticoid levels.

Rahe, R. H., Meyer, M., Smith, M., Kjaer, G., Holmes, T. H.: "Social stress and illness onset." *J. Psychosom. Res.* **8**: 35-48 (1964).

G18,232/64

Statistical studies suggest that various types of social stressors can predispose to *tuberculosis*, *skin diseases* and even *inguinal hernia*.

Blundo, S., Caponetti, R., Mazzaglia, E.: "La nostra esperienza nella terapia dell'iperplasia timica" (Our experience in the treatment of thymic hyperplasia). *Minerva Med. Sicil.* **11**: 96-102 (1966).

F75,708/66

Since thymus atrophy is a characteristic sign of the G.A.S., it is assumed that clinical cases of *thymus hyperplasia* may also be related to derangements of resistance to stress, although the underlying mechanism has not been explained.

Lambusta, A.: "Atrofia giallo-acuta del fegato e stress psico-emotivi" (Acute *yellow atrophy of the liver* and psycho-emotional stress). *Minerva Med. Leg.* **86**: 182-183 (1966).

J24,553/66

Belfer, M. L., Shader, R. I., Mascio, A. di, Harmatz, J. S., Nahum, J. P.: "Stress and *bronchitis*." *Br. Med. J.* **28**: 805-806 (1968).

H3,166/68

Border, J. R., Tibbetts, J. C., Schenk, W. G. Jr.: "Hypoxic hyperventilation and acute respiratory failure in the severely stressed patient: massive *pulmonary arteriovenous shunts*?" *Surgery* **64**: 710-719 (1968).

J22,741/68

L'Epée, P., Lazarini, H. J., N'Doky, T., Doignon, J.: "Oedème aigu du poumon post-émotionnel sur les lieux du travail" (Acute *pulmonary edema* after emotional stress on the job site). *Arch. Mal. Prof.* **30**: 72-73 (1969).

J22,112/69

Cianci, P., Donahoo, S., Minogue, T., Staver, R.: "Stress as a factor in the development of clinical malaria: a comparative study of malarial incidence in RVN casualties." *Milit. Med.* **137**: 113-114 (1972).

G89,300/72

In military personnel, *malaria* often "appeared after the added stress of surgery and anesthesia, including minor procedures."

Yousef, M. K. el, Bakewell, W. E. Jr.: "The Gaisböck syndrome." *J.A.M.A.* **220**: 864 (1972).

H55,016/72

The "Gaisböck syndrome" has been called a "*stress polycythemia*," as it often occurs in connection with psychic stress, particularly anxiety. It is associated with a number of biochemical and functional alterations characteristic of stress.

Brown, H. S., Turk, L. N., Hopkins, W. A.: "Management of the white lung syndrome." *Ann. Thorac. Surg.* **13**: 411-419 (1972).

J20,020/72

"Similar clinical pulmonary characteristics may develop after severe body stress and can be placed into one category for purposes of definition and treatment. Seventeen patients satisfying the criteria of so-called *white lung syndrome* were treated in private hospitals in metropolitan Atlanta during a three-year period."

Frimpter, G. W.: "Stress may precipitate cystathioninuria." *J.A.M.A.* **226**: 1068-1069 (1973).

H77,643/73

Cystathioninuria is a rare metabolic disorder compatible with normal life, but it renders subjects particularly sensitive to stressors which, in turn, aggravate its intensity.

Steen, R. E.: "Stress disorders in childhood. Second of 3 parts." *J. Ir. Med. Assoc.* **66**: 78-84 (1973).

J19,613/73

Steen, R. E.: "Third of 3 parts." *J. Ir. Med. Assoc.* **66**: 101-107 (1973).

J19,614/73

Review on stress diseases in childhood with special emphasis on various types of neurosis. A group of functional nervous disorders in childhood with a cyclic tendency is described as the "*periodic syndrome*." It is often associated with asthma, migraine headache, vomiting, diarrhea or fever. Both a hereditary predisposition and a stress-induced trigger mechanism appear to be involved.

Metz, G., Spiess, B., Classen, H. G., Mittermayer, C., Vogel, W.: "Akuter Stress und Lungenödem" (Acute stress and *pulmonary edema*). *Arzneim. Forsch.* **24**: 1625-1627 (1974).

J18,272/74

Paxton, J. W., Moore, M. R., Beattie, A. D., Goldberg, A.: "17-Oxosteroid conjugates in plasma and urine of patients with acute intermittent *porphyria*." *Clin. Sci. Molec. Med.* **46**: 207-222 (1974).

J9,742/74

"A wide variety of factors, such as drugs with different chemical structures, alcohol, infection, severe restriction of carbohydrate and protein intake, pregnancy and emotional stress, have been implicated as precipitating and aggravating acute episodes of the *hepatic porphyrias*, and there is the distinct possibility that the effects of these heterogeneous precipitating factors are mediated through interference with an endogenous regulatory system of steroid metabolism in the liver." Steroid metabolic studies suggest involvement of 17-KS, "especially dehydroepiandrosterone and aetiocholanolone, in the pathogenesis and control of acute intermittent porphyria."

McKenna, E. L.: "Nasal mastocytosis." *Laryngoscope* **84**: 112-125 (1974).

J9,670/74

Certain types of *chronic rhinitis* are due to often unidentifiable local stressors which lead to mast cell proliferation. They are considered to be dependent upon an L.A.S., and are treatable by glucocorticoids.

Wingard, D. W.: "Malignant hyperthermia: a human stress syndrome?" *Lancet* December 14, 1974, pp. 1450-1451.

H97,396/74

Clark, O. H., Hall, A. D., Schambelan, M.: "Clinical manifestations of adrenal hemorrhage." *Am. J. Surg.* **128**: 219-224 (1974).

J15,481/74

Katz, J. L., Weiner, H., Yu, T. F.: "Psychobiological variables in the onset and recurrence of gouty arthritis. A chronic disease model." *J. Chron. Dis.* **28**: 51-62 (1975).

J21,764/75

In man, the most common precipitants of *gouty attacks* "included alcohol and dietary indiscretion, local joint trauma, surgery and infection, not taking prescribed medication, and life experiences that were usually associated with feelings of tense anticipation."

Pluricausal Diseases

The concept that many maladies are not due to a single cause but to a "pathogenic situation" in which several potentially pathogenic agents must act concomitantly has proved to be very fruitful in the interpretation of the diseases of adaptation. These diseases are virtually always "pluricausal" or "multifactorial," depending as much upon stress as upon various internal and external conditioning factors.

In clinical medicine, countless observations have shown that in the presence of a potential disease producer, predisposition—that is, endogenous and exogenous conditioning—determines whether the malady will actually become evident or not. This is obvious from what we said in the preceding chapters about virtually every Disease of Adaptation. Whenever cardiovascular diseases, neuropsychiatric derangements, diabetes, hyperthyroidism, immune diseases, gastrointestinal maladies and so on become manifest upon exposure to stressful life events, it is always evident that such factors as genetic predisposition, nutrition, general physical fitness or pre-existent disease play a decisive role in determining whether or not morbid lesions develop.

In experimental medicine, a few particularly obvious examples of pluricausal diseases helped to illustrate this concept and to make it generally acceptable. At the same time, these clearcut models, in which diseases could be synthesized virtually at will by combined treatment with various in themselves innocuous agents, have answered two of the most often-voiced and best founded objections to the concept of stress and of the diseases of adaptation: (1) How could the most different agents produce the same result (namely, stress)? (2) How could the same causative factor (stress) produce the most different morbid changes?

Without the concept of pluricausal diseases, it was difficult to see how one could justify the idea of a stereotyped response to innumerable agents, when actually they all do cause different effects. This became acceptable only after we had shown that the specific effects of each agent (shivering after cold, hypoglycemia after insulin and so on) are superimposed upon the nonspecific effects of stress (for example, ACTH, corticoid and catecholamine secretion; in more severe forms, peptic ulcers, thymicolympathic involution, loss of weight and so on). On the other hand, depending upon predisposing factors, the same potential pathogen, stress, can cause more or less selective morbid lesions in the form of hypotension, cardiac infarction, peptic ulcers, neuropsychiatric derangements or migraine headache.

That this relatively simple concept has so long resisted general acceptance by the medical community is probably due to the fact that the clinical interpretation of any one case is always complicated by the unavoidable heterogeneity of the patient population; individuals differ widely from one another in terms of genetic background, nutrition, social environment and so on. The experiments on homogeneous populations of rats (in which genetic background, age, sex, nutrition and environment could be kept uniform while varying only a small number of potentially pathogenic factors) have helped us analyze pluricausal diseases under strictly reproducible conditions.

Among the clearcut pluricausal diseases that were instrumental in establishing this concept, the following are worthy of special mention:

In rats bearing a granuloma pouch, systemic stress could either inhibit or aggravate the topical damage caused by exposure of a limited tissue area to a pathogen (for example, croton oil). The result depended upon the intensity of topical irritation and of systemic stress. Mild stress usually inhibited the response to a moderately irritat-

ing topical pathogen, in that the resulting increased secretion of anti-inflammatory (syntoxic) glucocorticoids was useful in defending the tissue area against the damage of excessive defensive (inflammatory) responses. On the other hand, if the local stress (tissue irritation) was very severe, the inhibition of inflammation proved to be harmful, since it predisposed the adjacent tissue areas to necrosis and eventual perforation of the resulting abscesses, or to invasion of the blood with pathogenic bacteria which could, normally, be quarantined at the site of invasion. In fact, even when the local stimulus was only of moderate severity, extremely intense systemic stress produced such a pronounced increase in anti-inflammatory hormones that the resulting complete inhibition of the localization of an invading pathogen (by the virtual elimination of inflammatory or immunologic defense) proved to increase disease susceptibility to dangerous levels. The clarification of this constant interplay between local and systemic stress, that is to say between the L.A.S. and the G.A.S., represented an important step forward in the development of our knowledge not only of pluricausal diseases, but also of the mechanism of stress actions in general.

Since then, a great deal of work has been done in this field and several monographs have described the pluricausal nature of certain apparently quite specific morbid lesions with well-defined characteristics, both as regards their localization and the morphologic structure of the alterations that identify them.

Particular attention has been given in this connection to the various forms of *calciphylaxis* and *calcergy*, *thrombohemorrhagic phenomena*, *conditioned tissue necroses*, the *pluricausal cardiopathies* and *mineralocorticoid hypertension*. None of these depends upon any one particular pathogen in the way that paralysis of the leg muscles is caused by transection of the spinal cord, ischemic necrosis by obstruction of an end-artery, or a skin burn by contact with boiling water. In all these latter cases, we are dealing with direct pathogens that are damaging in themselves, and not with indirect pathogens, which cause disease mainly by the inappropriate or excessive defense reactions that they elicit. Here we are concerned with conditional pathogens that cause disease only under certain circumstances—that is, in the presence of special conditioning factors. For example, calciphylaxis and the thrombohemorrhagic phenomena are elicited by challengers only after suitable sensitization, which determines both the character and the localization of the resulting lesions.

It was the realization of the comparative frequency of such pluricausal diseases that led us in 1959 to state: "There begins to emerge a new and somewhat more complex pathology, in which the main objects of our study are no longer individual 'pathogens' but rather 'pathogenic situations.' "

Of course, this attempt to outline the essential characteristics of what we have called "pluricausal diseases" would be incomplete if we did not point out especially that most spontaneous maladies are between the two extremes, being neither completely moncausal nor equally dependent upon each constituent element of a "pluricausal pathogenic situation." In the vast majority of spontaneous maladies, one factor is of special importance; for example, a particular microbe, toxicant or dietary factor is the main cause of tuberculosis, botulinus poisoning or rickets. But hereditary or acquired predisposing factors for resistance may play an almost equally important part in determining whether these pathogens will or will not induce disease.

It is especially interesting in connection with the subject of this monograph that the diseases of adaptation, which are primarily due to pathogenic actions of stress, are virtually always pluricausal. Both the general predisposition to respond to stress

with disease and the particular character of the lesion developed depend primarily upon endogenous and exogenous conditioning.

Pluricausal Diseases

(See also our earlier stress monographs, p. xiii)

Skelton, F. R.: "On certain factors conditioning the action of the pituitary-adrenal system." In: Christman, R. C., *Pituitary-Adrenal Function*, pp. 39-48. Washington: American Association for the Advancement of Science, 1950.

B45,085/50

Selye, H.: "An experimental model illustrating the pathogenesis of the diseases of adaptation." *J. Clin. Endocrinol. Metab.* **14**: 997-1005 (1954).

B87,738/54

In rats bearing a granuloma pouch, systemic stress can either inhibit or aggravate the topical damage caused by exposure of a limited tissue area to a pathogen (for example, croton oil). The result is determined by the intensity of both the topical irritation and the systemic stress. Both the protective and the aggravating effects depend upon endogenous adrenal hormones, since they are abolished by adrenalectomy. These effects may be delayed and become manifest only long after the systemic stressor has ceased to act.

Selye, H.: "Le stress et l'infarctus du myocarde" (Stress and myocardial infarction). *Marseille Méd.* **95**: 575-580 (1958).

C53,144/58

Brief outline on the pluricausal cardiopathies, with special reference to infarctoid necroses and their prevention.

Selye, H.: "Perspectives in stress research." *Perspect. Biol. Med.* **2**: 403-416 (1959).

C60,261/59

Review on the perspectives in stress research, with special emphasis upon conditioning factors which can greatly modify stress-induced changes. We are beginning to see the importance of pluricausal or multifactorial diseases in which stress is not the causative agent but can be the decisive factor. "There begins to emerge a new and somewhat more complex pathology in which the main objects of our study are no longer individual 'pathogens,' but rather 'pathogenic situations.'"

Selye, H.: *Calciphylaxis*, p. 552. Chicago: University of Chicago Press, 1962.

D15,540/62

Monograph mainly concerned with calciphylaxis and calcergy, both of which appear to have some relationship to stress. Local application of stressors in calciphylactically conditioned animals may result in topical calcium deposits, whereas systemic stress may prevent various forms of calciphylaxis.

Selye, H., Tuchweber, B., Gabbiani, G.: "Prevention of cutaneous calciphylaxis by topical stress." *Arch. Dermatol.* **87**: 566-574 (1963).

D40,219/63

"A variety of agents such as distilled water, mechanical trauma (pinching the skin with a hemostat), formaldehyde, croton oil, or histamine liberators (e.g., compound 48/80, polymyxin) selectively inhibit skin calcification at the point where they are applied within the challenged area. Histologic studies show a relationship between this form of skin calcification, the distribution of mast cells, and the deposition of iron."

Marino, A., Mazzeo, F., Mezza, F. di, Bracale, G.: "Arteropatia periferica da adrenalina + ergotamina + psicostress nella cavia" (Peripheral arteriopathies caused by adrenaline + ergotamine + psychologic stress in guinea pigs). *Arch. Int. Pharmacodyn. Ther.* **156**: 455-466 (1965).

F49,371/65

Jahnke, V.: "Stress and pathologic calcification." *J. Am. Osteopath. Assoc.* **65**: 258-267 (1965).

J23,646/65

Most experimental calciphylactic syndromes can be prevented by pretreatment with stressors.

Selye, H., Tuchweber, B.: "El fenómeno trombohemorrágico como afección pluricausal" (The thrombohemorrhagic phenomenon as a pluricausal disease). *Prensa Med. Argent.* **52**: 2601-2607 (1965).

G32,011/65

Review on stress with special reference to its participation in the thrombohemorrhagic phenomenon.

Selye, H.: "Pluricausal diseases." *Exp. Med. Surg.* **24**: 191-209 (1966).

G32,043/66

Review on experimental pluricausal dis-

eases that are dependent upon the conjoint action of a "sensitizer," which gives them their special character, and an eliciting agent, which may be a specific factor or nonspecific stress. The main types are summarized in Fig. 6:

Selye, H.: *Thrombohemorrhagic Phenomena*, p. 337. Springfield, Ill.: Charles C Thomas, 1966. E5,986/66

Extensive monograph on thrombohemorrhagic phenomena, with special emphasis upon their pluricausal pathogenesis.*

Selye, H.: "Les maladies pluricausales" (Pluricausal diseases). *J. Réanim. Méd.-Chir.* 6: 521-539 (1966). G39,901/66

Detailed theoretical evaluation of the concept of pluricausal diseases, based mainly on clinical experiments on the stress factor in calciphylaxis, thrombohemorrhagic phenomena, infarctoid myocardial necroses, inflammation, and other disease models studied in the author's laboratory.

Selye, H.: "The thrombohemorrhagic phenomenon as a pluricausal disease." *Perspect. Biol. Med.* 9: 226-243 (1966). G23,231/66

Selye, H.: "Les maladies pluricausales" (Pluricausal diseases). *Rev. Méd. Fonct.* No. 1: 165-193 (1967). G32,045/67

Review on stress with special reference to its participation in pluricausal diseases.

Selye, H.: "Malattie da cause molteplici" (Pluricausal diseases). *Osped. Ital. Chir.* 16: 375-399 (1967). G46,780/67

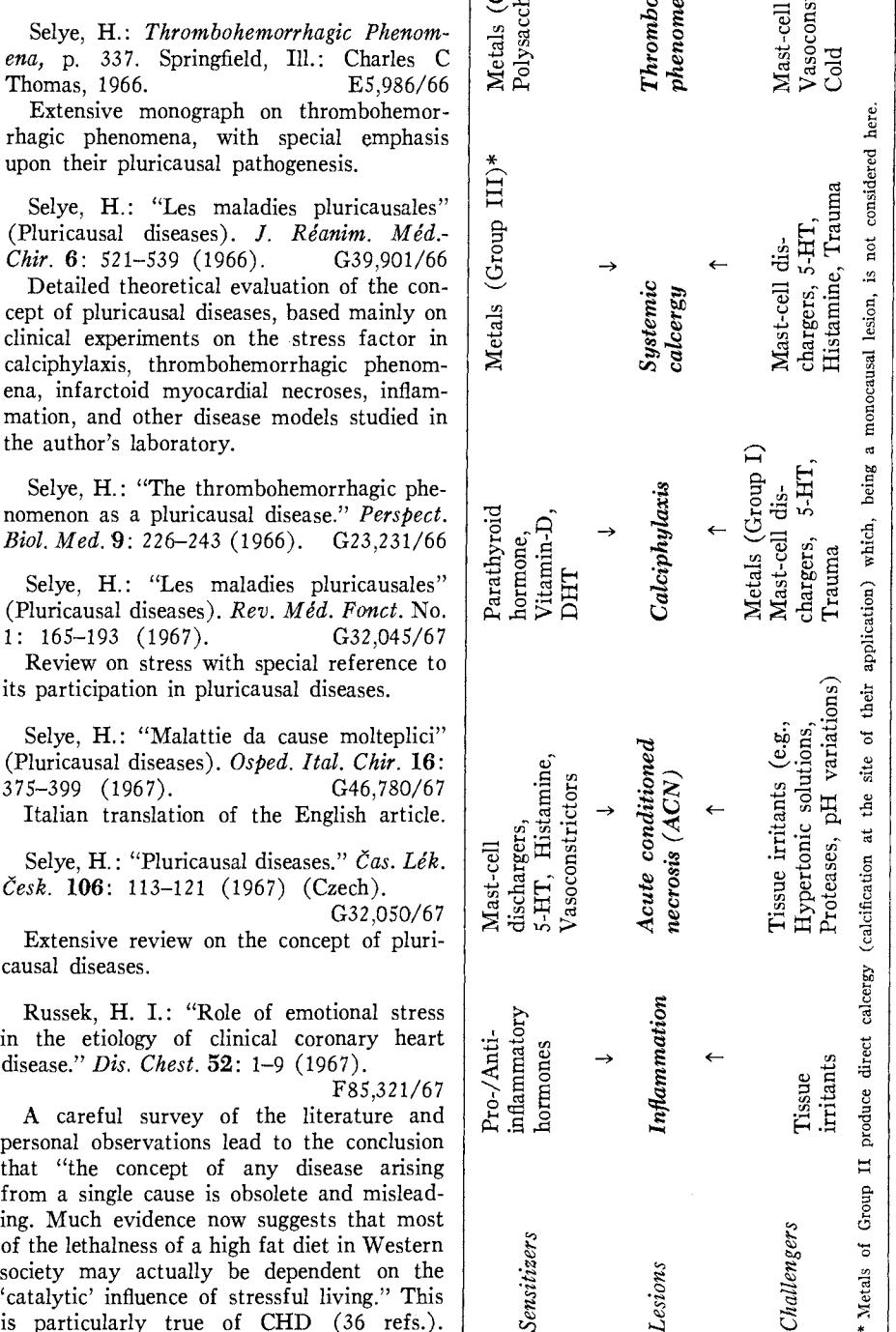
Italian translation of the English article.

Selye, H.: "Pluricausal diseases." *Čas. Lék. Česk.* 106: 113-121 (1967) (Czech). G32,050/67

Extensive review on the concept of pluricausal diseases.

Russek, H. I.: "Role of emotional stress in the etiology of clinical coronary heart disease." *Dis. Chest.* 52: 1-9 (1967). F85,321/67

A careful survey of the literature and personal observations lead to the conclusion that "the concept of any disease arising from a single cause is obsolete and misleading. Much evidence now suggests that most of the lethality of a high fat diet in Western society may actually be dependent on the 'catalytic' influence of stressful living." This is particularly true of CHD (36 refs.).



* Metals of Group II produce direct calcification at the site of their application which, being a monocausal lesion, is not considered here.

Figure 6. Prototypes of pluricausal lesions. (Reproduced from *Exp. Med. Surg.* 24 (1966) by permission.)

Selye, H.: "Pluricausal diseases." *Arkh. Patol.* **29** No. 5: 6-17 (1967) (Russian).
G32,042/67

Review on the concept of pluricausal diseases with special reference to inflammation, necrosis, calciphylaxis, calcergy, thrombosis and hemorrhage (15 refs.).

Selye, H.: "Le stress et les maladies pluri-causales" (Stress and pluricausal diseases). *Presse Méd.* No. 11 Supp.: 145-147 (1968).
G46,768/68

Description of a film summarizing the experimental pluricausal diseases and their possible clinical implications.

Stevenson, I.: "Single physical symptoms as residues of an earlier response to stress." *Ann. Intern. Med.* **70**: 1231-1237 (1969).

J22,514/69

"Single physical symptoms often persist after a general reaction to stress and after the other symptoms of the general reaction have subsided... Factors influencing the persistence and location of one symptom after a general reaction to stress form only

one group of the relevant causal factors in these disorders" (15 refs.).

Selye, H., Tuchweber, B.: "Il fenomeno tromboemorragico, malattia pluricausale" (The thrombohemorrhagic phenomenon. Pluricausal diseases). In: Nicola, P. de, *Coagulazione e Trombosi*, pp. 35-37. Roma: Edizioni Pem, 1971.
G60,021/71

Review on stress in relation to thrombohemorrhagic phenomena.

Hinkle, L. E. Jr.: "The concept of 'stress' in the biological and social sciences." *Sci. Med. Man* **1**: 31-48 (1973). J10,855/73

A review of the stress concept leads to the conclusion that "diseases may be as much a result of the adaptive reactions of the host as they are of the damaging effects of pathogenic agents, and it is widely accepted that the relationships of people to the other people around them and to the society in which they live are important causes of disease. The 'stress concept' has contributed to this change in point of view."

DISEASES OF ADAPTATION IN ANIMALS

(See also Experimental Diseases of Adaptation, which are discussed after the corresponding spontaneous maladies of man.)

Generalities

The fact that stress can be the decisive factor in the development of various diseases—not only in experimental animals, in which such maladies are purposely induced to serve as models, but also in spontaneous diseases of domestic animals—has attracted considerable attention on the part of veterinarians. The numerous reviews dealing with this subject in different languages have generally led to the conclusion that stress can cause essentially the same diseases in animals as in man. Among these, gastrointestinal derangements, cardiovascular diseases, loss of weight, growth retardation, and a special predisposition to various infections are the most common.

Shipping Fever

Shipping fever is among the diseases of farm animals most commonly ascribed to stress. It has no obvious counterpart in man but may be regarded as a variant of the disease proneness, and particularly the predisposition to infections, that is often caused by travel in search of diversion or work. Its symptomatology varies but it is usually

accompanied by a rise in temperature and gastrointestinal disturbances, presumably elicited by a decrease in resistance to various microorganisms, particularly *Pasteurella*, PPLO and *Salmonella*.

Shipping fever is most common among cattle and other large farm animals when they are transported by rail or truck over long distances. Irregular feeding, watering, unusual weather conditions, overcrowding and exposure to pathogens not previously encountered can all act as predisposing factors. Shipping fever in cattle is of enormous economic importance, especially in North America, where it takes a very large toll among cattle and beef transported from the range to the slaughterhouse or market. The outcome is often fatal, but even among surviving animals the loss of weight is usually of sufficient magnitude to reduce their market value considerably.

When the causative microorganism is known, specific treatment with antibiotics or antiserums is recommended, but usually such therapy comes too late, and since the nature of the pathogens cannot be predicted, no generally effective prophylaxis has yet been developed.

Decreased resistance to infection is probably the most important factor in shipping fever. This has been demonstrated experimentally in pigs taken for a "joy-ride" through the countryside in a clean truck; even under such hygienic conditions, *Salmonella* organisms readily proliferated. The fact that plasma corticoid levels are elevated during shipping fever is not of particular significance, since the malady obviously causes stress, and the hormonal disturbance may be a symptom rather than the cause of the disease.

Generalities

(See also our earlier stress monographs, p. xiii, and cf. individual Diseases of Adaptation)

Renaud, S.: "Stress and veterinary medicine." *Pfizer Rev.* No. 16: 1-4 (1957).

C31,131/57

Brief review on the G.A.S. and the L.A.S. as applied to veterinary medicine.

Faber, H. von: "Stress und Allgemeines Anpassungssyndrom bei Haustieren" (Stress and the general adaptation syndrome in domestic animals). *Züchtungskunde* **34**: 289-295 (1962).

G2,068/62

Brief review on the pathogenic effect of stress in veterinary medicine, with special emphasis upon domestic animals.

Tarczyński, S.: "Pathogenesis of invasive diseases in the light of stress theory." *Wiad. Parazytol.* **8**: 505-524 (1962) (Polish).

J24,545/62

Review of the G.A.S. as it relates to veterinary medicine. "Selye's theory is particularly useful for the synthetic presentation of the problem of the pathogenesis of parasitic diseases."

Veilleux, R.: "The stress concept as we see it today." *Adv. Vet. Sci.* **8**: 189-213 (1963).

D15,689/63

Review on the G.A.S. and the diseases of adaptation, mainly from a veterinarian's point of view.

Klussendorf, R. C.: "Salud y enfermedad relacionada con la nutrición animal" (Health and disease in relation to animal nutrition). *Rev. Med. Vet.* (B. Aires) **44**: 151-158 (1963).

E27,967/63

Brief notes on the role of stress in veterinary medicine, with special emphasis upon nutrition.

Szép, I.: *A Stress Jelentősége az Allattenyésztésben* (The importance of stress in animal husbandry), p. 100. Budapest: Agroinform, 1968 (Hungarian).

E849/68

Monograph with an extensive literature survey on relevant observations concerning the G.A.S. (264 refs.).

Skowik, J.: "Cytochemical reactions in white cell system of the bone marrow in rats due to thyroxin and methylthiouracil." *Weterynaria* **26**: 51-76 (1970) (Polish).

J7,639/70

Review on the G.A.S. in veterinary medicine.

Wilson, W. O.: "Evaluation of stressor agents in domestic animals." *J. Anim. Sci.* **32**: 578-583 (1971). J21,212/71

Bryant, M. J.: "The social environment: behaviour and stress in housed livestock." *Vet. Rec.* **90**: 351-358 (1972).

J20,517/72

Wohler, W. H.: "Force-feeding of nutrient slurry to feedlot cattle: another approach to the problem of stress." *Vet. Med. Small Anim. Clin.* **68**: 775-776 (1973).

J19,912/73

Hartmann, H., Meyer, H., Steinbach, G., Leirer, R.: "Allgemeines Adaptationssyndrom beim Jungtier" (General adaptation syndrome in young animals). *Monatsh. Vet. Med.* **28**: 64-70 (1973). J24,159/73

"Stress in farm animals." *Nature* **242**: 319-320 (1973). H77,659/73

Brief letter to editor.

Ewbank, R.: "Clinical signs of stress in farm animals. Changes in behaviour." *Br. Vet. J.* **130**: 90-91 (1974). J20,872/74

Loew, F. M.: "Stress and intensive livestock production in Canada." *Br. Vet. J.* **130**: 90 (1974). J20,871/74

Napier, J.: "Stress in farm animals. Proceedings of a joint symposium with the Royal Society for the Prevention of Cruelty to Animals (Introductory address)." *Br. Vet. J.* **130**: 85-86 (1974). J20,865/74

Brown, P. L.: "Summary: the synthesis of the stress entity." *Br. Vet. J.* **130**: 93-95 (1974). J20,877/74

Fraser, A. F.: "'Ethostasis': a concept of restricted behaviour as a stressor in animal husbandry." *Br. Vet. J.* **130**: 91-92 (1974). J20,873/74

Shipping Fever

(See also our earlier stress monographs, p. xiii)

Carter, G. R.: "Observations on the pathology and bacteriology of shipping fever in Canada." *Can. J. Comp. Med.* **18**: 359-364 (1954). C45,547/54

Shipping fever in cattle is frequently a

true pasteurellosis to which resistance is decreased by the stress of relocation.

Carter, G. R., McSherry, B. J.: "Further observations on shipping fever in Canada." *Can. J. Comp. Med.* **19**: 177-181 (1955).

C45,578/55

Cattle exposed to the stress of shipping become particularly sensitive to infections by *Pasteurella haemolytica* and PPLO.

King, N. B., Gale, C., Smith, H. R., Hamdy, A. H., Sanger, V. L., Pounden, W. D., Klosterman, E. W.: "Stress factors in shipping fever." *Vet. Med.* **53**: 67-72 (1958). D70,196/58

"Probably the most striking feature of the description of shipping fever is the severe stress to which cattle are subjected, after leaving the range. Some of the so-called stress factors are weaning, irregular feeding and watering, exposure to unusual weather conditions, overcrowding, exposure to pathogens, and contaminated quarters during transit, et cetera." Hemorrhagic septicemia antiserum was of little value in this study, whereas certain antibiotics given prophylactically and again after arrival at destination proved to be beneficial. Presumably the stress of shipping sensitizes to infections.

Manz, D.: "Der Einfluss von Belastungen auf den Gehalt an Lactatdehydrogenase (LDH) im Serum von Schlachtschweinen" (Influence of stress on the content of lactate dehydrogenase [LDH] in serum of slaughtered pigs). *Dtsch. Tierärztl. Wochenschr.* **71**: 597-601 (1964). J23,948/64

Shaw, K. E., Nichols, R. E.: "Plasma 17-hydroxycorticosteroids in calves—the effects of shipping." *Am. J. Vet. Res.* **25**: 252-254 (1964). J24,154/64

Hjerpe, C. A., Brownell, J. R.: "Bovine hypomagnesaemic tetany: two cases related to transportation." *Vet. Rec.* **79**: 396-397 (1966). J23,737/66

Howard, J. R.: "Observations of infectious diarrhea as part of the shipping fever syndrome in feedlot cattle." *J. Am. Vet. Med. Assoc.* **154**: 1201-1202 (1969). G73,227/69

Demonstration of various microorganisms in cattle affected by shipping fever.

Williams, L. P. Jr., Newell, K. W.: "Salmonella excretion in joy-riding pigs." *Am. J. Public Health* **60**: 926-929 (1970).

G74,611/70

"Stressed pigs." *Sciences (N.Y.)* **10**: 26-27 (1970). H32,029/70

In pigs, a "joy-ride" through the country-side in a clean truck enhances the proliferation of *Salmonella* organisms. "This increase could be considered to be a result of stress."

Osborne, J. C., Meredith, J. H.: "The influence of environmental and surgical stressors on susceptibility to bacterial endotoxin." *Exp. Med. Surg.* **28**: 39-44 (1970).

H39,299/70

In young piglets, "stress associated with transport, weaning, sunburn and a new environment appeared to be responsible for a state of decreased susceptibility to bacterial endotoxin."

Wegner, W., Greve, J. P.: "Tendenz zu Cor pulmonale bei verendeten Transportschweinen" (Tendency towards Cor pulmonare in pigs which died during transport). *Dtsch. Tierärztl. Wochenschr.* **77**: 637-640 (1970).

J21,806/70

Walla, F.: "Tiertransporte auf Kraftfahrzeugen" (Truck transport of animals). *Wien. Tierärztl. Monatsschr.* **58**: 206-211 (1971).

J21,807/71

Rocco, A., Aguggini, G.: "Eliminazione urinaria degli 11-idrossicorticosteroidi totali, dell'aldosterone e del testosterone nel vitellino" (Urinary excretion of total 11-hydroxycorticosteroids, aldosterone, and testosterone in cows). *Bol. Soc. Ital. Biol. Sper.* **47**: 485-487 (1971).

G88,973/71

In calves, aldosterone excretion is increased by the stress of travel. [The results do not lend themselves to statistical evaluation (H.S.).]

Wohler, W. H. Jr.: "Shipping stress in cattle: blood chemistry." *Mod. Vet. Pract.* **53**: 39-40 (1972).

J20,550/72

Schlecht, H., Pfund, L.: "Über die praktische Anwendung von Stresnil beim Schwein während der Mast und bei Transporten" (Practical use of Stresnil in swine during fattening and transportation). *Wien. Tierärztl. Monatsschr.* **59**: 76-80 (1972).

J21,576/72

Stresnil, a sedative drug, protects pigs against the stressor effect of transportation over long distances.

Kraft, W.: "Das Verhalten einiger Plasma-Enzyme und -Elektrolyte sowie von Glukose, unveresterten Fettsäuren und Laktat bei

Schweinen während der sich an den Transport zum Schlachthof anschliessenden Aufstellung" (The behavior of some plasma enzymes and electrolytes, as well as glucose, non-esterified fatty acids and lactate in pigs held in sheds after transportation to the slaughter house). *Zentralb. Veterinaermed. [A]* **20**: 357-369 (1973). J23,978/73

Völker, H., Furcht, G., Stolpe, J., Bauer, U.: "Zur Stressproblematik des Kälbertransports unter den Anforderungen industrielässiger Tierproduktion. Die Stresssituation und Stressreaktion transportierter Kälber" (Problems of transport stress in calves under conditions of intensive husbandry. The stress situation and reaction to stress in calves). *Arch. Exp. Veterinaermed.* **27**: 555-569 (1973).

J25,395/73

Allsup, T. N.: "Welfare problems associated with transportation." *Br. Vet. J.* **130**: 92 (1974).

J20,874/74

Gronstal, H., Osborne, A. D., Pethiyagoda, S.: "Experimental *Salmonella* infection in calves. 1. The effect of stress factors on the carrier state." *J. Hyg. (Camb.)* **72**: 155-162 (1974).

J11,903/74

In calves infected with *Salmonella*, resistance is decreased by stress factors, according to the earlier literature. During the present experiments in which infected calves were exposed to cold or transport "the symptoms were no more severe in the stressed calves than in the unstressed."

Varia

(See also our earlier stress monographs, p. xiii)

Vigue, R. F.: "Evaluation of some concepts of bovine ketosis from a practitioner's standpoint." *J. Am. Vet. Med. Assoc.* **127**: 101-119 (1955). D77,403/55

A review of the literature and personal observations on the role of stress in the production of *bovine ketosis* (125 refs.).

Marshak, R. R.: "The nutritional concept as the underlying cause of bovine ketosis." *Vet. Med.* **50**: 159-163 (1955). J12,168/55

Personal observations and review of the literature indicating that stress may be the eliciting factor in the development of *bovine ketosis*.

Fitko, R.: "Contemporary view of cystic

ovaries and nymphomania in animals." *Med. Weteryn.* **16:** 407-415 (1960) (Polish).

D1,235/60

Cystic ovaries and nymphomania may occur in various domestic animals as a consequence of stress.

Kowalczyk, T.: "Etiologic factors of gastric ulcers in swine." *Am. J. Vet. Res.* **30:** 393-400 (1969). J23,078/69

In pigs, *gastric ulcers* are common and probably often caused by stress (63 refs.).

Holmes, J. H. G., Robinson, D. W.: "*Hereditary muscular hypertrophy* in the bovine: metabolic response to nutritional stress." *J. Anim. Sci.* **31:** 776-780 (1970). J23,085/70

Cowan, D. F., Johnson, W. C.: "*Amyloidosis* in the white Pekin duck. I. Relation to social environmental stress." *Lab. Invest.* **23:** 551-555 (1970). G80,215/70

Martínek, Z., Horák, F.: "Development of

so-called 'genuine' epileptic seizures in dogs during emotional excitement." *Physiol. Bohemoslov.* **19:** 185-195 (1970).

J21,196/70

"Genuine" *epileptic seizures* are produced in isolated dogs of a special breed by exposure to the stressor effect of strong noise. These animals show a clear familial predisposition to epileptic seizures.

Gross, W. B.: "Effect of social stress on occurrence of Marek's disease in chickens." *Am. J. Vet. Res.* **33:** 2275-2279 (1972).

J20,137/72

Various stressors predispose chickens to the development of Marek's disease, when placed in cages previously occupied by chicks infected with the corresponding *virus*.

Holmes, J. H. G., Ashmore, C. R., Robinson, D. W.: "Effects of stress on cattle with *hereditary muscular hypertrophy*." *J. Anim. Sci.* **36:** 684-694 (1973). J19,908/73

V. TREATMENT

Generalities

(See also Drugs, and Multiple Stressors [Chapter II], and Diseases of Adaptation [Experimental, and in Animals, Chapter IV])

Since the treatment of individual diseases of adaptation has been discussed in the sections devoted to each of these maladies, I will now deal only with therapeutic measures applicable to any stress-induced derangement, that is, procedures meant to combat distress itself, irrespective of its cause.

Among these recommendations, the counsel most commonly given is to relax and refrain from any but the most unavoidable activities, or to seek diversion in leisure and play. However, this kind of advice is more easily given than followed, because active people are particularly dependent upon finding outlets for their pent-up energy, and cannot relax or play without continuously suffering from the feeling that they are wasting their time. For persons with an irrepressible drive to seek stress, it is much easier to find some comparatively unexacting diversionary activity than to do nothing. But because the so-called "leisure occupations" tend to become highly goal-oriented and intense efforts at outstanding achievement in sports, social, educational and civic events, they represent a poor antidote to the emotional stressors of daily work. This problem is particularly important for those who approach or have reached the retirement age and simply cannot go on utilizing their energy in the way to which they have become accustomed. As the progress of technology increasingly shortens work hours for most standard occupations, semiretirement will start as soon as a career begins. Not everyone knows how to play or to occupy additional leisure time with the more passive enjoyment of music, painting, sculpture, travel or spectator sports; hence, many people seek to release their pent-up energy through such dangerous outlets as drugs, violence and other forms of destructive behavior.

As explained in the General Outline, people also need a satisfactory motivation; for this I propose the principle of "altruistic egoism." Purely passive enjoyments (including even the pleasures of the flesh) are not sufficiently altruistic to furnish an aim that is satisfactory as the final purpose of our life. However, to discuss the entire philosophy of "altruistic egoism" would exceed the scope of this treatise; and hence I will limit myself here to simpler forms of dealing with individual problems of distress.

Among the procedures used to protect against the damaging effects of distress, some are activities employed by the individual as a means of diversion from daily routine, while others are more formal techniques or therapies. Most important among these kinds of treatment are:

Rest and Leisure
Psychotherapy in General
Handling and Gentling
Transcendental Meditation (TM) and Related Techniques—including the "relaxation response"
Zen and Yoga—including biofeedback
Hypnosis
Psychoanalysis
Acupuncture and Moxibustion
Chiropractic
Osteopathy
Various Stressors (Mental, Physical)—including balneotherapy, shortwave therapy, physiotherapy.
Diet—including "snacking behavior" which, like smoking, chewing gum and drugs is often used as a means of diversion.
Hormones and Related Substances
Vitamins
Psychotropic Drugs in General—including tranquilizers, analgesics, anesthetics, CNS stimulants.
Autonomic Blocking Agents
Ginseng, Eleutherococcus
Ethanol
Other Drugs
Smoking, which comprises ritualistic, behavioral and pharmacologic elements.

It would be impossible to present in this section a meaningful summary of all the psychotherapeutic and physical therapy procedures listed above, so for this the reader must be referred to the individual abstract sections. Essentially the same can be said about the various dietary, hormonal and other chemotherapeutic procedures.

Treatment with stress hormones, particularly catecholamines, ACTH and corticoids, is spectacularly effective against the stress produced by certain agents, but even here it is difficult to speak of nonspecific therapy for stress as such, except when an actual deficiency of these hormones has led to a general decrease in stress resistance, which may be rectified by exogenous administration of the same natural substances. Of course, in some instances the nonspecificity of such therapy is quite far-reaching. For example, in the case of the syntoxic glucocorticoids, beneficial results can be obtained against virtually any stressor that acts indirectly by eliciting excessive defense reactions (inflammation, immune responses), if these can be suppressed through steroids favoring coexistence with such indirect pathogens.

It may also be said that no single drug has been found that exerts a reliable, non-specific antistress effect irrespective of the pathogenic stressor agent.

There is some evidence that reserpine, chlorpromazine, nicotinic acid and various other drugs, especially tranquilizers, adrenergic or cholinergic blocking agents, anti-serotonins, and so on act as antistressors, possibly through their ability to block certain links in the mechanism mediating the stress response. However, in interpreting these results, the utmost care is recommended, as it is easy to confuse true anti-stress effects with the selective elimination of one or the other stress manifestation. For example, it appears quite unjustified to speak of an antistress effect merely because a drug specifically protects against stress-induced peptic ulcers or insomnia.

It is advisable to prescribe tranquilizers to patients who suffer mainly from certain psychogenic stressors, to give vasopressors to counteract the stress caused by vascular failure during shock and to administer antihistaminics when allergic-immunologic and other phenomena can be attributed to an excess of histamine. Even consumption of alcoholic beverages or tobacco smoking has a relaxing effect upon certain patients who suffer mainly from excessive nervous excitation. Yet in none of these instances are we justified in viewing the therapy as directed against the basic mechanism of stress itself.

In recent years, the Eastern remedies of ginseng and eleutherococcus (extracted from certain Asiatic plants and long used in Eastern medicine) have received a great deal of attention. There are many clinical and a few experimental observations suggesting that such preparations exert a nonspecific antistress effect, but much additional work will be necessary before these claims are widely accepted.

Treatment in General

(See also our earlier stress monographs, p. xiii, and *cf.* Drugs, and Multiple Stressors [Chapter II], and Diseases of Adaptation [Experimental, and in Animals, Chapter IV])

Mitchell, L.: "A technique for obtaining relaxation." *Physiotherapy* 49: 254-256 (1963).
J24,368/63

Bousingen, R. D. de: *Distensione e Training Autogeno* (Relaxation and autogenous training), p. 126. Roma: Edizioni Mediterranee, 1968.
E107/68

Translation of the French book, *La Relaxation*, which consists mainly of practical hints on how to relax in various conditions of stress and tension.

Martin, A. R.: "Idle hands and giddy minds. Our psychological and emotional unpreparedness for free time." *Am. J. Psychoanal.* 29: 147-156 (1969).
G77,622/69

Philosophic and psychoanalytic considerations concerning our psychologic and emotional unpreparedness for much free time, with ten interesting case reports on damage caused by idleness in patients.

Sherman, E. D.: "Retirement." *J. Am. Geriatr. Soc.* 18: 780-791 (1970).
G79,267/70

Lecture on the problems of retirement and ways of preventing its complications (10 refs.).

Davidson, P. O., Hiebert, S. F.: "Relaxation training, relaxation instruction, and repeated exposure to a stressor film." *J. Abnorm. Psychol.* 78: 154-159 (1971).
J20,333/71

Selye, H.: "Stress, work and leisure." *Totus Homo* 3: 3-6 (1971).
G39,918/71

Reflections on the activities that we call leisure and work, and their respective effects upon man under stress.

Rest and Leisure

(See also our earlier stress monographs, p. xiii)

Kennedy, J. A.: *Relax and Live*, p. 205. Englewood Cliffs, N. J.: Prentice-Hall, 1953.
B90,700/53

Advice on how to relax and avoid disease, given in lay language. One section is devoted to the relationship between aging and the G.A.S.

Russek, H. I.: "Role of heredity, diet, and emotional stress in coronary heart disease." *J.A.M.A.* 171: 503-508 (1959).
C74,784/59

In ninety-one out of one hundred patients, prolonged emotional strain related to occupational responsibilities preceded a coronary attack. Smoking is particularly frequent among coronary patients, but it may be a manifestation of inner stresses rather than an etiologic factor. Furthermore, much of our envied leisure time is regimented by participation in social, educational and civic events which "may represent a poor antidote for the emotional stresses of daily business competition."

Selye, H.: "Stress and the nation's health." *Addictions* **20**: 70-84 (1973).

G88,097/73

Lecture on the stressor effect of excessive leisure.

Selye, H.: "Stress and the executive." *Executive Health* **9**: 1-4 (1973).

G88,055/73

Popularized summary of stress in relation to work and leisure.

Löhr, G., Preiser, S.: "Regression und Recreation. Ein Beitrag zum Problem Stress und Erholung" (Regression and recreation. A contribution to the problem of stress and recovery). *Z. Exp. Angew. Psychol.* **21**: 575-591 (1974).

J25,113/74

"Different groups of subjects were subjected to different combinations of stress (work) and recreation (pause). The results showed that after the recreation pause, the efficiency increases proportional to the compensation to the stress activity (work) offered by the recreation activity."

Psychotherapy in General

(See also our earlier stress monographs, p. xiii)

Liddell, H.: "Some specific factors that modify tolerance for environmental stress." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 155-171. Baltimore: Williams & Wilkins, 1950.

B51,903/50

Résumé of the author's extensive investigations concerning the experimental induction of neurosis by stressful conditioning reflex techniques. In neurotic goats, "the presence of the mother regardless of her behavior toward her offspring, had an ameliorating effect on the young animal subjected to environmental stress."

Handlon, J. H., Wadeson, R. W., Fishman, J. R., Sachar, E. J., Hamburg, D. A., Mason, J. W.: "Psychological factors lowering plasma 17-hydroxycorticosteroid concentration." *Psychosom. Med.* **24**: 535-542 (1962).

D46,969/62

Viewing Disney nature-study films actually lowers 17-OHCS levels, whereas viewing arousing films has an opposite effect. The stimuli of either internal or external origin," former "may serve to narrow the subjects' attention away from other possibly stressful

Harris, M. R., Kalis, B. L., Freeman, E. H.: "Precipitating stress: an approach to brief therapy." *Am. J. Psychother.* **17**: 465-471 (1963).

J23,433/63

Chertok, L.: "An introduction to the study of tensions among psychotherapists." *Br. J. Med. Psychol.* **39**: 237-243 (1966).

J22,886/66

Review of the history of psychotherapy since the Société Royale de Médecine and the Académie des Sciences decided in 1784 to investigate "animal magnetism" as described by Mesmer. "As far back as 1780 Mesmer's disciple, Deslon, in his *Observations sur le Magnetisme Animal* said, 'If the medicine of imagination is the best, why shouldn't we use the medicine of imagination?'"

Kamakura, K.: "Autogenous training. Relief from stress." *J. Jap. Dent. Assoc.* **19**: 298-299 (1966).

J24,352/66

Campbell, J. H., Rosenbaum, C. P.: "Placebo effect and symptom relief in psychotherapy." *Arch. Gen. Psychiatry* **16**: 364-368 (1967).

J22,692/67

Kitamura, R.: "On the influence of Kendo training or home study upon uropepsin excretion." *Jap. Arch. Intern. Med.* **15**: 55-60 (1968).

J24,355/68

Baldwin, B. A.: "Autonomic stress resolution in repressors and sensitizers following microcounseling." *Psychol. Rep.* **31**: 743-749 (1972).

J19,724/72

Repressors tend to use avoidance mechanisms, such as withdrawal, denial and rationalization in response to stress, whereas sensitizers, under the same conditions, typically overinterpret threat, and utilize approach mechanisms such as obsessive rumination and intellectualization. Microcounseling based on this knowledge helps to resolve psychogenic stress.

Holmes, D. J.: *Psychotherapy: Experience, Behavior, Mentation, Communication, Culture, Sexuality, and Clinical Practice*, p. 1077, Sect. 1-6. Boston: Little, Brown, 1972.

E10,304/72

A voluminous yet very readable treatise on psychotherapy in which we counted fourteen pages that refer to stress without defining the sense in which the author uses the term. Nor were we able to locate in the subject index any reference to the hypophysis, the hypothalamus, the limbic system or the role played by corticoids or catecholamines.

Pilowsky, I.: "Psychiatric aspects of stress." *Ergonomics* **16**: 691-698 (1973).

J8,268/73

Reflections on the importance of preparing patients for impending stress (surgical operations, aggravation of disease) to help the subsequent coping process.

Gibson, H. B.: "Morita therapy and behavior therapy." *Behav. Res. Ther.* **12**: 347-353 (1974).

J18,663/74

Description of the ancient Japanese Morita therapy for neurotic disorders, the cause of which could now be ascribed to stress. "Although the theoretical model proposed by Selye (1952) is mainly applicable to the psychosomatic disorders, it is some such feed-back loop as this which is envisaged by the Morita theorists when they discuss 'psychic interaction.'"

Vernon, D. T. A., Bigelow, D. A.: "Effect of information about a potentially stressful situation on responses to stress impact." *J. Pers. Soc. Psychol.* **29**: 50-59 (1974).

J21,561/74

"Janis's explanation for the ameliorative effect of information on stress impact was tested in a study of 80 hernia-repair patients. It was proposed that subjects receiving accurate information regarding the impending surgery, etc., experience heightened anticipatory fear, develop specific problem-oriented ideas about the operation, profess greater confidence in the medical staff, and consequently manifest less postoperative depression and hostility." The concept was only partially confirmed.

Handling and Gentling

(See also our earlier stress monographs, p. xiii)

Weininger, O.: "Mortality of albino rats under stress as a function of early handling." *Can. J. Psychol.* **7**: 111-114 (1953).

B93,807/53

None of the rats gentled ten minutes daily for about ten days after weaning died in adulthood when exposed to a complex stress situation (cold, starvation, and water deprivation), but the same stressor procedure applied at the same time in adulthood to non-gentled controls caused adrenal enlargement, bleeding gastric erosions and other manifestations of the alarm reaction, as well as a high mortality rate.

Newton, G., Heimstra, N.: "Effects of early experience on the response to whole-body X-irradiation." *Can. J. Psychol.* **14**: 111-120 (1960).

D84,835/60

Weanling rats that have been previously handled lose less weight following x-irradiation than do controls.

McMichael, R. E.: "The effects of pre-weaning shock and gentling on later resistance to stress." *J. Comp. Physiol. Psychol.* **54**: 416-421 (1961).

G46,161/61

Rats handled during the early postnatal period grew better than controls, and their resistance to stressors was not very markedly influenced in later life.

Bell, R. W., Reisner, G., Linn, T.: "Recovery from electroconvulsive shock as a function of infantile stimulation." *Science* **133**: 1428 (1961).

J22,946/61

Rats handled during the first days of life show a stress reaction from which they recover within twenty-four hours. However, if exposed to electroshock days later, they manifest a subnormal concentration of blood sugar.

Schaefer, T. Jr.: "Early 'experience' and its effects on later behavioral processes in rats: II. A critical factor in the early handling phenomenon." *Trans. N.Y. Acad. Sci.* **25**: 871-889 (1963).

J23,586/63

Handling is effective in reducing later emotionality in the life of a rat, but only if applied very early. This study implies that "handling is ineffective unless it is accompanied by a temperature change." In fact, lowering the ambient temperature at the same early period of life produces an equal effect.

Hutchings, D. E.: "Early 'experience' and its effects on later behavioral processes in rats: III. Effects of infantile handling and body temperature reduction on later emotionality." *Trans. N.Y. Acad. Sci.* **25**: 890-901 (1963).

J23,587/63

Confirmatory evidence that handling during the immediate postnatal period decreases emotionality in rats only because of the associated drop in temperature.

Hunt, H. F., Otis, L. S.: "Early 'experience' and its effects on later behavioral processes in rats: I. Initial experiments." *Trans. N.Y. Acad. Sci.* **25**: 858-870 (1963).

J23,588/63

Salama, A. A., Hunt, J. M.: "'Fixation' in the rat as a function of infantile shocking,

handling, and gentling." *J. Genet. Psychol.* **105**: 131-162 (1964) (82 refs.).
J23,019/64

Levine, S.: "Maternal and environmental influences on the adrenocortical response to stress in weanling rats." *Science* **156**: 258-260 (1967). F82,015/67

Adrenocortical steroids in the plasma of newborn rats were reduced at weaning after the pups "were exposed to novel stimuli as compared with controls that were not handled."

Denenberg, V. H., Brumaghim, J. T., Haltmeyer, G. C., Zarrow, M. X.: "Increased adrenocortical activity in the neonatal rat following handling." *Endocrinology* **81**: 1047-1052 (1967). F89,864/67

Handling two-day-old rats increased their plasma corticosterone levels within half an hour of returning them to their mothers. However, this response could be prevented if the pups were placed in handling cans maintained at 35.5°C.

Ader, R., Friedman, S. B., Grota, L. J., Schaefer, A.: "Attenuation of the plasma corticosterone response to handling and electric shock stimulation in the infant rat." *Physiol. Behav.* **3**: 327-331 (1968).

H5,148/68

In newborn rats, stressor-induced elevations of plasma corticosterone were first seen at fifteen days, at which time the response to handling and electric shock was similar. Twenty-one-day-old unmanipulated rats showed a greater reaction to electric shock than to handling. Previously shocked animals displayed little adaptation, whereas repeated handling diminished the plasma corticosterone response.

Ader, R.: "Adrenocortical function and the measurement of 'emotionality'." *Ann. N.Y. Acad. Sci.* **159**: 791-805 (1969).

H18,024/69

Plasma and adrenal corticosterone measurements in rats failed to reveal any relationship to "emotionality," appraised by the response to handling and by open field activity.

Takahashi, K., Daughaday, W. H., Kipnis, D. M.: "Regulation of immunoreactive growth hormone secretion in male rats." *Endocrinology* **88**: 909-917 (1971).

H37,347/71

In gentled rats, plasma immunoreactive STH rose more than in nongentled controls,

whereas plasma corticosterone levels were less elevated. In both gentled and nongentled rats, pentobarbital anesthesia caused a significant rise in plasma STH and a corresponding decrease in plasma corticosterone. Ether, hypertonic glucose, 2-deoxyglucose, insulin and EP caused a marked suppression of plasma STH and an increase in plasma corticosterone which were partly or totally blocked by pentobarbital anesthesia.

Zarrow, M. X., Campbell, P. S., Denenberg, V. H.: "Handling in infancy: increased levels of the hypothalamic corticotropin releasing factor (CRF) following exposure to a novel situation." *Proc. Soc. Exp. Biol. Med.* **141**: 356-358 (1972). H60,966/72

Observations on rats confirmed "previous findings that handled animals release less corticosterone than nonhandled animals when exposed to a novel environment... A functionally different mechanism for release of CRF may exist as a result of infantile stimulation."

Transcendental Meditation (TM) and Related Techniques

(See also our earlier stress monographs, p. xiii)

Szirmai, E.: "Use of Jacobson's methods in different fields of medicine in connection with a case." *Agressologie* **7**: 641-645 (1966). J22,504/66

Successful application of "Jacobson's (progressive relaxation, anxiety and tension control) method in different fields of medicine."

Vanselow, K.: "Psychosomatische und psychotherapeutische Strömungen in der Medizin unserer Zeit. Konzepte und kritische Reflexion. 11. Meditative Übungen zur Beseitigung von Stress-Folgen" (Psychosomatic and psychotherapeutic trends in current medicine. Concepts and critical observations. 11. Meditative exercises for the removal of stress effects). *Hippokrates* **39**: 462-465 (1968). J23,243/68

Discussion of various meditative exercises (especially autogenic training, indirect suggestion and the "placebo effect," psychoanalysis and TM) used for the mastery of stress.

Fiske, E. B.: "Thousands finding meditation eases stress." *New York Times* December 11, 1972. J8,142/72

Popular review of the literature suggesting that Transcendental Meditation relieves the undesirable consequences of stress.

Benson, H., Wallace, R. K.: "Decreased drug abuse with transcendental meditation. A study of 1,862 subjects." In: Zarafonetis, C. J. D., *Drug Abuse (Proc. Int. Conf.)*, p. 369. Philadelphia: Lea & Febiger, 1972.

J16,137/72

Kanellakos, D. P., Lukas, J. S.: *The Psychobiology of Transcendental Meditation: A Literature Review*, p. 103. Menlo Park, Cal.: Stanford Research Institute, 1973.

E10,250/73

Annotated references and selected testimonials on the somatic and psychic effects of Transcendental Meditation, with a separate section on its ability to relieve distress.

Orme-Johnson, D. W.: "Autonomic stability and transcendental meditation." *Psychosom. Med.* 35: 341-349 (1973).

J19,677/73

Campbell, C.: "The facts on Transcendental Meditation: Part I. Transcendence is as American as Ralph Waldo Emerson." *Psychol. Today* April, 1974, pp. 37-38.

J17,286/74

"How the Maharishi Mahesh Yogi found fertile ground for a transplant from the banks of the Ganges, grew a huge and convinced bureaucracy, and may actually have something there."

Schwartz, G. E.: "The facts on Transcendental Meditation: Part II. TM relaxes some people and makes them feel better." *Psychol. Today* April, 1974, pp. 39-44.

J17,287/74

"Yes, 40 minutes of meditation a day, or just sitting on your bottom, may make you more alert but less tense. A demystifying report on research to date suggests that while oversold, this altered state fills specific psychological needs."

Otis, L. S.: "The facts on Transcendental Meditation: Part III. If well-integrated but anxious, try TM." *Psychol. Today* April, 1974, pp. 45-46.

J17,288/74

"Stanford Research Institute's staff divided themselves into control groups for meditation experiments. Self-paced desensitization to excessive stimuli, they found, helps more people than it hurts."

Kanellakos, D. P., Lukas, J. S.: *The Psychobiology of Transcendental Meditation. A*

Literature Review, p. 158. Menlo Park, Cal.: W A Benjamin, 1974. E10,766/74

Monograph with an epilogue on the relationship between Transcendental Meditation and the G.A.S.

Benson, H., Beary, J. F., Carol, M. P.: "The relaxation response." *Psychiatry* 37: 37-46 (1974). J10,474/74

Various self-induced states of altered consciousness (Transcendental Meditation, Zen, Subud, Nichiren Sho Shu, Hare Krishna, Scientology, Black Muslimism, Meher Baba and other religious practices consisting of sitting quietly and inhaling through the nose, then exhaling through the mouth) are reviewed as potential antistress measures. "Subjective and objective data exist which support the hypothesis that an integrated central nervous system reaction, the 'relaxation response,' underlies this altered state of consciousness." When elicited for periods of twenty to thirty minutes once or twice daily, these states do not appear to have any adverse effect. However, "when elicited more frequently, some subjects experience a withdrawal from life and symptoms which range in severity from insomnia to psychotic manifestations, often with hallucinatory behavior."

Benson, H.: "Your innate asset for combating stress." *Harv. Business Rev.* July-August, 1974, pp. 49-60. J14,229/74

Detailed description of the "relaxation response" as a prophylactic measure, especially against the stress of modern executive life. It is based on a combination of relaxation in a quiet environment, taking up a passive attitude in a comfortable position, and repeating silently, or in a low gentle tone, a single-syllable sound or word (for example, "one," "God"). The technique is closely related to Transcendental Meditation, Zen, yoga, autogenic training, progressive relaxation, hypnosis with suggested relaxation, and sientic cycles, with which its effects upon oxygen consumption, respiratory rate, heart rate, α -waves, blood pressure and muscle tension are compared. Its elements have been known for centuries, usually as religious rituals, but they are presented here in a noncultic factual manner and described in a language easily acceptable to the modern executive. The technique is recommended for the alleviation of certain toxicomanias, including alcoholism and cigarette smoking, and such diseases of adaptation as hypertension, peptic ulcers and some mental disturbances. It is suggested

that the relaxation response be induced once or twice daily for about twenty or thirty minutes. "When the response is elicited more frequently—for example, for many hours daily over a period of several days—some individuals have experienced a withdrawal from life and have developed symptoms which range from insomnia to hallucinatory behavior. These side effects of excessive elicitation of the relaxation response are difficult to evaluate on a retrospective basis, since many people with preexisting psychiatric problems might be drawn to any technique which evangelistically promises relief from tension and stress. However, it is unlikely that the twice daily elicitation of the response would do any more harm than would regular prayer." [The damaging side effects of overdoing this practice are singularly reminiscent of those known to be characteristic of prolonged sensory deprivation. In terms of our concept, this means that man needs stress and should use his faculties to the maximum of their tolerance for eustress, but brief periods of complete relaxation are as indispensable as sleep (H.S.).]

Eliot, R. S.: *Stress and the Heart*, Vol. 1, p. 415. Contemporary Problems of Cardiology. Mount Kisco, N.Y.: Futura, 1974.

E10,556/74

Monograph containing articles by numerous experts on the role of stress in the production of cardiovascular disease, with special reference to hypertension and myocardial infarction. Among the factors involved in the cardiovascular effects of stress, individual chapters deal with the role of occupation, homeostasis, sex, environmental influences, athletics, emotional arousal and stress tests. The therapeutic value of various techniques for relaxation, including Transcendental Meditation, yoga, Zen, sentic cycles, hypnosis and related practices, is examined.

Benson, H., Rosner, B. A., Marzetta, B. R., Klemchuk, H. M.: "Decreased blood-pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response." *Lancet* February 23, 1974, pp. 289-291. J14,532/74

Induction of a wakeful hypometabolic state by simple, noncultic mental techniques or by traditional meditational practices. It appears to derive from a hypothalamic response that decreases sympathetic activity and diminishes the blood pressure of moderately hypertensive patients. The results are

similar to those obtained by Transcendental Meditation.

Schneider, M.-J.: "Measuring meditation." *Sciences* 14: 6-10 (1974).

H86,769/74

Brief semipopular résumé of somatic changes achieved by Transcendental Meditation and yoga. The EEG was typical of relaxed wakefulness and not comparable to sleep, coma or hibernation. The blood concentrations of lactic acid, as well as the BMR were diminished. "Indian Yogis do it to reach nirvana. Japanese monks do it seeking satori. In the middle ages, Christian mystics did it to achieve union with God. More than 375,000 Americans have learned to meditate since 1965 in the hope of becoming less tense, more efficient and creative."

Avorn, J. L., Benson, H.: "Decreased variability of plasma cortisol in subjects practicing a relaxation technique." *Fed. Proc.* 33: 464 (1974).

H84,213/74

Beary, J. F., Benson, H.: "A simple psychophysiologic technique which elicits the hypometabolic changes of the relaxation response." *Psychosom. Med.* 36: 115-120 (1974).

J18,917/74

"Oxygen consumption, carbon dioxide production, and respiratory rate are significantly decreased during the practice of a new, easily-learned relaxation technique. The elements of the technique are a mental device to prevent distracting thoughts, a passive attitude, decreased muscle tonus, and a quiet environment which is as free of visual and auditory stimuli as possible. Sitting quietly with the eyes either open or closed failed to produce the same changes. These physiologic changes are consistent with an integrated hypothalamic response resulting in hypothesized decreased sympathetic activity." The procedure has been termed "relaxation response" and is closely related to TM (28 refs.).

Candelent, T., Candelent, G.: "Teaching transcendental meditation in a psychiatric setting." *Hosp. Community Psychiatry* 26: 156-159 (1975).

J22,324/75

Benson, H., Steinert, R. F., Greenwood, M. M., Klemchuk, H. M., Peterson, N. H.: "Continuous measurement of O₂ consumption and CO₂ elimination during a wakeful hypometabolic state." *J. Hum. Stress* 1: 37-44 (1975).

H97,895/75

Wilson, A. F., Honsberger, R., Chiu, J. T., Novey, H. S.: "Transcendental Meditation and asthma." *Respiration* **32**: 74-80 (1975).
J4,977/75

Selye, H.: "Foreword." In: Bloomfield, H. H., Cain, M. P., Jaffe, D. T.: *TM—Discovering Inner Energy and Overcoming Stress*, pp. ix-xii. New York: Delacorte Press, 1975.
J4,243/75

Bloomfield, H. H., Cain, M. P., Jaffe, D. T.: *TM—Discovering Inner Energy and Overcoming Stress*, p. 290. New York: Delacorte Press, 1975.
E10,920/75

General review on TM by a psychiatrist, an artist and a sociologist, with special emphasis upon its use as a means to combat distress.

Pasek, T., Romanowski, W.: "Role of steered rhythms in the prevention of psycho-neurologic disturbances." *Med. Latn.* **38**: 133-135 (1972) (Polish).
G99,071/72

Observations on the beneficial effect of yoga and Zen in normal and psychoneurotic patients. "After two years of training, increased resistance to stressors and improvement in psychoneurotic condition were seen." [It is not clear whether the physical training and/or the mental effect of these procedures was decisive (H.S.).]

Udupa, K. N., Singh, R. H., Yadav, R. A.: "Certain studies on psychological and biochemical responses to the practice of Hatha Yoga in young normal volunteers." *Indian J. Med. Res.* **61**: 237-244 (1973).

J9,580/73

Review of the literature and personal observations on the improvement of resistance to stress provided by the practice of Hatha Yoga.

Patel, C.: "Yoga and bio-feedback in hypertension." *Lancet* December 22, 1973, pp. 1440-1441.
H79,287/73

In a reply to Pickering's letter to the editor, it is claimed that yoga and biofeedback are beneficial in the treatment of hypertension.

Pickering, T.: "Yoga and bio-feedback in hypertension." *Lancet* December 22, 1973, p. 1440.
H79,286/73

Letter to the editor disputing Patel's conclusions. Yoga and biofeedback showed a limited and perhaps dubious effect in the treatment of hypertension.

Eliot, R. S.: *Stress and the Heart*, Vol. 1, p. 415. Contemporary Problems of Cardiology. Mount Kisco, N.Y.: Futura, 1974.
E10,556/74

Monograph containing articles by numerous experts on the role of stress in the production of cardiovascular disease with special reference to hypertension and myocardial infarction. Among the factors involved in the cardiovascular effects of stress, individual chapters deal with the role of occupation, homeostasis, sex, environmental influences, athletics, emotional arousal and stress tests. The therapeutic value of various techniques for relaxation, including Transcendental Meditation, yoga, Zen, sentic cycles, hypnosis, and related practices, is examined.

Patel, C.: "12-month follow-up of yoga and bio-feedback in the management of

Zen and Yoga

(See also our earlier stress monographs, p. xiii)

Ramamurthi, B.: "Yoga—An explanation and probable neurophysiology." *J. Indian Med. Assoc.* **48**: 167-170 (1967).

J12,073/67

"The background of the derivation and concept of Yoga in India is presented, followed by a simple exposition of yogic practices and some possible neurophysiologic explanations." [Little attention is given to objective neurophysiologic indicators of changes (H.S.).]

Hoenig, J.: "Medical research on yoga." *Confir. Psychiatr.* **11**: 69-89 (1968).

J12,076/68

The medical literature on "yoga exercises is reviewed and the conclusion is drawn that this field, which at one time appeared so promising to throw light on psychosomatic problems, is not likely to do so to any extent at all." Personal observations show that EEG allows certain conjectures regarding the state of mind of the yogi; a spontaneous change in heart rate was noted but could not be explained.

Sorenson, S.: *The Quest of Wholeness*, p. 138. Reykjavík: Prentsmidja Jóns Helgasonar, 1971.
E9,349/71

Painstaking efforts by a physician convertant with the original Sanskrit text on yoga to explain its effects upon the body and psyche in modern medical terms. A special section is devoted to the relief of distress by yoga (70 refs.).

hypertension." *Lancet* January 11, 1975, pp. 62-64. H98,088/75

In hypertensive patients, yoga exercises significantly reduced blood pressure over a 1-year period.

Hypnosis

(See also our earlier stress monographs, p. xiii)

Persky, H., Grosz, H. J., Norton, J. A., McMurtry, M.: "Effect of hypnotically-induced anxiety on the plasma hydrocortisone level of normal subjects." *J. Clin. Endocrinol. Metab.* **19**: 700-710 (1959). J11,141/59

Hypnotically induced anxiety states raised plasma cortisol levels, whereas hypnosis leading to a somnambulistic state had an inverse effect. Females were more readily influenced than males (25 refs.).

Levitt, E. E., Persky, H.: "Relation of Rorschach factors and plasma hydrocortisone level in hypnotically induced anxiety." *Psychosom. Med.* **22**: 218-223 (1960).

C88,083/60

Grosz, H. J.: "The relation of serum ascorbic acid level to adrenocortical secretion during experimentally induced emotional stress in human subjects." *J. Psychosom. Res.* **5**: 253-262 (1961). J11,152/61

A hypnotically-induced anxiety state increased the plasma ascorbic acid and cortisol levels in normal subjects.

Völgyesi, F. A.: "The general health syndrome produced by medical hypnosis." *Br. J. Med. Hypnot.* **14**: 25-32 (1963).

E25,104/63

Observations in man on the effect of hypnosis upon certain parameters of the G.A.S. [Presented in anecdotal style (H.S.).]

Thaler, V. H., Kisson, A. T.: "Thermal stress experiments and hypnosis (cold stress)." *Ann. Meet. Am. Soc. of Clinical Hypnosis*, Philadelphia (1964). J24,377/64

Liberson, W. T., Bernsohn, J., Wilson, A., Daly, V.: "Brain serotonin content and behavioral stress." *J. Neuropsychiatry* **5**: 363-365 (1964). D17,697/64

In guinea pigs, prolonged hypnosis training significantly decreased the 5-HT content of the cortex and hippocampus, and to a lesser degree, of the brain stem and cerebellum.

Wolffenbüttel, E.: "Um caso de hipertensão psicofisiológica de situação. Tratado com êxito pelo Hipno-Relaxamento Puro e Simples com follow-up de 4 anos e 4 meses" (A case of psychologic reactive hypertension treated successfully with pure and simple hypnorelaxation with a 4 year, 4 month follow-up). *Rev. Bras. Med.* **22**: 467-473 (1965) (Portuguese). J24,461/65

Volgyesi, F. A.: "Stress and hypnosis: hypnosis therapy in the case of organogenic and psychogenic disturbances of adolescents. Part I." *Br. J. Med. Hypnot.* **16**: 3-9 (1965). J24,007/65

Volgyesi, F. A.: "Part II." *Br. J. Med. Hypnot.* **16**: 8-13 (1965). J24,008/65

Volgyesi, F. A. "Part III." *Br. J. Med. Hypnot.* **17**: 22-29 (1965). J24,156/65

Sachar, E. J., Fishman, J. R., Mason, J. W.: "Influence of the hypnotic trance on plasma 17-hydroxycorticoid concentration." *Psychosom. Med.* **27**: 330-341 (1965). G31,897/65

During a deeply relaxing hypnotic trance, 17-OHCS elimination dropped markedly within nineteen minutes. However, this reaction was not consistent in all individuals observed (40 refs.).

Alnaes, R.: "Das Verhalten des Cortisol unter Hypnose oder autogenem Training mit besonderer Berücksichtigung der hypnosuggestiven Analgesie" (Cortisol activity under hypnosis or autogenic training, with special reference to hypnosuggestive analgesia). *Psychother. Psychosom.* **14**: 395-397 (1966). G58,155/66

Hypnosis may influence the blood cortisol level in both normal people and those under stress. [The brief anecdotal style of the presentation does not permit statistical evaluation (H.S.).]

Sachar, E. J., Cobb, J. C., Shor, R. E.: "Plasma cortisol changes during hypnotic trance. Relation to depth of hypnosis." *Arch. Gen. Psychiatry* **14**: 482-490 (1966). G38,955/66

Unusually low plasma cortisol concentrations were noted after ninety minutes of hypnosis (27 refs.).

London, P., McDevitt, R. A.: "Modification of stress responses to cold and electric shock; the use of autohypnotic techniques. AMRL-TR-67-142." *US Air Force Aerospace Med. Res. Lab.*, pp. 1-90 (1967). J24,396/7

Grüninger, O.: "Electrohypnosis and its effect on changes of electrical skin conductivity in the course of mental stress." *Bratisl. Lék. Listy* **50**: 516-523 (1968).

J23,786/68

Yanovski, A., Curtis, G. C.: "Hypnosis and stress." *Am. J. Clin. Hypn.* **10**: 149-156 (1968).

J22,510/68

"The relevance of hypnosis to the problem of stress as conceptualized by Selye is suggested by the results of neuro- and psychoendocrine studies" (51 refs.).

London, P., Ogle, M. E., Unikel, I. P.: "Effects of hypnosis and motivation on resistance to heat stress." *J. Abnorm. Psychol.* **73**: 532-541 (1968).

J22,410/68

During extreme "heat stress," performance in a task-solving test improved if the subjects were either hypnotized or exhorted to perform better. Exhortation has a slightly but nonsignificantly greater effect.

Frankenthal, K.: "Autohypnosis and other aids for survival in situations of extreme stress." *Int. J. Clin. Exp. Hypn.* **17**: 153-159 (1969).

J21,650/69

"Strong autosuggestion can be utilized to survive in situations of extreme stress by dissociating unbearable realities. Case histories in which this occurred are given."

London, P., McDevitt, R. A.: "Effects of hypnotic susceptibility and training on responses to stress." *J. Abnorm. Psychol.* **76**: 336-348 (1970).

J20,489/70

Lucas, O. N.: "Hypnosis and stress in hemophilia." *Bibl. Haematol.* No. 34: 73-82 (1970).

J21,249/70

McAmmond, D. M., Davidson, P. O., Kovitz, D. M.: "A comparison of the effects of hypnosis and relaxation training on stress reactions in a dental situation." *Am. J. Clin. Hypn.* **13**: 233-242 (1971).

J20,739/71

Bartlett, E. E.: "The use of hypnotic techniques without hypnosis per se for temporary stress." *Am. J. Clin. Hypn.* **13**: 273-278 (1971).

J21,210/71

Hypnotic techniques utilize ordinary suggestion to control inappropriate behavior without induction of formal hypnosis. "They are uniquely suitable for any patient's needs in any type of temporary stress."

Fogel, S.: "Muscular spasm diseases and body image distortions." *Am. J. Clin. Hypn.* **14**: 16-23 (1971).

G85,833/71

General discussion of hypnosis as a treat-

ment for stress-induced psychosomatic disease, illustrated with several case reports.

Cobb, L. A., Ripley, H. S., Jones, J. W.: "Free fatty acid mobilization during suggestion of exercise and stress using hypnosis and sodium amytal." *Psychosom. Med.* **35** No. 5: 367-374 (1973).

J7,261/73

"During hypnosis four of the six subjects readily relived past experiences of strenuous exercise and had significant increases in arterial FFA levels, and three showed rises in heart rate. In three of these four subjects there were further FFA increments with the reliving of past emotionally stressful situations." On the basis of observations with β -adrenergic blocking agents, the authors believe that "mechanisms other than circulating catecholamines, most likely neural adrenergic discharge, are also responsible for the FFA mobilization. A similar neurogenic mobilization of FFA may occur to some extent during physical exertion."

Psychoanalysis

(See also our earlier stress monographs, p. xiii)

Greenacre, P.: "Vision, headache and the halo; reactions to stress in the course of superego formation." *Psychoanal. Q.* **16**: 177-194 (1947).

B26,746/47

Alexander, F.: *Psychosomatic Medicine*, p. 300. New York: W W Norton, 1950.

B52,789/50

Simple textbook on psychosomatic medicine in relation to psychoanalysis and the G.A.S. (260 refs.).

Hartmann, H.: "Ego psychology and the problem of adaptation." In: Rapaport, D., *Organization and Pathology of Thought*, pp. 362-396. New York: Columbia University Press, 1951.

G27,004/51

Extensive analysis of the psychoanalytic approach to problems of psychologic adaptation, with almost no consideration of somatic stress (several hundred refs.).

Menninger, K.: "Regulatory devices of the ego under major stress." *Int. J. Psychoanal.* **35**: 412-420 (1962).

J3,936/62

Psychoanalytic study of the stress syndrome as a mental homeostatic reaction. It is concluded that "in its effort to control dangerous impulses under such circumstances and thereby prevent or retard the disintegrative process which threatens, the ego initi-

ates emergency regulatory devices which fall into five hierarchically arranged and specifically characterized groups, representing increasingly greater degrees of failure in integration."

Silverman, S.: *Psychologic Cues in Forecasting Physical Illness*, p. 403. New York: Appleton-Century-Crofts, 1970.

E10,672/70

Monograph on psychosomatic diseases, particularly stress-induced derangements, based largely on psychoanalytic investigations. The more of the following characteristics that appear together in a person, the greater the probability of the occurrence of somatic disease: "(1) exposure to critical psychologic stress inadequately compensated for by other environmental factors of a favorable nature; (2) some degree of physical dysfunction (ranging up to major illness) as part of a general style of adaptation to psychologic stress in the past, with previously sensitized body areas representing potential current target organs; (3) evidence of increasing instability and regressive shifts in psychologic equilibrium; (4) blocking of affects from adequate emotional expression or insufficient awareness of their significance if they are being so discharged; (5) presence of denial as a prominent psychologic defense; (6) existence of a high degree of egosuperego tensions despite lessening psychologic manifestations of their presence; (7) build-up of unmodified aggressiveness which is internalized; (8) a persisting increase in awareness of physical sensations and perceptions compared with previous levels; (9) recurrent dreams (and parapraxia) whose latent content contains prominent physical references especially to some form of dysfunction; (10) verbal references to somatic identification with an emotionally significant object, reinforced by actual occurrence of similar or related organ dysfunction in that person."

McLean, A.: "A psychoanalytic framework." In: McLean, A., *Occupational Stress*, pp. 27-30. Springfield, Ill.: Charles C Thomas, 1974.

E10,885/74

Acupuncture and Moxibustion

(See also our earlier stress monographs, p. xiii)

Gutstein, R. R.: *Trigger Treatment of Functional Ailments of the Skin, Muscles,*

Internal Organs, and Emotional States, p. 112. Ann Arbor, Mich.: Ann Arbor Publ., 1962.

E2,913/62

A rather unconventionally-written booklet on the cure of various allegedly stress-induced psychosomatic complaints through "trigger treatment" by ethylchloride freezing or injection of irritants to certain "trigger points." The treatment is somewhat reminiscent of acupuncture. [No systematic studies are reported which would lend themselves to statistical evaluation (H.S.).]

Toyama, P. M.: "The physiological basis of acupuncture and moxibustion therapy. *Am. J. Acupuncture* 3: 115-128 (1975).

J15,860/75

Lecture on acupuncture and moxibustion in the treatment of many diseases of adaptation.

Chen, G.: "Neurohumors in acupuncture." *Am. J. Clin. Med.* 3: 27-34 (1975).

J24,169/75

A review of the literature and personal observations lead the author to conclude that "among the substances to be considered are the neurohormones. Experimentally, the sympathetic and parasympathetic neurohormones are shown to be involved in analgesia and in the transmission of nerve impulses."

Chiropractic

(See also our earlier stress monographs, p. xiii)

Quigley, W. H.: "Physiological psychology of chiropractic in mental disorders." In: Schwartz, H. S., *Mental Health and Chiropractic*, pp. 107-119. New York: Sessions Publ., 1973.

E10,700/73

Résumé on the effect of chiropractic upon stress-induced mental illness.

Kimmel, E. H.: "Psychophysiological aspects of the subluxation." In: Schwartz, H. S., *Mental Health and Chiropractic*, pp. 135-147. New York: Sessions Publ., 1973.

E10,701/73

Observations on the effect of chiropractic upon stress-induced nervous derangements.

Schwartz, H. S.: "The psychotherapeutic experience of chiropractic." In: Schwartz, H. S., *Mental Health and Chiropractic*, pp. 161-173. New York: Sessions Publ., 1973.

E10,702/73

Summary on the effect of chiropractic upon stress diseases.

Schwartz, H. S. (ed.): *Mental Health and Chiropractic. A Multidisciplinary Approach*, p. 300. New York: Sessions Publ., 1973.

E10,696/73

Monograph mainly concerned with the effect of chiropractic on stress-induced psychologic disturbances.

(Histamine and stress). *Münch. Med. Wochenschr.* **97**: 466-469 (1955).

J25,677/55

Histamine liberation is considered to be a characteristic manifestation of the alarm reaction and may cause sudden death in corticoid-deficient patients receiving *short-wave therapy*.

Rusk, H. A.: "Convalescence, rehabilitation, and the therapeutic use of stress." *Ann. N.Y. Acad. Sci.* **73**: 476-481 (1958).

C61,572/58

Review on the importance of stress in the form of physical and mental *occupational therapy* during convalescence after various diseases.

Zimkin, N. V.: "Stress during *muscular exercises* and the state of non-specifically increased resistance." *Fiziol. Zh. SSSR* **47** No. 6: 741-751 (1961) (Russian). Eng. trans.: *Sechenov. Physiol. J. U.S.S.R.* **47** No. 6: 814-825 (1961).

J18,092/61

Unghváry, L., Hoványi, M., Kosztolnyik, J., Farkas, F.: "Veränderung des Blut-Glucocorticoid-Niveaus unter der Wirkung von physico-hydrotherapeutischen Verfahren" (Changes in the blood glucocorticoid level under the influence of physical *hydrotherapeutic procedures*). *Endokrinologie* **47**: 147-152 (1965).

F34,576/65

Sundberg, M., Kotovirta, M.-L., Pesola, E.-L.: "Effect of the Finnish sauna-bath on the urinary excretion of 17-OH-corticosteroids and blood eosinophil count in allergic and healthy persons." *Acta Allergol. (Kbh.)* **23**: 232-239 (1968).

G61,502/68

Urinary 17-OHCS elimination was essentially the same in allergic and normal individuals. "During the *sauna* day and 24 hours after the sauna bath the healthy subjects showed a statistically significant increase in the excretion of 17-OHCS. This kind of reaction was not found in the allergics and the difference between allergics and healthy subjects was also significant." The weak reaction of allergics was attributed to decreased reactivity to stressors. The eosinophil count was not consistently affected by the sauna.

Eigelsreiter, H., Schmid, H., Spielberger, M., Teichmann, W.: "Die Uropepsin-Ausscheidung bei hydrotherapeutischen Kuren (ohne und mit gleichzeitiger Bewegungstherapie)" (Uropepsin excretion during balneotherapy with and without simultaneous kin-

Osteopathy

(See also our earlier stress monographs, p. xiii)

Dunnington, W. P.: "A musculoskeletal stress pattern: observations from over 50 years' clinical experience." *J. Am. Osteopath. Assoc.* **64**: 366-371 (1964).

J22,344/64

Review of the treatment of stress diseases, especially those associated with musculoskeletal derangements, on the basis of the G.A.S.

Greenspan, J., Melchior, J.: "The effect of osteopathic manipulative treatment on the resistance of rats to stressful situations." *J. Am. Osteopath. Assoc.* **65**: 1205-1209 (1966).

J22,396/66

In rats, a treatment designed to mimic osteopathic manipulative therapy offered significant protection against various stressors.

Little, K. E.: "Toward more effective manipulative management of chronic myofascial strain and stress syndromes." *J. Am. Osteopath. Assoc.* **68**: 675-685 (1969).

J23,819/69

Detailed survey of the osteopathic treatment of myofascial derangements consequent to stress.

Various Stressors (Mental and Physical)

(See also our earlier stress monographs, p. xiii)

Wenzel, E.: "Die Bewegungen der Eosinophilen im Stress reizkörpertherapeutischer Methoden" (Changes of eosinophil count during stress produced by *nonspecific therapeutic stimuli*). *Z. Gesamte Inn. Med.* **8**: 551-560 (1953).

B99,246/53

Schnitzer, A.: "Histamin und Stress"

esiatics). *Z. Angew. Bader Klimaheilk.* **15:** 58-71 (1968). G58,525/68

Uropepsin elimination increases during *balneotherapy* possibly as a consequence of stimulation by corticoids produced under the stress of adaptation to this treatment. [The data do not lend themselves well to statistical evaluation (H.S.).]

Eiff, A. W. von, Czernik, A.: "Der Effekt einer elektrischen Carotis-Sinus-Stimulation auf autonome Funktionen während emotioneller Belastung" (Effect of electric stimulation of the carotid sinus on the autonomic functions during emotional stress). *Klin. Wochenschr.* **48:** 60-62 (1970).

J20,172/70

In patients exposed to psychogenic stress (mathematical problem-solving under difficult circumstances), there was hypertension, tachycardia, rapid respiration, increased muscular tone, and a rise in GSR. "By stimulating the carotid-sinus the reactions to stress such as blood pressure and pulse rate disappeared completely." Some earlier data on combatting stress by *electric stimulation* of the carotid-sinus are reviewed (7 refs.).

Nunneley, S. A., Troutman, S. J. Jr., Webb, P.: "Head cooling in work and heat stress." *Aerosp. Med.* **42:** 64-68 (1971).

J20,731/71

In man, *cooling of the head* decreased the BMR and relieved stress, especially in hot environments.

Malato, M.: "Funzionalità dell'asse diencefalo-ipofiso-surrenale nelle pazienti trattate con telecobaltoterapia per neoplasie dell'utero" (Function of diencephalo-hypophysio-adrenal axis in patients under *telecobaltotherapy* for uterine neoplasms). *Rass. Int. Clin. Ter.* **52:** 233-237 (1972).

J21,222/72

Brook, A.: "Mental stress at work." *Practitioner* **210:** 500-506 (1973). J1,772/73

Theoretical considerations and case reports illustrating the curative effect of *work satisfaction* on mental stress problems. It is noted that social factors connected with work, such as overpromotion, underpromotion and managerial indifference to personal problems of employees, cause pathogenic stress.

Haissly, J. C., Messin, R., Degre, S., Vandermoten, P., Demaret, B., Denolin, H.: "Comparative response to *isometric* (static) and *dynamic exercise* tests in coronary dis-

ease." *Am. J. Cardiol.* **33:** 791-796 (1974). H86,256/74

Amsterdam, E. A., Wilmore, J. H., Maria, A. N. de: "Symposium on *exercise* in cardiovascular health and disease." *Am. J. Cardiol.* **33:** 713-714 (1974).

H86,244/74

Pepine, C. J., Schang, S. J., Bemiller, C. R.: "Effects of perhexiline on symptomatic and hemodynamic responses to *exercise* in patients with angina pectoris." *Am. J. Cardiol.* **33:** 806-812 (1974).

H86,259/74

Scheuer, J., Penpargkul, S., Bhan, A. K.: "Experimental observations on the effects of *physical training* upon intrinsic cardiac physiology and biochemistry." *Am. J. Cardiol.* **33:** 744-751 (1974). H86,248/74

McHenry, M. M.: "Medical screening of patients with coronary artery disease." *Am. J. Cardiol.* **33:** 752-756 (1974).

H86,249/74

Wilmore, J. H.: "Individual *exercise* prescription." *Am. J. Cardiol.* **33:** 757-759 (1974). H86,250/74

Bonanno, J. A., Lies, J. E.: "Effects of *physical training* on coronary risk factors." *Am. J. Cardiol.* **33:** 760-764 (1974).

H86,251/74

Adams, W. C., McHenry, M. M., Bernauer, E. M.: "Long-term physiologic adaptations to *exercise* with special reference to performance and cardiorespiratory function in health and disease." *Am. J. Cardiol.* **33:** 765-775 (1974). H86,252/74

Haskell, W. L.: "Physical activity after myocardial infarction." *Am. J. Cardiol.* **33:** 776-783 (1974). H86,253/74

Stoedefalke, K. G.: "Physical fitness programs for adults." *Am. J. Cardiol.* **33:** 787-790 (1974). H86,255/74

Diet

(See also our earlier stress monographs, p. xiii)

Vasiutochkin, V. M.: "Physio-biochemical principles of rational nutrition in states of neuro-physical tension." *Vopr. Med. Zh.* No. 7: 50-56 (1959) (Russian).

J24,379/59

Allison, J. B.: "Stress diseases in relation to nutrition." *Rev. Invest. Clin.* **14**: 139-154 (1962). D29,232/62

Protein malnutrition, tumor growth and hypertension cause hyperlipemia in the dog and rat. They are considered to be stress diseases treatable by adequate protein intake.

Cuthbertson, D. P.: "Physical injury and its effects on protein metabolism. In: Munro, H. N. and Allison, J. B., *Mammalian Protein Metabolism*, pp. 373-414. New York and London: Academic Press, 1964.

G79,175/64

Review on the effect of stress upon protein metabolism. In man, protein loss within ten days of physical injury may amount to about 12 percent of the total body protein. In general, there is a catabolic loss during the first ten days and a maximum at about the third day with a secondary peak on the eighth day. With regard to dietary treatment, most observers hold that "during the first few days following the injury in the previously adequately nourished person it is probably unwise to push the intake of a well-balanced diet beyond appetite as this may fail during this early postinjury phase in severe injuries. Further, kidney function may not be normal for a day or two. Thereafter the patient should be encouraged, but not forced, to take as much as he can of a well-balanced diet, relatively rich in protein."

Balsley, M., Brink, M. F., Speckmann, E. W.: "Nutrition in disease and stress." *Geriatrics* **26**: 87-93 (1971). H36,185/71

Carlo, P. E.: "Nutritional therapy in surgery and trauma. Metabolic consequences of nutritional restriction and stress." *Agrestologie* **12**: 303-324 (1971). H51,864/71

Review on nutritional therapy for the metabolic consequences of trauma and other forms of stress. The so-called "obligatory, post-traumatic nitrogen loss" is part of the G.A.S. facilitated by, but not entirely dependent upon glucocorticoids. In acute stress, gluconeogenesis becomes essential at the expense of proteins to furnish a rapidly available source of energy. Lysosomes supply the enzymes required to catabolize proteins or synthesize sugar. Glucagon probably plays a very important role in this process, as it stimulates lysosomal activity and decreases insulin, thereby combatting stress-induced posttraumatic insulin resistance, since insulin inhibits gluconeogenesis. The main pertinent questions are answered as follows: "a) post-

traumatic nitrogen loss is due to starvation and stress; b) it is harmful because of the protein loss and metabolic imbalances it induces; c) it can be prevented or considerably limited by preventing the development of intense gluconeogenesis before surgery, and pharmacological control of adrenergic reactions; d) it helps the patient because it decreases the chances and severity of complications and speeds up recovery." In severe surgical stress, parenteral nutrition is advocated.

King, A. J.: "Stress, cigarette smoking and snacking behaviour in adolescent males." *Can. J. Public Health* **62**: 297-302 (1971). G86,388/71

Among male adolescents, stress (caused by examinations) produced more significant changes in snacking than in smoking. "Stressed non-smokers snacked significantly more than unstressed non-smokers. Unstressed smokers snacked significantly more than unstressed non-smokers."

Hartig, W.: "Ernährung des Patienten im Stress" (Diet of the patient in stress). *Zentralbl. Chir.* **99**: 577-586 (1974).

J14,052/74

Clinical suggestions concerning diets for patients under stress (28 refs.).

Hormones and Related Substances

(See also our earlier stress monographs, p. xiii)

Selye, H., Dosne, C.: "Treatment of wound shock with corticosterone." *Lancet* July 20, 1940, pp. 70-71. A33,299/40

In rats the damaging effect of stressors (surgical trauma, formaldehyde) can be combatted by corticosterone but not by DOC. "From this it appears that the hydroxyl group on carbon atom 11 is important for the shock-combating action of cortical steroids."

Selye, H., Dosne, C., Bassett, L., Whitaker, J.: "On the therapeutic value of adrenal cortical hormones in traumatic shock and allied conditions." *Can. Med. Assoc. J.* **43**: 1-8 (1940). A32,768/40

During the shock phase of the alarm reaction produced by heavy formaldehyde dosage in the rat, there is hypochloremia, hypoglycemia and hemoconcentration, all of which can be at least partially inhibited by a crude cortical extract (cortin). This is

even more obvious in surgical shock produced by partial hepatectomy, but here a specific effect of hepatic insufficiency cannot be excluded.

Harrower, H. R.: "The adrenal glands in stress, toxemia and infections." *Med. Rec. (N.Y.)* **155**: 497-501 (1942).

B26,260/42

Review of clinical data suggesting that the most diverse diseases "may have adrenal-depleting effects. There now can be no doubt that minor degrees of adrenal insufficiency are far more common, far more responsive to treatment (and, therefore, far more important to the average physician) than major degrees of adrenal insufficiency such as Addison's disease." Hence, corticoid therapy is recommended for the first time as a treatment in quite disparate maladies.

Pincus, G., Hoagland, H.: "Effects of administered pregnenolone on fatiguing psychomotor performance." *J. Aviat. Med.* **15**: 98-115 (1944).

B11,448/44

Pregnenolone improved stress resistance as indicated by performance scores on the Stevens serial coordination meter and the Hoagland-Werthessen pursuit meter. No such effects were obtained under similar conditions by placebos, progesterone or adrenocortical extracts. [We have found no evidence that these promising results have ever been confirmed (H.S.).]

Sprague, R. G.: Cortisone and ACTH. A review of certain physiologic effects and their clinical implications." *Am. J. Med.* **10**: 567-594 (1951).

B58,575/51

Levine, R., Goldstein, M. S., Ramey, E. R., Fritz, I.: "Studies on the mode of action of cortisone in stress situations." *Bull. N. Engl. Med. Cent.* **13**: 114-120 (1951).

B65,214/51

Studies on the Chambers-Zweifach mesoappendix preparation suggest that the beneficial effect of adrenocortical extract in stress is due largely to its action upon vascular contractility.

Duncan, J. T. Jr.: "Adrenal insufficiency in thermal burn with septicemia. Successful replacement therapy." *Am. Surg.* **20**: 57-59 (1954).

J10,792/54

In a patient with adrenal insufficiency following a burn and septicemia, cortisone was very efficacious.

Scholz, H.: "Die Behandlung des Bestrahlungssyndroms mit Prednisolon" (Treatment

of the radiation syndrome with prednisolone). *Zentralbl. Gynaekol.* **81**: 1065-1075 (1959).

C78,296/59

Review of the literature and personal observations suggest that the radiation syndrome is essentially related to the G.A.S. and associated with adrenocortical deficiency. Prednisolone allegedly has a therapeutic effect on both the generalized radiation syndrome and on local x-ray damage.

Hall, C. E., Hall, O.: "Effect of stress on response to fluorocortisone excess in the rat." *Proc. Soc. Exp. Biol. Med.* **107**: 799-802 (1961).

E99,293/61

Hale, H. B., Mefferd, R. B. Jr.: "Effects of somatotropin in rats acutely exposed to adverse environments." *J. Appl. Physiol.* **16**: 123-126 (1961).

D191/61

In rats, "somatotropin modified environmentally induced changes in 24-hour urinary excretion of urea, uric acid and phosphate and the urinary Na/K, Ca/P and uric acid/creatinine ratios. Suggestive evidence was thus obtained to support the hypothesis that somatotropin contributes to homeostasis."

Zambarda, E.: "Urinary excretion of corticoids in patients undergoing minor surgical stress and treated with aldosterone." *Riv. Patol. Clin.* **18**: 833-836 (1963).

J24,639/63

Sambhi, M. P., Weil, M. H., Udhaji, V. N., Shubin, H.: "Adrenocorticoids in the management of shock." In: Hershey, S. G., *Shock*, Vol. 2, pp. 421-433. Boston: Little, Brown, 1964.

G68,985/64

Review of the literature on the limited use of glucocorticoids in the management of shock (50 refs.).

Livanou, T., Ferriman, D., James, V. H. T.: "The response to stress after corticosteroid therapy." *Proc. R. Soc. Med.* **58**: 1013-1015 (1965).

F59,005/65

In patients, shortly after discontinuing glucocorticoid therapy, the plasma cortisol level following insulin hypoglycemia does not increase as much as in unpretreated controls.

Dobkin, A. B., Byles, P. H., Neville, J. F. Jr.: "Neuroendocrine and metabolic effects of general anaesthesia and graded haemorrhage." *Can. Anaesth. Soc. J.* **13**: 453-475 (1966).

G41,075/66

In dogs, various parameters of the stress reaction were compared following anesthesia induced by different agents, in combination with severe bleeding, and after pretreatment

with methylprednisolone and ampicillin. Individual responses varied, depending upon the anesthetic used: "It is likely that the rapid recovery from the stress of the combination of haemorrhage and general anaesthesia may be attributed to the use of a relatively large dose of the corticoid and antibiotic drugs." [Lack of adequate controls makes it difficult to identify the relative role of each factor in this complicated procedure (H.S.).]

VanderWall, D. A., Stowe, N. T., Spangenberg, R., Hook, J. B.: "Effect of glucagon in hemorrhagic shock." *J. Surg. Oncol.* **2**: 177-187 (1970). G77,407/70

In dogs, some of the circulatory disturbances elicited by hemorrhagic shock were prevented by chronic intravenous infusions of glucagon. Hence, "glucagon has potential usefulness in clinical situations in which cardiac output and renal blood flow are compromised."

Kostowski, W., Rewerski, W., Piechocki, T.: "Effects of some steroids on aggressive behaviour in mice and rats." *Neuroendocrinology* **6**: 311-318 (1970). H34,036/70

DOC decreased the muricide reaction in rats, but failed to change the aggressive response of isolated mice. Cortisol increased aggressiveness, whereas hydroxydione (an anesthetic steroid) decreased it in both these tests.

Madden, J. J. Jr., Ludewig, R. M., Wangensteen, S. L.: "Failure of glucagon in experimental hemorrhagic shock." *Am. J. Surg.* **122**: 502-504 (1971). G86,060/71

In dogs with hemorrhagic shock, glucagon (given at the time of re-infusion of the shed blood) had no beneficial hemodynamic effect and did not increase survival rates.

Lefer, A. M., Glenn, T. M., Lopez-Rasi, A. M., Kiechel, S. F., Ferguson, W. W., Wangensteen, S. L.: "Mechanism of the lack of a beneficial response to inotropic drugs in hemorrhagic shock." *Clin. Pharmacol. Ther.* **12**: 506-516 (1971). G83,070/71

Despite its inotropic effect, glucagon did not exhibit any beneficial action in dogs with hemorrhagic shock.

Bendikov, E. A., Basaeva, A. I.: "The use of DOPA in replacement therapy in disturbances of circulatory regulation during stress." *Biull. Éksp. Biol. Med.* **76** No. 12: 36-39 (1973) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **76**: 1414-1416 (1973). J20,146/73

In cats, stress produced by injection of potassium chloride into the lateral ventricles caused depletion of NEP in the hypothalamus, with inhibition of sympathetic vasomotor tone. These changes could be corrected by injection of DOPA.

Novelli, G. P., Marsili, M., Pieraccioli, E.: "Anti-shock action of steroids other than cortisone." *Eur. Surg. Res.* **5**: 169-174 (1973). J7,837/73

In rats, mortality induced by trauma (drum-shock) can be combatted by massive doses of glucocorticoids, estrogens and testosterone. Apparently, the therapeutic effect is not due to the specific action of glucocorticoids, but rather to overdosage with various steroids.

Kobayashi, A., Utsunomiya, T., Sentoh, H., Tomita, K., Ohbe, Y.: "Adrenocortical responsiveness after long-term corticosteroid therapy in childhood nephrosis." *Helv. Paediatr. Acta* **28**: 341-348 (1973). J8,226/73

In children who received long-term glucocorticoid treatment for nephrosis, ACTH caused a greatly diminished response in the hormone production of the adrenals following discontinuation of the therapy. Depending upon the length and dosage of treatment with betamethasone, complete recovery of adrenocortical responsiveness may take six months.

Bismuth, C.: "Utilisation des corticoïdes dans le choc toxique" (Utilization of corticoids in toxic shock). *Eur. J. Toxicol.* **6**: 168-170 (1973). J9,345/73

Brief summary of the uses and limitations of corticoid therapy for allergic shock and pneumopathies due to inhalation of gastric juice.

Bouzarth, W. F., Shenkin, H. A.: "Possible mechanisms of action of dexamethasone in brain injury." *J. Trauma* **14**: 134-136 (1974). J10,329/74

Dexamethasone may be beneficial in the treatment of brain injury by relieving the associated cerebral edema. It is dubious whether its effect upon systemic stress also plays a role here (16 refs.).

Court, J. M., Dunlop, M. E., Boulton, T. J. C.: "Effect of ephedrine in ketotic hypoglycaemia." *Arch. Dis. Child.* **49**: 63-65 (1974). J10,138/74

In children receiving a "ketogenic stress diet," it has been shown that "while adequate glycogen stores exist, ephedrine may help

maintain glucose homoeostasis under conditions of stress."

Vitamins

(See also our earlier stress monographs, p. xiii)

Dugal, L. P., Thérien, M.: "The influence of ascorbic acid on the adrenal weight during exposure to cold." *Endocrinology* **44**: 420-426 (1949). B36,429/49

In guinea pigs as in rats, exposure to cold elicits all the manifestations of the alarm reaction, including ascorbic acid depletion. Treatment with ascorbic acid inhibits adrenal enlargement and raises resistance to cold.

Stepto, R. C., Pirani, C. L., Consolazio, C. F., Bell, J. H.: "Ascorbic acid intake and the adrenal cortex." *Endocrinology* **49**: 755-773 (1951). B66,289/51

In guinea pigs kept on a vitamin C-deficient diet, adrenal ascorbic acid drops concurrently with adrenal lipids and cholesterol. This may interfere with corticoid synthesis or merely indicate that, for the guinea pig, vitamin C deficiency is a strong stressor. In such a situation, vitamin C administration is of therapeutic value.

Bacchus, H.: "Leukocyte response to stress in normal and adrenalectomized rats pretreated with ascorbic acid." *Proc. Soc. Exp. Biol. Med.* **77**: 167-169 (1951). B59,311/51

In rats, stress caused by sham adrenalectomy induces eosinopenia, with polymorphonuclear leukocytosis developing within three hours. Pretreatment with ascorbic acid or adrenalectomy prevents, and may even reverse, the eosinopenia.

Bacchus, H., Altszuler, N.: "Eosinophil response to stress in ascorbic acid pretreated mice." *Endocrinology* **51**: 1-4 (1952). B74,531/52

In mice, ascorbic acid pretreatment prevents the eosinopenia caused by EP, but not that elicited by ACTH. "These observations were interpreted as indicating that the vitamin operated in this mechanism by depressing the release of pituitary corticotrophic hormone."

Pirani, C. L.: "Review: relation of vitamin C to adrenocortical function and stress phenomena." *Metabolism* **1**: 197-222 (1952).

B70,172/52

Review of the literature which leads to the conclusion that "under normal conditions man is supplied with stores of ascorbic acid more than adequate to cope with the metabolic need of acute stress. Administration of ascorbic acid, however, would seem indicated in severe chronic stress, especially after traumatic injuries or burns, and during protracted stimulation of the adrenal cortex" (242 refs.).

Salomon, L. L.: "Studies on adrenal ascorbic acid. II. On ascorbic acid neogenesis in rat adrenal glands." *Tex. Rep. Biol. Med.* **15**: 934-939 (1957). C45,566/57

Studies with labeled vitamin C indicate that, in both hypophysectomized and intact rats, local synthesis of this vitamin contributes little or nothing to its concentration in the adrenal.

Goldstein, A., Bailey, G. W. H.: "The effect of ascorbic acid on mental and physical well-being in human subjects under mild stress." *Stanf. Med. Bull.* **17**: 175-177 (1959).

J23,580/59

In a double-blind experiment on male medical students, vitamin C, administered daily in large amounts, was "no more effective than a placebo in improving the state of mental and physical well-being, as evaluated by the subjects themselves. Ascorbic acid also had no effect on the incidence of colds among the subjects."

Juszkiewicz, T., Jones, L. M.: "Effects of chlorpromazine and ascorbic acid in rats during simulated transportation conditions at normal and high temperatures." *Am. J. Vet. Res.* **22**: 544-548 (1961). J24,117/61

"Under simulated transport conditions, chlorpromazine protects rats against excessive weight losses, excessive depletion of the adrenal ascorbic acid, and the excessive mortality experienced at high temperature. The simultaneous administration of ascorbic acid with chlorpromazine seemed to promote anti-stress effects, particularly at high temperatures."

Wiswell, O. B.: "Influence of vitamin E and high and low thermal environments on weight and body temperature of the rabbit." *Aerosp. Med.* **33**: 685-688 (1962).

J23,017/62

In rabbits exposed to cold or heat, the body weight loss ascribed to stress is diminished by vitamin E supplements to the diet.

Rokicki, W.: "On the anti-stress activity of vitamin C." *Patol. Pol.* **17**: 34-38 (1966) (Polish).

J24,613/66

Levi, L.: "Das Experiment am Menschen in der Psychosomatik" (Psychosomatic studies in man). *Verh. Dtsch. Ges. Inn. Med.* **73**: 58-70 (1967). G85,102/67

In man, various psychic stressors cause hyperlipoproteinemia as well as increased blood FFA. Nicotinic acid treatment diminishes the blood lipids without influencing the tachycardia, hypertension or catecholamine secretion. Hence, it is assumed that nicotinic acid inhibits fatty acid mobilization within the adipose tissue itself.

Green, J., Muthy, I. R., Diplock, A. T., Bunyan, J., Cawthorne, M. A., Murrell, E. A.: "Vitamin E and stress. 7. The interrelationships between polyunsaturated fatty acid stress, vitamin A and vitamin E in the rat and the chick." *Br. J. Nutr.* **21**: 845-864 (1967). F92,058/67

In rats, vitamin E has no obvious protective effect against stressors.

Carlson, L. A., Levi, L., Orö, L.: "Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid." *J. Clin. Invest.* **47**: 1795-1805 (1968). H1,440/68

In male volunteers, emotional stressors (dazzling light, standardized criticism, sorting steel balls of different sizes) caused a rise in plasma FFA and triglycerides as well as increased catecholamine excretion. Concurrent treatment with nicotinic acid prevented the elevation in FFA and triglycerides but not the stressor-induced increase in catecholamine elimination or the associated rise in heart rate and blood pressure.

Piroth, M.: "Experimenteller Stress und Ascorbinsäurezufuhr" (Experimental stress and supply of ascorbic acid). *Verh. Dtsch. Ges. Pathol.* **52**: 478-480 (1968).

H34,240/68

In rats chronically exposed to cold, the manifestations of the G.A.S. could not be beneficially influenced by vitamin C supplements, except for a doubtful increase in resistance during the first week.

Beneš, V., Hrubeš, V.: "Serum free fatty acids level after an experimentally induced emotional stress and its modification by nicotinic acid in rats with different characteristics of higher nervous activity." *Activ. Nerv. [Supp.]* (Praha) **10**: 395-399 (1968). J11,743/68

For rats in which fear was induced by intermittent electric shocks, serum FFA

rises were particularly obvious among animals with extremely low spontaneous exploratory activity. Intraperitoneal nicotinic acid completely blocked this change.

Rokicki, W.: "Effect of vitamin C on the ovaries and adrenal glands in stress states." *Patol. Pol.* **20**: 455-459 (1969) (Polish).

J24,612/69

Mikhelson, D. A.: "The effect of the B₁ vitamin and niacin on the course of biochemical processes in the organism exposed to the action of vibration." *Vopr. Pitan.* **28** No. 6: 54-58 (1969) (Russian). J25,110/69

In rats, stress induced by vibration appears to have been alleviated by thiamine and niacin, but especially by the combined administration of both vitamins.

Pohujani, S. M., Chittal, S. M., Raut, V. S., Sheth, U. K.: "Studies in stress induced changes on rat's adrenals. Part III. Effect of pre-treatment with ascorbic acid." *Indian J. Med. Res.* **57**: 1091-1094 (1969).

H43,275/69

Ellerbrook, R. C., Purdy, M. B.: "Capacity of stressed humans under mega dosages of nicotinic acid to synthesize methylated compounds." *Dis. Nerv. Syst.* **31**: 196-197 (1970). G74,382/70

"How much vitamin C?" *Nature* **243**: 117-118 (1973). H77,668/73

Review of literature suggesting that, during surgical stress, guinea pigs need many times the basic amount of vitamin C.

Khomulo, P. S., Mytareva, L. V., Zakrinichnaya, G. A.: "Oxygen and glucose utilization by aortic tissue with administration of cholesterol and nervous system stress." *Kardiologija* **13** No. 1: 116-120 (1973) (Russian). H80,123/73

In rats, vitamin B₁₅ (calcium pangamate) allegedly diminishes certain metabolic changes produced by restraint.

Rasche, R., Butterfield, W. C.: "Vitamin A pretreatment of stress ulcers in rats." *Arch. Surg.* **106**: 320-321 (1973).

J641/73

Studies on rats which received 10,000 international units of vitamin A prior to an eight-hour period of immobilization in a wire gauze device suggest that this vitamin "exerts a negligible, if any, protective effect on the occurrence of gastric ulceration."

Nandi, B. K., Subramanian, N., Majumder, A. K., Chatterjee, I. B.: "Effect of

ascorbic acid on detoxification of histamine under stress conditions." *Biochem. Pharmacol.* **23**: 643-647 (1974). H81,833/74

In both rats and guinea pigs kept on an ascorbic acid-free diet, a variety of stressors (vaccines, toxoids, malnutrition, cold, heat, pregnancy) increased histamine formation or excretion into the urine. "Administration of large doses of ascorbic acid in any of the stressful situations resulted in a marked decrease in the urinary histamine level indicating detoxification of histamine in vivo."

Cheney, C. D., Rudrud, E.: "Prophylaxis by vitamin C in starvation induced rat stomach ulceration." *Life Sci.* **14**: 2209-2214 (1974) (16 refs.). J14,496/74

Gori, E.: "Les hypnotiques et le stress" (Hypnotics and stress). *20th Int. Congr. Physiol.*, 357-358. Brussels, July-August, 1956. C23,393/56

Even fatal doses of *barbiturates* fail to produce an alarm reaction (adrenal ascorbic acid depletion) in the rat, and actually inhibit the stressor effect of various agents. On the other hand, many *hypnotics* and *anesthetics* stimulate ACTH secretion and may thereby overcome their own antistress effect, which might be due to depression of the reticular formation. [The brief abstract does not lend itself to critical analysis (H.S.).]

Mason, J. W., Brady, J. V.: "Plasma 17-hydroxycorticosteroid changes related to reserpine effects on emotional behavior." *Science* **124**: 983-984 (1956). C25,325/56

In rhesus monkeys, moderate doses of *reserpine* inhibited not only experimentally induced anxiety and fear responses, but also the associated increase in plasma 17-OHCS levels. This fact is all the more interesting since, in themselves, comparable doses of reserpine produce a transient increase in 17-OHCS levels.

Mahfouz, M., Ezz, E. A.: "The action of chlorpromazine and serpasil on the response of the rat to acute stress." *20th Int. Congr. Physiol.*, pp. 601-602. Brussels, July-August, 1956. C23,436/56

Both *chlorpromazine* and *serpasil* pretreatment "seemed to have protected" rats against the stressor effect (adrenal ascorbic acid depletion) of various agents, such as ether anesthesia, hemorrhage, heat and cold. [The brief abstract does not lend itself to critical evaluation (H.S.).]

Bias, D. A. de, Paschkis, K. E., Cantarow, A.: "Effects of *chlorpromazine* and autonomic nervous system blocking agents in combating heat stress." *Am. J. Physiol.* **193**: 553-556 (1958). C54,401/58

Brief review of the literature and personal observations on the effect of various drugs upon resistance to diverse stressors in intact and adrenalectomized rats. Since different drugs are effective against different stressors, the mechanisms of protection must be dissimilar.

Mahfouz, M., Ezz, E. A.: "The effect of reserpine and chlorpromazine on the response of the rat to acute stress." *J. Pharmacol. Exp. Ther.* **123**: 39-42 (1958). C53,654/58

In rats, both *chlorpromazine* and *reserpine*

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(See also our earlier stress monographs, p. xiii)

Holzbauer, M., Vogt, M.: "The action of chlorpromazine on diencephalic sympathetic activity and on the release of adrenocorticotrophic hormone." *Br. J. Pharmacol.* **9**: 402-407 (1954). C7,651/54

In rats, ACTH release following surgical shock or EP injection was not prevented by *chlorpromazine*. In fact, the latter caused some ACTH release by itself. These observations contradict certain earlier claims.

Nasmyth, P. A.: "The effect of *chlorpromazine* on adrenocortical activity in stress." *Br. J. Pharmacol.* **10**: 336-339 (1955).

C27,637/55

Kothari, N. J., Rindani, T. H.: "Effect of reserpine-free extract of *Rauwolfia serpentina* on stress induced activation of adrenal cortex." *Arch. Int. Pharmacodyn. Ther.* **105**: 68-72 (1956). C15,329/56

In man, the eosinopenia "in response to systemic stress by electroshock" is decreased by pretreatment with *Rauwolfia serpentina*, indicating a blockade of the stress response.

Huguenard, P.: "Atténuation du 'stress' par l'hypométabolisme (Physiologie et méthodes)" (Attenuation of "stress" by hypometabolism [physiology and methods]). *Anesth. Analg.* **13**: 16-40 (1956). C15,557/56

Summary of the results on the prevention by artificial hibernation of surgically-induced stress in man.

inhibited the stressor effect (adrenal ascorbic acid depletion) of cold, heat, and hemorrhage under ether anesthesia. Neither drug prevented the adrenal ascorbic acid depletion caused by ACTH. They may act upon the hypothalamus.

Kivalo, E., Rinne, U. K.: "The effect of *perphenazine* on the ACTH release induced by neurotropic stress." *Psychopharmacologia* **1**: 288-293 (1960). J23,393/60

Weiss, B., Laties, V. G., Blanton, F. L.: "Amphetamine toxicity in rats and mice subjected to stress." *J. Pharmacol. Exp. Ther.* **132**: 366-371 (1961). D6,968/61

The toxicity of amphetamine is increased in rats and mice exposed to aversive electroshock. This effect can be counteracted by *chlorpromazine* and *phenoxybenzamine*.

Juszkiewicz, T., Jones, L. M.: "Effects of *chlorpromazine* and ascorbic acid in rats during simulated transportation conditions at normal and high temperatures." *Am. J. Vet. Res.* **22**: 544-548 (1961). J24,117/61

"Under simulated transport conditions, *chlorpromazine* protects rats against excessive weight losses, excessive depletion of the adrenal ascorbic acid, and the excessive mortality experienced at high temperature. The simultaneous administration of ascorbic acid with *chlorpromazine* seemed to promote anti-stress effects, particularly at high temperatures."

Chaudhury, R. R., Chaudhury, M. R., Lu, F. C.: "Stress-induced block of milk ejection." *Br. J. Pharmacol.* **17**: 305-309 (1961). D61,414/61

The stress-induced block of milk ejection in guinea pigs can be largely inhibited by *tranquillizers*.

Mallov, S., Witt, P. N.: "Effect of stress and tranquilization on plasma free fatty acid levels in the rat." *J. Pharmacol. Exp. Ther.* **132**: 126-130 (1961). D3,463/61

In rats, electroshocks raise the plasma FFA concentration. This in turn can be inhibited by tranquilizers (*chlorpromazine*, *meprobamate*), but only when given at certain dose levels at critical times.

Betz, D., Ganong, W. F.: "Effect of *chlorpromazine* on pituitary-adrenal function in the dog." *Acta Endocrinol. (Kbh.)* **43**: 264-270 (1963). D68,211/63

Petri, G., Kovács, G. S.: "The effect of operation stress on the metabolism of

patients." *Pol. Tyg. Lek.* **18**: 674-680 (1963) (Polish). G2,166/63

"It has been found that in response to surgery urine flow promptly decreased, osmolality increased; infusion of 5 per cent dextrose did not influence this phenomenon. The urinary output of sodium and chloride fell promptly after operation, potassium excretion increased. . . . *Barbiturate* anaesthesia prevented the development of postoperative metabolic changes as long as anaesthesia was maintained but once it was over, the above changes developed in their characteristic form."

Girod, C.: "Influence de la réserpine sur l'axe hypophysocortico-surrénalien, chez le singe *Macacus sylvanus L.*" (The influence of reserpine on the pituitary-adrenocortical axis in the *Macacus sylvanus L.* monkey). *C.R. Acad. Sci. (Paris)* **256**: 1600-1602 (1963). D62,899/63

In the monkey *Macacus sylvanus L.*, *reserpine* causes adrenal hyperactivity with pituitary changes suggestive of increased ACTH secretion.

Buckley, J. P., Kato, H., Kinnard, W. J., Aceto, M. D. G., Estevez, J. M.: "Effects of reserpine and *chlorpromazine* on rats subjected to experimental stress." *Psychopharmacologia* **6**: 87-95 (1964). G19,794/64

In rats, combined treatment with various stressors (sound, light, vibration, conditioned avoidance) elicited peak pressor responses after eleven weeks. This was not influenced by *reserpine* or *chlorpromazine*, which actually increased mortality. Possibly, under certain conditions (prolonged chronic stress rather than severe acute stress), both reserpine and *chlorpromazine* exert a potentiating or additive effect on the pituitary-adrenal response to stress, "thus producing adrenal insufficiency leading to the death of the animal."

Tullner, W. W., Hertz, R.: "Suppression of corticosteroid production in the dog by monase." *Proc. Soc. Exp. Biol. Med.* **116**: 837-840 (1964). F17,084/64

Etryptamine (Monase), formerly used as an antidepressant, often causes syncope and hypotension in patients, and sharply decreases corticoid output in pentobarbital-anesthetized dogs. This effect is prevented by ACTH, even after hypophysectomy. Presumably, the action of *etryptamine* "in intact dogs is a result of suppression either of formation or release of ACTH."

Bernis, R., Vanek, R., Delferiere, A., Trop, D.: "Etude clinique et biochimique de l'anesthésie à l'hydroxydione dans l'agression chirurgicale" (Clinical and biochemical study of anesthesia with hydroxydione in surgical stress). *Acta Anaesthesiol. Belg.* **15**: 97-110 (1964). J24,074/64

In man, *hydroxydione* anesthesia does not prevent the increase in corticoid output produced by surgery.

Bohus, B., Endrőczi, E.: "Untersuchungen über die Wirkung von Chlorpromazin auf das Hypophysen-Nebennierenrinden-System bei Ratten" (Studies on the effect of chlorpromazine on the hypophysis-adrenal cortex system in rats). *Endocrinologie* **46**: 126-133 (1964). F16,012/64

In rats, large doses of subcutaneous *chlorpromazine*, particularly when injected into the reticular formation of the brain, produced high corticosterone secretion. It was not possible to inhibit the blood corticosterone rise normally caused by stressors (formalin, restraint) through pretreatment with chlorpromazine.

Rerup, C.: "Corticotrophin release in mice: failure of pentobarbital-morphine to block the effect of non-specific stress." *Acta Endocrinol. (Kbh.)* **46**: 387-392 (1964). F14,817/64

In mice, the nonspecific stress of histamine injections could not be blocked by *pentobarbital* plus *morpheine*; hence, such preparations are inappropriate for testing CRF activity.

Tournut, J., Le Bars, H., Labie, C., Khamouma, M.: "Prévention des effets de l'immobilisation forcée chez le Porc par certains neuroleptiques" (Prevention of the effects of forced immobilization in the pig by certain neuroleptics). *C. R. Acad. Sci. (Paris)* **260**: 5415-5418 (1965). G66,777/65

In pigs, immobilization causes loss of weight and gastric ulcers which can be considerably diminished by *chlorpromazine* and other neuroleptic agents.

Schulz-Baldes, J. G.: "Prüfung einiger alter Sedativa und des Phenacetins auf antistressorische Wirkungen" (Investigation of some old sedatives and of phenacetin for anti-stress activity). *Arzneim. Forsch.* **15**: 835-837 (1965). F49,128/65

Ascorbic acid depletion produced in rats by various stressors was not significantly prevented by hop meal, *phenacetin*, *sodium bromide*, *valerian* and magnesium sulfate. None of these substances exhibited "any noteworthy anti-stress activity—not even

phenacetin. Hence, they have no specific sedative effect on the hypophyseal-adrenal system."

Rosecrans, J. A., Feo, J. J. de: "The interrelationships between chronic restraint stress and reserpine sedation." *Arch. Int. Pharmacodyn. Ther.* **157**: 487-497 (1965).

F54,866/65

In rats, stress by restraint initially increased the 5-HT and decreased the NEP content of the brain. "Reserpinated stress animals were more easily handled at first, but became more excitable and difficult to handle as the experiment progressed." This change appeared to correlate with the continued depletion of brain NEP because the brain 5-HT remained approximately constant. The possible protective effect of *reserpine* is considered in connection with the G.A.S.

Barrett, A. M., Stockham, M. A.: "The response of the pituitary-adrenal system to a stressful stimulus: the effect of conditioning and pentobarbitone treatment." *J. Endocrinol.* **33**: 145-152 (1965).

F49,945/65

In rats, deep *pentobarbital* anesthesia diminished the rise in plasma corticosterone normally elicited by various stressors.

Michalová, C., Hrubeš, V., Beneš, V.: "The influence of *chlordiazepoxide* on biochemical reactions to experimental stress in rats." *Activ. Nerv. Sup. (Praha)* **8**: 458-459 (1966).

J23,495/66

Ordy, J. M., Samorajski, T., Schroeder, D.: "Concurrent changes in hypothalamic and cardiac catecholamine levels after anesthetics, tranquilizers and stress in a subhuman primate." *J. Pharmacol. Exp. Ther.* **152**: 445-457 (1966).

F67,727/66

In squirrel monkeys, various stressors cause a concurrent depletion of hypothalamic and cardiac NEP. Pretreatment with *chlorpromazine* or *haloperidol* inhibits both these effects.

Martinez, L. R., Euler, C. von, Norlander, O. P.: "The sedative effect of *premedication* as measured by catecholamine excretion." *Br. J. Anaesth.* **38**: 780-786 (1966).

G42,455/66

Buckley, J. P., Vogen, E. E., Kinnard, W. J.: "Effects of pentobarbital, acetylsalicylic acid, and reserpine on blood pressure and survival of rats subjected to experimental stress." *J. Pharm. Sci.* **55**: 572-575 (1966).

F67,051/66

Chronic exposure of rats to a variety of

stressors (strong light, sound, electric shock) produces hypertension which is not prevented by *pentobarbital* or *acetylsalicylic acid* but is diminished by *reserpine*. The ulcerogenic effect of stressors is aggravated by *acetylsalicylic acid*.

Ganong, W. F., Boryczka, A. T., Lorenzen, L. C., Egge, A. S.: "Lack of effect of α -ethyltryptamine on ACTH secretion when blood pressure is held constant." *Proc. Soc. Exp. Biol. Med.* **124**: 558-559 (1967).

F77,622/67

In dogs, increased ACTH secretion produced by hemorrhage is prevented by *α -ethyltryptamine* (etryptamine) in doses that restore the blood pressure. Presumably, "it is the rise in blood pressure produced by *α -ethyltryptamine* that causes the inhibition of ACTH secretion."

Pishkin, V., Shurley, J. T., Wolfgang, A.: "Stress. Psychophysiological and cognitive indices in an acute double-blind study with hydroxyzine in psychiatric patients." *Arch. Gen. Psychiatry* **16**: 471-478 (1967).

G46,638/67

In psychiatric patients with "cognitive stress," it was found that "(1) anxiety and muscle tension were reduced in *hydroxyzine* groups with no impairment of decision making capability; (2) antecedent unavoidable failure interfered with decision making in placebo and control groups, while the interference was significantly reduced in *hydroxyzine* groups; (3) autonomic levels of activation decreased at a significantly higher rate in *hydroxyzine*-treated Ss during the extinction phase than in the placebo and the no-drug groups, and pain thresholds of *hydroxyzine* patients were significantly higher than those in the no-drug groups; and (4) physiological levels of activation increased with increase in the amount of information input" (27 refs.).

Dandiya, P. C., Varma, R. R., Sogani, R. K., Khuteta, K. P.: "Effect of *reserpine* and *chlorpromazine* on some cold stress-induced biochemical alterations." *J. Pharm. Sci.* **56**: 300-301 (1967).

F76,430/67

Dasgupta, S. R., Mukherjee, B. P.: "Effect of *chlordiazepoxide* on eosinopenia of stress in rabbits." *Nature* **213**: 199-200 (1967).

F75,231/67

Dasgupta, S. R., Mukherjee, B. P.: "Effect of *chlordiazepoxide* on stomach ulcers in rabbit induced by stress." *Nature* **215**: 1183 (1967).

F87,560/67

In rabbits, the gastric ulcers and eosinopenia produced by electroshock or restraint were inhibited by *chlordiazepoxide*.

Vunder, P. A., Fefer, M. I., Batanova, G. K., Dorofeeva, R. V.: "Stress and compensatory hypertrophy of the adrenal gland in conditions of prolonged *reserpin* administration." *Probl. Endokrinol.* **14** No. 5: 82-86 (1968) (Russian). H4,672/68

Buckley, J. P., Parham, C., Smookler, H. H.: "Effects of *reserpine* on rats subjected to prolonged experimental stress." *Arch. Int. Pharmacodyn. Ther.* **172**: 292-300 (1968). F99,053/68

Reserpine prevented the hypertension which develops in rats exposed to diverse stressors.

Brown, M. L., Sletten, I. W., Kleinman, K. M., Korol, B., "Effect of *oxazepam* on physiological responses to stress in normal subjects." *Curr. Ther. Res.* **10**: 543-553 (1968). J23,435/68

Prabhu, S., Sharma, V. N.: "Study of thermal stress induced haematological changes and their modification by *chlorpromazine* in rats." *Indian J. Med. Res.* **56**: 742-753 (1968). G61,228/68

Usher, D. R., Ling, G. M., MacConaill, M.: "Some endocrine and behavioural effects of *chlordiazepoxide* in septal-lesioned rats." *Int. J. Clin. Pharmacol.* **1**: 191-196 (1968). G64,766/68

Rats with septal lesions developed a typical behavioral pattern, the "septal syndrome," with enhanced ACTH synthesis, but diminished release of this hormone during stress. "*Chlordiazepoxide*" reduced the hyper-reactivity of septal-lesioned rats, but had no effect on endocrine organ weights; the reduction of hyper-reactivity was more marked in the stressed animals. Lesioned rats had larger adenohypophyses than sham-operated animals. The weight of this gland was reduced in all stressed animals, whether sham-operated or lesioned. It is postulated that mild stress and *chlordiazepoxide* both contribute to a diminished hyper-reactivity of rats with septal lesions."

Levi, L.: "Emotional stress and biochemical reactions as modified by psychotropic drugs with particular reference to cardiovascular pathology." *Proc. Int. Symp. Psychotropic Drugs in Internal Medicine*, Baia Domizia, Italy, 1968. *Int. Congr. Ser.* No.

182, pp. 206-220. Amsterdam: Excerpta Medica, 1969. G59,520/69

Review on the effectiveness of *psycho-tropic drugs* in the treatment of emotional stress reactions in man.

Reeder, L. G., Chapman, J. M., Coulson, A. H.: "Socio-environmental stress, *tranquillizers* and cardiovascular disease." Proc. Int. Symp. Psychotropic Drugs in Internal Medicine, Baia Domizia, Italy, 1968. *Int. Congr. Ser. No. 182*, pp. 226-238. Amsterdam: Excerpta Medica, 1969. J17,504/69

Pohujani, S. M., Chittal, S. M., Raut, V. S., Sheth, U. K.: "Studies in stress induced changes on rat's adrenals. Part I. Effect of *central nervous depressants*." *Indian J. Med. Res.* **57**: 1081-1086 (1969). H43,274/69

Oren, B. G.: "Stress-related gastrointestinal dysfunction and combined *antidepressant-tranquilizer* therapy." *Psychosomatics* **10**: 258-263 (1969). J21,950/69

Sharma, V. N., Prabhu, S.: "Influence of chlorpromazine in rats subjected to electroshock and restraint stress." *Indian J. Med. Res.* **57**: 106-117 (1969). G68,885/69

Chlorpromazine provides partial protection to rats against eosinopenia and various other manifestations of stress caused by restraint or electroshock.

Ecanow, B., Gold, B. H., Tunkunas, P.: "Rheological effects of stress and *ataractic drugs* (Implications for a theory of schizophrenia)." *Dis. Nerv. Syst.* **30**: 172-177 (1969). H33,857/69

Brand, E. D., Stetson, R. E., Beall, J. R., Lennard, H. L., Epstein, L. J., Ransom, D. C.: "Relieving stress with *drugs*." *Science* **170**: 928-930 (1970). J21,422/70

Harrer, G., Harrer, H.: "Untersuchungen zur Objektivierung von Tranquillizer-Effekten" (Objective studies of the effects of *tranquilizing agents*). *Arzneim. Forsch.* **20**: 921-923 (1970). J20,323/70

Świątecka, G.: "The influence of ipronal on chronic neurotropic stress in white rats." *Arch. Immunol. Ther. Exp. (Warszawa)* **19**: 911-914 (1971). J20,325/71

In rats, various *tranquillizers* and *barbiturates*, particularly *ipronal*, suppress the typical consequences of psychogenic stress.

Corrodi, H., Fuxé, K., Lidbrink, P., Olson, L.: "Minor tranquilizers, stress and central

catecholamine neurons." *Brain Res.* **29**: 1-16 (1971). G85,849/71

Chlordiazepoxide, diazepam and *nitrazepam* blocked the stress-induced stimulation of NEP neurons by decreasing their nervous activity. Chlordiazepoxide and diazepam potentiated the stress (restraint)-induced fall in nervous activity in ascending dopaminergic neurons. Stress combined with these drugs therefore decreased dopamine turnover in the telencephalon in comparison with normal rats (67 refs.).

Krulik, R., Černý, M.: "Effect of chlordiazepoxide on stress in rats." *Life Sci. [I]* **10**: 145-151 (1971). G84,266/71

In rats, electroshock caused an important increase in blood corticosterone. "*Chlordiazepoxide* or *diazepam* injected to the animals before the stress decreased significantly the level of corticosterone in blood of stressed animals."

Neshev, G.: "The effect of chlorpromazine and phenamine on the basal metabolism and conditioned reflex activity of rats under stress conditions." *Farmakol. Toksikol.* **34**: 674-676 (1971) (Russian). J22,360/71

Experiments on rats showed that "stress factors lessen the depressive influence of *chlorpromazine* on the basal metabolism and potentiate the effect of *phenamine*. Stress weakens the action of chlorpromazine on the inhibitory processes in the brain cortex, intensifying the processes of excitation and summing up the effects of *phenamine* and stress factors on the higher nervous activity."

Lehmann, H. E., Ban, T. A.: "Pharmacotherapy of tension and anxiety." *Curr. Psychiatr. Ther.* **12**: 70-80 (1972) (55 refs.). J16,983/72

Ehrenstein, W., Schaffler, K., Müller-Limmroth, W.: "Die Wirkung von Oxazepam auf den gestörten Tagschlaf nach Nachschichtarbeit" (The effect of oxazepam on day sleep disturbed due to night work). *Arzneim. Forsch.* **22**: 421-427 (1972). J15,868/72

In nurses doing night shift work, *oxazepam* aided adjustment to sleeping during the day. "In oxazepam day sleep, the sleep of stage 3 and 4 and the REM sleep were increased to the values registered in night sleep. In oxazepam day sleep the share of waking periods remained clearly below the reference values of normal day and night sleep. Stage 1 and 2 of orthodox sleep were increased in oxazepam

day sleep as compared to normal day sleep but did not reach the values of night sleep."

Ajika, K., Kalra, S. P., Fawcett, C. P., Krulich, L., McCann, S. M.: "The effect of stress and Nembutal on plasma levels of gonadotropins and prolactin in ovariectomized rats." *Endocrinology* **90**: 707-715 (1972). H52,545/72

"The stress of etherization and bleeding produced an elevation within 2 min in the plasma levels of prolactin, LH, and FSH in ovariectomized rats. . . . Nembutal blocked the stress-induced elevations of plasma prolactin and LH but did not affect the levels of FSH. The effect of Nembutal is thought to be on the CNS since the Nembutalized rats responded to hypothalamic extract or ovine LRF with dramatic elevations in plasma LH."

Turton, M. B., Deegan, T., Geddes, I. C.: "The effects of intraperitoneal injection of lignocaine on plasma catecholamine levels in unstressed and stressed rats." *Br. J. Anaesth.* **44**: 460-464 (1972). G91,803/72

Krulík, R., Černý, M.: "Influence of chlordiazepoxide on blood corticosterone under repeated stress." *Activ. Nerv. Sup.* (Praha) **14**: 31-34 (1972). J20,548/72

In rats, chlordiazepoxide can inhibit the rise in blood corticosterone normally elicited by electric shocks.

Smith, R. B., Balchius, D., Mueller, M.: "Comparative use of alcohol and chlorpromazine by experimentally stressed CF/1 mice." *Med. Ann. D.C.* **41**: 619-621 (1972).

J20,511/72

Reyntjens, A. M., Mierlo, F. P. van: "A comparative double-blind trial of pimozide in stress-induced psychic and functional disorders." *Curr. Med. Res. Opin.* **1**: 116-122 (1972). J1,649/72

In patients under severe psychic stress, pimozide was significantly superior to diazepam as a tranquilizer.

Schlecht, H., Pfund, L.: "Über die praktische Anwendung von Stresnil beim Schwein während der Mast und bei Transporten" (Practical use of Stresnil in swine during fattening and transportation). *Wien. Tierärztl. Monatsschr.* **59**: 76-80 (1972).

J21,576/72

Stresnil, a sedative drug, protects pigs against the stressor effect of transportation over long distances.

James, B., James, N. M.: "Tranquilizers and examination stress." *J. Am. Coll. Health Assoc.* **21**: 241-243 (1973). J19,898/73

Konzett, H., Berner, W., Lochs, H.: "Emotionally induced cardiovascular changes in man as a means for the investigation of tranquillizing drugs." *Psychopharmacologia* **30**: 75-82 (1973). J19,725/73

Herrera-Ramos, F.: "Anxiety and anguish in somatic illness: clinical experience with lorazepam." *Curr. Med. Res. Opin.* **1**: 528-534 (1973). J22,003/73

Strasser, H., Müller-Limmroth, W.: "Komplexe Auswirkungen der Faktoren Lärm, Tranquillizer, erschwerte Arbeitsbedingung und Versuchszeit auf eine Pursuit Tracking-Leistung und das kontinuierliche Puls-zu-Puls-Verhalten" (Complex effects of different factors [noise, tranquilizers, difficult working conditions, test time] on pursuit tracking performance and beat-to-beat heart rate behavior). *Int. Arch. Arbeitsmed.* **31**: 81-103 (1973) (about 50 refs.). J17,472/73

Reier, C. E., George, J. M., Kilman, J. W.: "Cortisol and growth hormone response to surgical stress during morphine anesthesia." *Anesth. Analg. (Cleve.)* **52**: 1003-1010 (1973). J8,185/73

After surgery, the usual increase in plasma cortisol and STH was blocked by large doses of morphine used in connection with anesthesia. Adrenocortical responsiveness was not affected, as indicated by the continued efficacy of exogenous ACTH in raising plasma cortisol. The blockade of these hormone secretions during stress did not seem to influence the clinical condition. "Nonetheless, since it is thought that the adrenocortical response is essential for stress survival, the recommendation that morphine in doses larger than 2 mg./kg. be avoided, appears prudent."

Davies, J. A., Navaratnam, V., Redfern, P. H.: "The effect of phase-shift on the passive avoidance response in rats and the modifying action of chlordiazepoxide." *Br. J. Pharmacol.* **51**: 447-451 (1974).

H92,485/74

"In rats trained to a 12 h light-12 h dark cycle, advancing the phase by 6 h produced a resynchronization of the 24 h variation in passive avoidance response (PAR) which was completed after 10 days." Chlordiazepoxide lessened the disruptive effect of phase-shift. The clinical implications of this work are discussed.

Boucsein, W., Janke, W.: "Experimental-psychologische Untersuchungen zur Wirkung von Propiramfumarat und Promethazin unter Normal- und Stress-bedingungen" (Experimental-psychologic studies on the action of propiram fumarate and promethazine under normal and stress conditions). *Arzneim. Forsch.* **24**: 675-693 (1974). H86,778/74

A new tranquilizer, *propiram fumarate*, as well as *promethazine*, proved beneficial in decreasing various manifestations of sound-induced psychogenic stress in man.

Hodges, J. R., Vellucci, S.: "The effect of reserpine on pituitary-adrenocortical function in the rat." *Br. J. Pharmacol.* **50**: 466P (1974). H86,673/74

In rats, a single intraperitoneal injection of *reserpine* caused adrenal ascorbic acid depletion and plasma corticosterone increases. After a week of daily injections, these changes no longer developed, "indicating that the alkaloid no longer acted as a stressful stimulus, i.e. some form of 'adaptation' occurred." Yet at this time exposure to "cold stress" still caused an increase in plasma corticosterone, although without concomitant ascorbic acid depletion. The authors conclude that reserpine inhibits the hypothalamus-pituitary-adrenocortical system only under very special conditions.

Cosgrove, D. O., Jenkins, J. S.: "The effects of epidural anesthesia on the pituitary-adrenal response to surgery." *Clin. Sci. Molec. Med.* **46**: 403-407 (1974).

J10,530/74

In women undergoing pelvic operations under *epidural anesthesia*, cortisol secretion was very low compared to its level in others operated on under general anesthesia. Despite this deficient cortisol discharge, surgery was not impeded. The observations may be interpreted as indicating that "these pathways travel solely through the spinal cord" and hence are blocked by epidural anesthesia.

Rayfield, E. J., George, D. T., Beisel, W. R.: "Altered growth hormone homeostasis during acute bacterial sepsis in the rhesus monkey." *J. Clin. Endocrinol. Metab.* **38**: 746-754 (1974). H86,214/74

Studies on monkeys demonstrate an exaggerated STH response following an intravenous glucose load during the stress of acute infection, and suggest that the reaction may be suppressed with *chlorpromazine*.

Villeneuve, C.: "Effets du Chlordiazepoxide et du Diazepam sur les changements

morphologiques et biochimiques induits par le stress" (Effects of chlordiazepoxide and diazepam on the morphologic and biochemical changes induced by stress). *Ann. ACFAS* **41**: 165 (1974). H88,191/74

Chlordiazepoxide and *diazepam* suppress only some of the manifestations of stress caused by sound in the rat. Their effect is not conspicuous.

Schumpelick, V., Paschen, U.: "Vergleich der protektiven Wirkung von Diazepam und Vagotomie auf das Stressulkus der Ratte" (Comparison of the protective activity of diazepam and vagotomy on stress ulcers in rats). *Arzneim. Forsch.* **24**: 176-179 (1974). H82,750/74

In rats, stress ulcers produced by restraint can be inhibited by *diazepam* pretreatment or vagotomy, but combined application of both agents offers the best protection. "This fact demonstrates a different mode of action. The antiulcerative effect of diazepam is explained by its direct action on the vegetative regulation centres in the hypothalamic and limbic system, leading to a partial inhibition of the vagally controlled HCl-pepsin component and the splanchnic nerve dependent vascular factor of ulcerogenesis as well."

Lahti, R. A., Barsuhn, C.: "The effect of minor tranquilizers on stress-induced increases in rat plasma corticosteroids." *Psychopharmacologia* **35**: 215-220 (1974).

J11,100/74

In rats the increase in plasma corticoids produced by the stressor effect of a noisy environment could be inhibited by *meprobamate*, *phenobarbital*, *diazepam* and several other benzodiazepines with anxiolytic properties. "U-33,030 and U-31,889, two triazolo-benzodiazepine derivatives, were the most potent compounds tested. No other type of psychoactive compound demonstrated this activity."

Boucsein, W.: "Die Wirkung von Chlordiazepoxyd unter Angstbedingungen im psychophysiologischen Experiment" (The effect of chlordiazepoxide on anxiety. A psychophysiological experiment). *Arzneim. Forsch.* **24**: 1112-1114 (1974). H91,785/74

In anxious patients the expectation of an electric shock produces a typical stress response, as indicated by heart rate, GSR and breathing. Pretreatment with *chlordiazepoxide* largely combats this response.

Niemegeers, C. J. E., Nueten, J. M. van, Janssen, P. A. J.: "Azaperone, a sedative

neuroleptic of the butyrophenone series with pronounced anti-aggressive and anti-shock activity in animals." *Arzneim. Forsch.* **24**: 1798-1806 (1974). H97,389/74

Hiebert, L. M., Jaques, L. B.: "Blocking of stress by pentobarbital-morphine as related to training and age of rats." *Steroids Lipids Res.* **5**: 255-261 (1974). K1,176/74

In experiments with several stressors, "pentobarbital-morphine" blocked the adrenal ascorbic acid depletion by stress when young trained rats were used. No block in adrenal ascorbic acid depletion occurred in untrained rats or in older trained rats."

Weiger, E.: "Medikamentöse Anxiolyse im Rahmen der Operationsvorbereitung" (Treatment of preoperative anxiety with tranquilizers). *Med. Welt.* **25**: 1774-1782 (1974). H96,097/74

Roudier, R.: "Etude des modifications neuro-sécrétaires hypothalamo-hypophysaires en fonction de différents stress. Essai de correction par le méclofénoxate" (The influence of various stressors on hypothalamo-hypophyseal neurosecretory modifications. Attempt at correction by meclofenoxate). *Ann. Anesth. Fr.* **15**: 517-522 (1974).

J19,327/74

In rats, various stressors cause an immediate disappearance of Gomori granulations from the hypothalamus, with hemorrhagic lesions in the adrenals. *Meclofenoxate* (an analeptic drug) inhibits these changes and acts as an "antistress substance."

Neshev, G.: "The effect of aminazinum and phenaminum on stress in experimental conditions." *Patol. Fiziol. Éksp. Ter.* **14** No. 5: 42-46 (1974) (Russian). J24,151/74

In rats, *chlorpromazine* and *phenocoll* (phenamine) counteract the stress produced by burns, as judged by its classic morphologic and hormonal indicators.

Hodges, J. R., Vellucci, S.: "Pituitary-adrenocortical function in the reserpine-treated rat." *J. Endocrinol.* **61**: xxvi (1974). H87,552/74

In rats, *reserpine* causes a pronounced initial increase in plasma corticosterone with a diminution of adrenal ascorbic acid; upon continued daily injections, this response gradually fades, and even ACTH secretion after "cold stress" is inhibited.

Webb, S. D., Collette, J.: "Urban ecological

and household correlates of *stress-alleviative drug use*." *Am. Behav. Sci.* (In press).

J23,442/75

Hodges, J. R., Vellucci, S. V.: "The effect of *reserpine* on hypothalamo-pituitary-adrenocortical function in the rat." *Br. J. Pharmacol.* **53**: 555-561 (1975).

K1,166/75

In rats, "inhibition of stress-induced ACTH release was due neither to depletion of pituitary stores of the hormone, nor to a corticosteroid feedback effect."

Autonomic Blocking Agents

(See also our earlier stress monographs, p. xiii)

Peterfy, G., Pinter, E. J., Cleghorn, J. M., Pattee, C. J.: "Observations on the adrenergic mechanism of hyperadipokinesis of emotional stress." *Proc. Can. Fed. Biol. Soc.* **9**: 64 (1966). F66,182/66

In men and women, the emotional stress of threatening suggestions leads to hyperadipokinesis. "The primary factor appears to be the adrenergic nervous system." This response, associated with marked increases in plasma FFA and catecholamine levels, is prevented by a β -adrenergic-blocking agent (propranolol).

Smookler, H. H., Buckley, J. P.: "Effect of drugs on animals exposed to chronic environmental stress." *Fed. Proc.* **29**: 1980-1984 (1970). H32,862/70

In rats exposed to various stressors (sound, flashing lights, vibration), α -MT prevented the increase in blood pressure without raising mortality. Presumably, this result occurs because α -MT reduces the catecholamine level by inhibiting their synthesis, but leaves the catecholamine-binding system intact. "The combination of a reduced amount of liberated transmitter plus rapid inactivation by an intact binding system may serve to dampen the stress-induced activation of central sympathetic centers" (29 refs.).

Cleghorn, J. M., Peterfy, G., Pinter, E. J., Pattee, C. J.: "Verbal anxiety and the beta adrenergic receptors: a facilitating mechanism?" *J. Nerv. Ment. Dis.* **151**: 266-272 (1970). J20,728/70

Studies on man "indicate that beta adrenergic blockade with propranolol has no inhibiting effect on psychological anxiety in

healthy subjects when an operational measure of anxiety is used, and where bodily symptoms are absent."

Taggart, P., Carruthers, M.: "Suppression by oxprenolol of adrenergic response to stress." *Lancet* August 5, 1972, pp. 256-258.

H57,669/72

In racing-car drivers, oxprenolol given one hour before the race suppresses tachycardia, plasma FFA and total plasma catecholamine concentrations, as compared with values obtained for the same drivers on previous occasions. This β -blockade appears to diminish emotional stress without interfering with performance.

Lidén, S., Gottfries, C. G.: "Beta-blocking agents in the treatment of catecholamine-induced symptoms in musicians." *Lancet* August 31, 1974, p. 529.

H84,664/74

"Beta-blocking agents have been found to be of value in certain stress situations. In such situations the catecholamine output can be raised to a level which causes tremor. These effects may be unpleasant enough (e.g., when speaking before an audience), but they can be truly incapacitating for musicians." Alprenolol, a β -blocking agent, relieves the palpitation, increased muscular tonus, tremor and many other manifestations of the "catecholamine syndrome" in musicians playing various instruments.

Gupta, M. B., Tangri, K. K., Bhargava, K. P.: "Mechanism of ulcerogenic activity of reserpine in albino rats." *Eur. J. Pharmacol.* 27: 269-271 (1974).

H89,397/74

In rats, reserpine-induced gastric ulcers were prevented by α -adrenergic blockers, 6-hydroxydopamine and atropine, but not by adrenalectomy. Presumably, both adrenergic and cholinergic mechanisms are involved in reserpine-induced stress ulcers.

Backström, E., Nyberg, G.: "Effets de l'inhibition des récepteurs β sur les symptômes qui précèdent les examens universitaires" (Effects of β -receptor inhibition on the symptoms preceding university examinations). *Coeur Méd. Interne* 13: 149-154 (1974).

J21,826/74

"The β -inhibiting agents provide an advantage over the central acting sedatives, the tranquilizers: they do not affect cerebral efficiency."

Harvey, W. D., Falloona, G. R., Unger, R. H.: "The effect of adrenergic blockade on

exercise-induced hyperglucagonemia." *Endocrinology* 94: 1254-1258 (1974).

H85,696/74

In rats, forced swimming increases the plasma glucagon level. This response can be prevented by pretreatment with the α -adrenergic blocker, phentolamine, but not by propranolol. Presumably, exercise-induced hyperglucagonemia is largely mediated via α -adrenergic stimulation.

Ginseng, Eleutherococcus

(See also our earlier stress monographs, p. xiii)

Petkov, W., Staneva, D.: "Der Einfluss eines Ginseng-Extraktes auf die Funktionen der Nebennierenrinde" (The influence of ginseng extract on adrenal cortex functions). *Arzneim. Forsch.* 13: 1078-1081 (1963).

E38,058/63

"Substantial stress caused a mild drop in eosinophils in Ginseng-treated rats, while it produced a statistically significant rise in control animals." Curiously, large doses of ginseng elicited adrenal hypertrophy and eosinopenia in control rats.

Tsung, J. Y., Chen, C., Tang, S.: "The sedative, fatigue-relieving and temperature stress-combating effects of Panax ginseng." *Acta Physiol. Sinica* 27: 324-328 (1964) (Chinese).

J25,533/64

Iaremenko, K. V., Moskalik, K. G.: "The combined action of some stress effects and eleutherococcus extract on inoculation of tumor cells injected intravenously." *Vopr. Onkol.* 13 No. 9: 65-69 (1967) (Russian).

H4,112/67

In mice inoculated with Ehrlich tumor cells intravenously, intermittent cooling or injection of ACTH enhanced the take of neoplastic cells, but this effect could be eliminated by administering the eleutherococcus extract.

Brekhan, I. I.: "Panax ginseng. I." *Med. Sci. Serv.* 4 No. 3: 1-11 (1967).

J18,635/67

Brief English summary of the author's work (originally published in Russian, Chinese and Japanese) on the biochemistry and pharmacology of ginseng and related glycosides. The ginseng root itself, taken orally, allegedly increases work capacity in man and various species of animals. It may

also inhibit inflammation and cause premature sexual maturity in female mice. In rats, ginseng counteracts the thymicolympathic atrophy as well as the adrenal hypertrophy and hyperactivity elicited by the stress of restraint (11 refs.).

Golotin, V. G., Berdyshev, G. D., Brekhman, I. I.: "The effect of ginseng and eleutherococcus on the lifespan of white rats." *USSR Conf. on the Medicament Treatment in Advanced and Old Age*, USSR Acad. Med. Sci., USSR and Ukraine, p. 94 (1968).

J18,636/68

Brief abstract of an orally presented paper on the beneficial effect of ginseng and eleutherococcus upon the lifespan of rats alternatingly exposed to the stress of electric current and swimming. [The short résumé is difficult to evaluate (H. S.).]

Brekhman, I. I., Dardymov, I. V.: "New substances of plant origin which increase nonspecific resistance." *Annu. Rev. Pharmacol.* **9**: 419-430 (1969). J18,983/69

Review on the rise in nonspecific resistance obtainable by ginseng and related plant products. Special emphasis is placed upon their "antistress effect."

Brekhman, I. I., Kirillov, O. I.: "Effect of eleutherococcus on alarm-phase of stress." *Life Sci.* **8**: 113-121 (1969). G65,251/69

Observations in rats led the authors to the conclusion that "like Panax ginseng, eleutherococcus increases the resistance of an organism to stressors of various nature. This phenomenon finds some explanation in experiments which certify that eleutherococcus changes the course of the alarm-reaction, reducing activation of the adrenal cortex, thymus involution and stomach bleeding."

Kim, C., Kim, C. C., Kim, M. S., Hu, C. Y., Rhe, J. S.: "Influence of ginseng on the stress mechanism." *Lloydia* **33**: 43-48 (1970). J20,883/70

Experiments on rats suggested that the initial adrenal ascorbic acid depletion caused by heat or cold could be slightly diminished by feeding Korean ginseng root, and a similar inhibition occurred as regards the adrenal effects of ACTH, even after hypophysectomy. Hence apparently "ginseng acts upon the peripheral site of the stress mechanism in response to stress."

Brekhman, I. I., Berdyshev, G. D., Golotin, V. G.: "Effect of eleutherococcus and ginseng extracts on the activity and adaptive

synthesis of tryptophan pyrolase in rats." *Izv. Akad. Nauk SSSR [Biol.] No. 1: 31-37 (1971)* (Russian). J21,371/71

Eleutherococcus increases the activity and enhances the induction of tryptophan pyrolase in both intact and adrenalectomized rats, whereas ginseng decreases its induction only in the presence of the adrenals.

Ethanol

(See also our earlier stress monographs, p. xiii)

Greenberg, L. A., Lester, D.: "The effect of alcohol on audiogenic seizures of rats." *Q. J. Stud. Alcohol* **14**: 385-389 (1953). J23,511/53

In rats, audiogenic seizures were largely inhibited by moderate ethanol intake.

Korn, S. J.: "The relationship between individual differences in the responsiveness of rats to stress and intake of alcohol." *Q. J. Stud. Alcohol* **21**: 605-617 (1960).

D432/60

Rats "more responsive to stress may select alcohol solutions as a learned adaptive response. The alcohol may function to attenuate the effects of stress."

Coopersmith, S.: "Adaptive reactions of alcoholics and nonalcoholics." *Q. J. Stud. Alcohol* **25**: 262-278 (1964). J23,223/64

Study of the ability of alcoholics and nonalcoholics to tolerate threatening stimuli. "A review of literature led to the hypotheses that alcoholics were limited in such capacities and that alcohol both provided a relief from distress and increased adaptive capacities."

Geber, W. F., Anderson, T. A., Dyne, B. van: "Influence of ethanol on the response of the albino rat to audiovisual and swim stress." *Exp. Med. Surg.* **24**: 25-35 (1966). F67,524/66

In rats, ethanol blocked the stressor effect of forced swimming and audiovisual stimulation as judged by adrenal and brain ascorbic acid levels, serum cholesterol and other indicators (39 refs.).

Geber, W. F., Anderson, T. A.: "Ethanol inhibition of audiogenic stress induced cardiac hypertrophy." *Experientia* **23**: 734-736 (1967). F88,482/67

Morra, M.: "Ethanol and maternal stress on rat offspring behaviors." *J. Genet. Psychol.* **114**: 77-83 (1969). J22,650/69

A review of the literature concerning the effect of stress during pregnancy upon the offspring of rats. Administration of ethanol to the mother significantly diminished the influence of stress upon her young.

Wright, J. M. von, Pekannmäki, L., Malin, S.: "Effects of conflict and stress on alcohol intake in rats." *Q. J. Stud. Alcohol* **32**: 420-433 (1971). G84,239/71

In rats repeatedly exposed to the stressor effect of electroshocks, voluntary alcohol consumption may increase, although drinking water is also available *ad libitum*.

Smith, R. B., Balchius, D., Mueller, M.: "Comparative use of alcohol and chlorpromazine by experimentally stressed CF/1 mice." *Med. Ann. D.C.* **41**: 619-621 (1972).

J20,511/72

Other Drugs

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937).

38,798/37

First description of the anaphylactoid inflammation produced in the rat by parenteral administration of egg white. This response was aggravated by adrenalectomy and hence, presumably, some adrenal factor had anti-phlogistic effects. The experiment also showed that "in this case an alarm reaction, elicited by another drug [*formaldehyde*], exerted a protective influence" against egg white. Thus, we are dealing with a type of cross-resistance.

Tepperman, J., Rakieten, N., Birnie, J. H., Diermeier, H. F.: "Effect of antihistamine drugs on the adrenal cortical response to histamine and to stress." *J. Pharmacol. Exp. Ther.* **101**: 144-152 (1951). B59,242/51

In rats, various *antihistaminics* (Phenoxyadrine, Benadryl, Pyribenzamine) did not significantly alter the adrenal ascorbic acid concentration, but intraperitoneal injection of histamine reduced it remarkably. "Pre-treatment with an antihistamine drug did not prevent or modify the adrenal ascorbic acid response to the stress of intraperitoneal carbon tetrachloride administration."

Dufour, D., Rochette, A.: "Etude de l'influence des acides nucléiques du thymus sur la réponse non-spécifique à l'agression" (Study of the influence of thymic nucleic

acids on the nonspecific response to stress). *Ann. Endocrinol. (Paris)* **22**: 9-13 (1961). D3,652/61

Kraus, S. D.: "Beta-glycyrrhetic acid on the adrenal ascorbic acid of unstressed and stressed immature female rats." *Nature* **193**: 1082 (1962). D21,167/62

Dandiya, P. C., Menon, M. K.: "Actions of asarone on behavior, stress, and hyperpyrexia, and its interaction with central stimulants." *J. Pharmacol. Exp. Ther.* **145**: 42-46 (1964). F15,976/64

In rats, the stressor effect of cold (as indicated by adrenal ascorbic acid depletion) is inhibited by *asarone*, the active principle of the volatile oil of an Indian indigenous plant, *Acorus calamus Linn.*

Vaškú, J., Urbánek, E., Doležel, S.: "Über den abweichenden Verlauf der Alarmreaktion im lymphoepithelialen und lymphoretikulären Gewebe unter dem Einfluss von K-Mg-Aspartat" (Irregular evolution of the alarm reaction in lymphoepithelial and lymphoreticular tissues under the influence of K-Mg-aspartate). *Arzneim. Forsch.* **16**: 559-565 (1966). F65,898/66

In rats, the development of the alarm reaction can be modified by *K-Mg-aspartate*.

Debrezeni, L., Csonka-Takács, L., Csete, B.: "The effect of *dehydrobenzperidol* and *fentanyl* on corticosteroid secretion and the stress-induced ACTH-release in the rat." *Acta Physiol. Acad. Sci. Hung.* **36**: 425-430 (1969). G76,188/69

Reznikov, A. G., Kravtsova, E. L.: "Effect of o,p'-DDD on the secretion of 11- and 17-hydroxy-corticosteroids in dogs during stress." *Patol. Fiziol. Éksp. Ter.* **14** Nos. 7-8: 38-40 (1970) (Russian). J21,368/70

In dogs, o,p'-DDD diminished the 17-OHCS and 11-OHCS content of adrenal venous blood. They also showed decreased corticoid production when exposed to stress. o,p'-DDD disturbed the synthesis of cortisol and cortisone to the same extent.

Schultis, K.: "Xylitol als Glucoseaustauschstoff bei der gestörten Glucoseassimilation im Postaggressions-Syndrom.—Eine Übersicht über tierexperimentelle und klinische Studien" (Xylitol used as a glucose substitute in disordered glucose assimilation of the post-aggression syndrome. Review of animal experiments and clinical studies). *Z. Ernährungswiss.* **11** Supp.: 87-97 (1971). J20,730/71

Fox, C. L. Jr., Stanford, J. W.: "Comparative efficacy of hypo-, iso-, and hypertonic sodium solutions in experimental burn shock." *Surgery* **75**: 71-79 (1974).

J9,143/74

Comparative studies on the effect of hypotonic, isotonic and hypertonic *sodium chloride* solutions upon experimental burn shock in mice (43 refs.).

Brachfeld, N.: "Ischemic myocardial metabolism and cell necrosis." *Bull. N.Y. Acad. Med.* **50**: 261-293 (1974).

J10,994/74

Review of metabolic factors involved in stress-induced myocardial necrosis, with a section on the prophylactic and/or therapeutic role of *potassium*.

Smoking

(See also our earlier stress monographs, p. xiii)

Russek, H. I., Zohman, B. L.: "Relative significance of heredity, diet and occupational stress in coronary heart disease of young adults. Based on an analysis of 100 patients between the ages of 25 and 40 years and a similar group of 100 normal control subjects." *Am. J. Med. Sci.* **235**: 266-277 (1958).

A352/58

Hereditary predisposition and high-fat diets are undoubtedly important conditioning factors in CHD. However, among one hundred young coronary patients, "severe emotional strain of occupational origin was observed in 91% of the test subjects as compared with 20% of normal controls. Emotional stress associated with job responsibility appears far more significant in the etiologic picture of coronary disease in young adults than heredity or a prodigiously high-fat diet." Smoking would seem "to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease."

Russek, H. I.: "Stress, tobacco, and coronary disease in North American professional groups. Survey of 12,000 men in 14 occupational groups." *J.A.M.A.* **192**: 189-194 (1965).

F36,826/65

Statistical studies on twelve thousand professional men in fourteen occupational categories in the United States. On the basis of questionnaires evaluated by specialists in each field, CHD was "strikingly related to

the relative stressfulness of occupational activity" among physicians, lawyers, security analysts and traders. High-fat diets and smoking were associated with a high incidence in combination with emotional stress. Smoking was most frequent in stressful occupations, but unexpectedly, CHD was more common among nonsmokers than among persons who once smoked but gave it up. Possibly, "the ability to stop smoking may imply a resilient personality response to stress and diminished vulnerability to atherogenic influences."

Pincherle, G., Williamson, J.: "Smoking and neuroticism." *Lancet* October 30, 1971, p. 981.

J20,174/71

Statistical study showing that smoking was more frequent in patients under excessive stress than in nonstressed controls. "There was no difference between those stressed from work and those stressed from their home circumstances. One of the main reasons given by patients for smoking is the tranquillising effect, so it is not surprising to find a relationship with stress."

King, A. J.: "Stress, cigarette smoking and snacking behaviour in adolescent males." *Can. J. Public Health* **62**: 297-302 (1971).

G86,388/71

Among male adolescents, stress (caused by examinations) produced more significant changes in snacking than in smoking. "Stressed non-smokers snacked significantly more than unstressed non-smokers. Unstressed smokers snacked significantly more than unstressed non-smokers."

Ashton, H., Savage, R. D., Telford, R., Thompson, J. W., Watson, D. W.: "The effects of cigarette smoking on the response to stress in a driving simulator." *Br. J. Pharmacol.* **45**: 546-556 (1972).

J14,838/72

Lindenthal, J. J., Myers, J. K., Pepper, M. P.: "Smoking, psychological status and stress." *Soc. Sci. Med.* **6**: 583-591 (1972).

G95,675/72

Report on a statistical survey concerning the relationship between life crises and smoking behavior.

Luban-Plozza, B.: "Das Problem der Tabakentwöhnung" (The problem of nicotine withdrawal). *Öst. Arzteztg.* **28**: 1093-1111 (1973).

J13,887/73

Review on breaking the smoking habit. The author distinguishes between "pleasure

smokers" and "stress smokers." The latter smoke to relieve anxiety or other psychogenic stresses. For them, it is very difficult to stop smoking because they develop depressions and impairment of performance if they do not smoke, so that those around them usually try to talk them into resuming the habit. Various practical suggestions are made (numerous refs.).

Hall, G. H., Morrison, C. F.: "New evidence for a relationship between tobacco smoking, nicotine dependence and stress." *Nature* **243**: 199-201 (1973).

H78,377/73

Rats that have learned to avoid electric shock under the influence of nicotine can become dependent upon this drug for successful performance. Presumably, "this dependence is related to the degree of stress to which the animal is exposed."

Schechter, M. D.: "Effect of nicotine on response to frustrative non-reward in the rat." *Eur. J. Pharmacol.* **29**: 312-315 (1974).

H96,851/74

"Rats were subjected to frustrative non-reward in the Amsel double runway after administration of nicotine and saline. Results revealed that nicotine decreases the magnitude of the frustrative effect when compared to saline."

Agué, C.: "Urinary catecholamines, flow

rate and tobacco smoking." *Biol. Psychol.* **7**: 229-236 (1974).
J12,382/74

Cigarette smoking significantly raised EP but not NEP excretion. The increased EP excretion was interpreted as "an adaptive mechanism to unspecific stress." However, in this respect, ordinary and nicotine-free cigarettes were equivalent, and the results may have been of psychogenic origin.

Luban-Plozza, B.: "Psychologische Motive des Rauchens" (Psychologic motives for smoking). *Münch. Med. Wochenschr.* **116**: 547-552 (1974).
H85,110/74

An analysis of motivation for smoking permits the distinction of four types, one of which is the "stress smoker," who turns to cigarettes mainly for their tranquilizing value and who allegedly tolerates pain much better if permitted to smoke. It appears paradoxical that although nicotine increases pulse rate and blood pressure, it has nevertheless been found to have a favorable effect upon stress tolerance, at least under certain circumstances. It remains to be shown to what extent this is due to pharmacologic actions or to social and psychic influences; for example, being offered a cigarette by an examining professor relaxes the candidate largely because of the friendliness of such a gesture. A "smoker personality" is often characterized by a tendency towards depression and intense variations in mood.

VI. THEORIES

GENERAL MECHANISMS

In this section, foremost emphasis will be laid upon the neurohumoral responses most characteristic of stress, especially the control of the discharge and action of corticoids and catecholamines. Additional data on the participation of many other hormones (STH, TTH, LH, FSH, thyroid hormone, insulin, glucagon), hormone-like substances (5-HT, histamine) and other chemical and morphologic parameters of the stress response will be found in the section Characteristic Manifestations of Stress; here, they will be discussed only in proportion to the little information we have about the functional role they play in the G.A.S.

To assist in an overview of this chapter, let us state at the outset that the material will be subdivided into the following sections:

Nervous mechanisms

Hormonal mechanisms

Various mechanisms

Some of the data pertaining to this last category have already been discussed in the introductory Outline—for example, the distinctions between syntoxic and cataxic hormones and between homeostasis and heterostasis. Here, we will present a general résumé of the neurohumoral coordinating mechanisms, that is, the pathways through which a stressor applied at any one target area spreads throughout the body. Finally, we will touch upon the very important behavioral implications of somatic research on stress.

NERVOUS MECHANISMS

Generalities

It would be almost impossible to present a well-balanced synoptic summary of the participation of nervous mechanisms in stress reactions since, depending upon the nature of the stressor and of the conditioning factors, virtually any pathway of the central and peripheral nervous system may be involved. Yet this system plays such a cardinal role in the mediation of stress responses, especially in man and other higher animals, that it does deserve detailed consideration.

After giving this matter much thought and discussing it with many competent specialists in the field of neurophysiology, I seriously considered two possibilities: (1) to describe the pathways on an anatomic basis, following the course of impulses

that lead to the mobilization of the stress mechanism or (2) to use a biochemical basis for classification and consider pathways separately, according to the neurohumoral mediators responsible for their activation, irrespective of the anatomic regions through which they travel (for example, mediation through NEP, dopamine, 5-HT, acetylcholine and other less-researched possible mediators, such as histamine or GABA).

However, the enormous number of pertinent observations in the literature and their apparently contradictory nature convinced me that I could not present a balanced picture using either of these classifications. It was decided instead to construct a practical index, putting major emphasis upon a correct, objective description of individual key publications. Thus, I will cite data on each morphologic nervous structure merely in alphabetic order in the present section and I will discuss the neurohumoral mechanisms conjointly with the purely hormonal ones in the next division, which is devoted to Hormonal Mechanisms. I will deviate from this principle only in the case of: (1) the corticotropin-releasing factor (CRF) because its discharge and mediation through nerves and vascular pathways are primarily morphologic problems and (2) the cerebrospinal fluid (CSF) whose participation in stress as a morphologic unit has attracted much more attention than has its chemical composition.

Thus, this section does not represent so much an analysis and criticism of the literature as a simple key, designed merely to give ready access to the principal facts known about the participation of various nervous structures in the stress response. It is based mainly on the observations and interpretations of those who selectively explored one or the other of these structures, either by producing localized lesions, by stimulating circumscribed parts of the nervous system or by examining microscopic changes in them during stress.

Since I have tried to make this encyclopedia accessible to scientists interested in any aspect of stress, it is evident that many of my readers (physiologists, clinicians, biochemists, or even psychologists and psychiatrists) will not be sufficiently familiar with the more complex aspects of modern neuroanatomy to make good use of this section. Therefore, by way of an introduction, I present a concise dictionary of the more common technical terms and a few especially illustrative anatomic drawings and explanatory charts for general orientation. Most of these were taken from the excellent text, *A Neurophysiological Model of Emotional and Intentional Behavior* by John L. Weil of Harvard Medical School, with the kind permission of the author and Charles C Thomas, Publisher.

They will help give an overview of the location of various subsequently-mentioned structures, as well as provide a key to the nomenclature, which is often confusing because in many cases several synonymous designations are used.

In addition, I felt that at least a brief outline of the established basic facts concerning CRF and the total deafferentation of the hypophysiotropic area should be stated at the outset. After all, whatever other pathways are followed during the early mediation of stress responses, eventually they mobilize the pituitary-adrenocortical system through CRF, which is produced in an area of the hypothalamus that can now be isolated by surgical deafferentation. I did not see any way of discussing all other aspects in a similar manner. However, it was hoped that even the most superficial outline of these two basic areas of information, combined with the introductory illustrations explaining the structure and nomenclature of the regions to be discussed, would be of considerable help to the nonspecialist in this field. For more precise in-

formation, readers will have to turn to the corresponding abstract sections and in many cases even obtain the original publications in order to clarify apparent contradictions due to differences in methodology or actual errors in observation or interpretation.

Finally, those who wish to cover a particular field as completely as possible can refer to the sections Generalities, Hypothalamus, Limbic System, which contain data pertinent to virtually any other specifically-mentioned structure as they present an overview of the principal pathways of impulses through which the stressor's stimulus is transmitted from the nervous to the hormonal system.

Dictionary

Of course, every term and synonym mentioned in the publications subsequently cited cannot be enumerated here. Hence, this dictionary will be limited to the clarification of frequently-used synonyms or variably-formulated anatomic descriptions that may be confusing. Other nervous structures that have been discussed in separate sections, though unlikely to cause confusion, are merely listed for the sake of completeness, thereby giving the reader an index of what is to come.

Amygdala Amygdaloid body. The cerebellar tonsil.

Brain Stem See *Mesencephalon*.

Cerebrospinal fluid (CSF).

Cerebrum.

Cortex The covering gray area of the brain and cerebellum.

Corticotropin-releasing factor (CRF).

Diencephalon Between brain, interbrain. Posterior part of the prosencephalon including the epithalamus, thalamus, hypothalamus, subthalamus and metathalamus.

Ependyma The epithelial cells which cover all cavities of the brain and spinal cord.

Their elements are not nervous, but probably are more closely related to glia cells.

Fornix A paired structure consisting primarily of longitudinal white fibers, lying beneath the corpus callosum and just above the tela chorioidea of the third ventricle.

Habenula The dorsal peduncles of the pineal body. These are parts of the epithalamus of the diencephalon and each contains medial and lateral habenular nuclei. They continue on both sides with the striae medullares of the thalamus and the habenular commissure.

Hindbrain See *Rhombencephalon*.

Hippocampus Hippocampus major; cornu Ammonis (Ammon's horn), a curved elevation consisting mainly of gray matter, in the floor of the inferior horn of the lateral ventricle.

Hypothalamic Deafferentation A surgical procedure that permits the complete separation of the hypophysiotropic area of the hypothalamus, which can then receive no nervous input but remains in contact with the pituitary through the blood vessels of the stalk.

Hypothalamus Part of the region of the diencephalon that forms the floor of the third ventricle, including neighboring associated nuclei. It is divided into: (1) The anterior region, or pars supraoptica, above the optic chiasma. This includes the supraoptic and paraventricular nuclei and a less differentiated nucleus that merges with the preoptic area (the anterior hypothalamic nucleus). (2) The middle region,

the pars tuberalis (tuber cinereum), including the lateral hypothalamic and tuberal nuclei, lateral to a sagittal plane passing through the anterior column of the fornix, and the dorsomedial, ventromedial and posterior hypothalamic nuclei, medial to the above plane. (3) The caudal region, or mammillary bodies, including medial, lateral and intercalated mammillary nuclei and premammillary and supramammillary nuclei.

Insula of Reil The portion of the cerebral cortex that overlies the corpus striatum. In adult human brains, it is not visible from the outside because it is underneath the bottom of the lateral fissure.

Limbic System A ring of cerebral cortex, composed of the limbic lobe and associated subcortical nuclei, such as the amygdaloid complex, septal nuclei, hypothalamus, habenula, anterior thalamic nuclei and parts of the basal ganglia. It is the oldest portion of the cortex possessing evolutionary rudiments even in reptiles, amphibians and fish. Probably controls various emotional and behavioral patterns.

Median Eminence (ME) A longitudinal ridge in the floor of the fourth ventricle, bounded medially by the median sulcus and laterally by the sulcus limitans.

Medulla Oblongata, Pons, Locus caeruleus.

Mesencephalon The part of the brain developed from the middle cerebral embryonic vesicle. It consists of the tectum with the corpora quadrigemina and the cerebral peduncles, and is traversed by the cerebral aqueduct of Sylvius (synonym: mid-brain).

Midbrain See *Mesencephalon*.

Peripheral Nerves.

Reticular Activating System The reticular formation of the superior levels of the brain stem and the adjacent subthalamus, hypothalamus and medial thalamus. As indicated by animal experiments, it plays a basic role in coordinating the activity of the CNS. It is connected by collaterals with long afferent and efferent nervous pathways, and thus interacts with them. Caudal impulses upon spinal cord levels contribute to optimum motor performance. Cephalic influences upon the cerebral hemispheres form the basis of wakefulness and arousal on which higher CNS functions depend. Many hypnotic and ataractic drugs block transmission of impulses from this area, and lesions in it cause states similar to coma.

Reticular Formation or Substance Also called *formatio reticularis*. A part of the CNS consisting of small islands of gray matter separated by fine nerve fiber bundles. These run in every direction and fill the interspaces between the larger fiber tracts and nuclei.

Rhinencephalon (Archicortex) The portion of the brain believed to receive and integrate olfactory impulses, and to regulate appropriate motor activities in response to these. It comprises the hippocampal formation, the olfactory and the piriform lobes, including the olfactory bulb and peduncle, parolfactory (Broca's) area, subcallosal gyrus and anterior perforated substance. However, a portion of this area is not concerned with olfaction.

Rhombencephalon The hindbrain or afterbrain, divided secondarily into the metencephalon and myelencephalon. It is derived from the most caudal of the three primary embryonic brain vesicles and includes the pons, cerebellum and medulla oblongata.

Septum A translucent membrane that separates the lateral vesicles of the brain and comprises two laminae which surround the so-called fifth ventricle.

Spinal Cord.

Stalk, Portal Vessels The hypophyseal stalk connects this gland with the hypothalamic part of the brain and contains portal vessels. The latter are comparatively large veins that bring blood from the capillary plexus in the ME to another capillary plexus in the anterior lobe of the hypophysis.

Telencephalon The anterior part of the primary embryonic forebrain that develops into the olfactory lobes, cerebral lobes and corpora striata.

Thalamus See *Hypothalamus*.

Nervous vs. Systemic Stressors

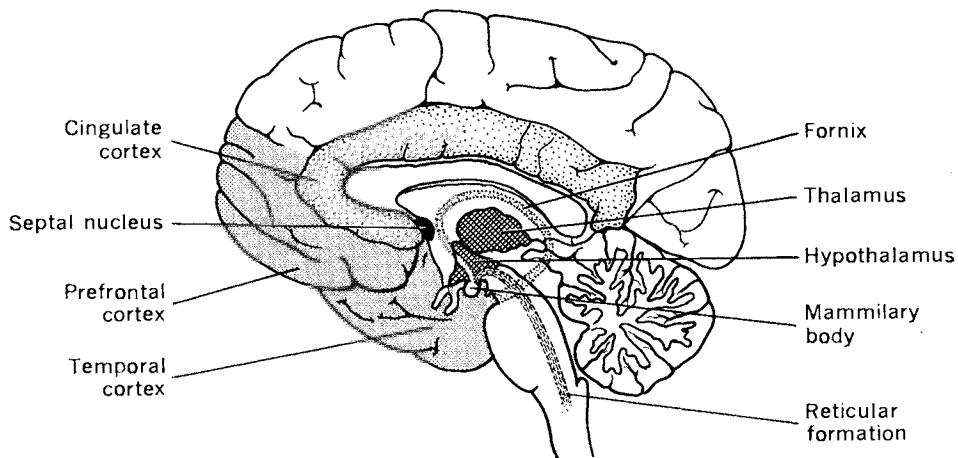
Anatomic Drawings and Explanatory Tables

Figure 7. The limbic system, medial sagittal view. (From Weil, John L., *A Neurophysiological Model of Emotional and Intentional Behavior* (1974), Fig. 1-3, p. 9. Courtesy of Charles C Thomas, Publisher, Springfield, Ill. Prepared by Gayanne DeVry.)

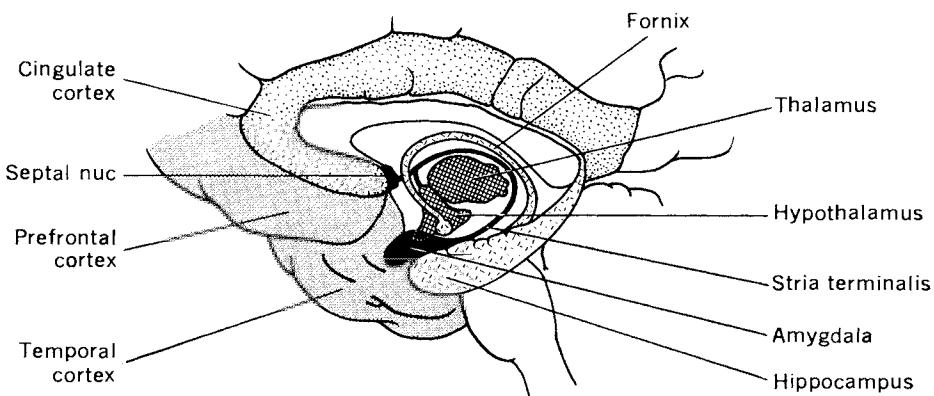


Figure 8. The limbic system, sagittal view. (From Weil, John L., *A Neurophysiological Model of Emotional and Intentional Behavior* (1974), Fig. 1-4, p. 11. Courtesy of Charles C Thomas, Publisher, Springfield, Ill. Prepared by Gayanne DeVry.)

THE LIMBIC SYSTEM

Limbic System Constituent	Position Within the Limbic System	General Structure and Position Within the Central Nervous System	Reference
Reticular formation	Lower limbic	An internuncial network within the brainstem, midbrain, and thalamus; contains the tegmental reticular nuclei	French, 1960:1281-4 Brady, 1958:195-202
Hypothalamus	Central limbic	Diencephalic core of the limbic system	Brady, ibid:195 House and Pansky, 1967:403-10
Septal nucleus	Upper limbic	A subcortical component of the limbic system, anterior and superior to the hypothalamus	Brady, ibid:195 Crosby, 1962:419
Amygdaloid nucleus	Upper limbic	A subcortical component of the limbic system, embedded within the temporal cortex	Gloor, 1960:1395 Brady, 1958:195
Hippocampus	Upper limbic	Primitive ancient "paleo-" ("archi") three-layered cortex which together with the pyriform cortex forms the bulk of the cerebral hemispheres in lower vertebrates	Green, 1960:1374 Brady, 1958:195 Grossman, 1967:528
Pyriform, (Entorhinal) cortex	Upper limbic	Primitive ancient "paleo-" three-layered cortex lying on the ventral aspect of the temporal lobe	Brady, 1958:195 Green, 1960: 1373
Cingulate cortex	Upper limbic	"Meso-" four to five-layered newer limbic cortex medially forming an arch above the corpus callosum	Brady, 1958:195 Kaada, 1960:1345-6 Grossman, 1967:528
Orbito-insular-temporal cortex	Upper limbic	"Meso-" four to five-layered limbic cortex contributing to the formation of the anterior-medial and basal cerebrum	Kaada, ibid: 1346-7 Grossman, 1967:528
Prefrontal cortex	Upper limbic	Six-layered limbic "neo-" cortex of the anterior cerebrum	Nauta, 1964:405 Akert, 1964:377-8

(From Weil, John L., *A Neurophysiological Model of Emotional and Intentional Behavior* (1974), Table II, p. 10.
Courtesy of Charles C Thomas, Publisher, Springfield, Ill.)

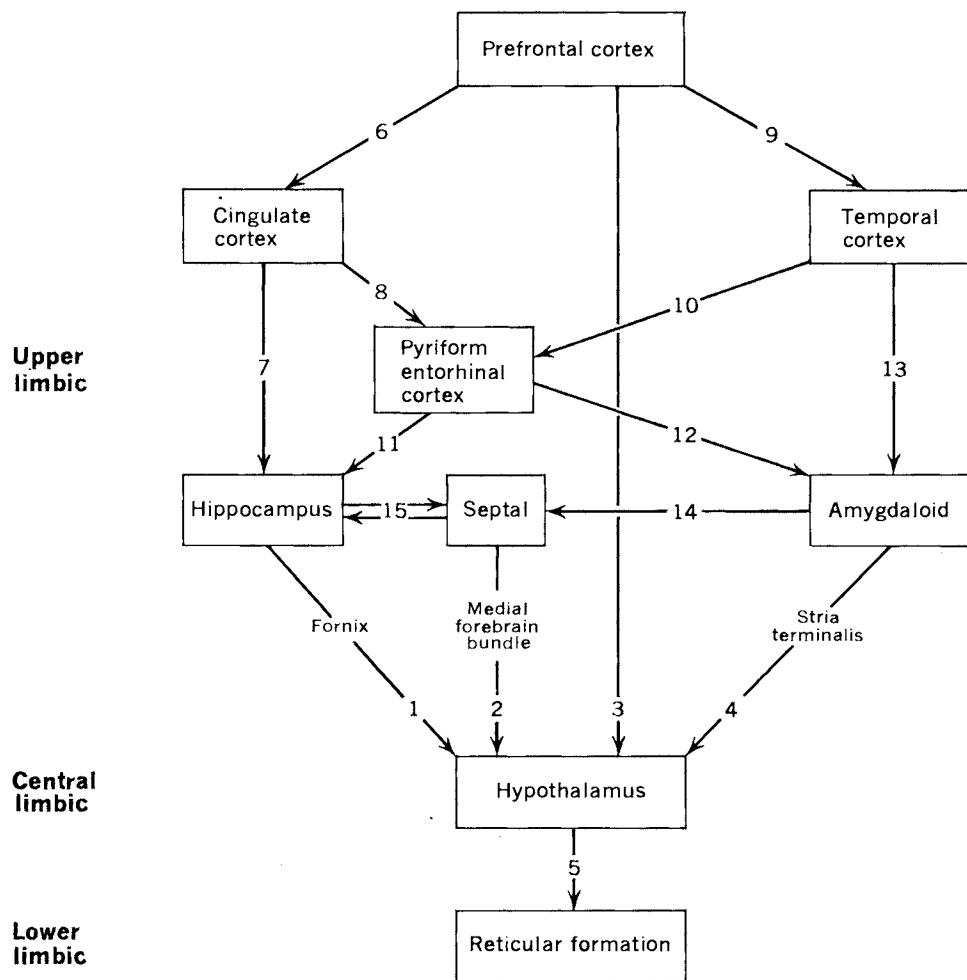


Figure 9. All limbic roads lead to the hypothalamus and reticular formation. (From Weil, John L., *A Neurophysiological Model of Emotional and Intentional Behavior* (1974), Fig. 1-5, p. 12. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.)

ANATOMICAL CONNECTIONS WITHIN THE LIMBIC SYSTEM*

Connection		Reference
1. Hippocampus	Hypothalamus	House and Pansky, 1967:403
2. Septal Nuclei	Hypothalamus	House and Pansky, 1967:220
3. Prefrontal Cortex	Hypothalamus	Nauta, 1964:403
4. Amygdala	Hypothalamus	Ingram, 1960:964 Ruch, 1965:240
5. Hypothalamus	Reticular Formation	Ingram, 1960:964-5 House and Pansky, 1967:409 Ruch, 1965:240
6. Prefrontal Cortex	Cingulate Cortex	Nauta, 1964:397-9
7, 8. Cingulate Cortex	Hippocampus and Pyriform Cortex	Nauta, 1964:397 Green, 1960:1377
9. Prefrontal Cortex	Temporal Cortex	Nauta, 1964:399-400
10. Temporal Cortex	Pyriform Cortex	Crosby, 1962:428
11. Pyriform Cortex	Hippocampus	Nauta, 1964:397 Green, 1960:1376 Brady, 1958:196
12. Pyriform Cortex	Amygdala	Kappers, 1936:1436
13. Temporal Cortex	Amygdala	Nauta, 1964:401
14. Amygdala	Septal Nuclei	Gloor, 1960:1399
15. Septal Nuclei	Hippocampus	Kappers, 1936:1408

* Numbers employed in the table refer to specific tracts listed in Figure 9.

(From Weil, John L., *A Neurophysiological Model of Emotional and Intentional Behavior* (1974), Table III, p. 13.
Courtesy of Charles C Thomas, Publisher, Springfield, Ill.)

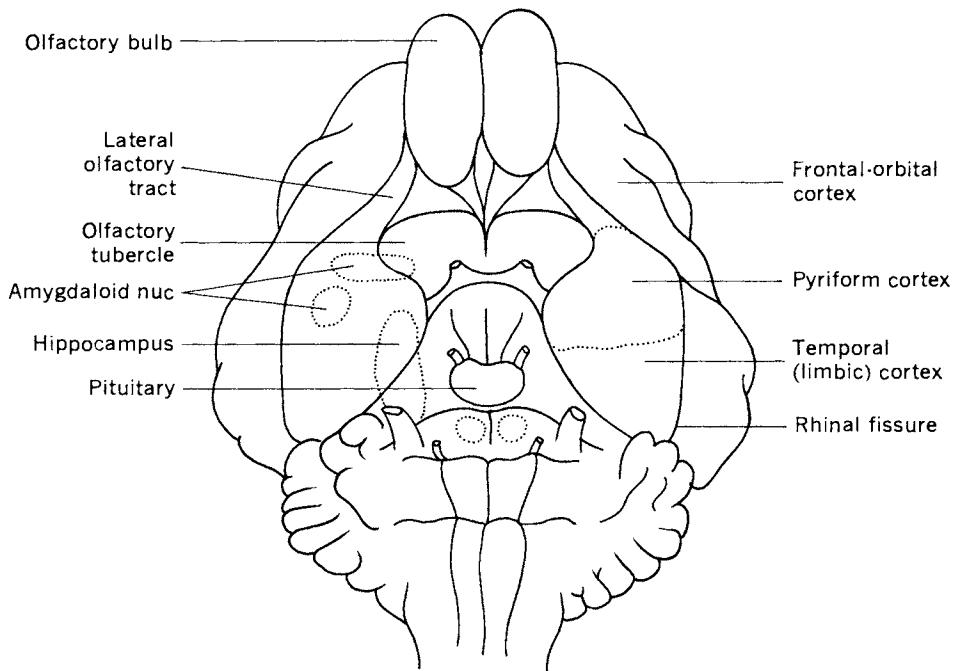


Figure 10. The limbic system, basal view of the cat brain. (From Weil, John L., *A Neurophysiological Model of Emotional and Intentional Behavior* (1974), Fig. 1-6, p. 14. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.)

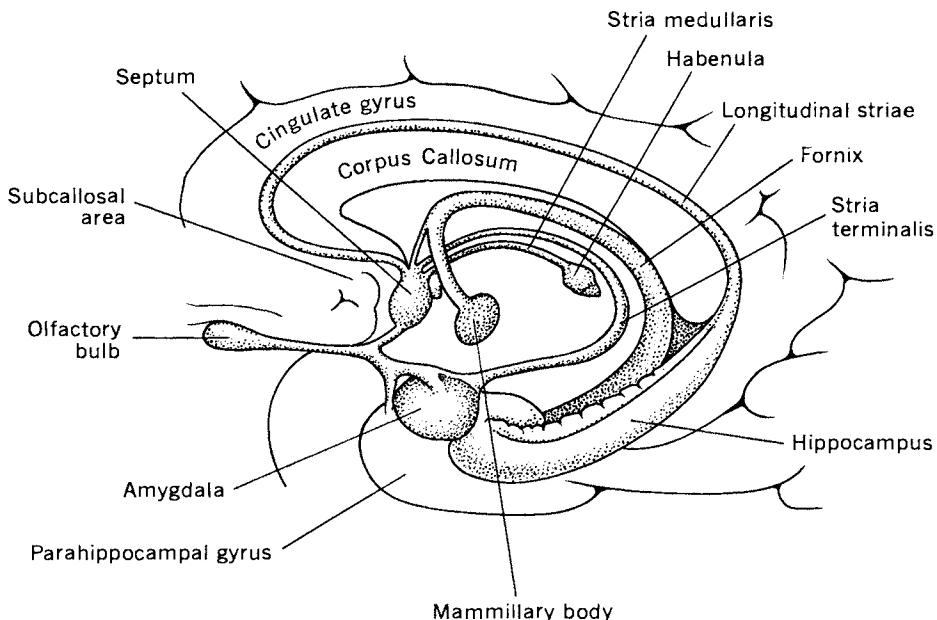


Figure 11. Semischematic drawing of rhinencephalic structural relationships as seen in medial view of the right hemisphere. Both deep and superficial structures are indicated. (Reproduced from *Human Neuroanatomy* (6th ed., 1969), Fig. 21-4, p. 522, by permission of R. C. Truex and M. B. Carpenter, and the Williams & Wilkins Co.)

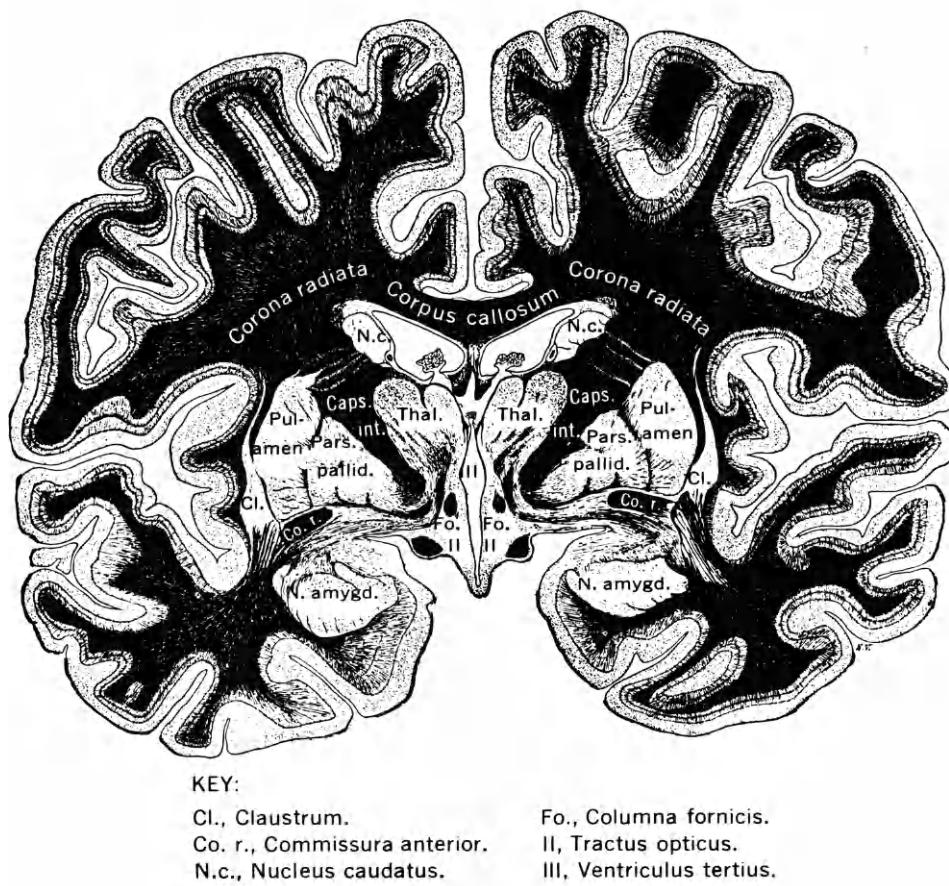


Figure 12. (Reproduced from *Atlas of Cross Section Anatomy of the Brain* (1951), Fig. 37. Used with permission of T. Rasmussen and the McGraw-Hill Book Co.)

General Discussion of CRF and the Results of Experiments with Deafferentation of the Hypophysiotrophic Area

CRF. CRF activity has been demonstrated in hypothalamic tissue, and there is overwhelming evidence to indicate that this substance occurs in the ME, a region of the MBH, also called the "hypophysiotrophic area." The circadian peak in the CRF concentration of the hypothalamus precedes that of corticosterone in the blood by three hours.

Anterior pituitary homografts can maintain ACTH secretion only if they are placed in immediate contact with the ME and if the development of vascular connections between the two structures is not prevented by some impenetrable membrane. The neurons of the hypophysiotrophic area terminate in the ME, which is supplied with no other nerve endings.

The posterior pituitary is extremely rich in CRF activity and it is commonly as-

sumed today that the latter merely represents a store of the CRF that comes from the ME. Yet we still have no definite proof that the CRF of the ME is chemically identical with that found in the neurohypophysis.

Deafferentation. Our understanding of the mechanism through which ACTH secretion can be stimulated under various conditions has been considerably clarified by the important discovery that the entire hypophysiotrophic area can be isolated from the rest of the brain by surgical intervention, using a circular knife pushed from the cortex down to the base of the skull. With this instrument (generally known as the Halász knife), it is possible to accomplish a complete deafferentation of the hypophysiotrophic area, which remains in contact with the pituitary only through the stalk.

After this intervention, there is no reduction in the basal secretion of ACTH which, in fact, is usually above normal. Furthermore, the anterior lobe can still respond to various stressors, such as ether, restraint, tourniquet shock, formalin and so on, by a rise in plasma ACTH, reflected in increased plasma corticosterone levels. Removal of one adrenal also causes compensatory hypertrophy of the contralateral gland. All these reactions fail to occur if the ME is destroyed.

However, the diurnal rhythm in pituitary ACTH secretion is abolished after deafferentation of the hypophysiotrophic area. Apparently, this ACTH release is regulated by nervous stimuli reaching the hypothalamo-hypophyseal system from other parts of the CNS. There is a good deal of evidence that the fibers regulating circadian ACTH secretion originate in the hippocampus. The rhythm is abolished about one week after transection of the fornix, yet it reappears three weeks later, suggesting that the fornix is not the only decisive structure.

Generalities

(See also our earlier stress monographs, p. xiii)

Houssay, B. A., Biasotti, A., Sammartino, R.: "Modifications fonctionnelles de l'hypophyse après les lésions infundibulo-tubérennes chez le crapaud" (Functional changes of the hypophysis after lesions of the lobus infundibularis in toads). *C.R. Soc. Biol. (Paris)* **120**: 725-727 (1935). B6,016/35

In the toad the hypothalamus consists of a pars basalis, lamina terminalis and lobus infundibularis. The latter is attached to the hypophysis. Lesions of the lobus infundibularis cause circulatory arrest in the principal lobe of the hypophysis with increased absorption of MTH, darkening of the animal, and other hormonal derangements.

Sayers, G., Sayers, M.A.: "The pituitary-adrenal system." *Rec. Prog. Horm. Res.* **2**: 81-115 (1948) (124 refs.). B18,350/48

Harris, G. W.: "Neural control of the

pituitary gland." *Physiol. Rev.* **28**: 139-179 (1948). B26,619/48

A classic review on nervous factors controlling pituitary activity in which the author describes his first observations on the regulation of ACTH secretion by the hypothalamus during stress (450 refs.).

Fortier, C.: "Facteurs humoraux et nerveux de la réponse hypophysio-surrénaliennes au stress" (Humoral and nervous factors in the hypophyseal-adrenal response to stress). *Acta Neuroveg. (Wien)* **5**: 55-131 (1952) (793 refs.). B67,408/52

Graham, B. F.: "Neuroendocrine components in the physiological response to stress." *Ann. N.Y. Acad. Sci.* **56**: 184-194 (1953). B95,499/53

Review of the early development of our concepts concerning the neurohumoral mediation of stress phenomena (38 refs.).

Bargmann, W.: *Das Zwischenhirn-Hypophysensystem* (The hypothalamic-hypophy-

seal system), p. 138. Berlin, Göttingen and Heidelberg: Springer-Verlag, 1954.

C3,410/54

Extensive monograph concerning the structure of the midbrain-hypophyseal system, with special reference to neurosecretion (several thousand refs.).

Siedek, H.: "Ueber die Bedeutung des vegetativen Dreitaktes" (The importance of the vegetative triphasic reaction). *Wien. Klin. Wochenschr.* **68**: 651-656 (1956).

C34,208/56

Analysis of the similarities and dissimilarities between the G.A.S. and the vegetative syndrome of Hoff. Both reaction forms are triphasic, and probably are closely related.

Ramey, E. R., Goldstein, M. S.: "The adrenal cortex and the sympathetic nervous system." *Physiol. Rev.* **37**: 155-195 (1957).

C35,830/57

Review of the literature on the relationship between Cannon's emergency theory and the G.A.S. (455 refs.).

Mason, J. W.: "The central nervous system regulation of ACTH secretion." In: Jasper, H. H., Proctor, L. D. et al., *Reticular Formation of the Brain*, pp. 645-670. Boston: Little, Brown, 1958 (10 refs.).

C78,258/58

Sayers, G., Redgate, E. S., Royce, P. C.: "Hypothalamus, adenohypophysis and adrenal cortex." *Ann. Rev. Physiol.* **20**: 243-274 (1958) (175 refs.).

C49,916/58

Hume, D. M., Egdahl, R. H.: "The importance of the brain in the endocrine response to injury." *Ann. Surg.* **150**: 697-712 (1959).

C75,539/59

The literature and personal experiments on dogs with sections through various regions of the spinal cord and removal of diverse brain areas suggest that "the secretion of ACTH and adrenal corticosteroid following trauma is under the control of a complex neurohumoral mechanism located in various areas of the brain" (28 refs.).

Bovard, E. W.: "A note on the threshold for emotional stress." *Psychol. Rev.* **68**: 216-218 (1961).

D15,112/61

A review on the nervous centers regulating psychogenic stress as manifested by the response of the pituitary-adrenocortical axis.

Sawyer, W. H.: "Neurohypophysial hormones." *Pharmacol. Rev.* **13**: 225-277 (1961).

D10,631/61

Extensive review on neurosecretory materials regulating anterior and posterior pituitary functions (369 refs.).

Saffran, M.: "Mechanisms of adrenocortical control." *Br. Med. Bull.* **18**: 122-126 (1962).

D23,888/62

Review on the mechanism controlling corticoid secretion, especially during stress and under the influence of hypothalamic mediators.

Fortier, C.: "Adenohypophysis and adrenal cortex." *Ann. Rev. Physiol.* **24**: 223-258 (1962).

D21,959/62

Review on the regulation of ACTH secretion by neurohumoral substances, with special reference to stress (315 refs.).

Ganong, W. F.: "The central nervous system and the synthesis and release of adrenocorticotropic hormone." In: Nalbandov, A. V., *Advances in Neuroendocrinology*, pp. 92-149. Urbana, Ill.: University of Illinois Press, 1963.

J11,446/63

Review of the major hypotheses on the mechanism of ACTH release. The principal conclusion is that, *in vivo*, only ACTH and angiotensin have an established regulatory function in corticoid secretion. The hypothalamus and pituitary serve as an independent unit in the response to stress. With the possible exception of hindbrain pituitary pathways, no extrahypothalamic pathway has been shown to influence ACTH secretion during stress. Vasopressin may have some intrinsic CRF activity, but it is not the principal mediator. Corticoids inhibit ACTH synthesis more than its secretion. The ME increases ACTH release to meet emergencies, but there is a basal level at which the hormone is produced without necessarily being dependent upon neural control (700 refs.).

Scharrer, E., Scharrer, B.: *Neuroendocrinology*, p. 289. New York: Columbia University Press, 1963.

E4,032/63

Highly technical treatise on the relationships between endocrine glands and the nervous system. A separate chapter is devoted to the stress concept based on the works of Cannon and Selye. An extensive bibliography (74 pp.) gives easy access to the relevant technical literature.

Hrazdilová, V.: "Klinisch-experimentelle Untersuchungen über die Rolle des ZNS bei Stress-Reaktionen" (The role of the CNS in stress reactions. Clinical-experimental studies). *Psychiatr. Neurol. Med. Psychol.*

(Leipz.) **16**: 321-329 (1964). D19,823/64
Theoretical interpretation of clinical observations suggesting that the hormonal mechanisms of the G.A.S. are controlled by the CNS (32 refs.).

Everett, J. W.: "Central neural control of reproductive functions of the adenohypophysis." *Physiol. Rev.* **44**: 373-431 (1964).

F14,325/64

Review on the neural control of gonadotrophic hormone production by the adenohypophysis, with a short section on stressors (471 refs.).

McCann, S. M., Ramirez, V. D.: "The neuroendocrine regulation of hypophyseal luteinizing hormone secretion." *Rec. Prog. Horm. Res.* **20**: 131-170 (1964).

E4,214/64

Review on the neural control of pituitary LH secretion, with a brief section on the effect of stressors (66 refs.).

Welch, B. L.: "Psychophysiological response to the mean level of environmental stimulation: A theory of environmental integration." *Symp. Medical Aspects of Stress in the Military Climate*, pp. 39-99. Publication No. 778-714. Washington, D.C.: U.S. G.P.O., 1965.

G41,327/65

Review on the relationship between stress and Mean Level of Environmental Stimulation (MLES). Detailed survey of the literature and personal observations on the effect of isolation with sensory deprivation or crowding on nonspecific responsiveness. Particular attention is given to the role of the Ascending Reticular Activating System (ARAS) upon the hypothalamus, and through it upon ACTH, glucocorticoid and catecholamine discharges. The numerous feedbacks in several mechanisms involved in arousal and relaxation are critically analyzed (205 refs.).

Ruedi, B., Felber, J. P., Wertheimer, J., Vannotti, A.: "Perturbations hypophysosurréaliennes en rapport avec des lésions du système nerveux central" (Hypophyseal-adrenal disturbances in connection with lesions of the central nervous system). *Rev. Méd. Suisse Romande* **86**: 691-704 (1966).

G42,804/66

Mangili, G., Motta, M., Martini, L.: "Control of adrenocorticotrophic hormone secretion." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 1, pp. 297-370. New York and London: Academic Press, 1966.

E6,488/66

Extensive review on the neurohumoral regulation of ACTH secretion with special reference to stress (several hundred refs.).

Martini, L., Ganong, W. F. (eds.): *Neuroendocrinology*, Vol. 1, p. 774. New York and London: Academic Press, 1966.

E6,480/66

Extensive monograph on neuroendocrine mechanisms, with sixteen chapters by authorities recognized in their respective fields. Individual chapters deal with the anatomy of the hypothalamus and pituitary, the limbic and other neural pathways that regulate endocrine function, stereo-tactic techniques, hypothalamic releasing factor, the regulation of ACTH secretion in adults, fetuses and infants, regulation of aldosterone secretion, STH, gonadotrophins, prolactin and so on (several hundred refs.).

Kurzin, J. T.: "Konzeption über das allgemeine Adaptationssyndrom und die kortikoviszerale Theorie" (The concept of the general adaptation syndrome and the corticovisceral theory). *Dtsch. Gesundheitsw.* **21**: 906-912 (1966).

J23,668/66

Young, I. J., Rowley, W. F.: "The logic of disease." *Int. J. Neuropsychiatry* **3**: 201-208 (1967).

J23,673/67

Mason, J. W.: "'Over-all' hormonal balance as a key to endocrine organization." *Psychosom. Med.* **30**: 791-808 (1968).

H6,465/68

Review on the relative participation of the endocrine and nervous systems in stress reactions (50 refs.).

McCann, S. M., Dhariwal, A. P. S., Porter, J. C.: "Regulation of the adenohypophysis." *Annu. Rev. Physiol.* **30**: 589-640 (1968).

H5,556/68

Brief but well-documented review on the releasing factors for all anterior pituitary hormones, with only brief consideration of ACTH (415 refs.).

Hodges, J. R., Jones, M. T., Stockham, M. A.: "Control of corticotrophin secretion." In: Eichler, O., Farah, A. et al., *Handbuch der Experimentellen Pharmakologie*, Vol. XIV/3, pp. 215-255. Berlin, Heidelberg and New York: Springer-Verlag, 1968.

E7,895/68

Handbook article on the neurohumoral control of ACTH secretion under various conditions, particularly stress (several hundred refs.).

Ganong, W. F., Martini, L. (eds.): *Frontiers in Neuroendocrinology*, p. 442. London, New York and Toronto: Oxford University Press, 1969. E10,576/69

Extensive monograph on the structure and function of the hypothalamus-pituitary system, with special reference to stress reactions, the structure of the ME, the role of catecholamines and releasing factors in the hypothalamus, short and long feedback control of ACTH, and the conclusions to be drawn from animals with deafferented hypophyseal-hypothalamic islands.

Sawyer, C. H., Gorski, R. A. (eds.): *Steroid Hormones and Brain Function* (Proc. Conf. UCLA, 1970), p. 388. Berkeley, Los Angeles and London: University of California Press (UCLA Forum Med. Sci. No. 15), 1971. E10,579/70

Extensive monograph devoted to interrelations between steroid hormones and the nervous system. Several sections deal specifically with the effect of steroids upon the brain and with the mechanism of neurohormonal regulation during stress (several hundred refs.).

Yates, F. E., Russell, S. M., Maran, J. W.: "Brain-adenohypophysial communication in mammals." *Annu. Rev. Physiol.* 33: 393-444 (1971). H36,376/71

Review of data on the structural and functional aspects of the neural control of all anterior pituitary hormones, with only a brief section on ACTH (312 refs.).

Kositskii, G. I., Smirnov, V. S.: *The Nervous System and "Stress"*, p. 265. Washington, D.C.: NASA, 1972. E8,958A/72

A well-documented technical monograph on the relationship between the role played by the nervous system (Pavlov) in resistance phenomena, and hormonal reactions to stress (Selye). The nonhormonal aspects (including nervous mediation) of the G.A.S. are not considered. The extensive bibliography in this English translation will be a valuable source of references to the pertinent Soviet literature for those not reading Russian. [The original Russian edition was published by Nauka in 1970 under the same title (H. S.).]

Murgaš, K., Jonec, V.: "Central nervous influence upon the adrenocortical reaction during stress situations." *Adv. Exp. Med. Biol.* 33: 655-660 (1972). J23,812/72

Naumenko, E. V.: *Central Regulation of*

the Pituitary-Adrenal Complex, p. 195. Leningrad: Nauka Press, 1971 (Russian). Engl. trans.: New York and London: Consultants Bureau, 1973. E10,650/73

Monograph mainly concerned with the central regulation of the hypophyseal-adrenocortical axis in relation to the G.A.S. Special chapters deal with the nervous centers and neurohumoral substances involved in the transmission of impulses. The English translation furnishes ready access to the many pertinent publications that have appeared in Russian (about 800 refs.).

Brown, G. M., Martin, J. B.: "Neuroendocrine relationships." *Prog. Neurol. Psychiatry* 28: 193-240 (1973). J10,042/73

Chapter on the regulation of hormone secretion by the nervous system, including the release of hormones during stress (587 refs.).

Lissák, K. (ed.): *Hormones and Brain Functions* (Proc. 2nd Congr. Int. Soc. Psychoneuroendocrinology. Budapest, 1971), p. 544. New York: Plenum Press, 1973.

E10,608/73

Report on the proceedings of an international congress with the participation of many outstanding specialists. Among the main topics considered are neonatal and ontogenetic aspects of neuroendocrinology; the control, biosynthesis and release of pituitary hormones; and hormonal influences on brain function.

Fortier, C., Labrie, F.: "Regulation of secretion." In: Berson, S. A. and Yalow, R. S., *Peptide Hormones*, pp. 383-391. Amsterdam: North-Holland, 1973. J12,062/73

Fortier, C.: *Cours d'Endocrinologie* (Course on endocrinology). (mimeographed, 1974). J12,063/74

Greatly simplified but excellent review on the neurohumoral control of the adenohypophysis.

Weil, J. L.: *A Neurophysiological Model of Emotional and Intentional Behavior*, p. 189. Springfield, Ill.: Charles C Thomas, 1974. E10,841/74

Papaikonomou, E.: *Biocybernetics, Biosystems Analysis and the Pituitary Adrenal System*, p. 334. Purmerend, Netherlands: Nooy's Drukkerij, 1974. E10,437/74

A monograph that combines insight and wit in applying the principles of biosystems analysis and biocybernetics to the pituitary-adrenocortical system in relation to the G.A.S.

Sayers' hypothesis about the activation of ACTH secretion by a negative feedback due to increased utilization of glucocorticoids during stress was not supported by subsequent experiments. It was replaced by the hypothesis of Yates that stress activates a controller of the system in the hypothalamus. Then Smelik provided evidence of an integral controller of the system with a derivative controller sensitive to negative rates of change of blood glucocorticoids. It is essential in studies concerning the regulation of corticoid secretion to consider the ACTH concentration of the blood and the blood flow as separate input variables, and to distinguish between the effect of unbound and protein-bound corticoids (about 450 refs.).

Amygdala

(See also our earlier stress monographs, p. xiii,
and cf. Limbic System)

Martin, J., Endrőczi, E., Bata, G.: "Effect of the removal of amygdaloid nuclei on the secretion of adrenal cortical hormones." *Acta Physiol. Acad. Sci. Hung.* **14**: 131-134 (1958). C63,999/58

In cats and dogs, the corticoid concentration in the adrenal venous blood rose considerably after surgical removal of the amygdaloid nuclei and the periamygdaloid cortical areas. These animals showed neither rage nor sexual reactions but an extreme reduction in activity and in resistance to emotional stimuli.

Mason, J. W.: "Plasma 17-hydroxycorticosteroid levels during electrical stimulation of the amygdaloid complex in conscious monkeys." *Am. J. Physiol.* **196**: 44-48 (1959). C63,562/59

In unanesthetized rhesus monkeys, electric stimulation of the amygdaloid complex invariably caused substantial elevations of plasma 17-OHCS levels, while no rises were observed during stimulation of the putamen (22 refs.).

Endrőczi, E., Lissák, K., Bohus, B., Kovács, S.: "The inhibitory influence of archicortical structures on pituitary-adrenal function." *Acta Physiol. Acad. Sci. Hung.* **16**: 17-22 (1959). C77,912/59

In cats, rabbits, dogs and rats, electric stimulation of the amygdaloid nucleus increases ACTH secretion, whereas under

similar conditions stimulation of the hippocampus inhibits the rise in ACTH release characteristic of stress (electroshock, EP, histamine, formalin). ACTH activity is estimated by adrenal ascorbic acid, corticoid content of adrenal venous blood, and lymphopenia.

Yamada, T., Greer, M. A.: "The effect of bilateral ablation of the amygdala on endocrine function in the rat." *Endocrinology* **66**: 565-574 (1960). C84,079/60

In rats, bilateral electrolytic destruction of the amygdala does not significantly interfere with TTH or ACTH secretion, but gonadotrophin production is definitely reduced. The amygdalectomized rats become adipose and aphagic. [The published curve showed a transitory rise of adrenal weight after the operation, and there was definite thymus involution, but this might have been a non-specific stress manifestation (H.S.).]

Bovard, E. W., Gloor, P.: "Effect of amygdaloid lesions on plasma corticosterone response of the albino rat to emotional stress." *Experientia* **17**: 521-523 (1961).

D14,959/61

Destruction of the central nucleus of the amygdala increases plasma corticosterone in the rat exposed to brief periods of restraint. It is suggested that separate inhibitory and facilitatory mechanisms for the pituitary-adrenocortical response to stress exist in the amygdaloid complex.

Slusher, M. A., Hyde, J. E.: "Alteration of adrenal effluent corticoid levels following forebrain stimulation in cats." *J. Clin. Endocrinol. Metab.* **21**: 100 (1961). D6,490/61

In cats, stimulation of lateral amygdala or rostral midline structures decreased the corticoid content of adrenal venous blood, whereas stimulation of the medial amygdala or hypothalamus induced rises. Stimulation of the hippocampus caused decreases in some cats and increases in others. [The brief abstract is difficult to evaluate (H.S.).]

Slusher, M. A., Hyde, J. E.: "Effect of limbic stimulation on release of corticosteroids into the adrenal venous effluent of the cat." *Endocrinology* **69**: 1080-1084 (1961).

D15,597/61

In cats with "encéphale isolé," adrenal venous corticoid levels decreased significantly after stimulation of the uncus, the lateral amygdala, the preoptic region, the diagonal band of Broca, or the septum. On the other hand, corticoid levels rose after stimulation

of the hippocampus or anterior medial amygdala. "The limbic system would appear to contain separate components functionally related to inhibition or facilitation of ACTH release."

Gunne, L. M., Reis, D. J.: "Changes in brain catecholamines associated with electrical stimulation of amygdaloid nucleus." *Life Sci.* **2**: 804-809 (1963). E36,459/63

In unanesthetized rats, intermittent electric stimulation of the right amygdaloid nucleus caused autonomic behavioral defense reactions and a decrease in NEP in the left hemisphere of the brain, while brain dopamine was unaffected. There was a decrease of EP and NEP in the adrenals.

Eleftheriou, B. E., Zolovick, A. J., Pearse, R.: "Effect of amygdaloid lesions on pituitary-adrenal axis in the deer mouse." *Proc. Soc. Exp. Biol. Med.* **122**: 1259-1262 (1966). F72,633/66

In the deer mouse, lesions in the medial amygdaloid complex increased plasma ACTH and corticosterone levels within twelve hours, presumably by eliminating an inhibitory effect.

McHugh, P. R., Smith, G. P.: "Plasma 17-OHCS response to amygdaloid stimulation with and without afterdischarges." *Am. J. Physiol.* **212**: 619-622 (1967). F78,351/67

In conscious rhesus monkeys, electric stimulation of the amygdaloid complex evoked afterdischarges and increased the plasma 17-OHCS concentration. Comparable stimuli which did not elicit afterdischarges had no effect on plasma 17-OHCS.

Matheson, G. K., Branch, B. J., Taylor, A. N.: "Facilitation and inhibition of ACTH release with amygdaloid stimulation in conscious cats." *Physiologist* **12**: 296 (1969).

H16,139/69

Various amygdaloid nuclei have different effects on ACTH release.

Matheson, G. K., Branch, B. J., Taylor, A. N.: "Effects of amygdaloid stimulation on pituitary adrenal activity in conscious cats." *Brain Res.* **32**: 151-167 (1971).

H73,938/71

In conscious cats with implanted electrodes, "facilitation of ACTH release, as determined by changes in plasma levels of cortisol and corticosterone, occurred primarily in response to stimulation of the corticomedial, basal and lateral amygdaloid nuclei; inhibition, primarily upon stimulation of the

corticomedial nuclei. The basal nuclear group also exerted differential inhibitory effects on corticosterone, while the major effect of anterior amygdaloid stimulation was no change in both steroids." The direction of ACTH response was directly related to the existing level of pituitary-adrenal activity; when this was low, stimulation caused facilitation of ACTH release, whereas inhibition occurred when the initial levels were high. Thus, the amygdala is a potent modulator of pituitary-adrenal activity. The literature on the neural regulation of ACTH secretion is carefully reviewed and criticized (33 refs.).

Winson, J., Gerlach, J. L.: "Stressor-induced release of substances from the rat amygdala detected by the push-pull cannula." *Nature [New Biol.]* **230**: 251-253 (1971). G83,348/71

Zolovick, A. J.: "Effects of lesions and electrical stimulation of the amygdala on hypothalamic-hypophyseal regulation." In: Eleftheriou, B. E., *The Neurobiology of the Amygdala*, pp. 643-683. New York and London: Plenum Press, 1972 (more than 150 refs.). J17,218/72

Leppäläluoto, J.: "Electrical stimulation of human thalamic and amygdaloid area and plasma cortisol concentration." *Acta Physiol. Scand.* **89**: 187-191 (1973). J8,407/73

In five patients, electric stimulation of the thalamus and amygdala by electrodes (chronically implanted for the treatment of psychomotor seizures) caused bursts of plasma cortisol (indwelling catheters). However, similar rapid changes in plasma cortisol were also observed in normal controls, and hence "no conclusion about the function of the pituitary-adrenal cortex axis in relation to electrical stimulation of thalamus or amygdala was drawn."

Allen, J. P., Allen, C. F.: "Role of the amygdaloid complexes in the stress-induced release of ACTH in the rat." *Neuroendocrinology* **15**: 220-230 (1974). H91,996/74

Plasma corticosterone determinations in the rat "suggest that the amygdalae facilitate rather than directly transmit neurogenic stress-induced signals (leg break) but not signals from systemic stresses (ether)." However, "bilateral paired amygdaloid lesions blocked the effect of the leg break but not of ether or tourniquet. Bilateral paired lesions between the lateral hypothalamic area and the amygdalae also blocked the effect of the leg break but not ether or tourniquet, whereas

bilateral lesions in the anterior portion of the striae terminali did not block the leg-break effect."

Brain Stem

(See also our earlier stress monographs, p. xiii)

Moll, J.: "Localization of brain-stem lesions inhibiting compensatory adrenal hypertrophy following unilateral adrenalectomy." *Z. Zellforsch. Mikrosk. Anat.* **49**: 515-524 (1959). C67,656/59

Slusher, M. A.: "Effect of brainstem lesions on stress-induced corticosteroid release in female rats." *Endocrinology* **67**: 347-352 (1960). C90,692/60

In rats five days after unilateral adrenalectomy and brain stem lesions, adrenal corticoids were measured following laparotomy. "At the rostral pons level, dorsal as well as ventral tegmental lesions were associated with high initial (0-15 minutes) release levels of corticosteroids into the adrenal venous effluent. Dorsal tegmental lesions were associated with an augmented corticosteroid release following acute stress while ventral tegmental lesions inhibited this response. Neither lesion site significantly altered compensatory adrenal hypertrophy."

Egdahl, R. H.: "The effect of brain removal, decortication and mid brain transection on adrenal cortical function in dogs." *1st Int. Congr. Endocrinology*, pp. 49-50. Copenhagen, 1960. J12,258/60

Comparative studies on dogs with complete bilateral decortication, brain removal, spinal cord and midbrain transection. The high resting corticoid outputs after midbrain transection suggest that cerebral inhibition of some hindbrain factor-releasing area is effected through nervous, and not humoral, pathways. "Adrenal cortical responses to nerve stimulation are less than maximal in these animals, and this would seem to indicate that it is the hind brain center rather than the hypothalamic one which has been activated to result in ACTH release." [The brief abstract does not lend itself to critical evaluation (H.S.).]

Slusher, M. A., Hyde, J. E.: "Effect of diencephalic and midbrain stimulation on ACTH levels in unrestrained cats." *Am. J. Physiol.* **210**: 103-108 (1966). F59,593/66

In unrestrained cats with chronically implanted electrodes, "measurable ACTH was released 1-2 min after stimulation of sites in dorsal midbrain, or four of eight sites in diencephalon; 30 min later, levels were again below the minimum detectable. Inhibition of the pituitary-adrenal axis was demonstrated by paired stimulation of a potentially inhibitory site with a demonstrably facilitative one: diencephalically evoked release of ACTH was blocked by concurrent stimulation of sites in the ventral midbrain or the preoptic region."

Zigmund, R. E., Schon, F., Iversen, L. L.: "Increased tyrosine hydroxylase activity in the locus coeruleus of rat brain stem after reserpine treatment and cold stress." *Brain Res.* **70**: 547-552 (1974). J11,658/74

Cerebrum, Brain in General

(See also our earlier stress monographs, p. xiii)

Scarf, J. E.: "Reaction to life stresses following unilateral prefrontal lobectomy or lobotomy." In: Wolff, H. G., Wolf, S. G. Jr. et al., *Life Stress and Bodily Disease*, pp. 121-126. Baltimore: Williams & Wilkins, 1950. B51,899/50

Egdahl, R. H., Story, J. L., Melby, J. C.: "Effect of progressive removal of the brain on adrenal cortical hypersecretion due to operative trauma." *Fed. Proc.* **17**: 435 (1958). H22,039/58

The rise in 17-OHCS produced by surgical trauma in the adrenal vein of the dog was not prevented by progressive removal of brain parts down to the hypothalamus, but disappeared after extirpation of the latter.

Egdahl, R. H.: "Adrenal cortical and medullary responses to trauma in dogs with isolated pituitaries." *Endocrinology* **66**: 200-216 (1960). J11,920/60

In dogs the urinary 17-OHCS content was raised for about five days after removal of the brain above the inferior colliculus. The dogs responded to burns with a further increase. Catecholamine levels were low, but rose after burns.

Egdahl, R. H.: "Corticosteroid secretion following caval constriction in dogs with isolated pituitaries." *Endocrinology* **68**: 226-231 (1961). J12,285/61

In dogs, partial constriction of the thoracic inferior vena cava strongly stimulates ACTH secretion, even after removal of the entire brain, which totally isolates the pituitary from its cerebral connections. The resting control 17-OHCS output is above normal even in decerebrated dogs.

Egdahl, R. H.: "Further studies on adrenal cortical function in dogs with isolated pituitaries." *Endocrinology* 71: 926-935 (1962). D45,363/62

In dogs, removal of the brain down to the pons and preparation of "hypothalamic islands," as well as ablation of the entire brain and spinal cord, depressed adrenal cortical function at first and then elevated the resting secretion. Removal of the posterior pituitary or abdominal evisceration did not alter this response.

Wise, B. L., Brunt, E. E. van, Ganong, W. F.: "Effect of removal of various parts of the brain on ACTH secretion in dogs." *Proc. Soc. Exp. Biol. Med.* 112: 792-795 (1963). D61,018/63

In dogs, 17-OHCS output in adrenal venous blood following trauma was slightly decreased after ablation of all brain tissue above the pons except the hypothalamus. The output was significantly lowered, but still above basal levels, after removal of the entire brain above the pons. Acute section of the pituitary stalk decreased the corticoid response to approximately the same degree. Hypophysectomy plus removal of the brain reduced output to very low levels. "These data do not support the hypothesis that the hindbrain secretes a factor which stimulates the pituitary to secrete ACTH."

Wise, B. L., Brunt, E. E. van, Ganong, W. F.: "Effect of brain removal in dogs previously subjected to pituitary stalk section." *Proc. Soc. Exp. Biol. Med.* 116: 306-310 (1964). F14,878/64

In dogs, transection of the pituitary stalk does not prevent 17-OHCS secretion into the adrenal venous blood. Following subsequent brain removal, 17-OHCS output is elevated and all neurohypophyseal tissue below the plastic plate separating the stalk becomes atrophic, but the adrenals retain their normal size. "The results suggest that the stress response in severely stressed dogs is not due entirely to CRF from the hypothalamus, and may be due in part to an ACTH-stimulating humoral agent liberated from traumatized tissues."

Matheson, G. K.: "Aspects of forebrain regulation of plasma glucocorticoids." *Diss. Abstr.* 30: 470B (1969). J11,477/69

Doctoral dissertation on the effect of electrically stimulating various forebrain regions of the rhesus monkey by chronically-implanted electrodes. As regards corticoid secretion, "the facilitatory loci were: the basal, accessory basal and lateral basal amygdaloid nuclei; the lateral hypothalamus (tuberal level); the fibers of the direct amygdalo-hypothalamic pathway; and the anterior commissure. Inhibitory loci were: the cortical, medial and anterior amygdaloid nuclei; fibers from the insular cortex; the stria terminalis and the olfactory area between the preoptic and anterior hypothalamic areas and the amygdala. Neutral areas were: the globus pallidus, the optic tract, the zona incerta and the subthalamus."

Kawakami, M., Kimura, F., Yoshida, K., Yanase, M., Seto, K.: "Reorganization of the brain mechanisms on the response to the repeated stress." *J. Physiol. Soc. Jap.* 32: 727-747 (1970) (Japanese). J21,406/70

Papaikonomou, E., Smelik, P. G.: "Evidence for derivative control in the rat pituitary-adrenal system." *Am. J. Physiol.* 227: 137-143 (1974). J10,731/74

In Nembutal-anesthetized rats with a carotid artery cannulated and one adrenal exposed, the plasma corticosterone level was fairly constant, but after removal of one adrenal it started to oscillate with periods of ten or twelve minutes. Similar oscillations were found when the blood from one adrenal was delayed on its way to the systemic circulation by about twenty-four minutes. In hypophysectomized rats receiving constant ACTH infusions, as well as in rats with corticosterone implants in the hypothalamus, unilateral adrenalectomy caused no such oscillations. The authors assume "the existence of a derivative controller, probably located in the brain, which is sensitive for negative rates of change in blood levels of corticosterone."

Cortex

(See also our earlier stress monographs, p. xiii)

Ferguson, R. W., Folkow, B., Mitts, M. G., Hoff, E. C.: "Effect of cortical stimu-

lation upon epinephrine activity." *J. Neurophysiol.* **20**: 329-339 (1957). C37,699/57

In cats, electric stimulation of the anterior sigmoid gyri greatly increased EP secretion, whereas stimulation of the cortical vasodepressor areas actually diminished it. "In electrode positions permitting stimulation of corticofugal fibers in the internal capsule, it was possible to differentiate loci giving blood pressure rise plus contraction of the denervated nictitating membrane from closely adjacent loci evoking pressor response with relaxation of the membrane. This is interpreted to mean that vasomotor and adrenal medullary secretory response may be mediated by discrete pathways from the cortex" (15 refs.).

Endrőczi, E., Kovács, S., Bohus, B.: "Changes in behavior and endocrine activation in response to the stimulation of orbito-frontal cortical areas." *Acta Physiol. Acad. Sci. Hung.* **14**: 39-44 (1958). C59,559/58

In rats, stimulation of the orbito-frontal cortical areas with chronically implanted electrodes elicited effective defensive and escape reactions, invariably accompanied by activation of the pituitary-adrenal cortical system. The most intense reactions were elicited from the paramedian areas of the posterior orbital cortex.

Euler, U. S. von, Folkow, B.: "The effect of stimulation of autonomic areas in the cerebral cortex upon the adrenaline and noradrenaline secretion from the adrenal gland in the cat." *Acta Physiol. Scand.* **42**: 313-320 (1958). C54,880/58

In cats, stimulation of certain autonomic areas in the cerebral cortex causes selective changes in the EP secretion of the adrenal medulla. Inhibition is obtained most consistently upon stimulation of ventral parts of the cerebral cortex, whereas NEP release is but slightly affected.

Egdahl, R. H.: "Cerebral cortical inhibition of pituitary-adrenal secretion." *Endocrinology* **68**: 574-581 (1961).

J12,284/61

In bilaterally decorticated dogs, 17-OHCS output into the adrenal blood was markedly elevated under ordinary conditions. "Sciatic nerve stimulation in the anesthetized decorticated animal resulted in a significant adrenal cortical response which was not further increased by exogenous ACTH. These studies indicate that the cerebral cortex exerts a tonic inhibition on lower central nervous sys-

tem areas which are involved in the control of ACTH release."

Gollender, M.: "Eosinophil and avoidance correlates of stress in anterior cingulate cortex lesioned rats." *J. Comp. Physiol. Psychol.* **64**: 40-48 (1967). G48,960/67

"Bilateral Area 24 lesions in rats disrupt mediation of normal conditioned eosinopenia to a learned fear situation, but are insufficient to damage mediation of original stressful stimulus or complex neural systems involved in performance of avoidance tasks."

McEwen, B. S., Weiss, J. M., Schwartz, L. S.: "Retention of corticosterone by cell nuclei from brain regions of adrenalectomized rats." *Brain Res.* **17**: 471-482 (1970).

J12,015/70

In adrenalectomized rats, nuclear uptake of labeled corticosterone was highest in the hippocampus, but was also demonstrable in the amygdala and cerebral cortex.

Semiginovsky, B., Jakoubek, B., Kraus, M., Erdőšová, R.: "Effect of restraint stress on the oxygen consumption and [¹⁴C] leucine incorporation into brain cortex slices of rats." *Brain Res.* **23**: 298-301 (1970).

H47,527/70

Bito, L. Z., Myers, R. E.: "On the physiological response of the cerebral cortex to acute stress (reversible asphyxia)." *J. Physiol. (Lond.)* **221**: 349-370 (1972).

G89,354/72

Newborn rhesus monkeys delivered by Cesarean section and then exposed to various stressors showed stereotyped chemical changes in the brain. "It is proposed that the release of intracellularly bound cations is a result of their displacement from their binding sites by NH₄⁺ which is released to, and recovered from, these cation binding sites by a glutamate-glutamine interconversion. It is concluded that the apparent organized 'shutdown' of the cortical cells in response to acute stress may contribute to the relative insensitivity of this area of the brain to permanent histopathological damage."

Aleksandrovskaia, M. M., Kruglikov, R. I., Shevtsov, V. V.: "Structure and protein metabolism of the cerebral cortex during repeated electric shocks." *Dokl. Akad. Nauk SSSR* **203**: 251-253 (1972) (Russian). Engl. trans.: *Proc. Acad. Sci. USSR, Biol. Sci.* **203**: 243-245 (1972). J20,135/72

Corticotrophin-releasing Factor (CRF)

(See also our earlier stress monographs, p. xiii)

Hume, D. M.: "The role of the hypothalamus in the pituitary-adrenal cortical response to stress." *J. Clin. Invest.* **28**: 700 (1949).

B33,420/49

Brief abstract of observations suggesting that certain hypothalamic extracts produce eosinopenia in both normal animals and in those with lesions in the anterior hypothalamus which make them unable to respond to stressors by eosinopenia. It is assumed that a mechanism located in the anterior hypothalamus elicits a substance capable of causing increased ACTH secretion during stress. [The particular region in the "anterior hypothalamus" has not been further identified in this brief abstract (H.S.).]

Groot, J. de, Harris, G. W.: "Hypothalamic control of the anterior pituitary gland and blood lymphocytes." *J. Physiol. (Lond.)* **111**: 335-346 (1950). B54,598/50

"Electrical stimulation of the posterior region of the tuber cinereum or of the mammillary body, of unanaesthetized, unrestrained rabbits resulted in a lymphopenia, which was similar in time relations and magnitude to that following an emotional stress stimulus." This response was not abolished by cervical sympathectomy and could not be duplicated by stimulation of other hypothalamic areas. A similar psychogenic stress lymphopenia was abolished by lesions in the zona tuberalis and by transverse lesions in the posterior tuber cinereum or mammillary body, but not by lesions in the pars distalis and pars intermedia, or by interruption of the infundibular stem. It is concluded that stress-induced ACTH secretion "is under neural control via the hypothalamus and the hypophysial portal vessels of the pituitary stalk." [This is the first clearcut demonstration of the hypothalamic regulation of stress-induced ACTH secretion (H.S.).]

Saffran, M., Schally, A. V., Benfey, B. G.: "Stimulation of the release of corticotropin from the adenohypophysis by a neurohypophysial factor." *Endocrinology* **57**: 439-444 (1955). C8,454/55

"Posterior pituitary extracts contain a corticotropin-releasing factor (CRF) that stimulates the release of ACTH from rat anterior pituitary tissue in vitro." CRF can be separated from vasopressin, and its activity is enhanced by NEP.

Guillemin, R., Rosenberg, B.: "Humoral hypothalamic control of anterior pituitary: a study with combined tissue cultures." *Endocrinology* **57**: 599-607 (1955). C9,787/55

If the dog or rat adenohypophysis is cultured in roller tubes, ACTH activity in the fluid medium disappears after the first four days, despite excellent growth and differentiation of the pituitary outgrowth. When explants of hypothalamus or ME are added to such cultures, the surrounding medium contains no histamine, acetylcholine, EP, NEP, 5-HT, oxytocin or vasopressin, but ACTH activity is demonstrable. "There exists some hypothalamic hypophysiotropic mediator involved in ACTH release, which is different from the above mentioned substances."

Porter, J. C., Rumsfeld, H. W. Jr.: "Effect of lyophilized plasma and plasma fractions from hypophyseal-portal vessel blood on adrenal ascorbic acid." *Endocrinology* **58**: 359-364 (1956). C12,745/56

Lyophilized extracts of hypothalamic venous plasma from dogs injected into cortisol-treated or hypophysectomized rats caused adrenal ascorbic acid depletion in the latter. "The active substance is either a large protein molecule or is bound to a large protein and is probably not identical with vasopressin."

Schapiro, S., Marmorston, J., Sobel, H.: "Pituitary stimulating substance in brain blood of hypophysectomized rat following electric shock 'stress.'" *Proc. Soc. Exp. Biol. Med.* **91**: 382-386 (1956) (18 refs.).

C14,584/56

Porter, J. C., Jones, J. C.: "Effect of plasma from hypophyseal-portal vessel blood on adrenal ascorbic acid." *Endocrinology* **58**: 62-67 (1956). J11,918/56

Plasma obtained from the hypophyseal-portal veins of hypophysectomized dogs decreased the adrenal ascorbic acid content in cortisol-overdosed rats, but not in hypophysectomized rats. "These observations suggest that blood from the hypophyseal portal vessels contains a substance(s) which accelerates the release of ACTH from the anterior lobe. These observations further suggest that a block in the response of the rat to the stress of unilateral adrenalectomy occurs at some site other than the anterior lobe, perhaps the hypothalamus."

Guillemin, R., Hearn, W. R., Cheek, W. R., Housholder, D. E.: "Control of corticotrophin release: further studies with in

vitro methods." *Endocrinology* **60**: 488-506 (1957). C32,056/57

A substance has been isolated from the hypothalamus and posterior pituitary of the hog and cattle in the form of a small peptide, "different from vasopressin, oxytocin, ACTH, histamine, acetylcholine, adrenalin, nor-adrenalin and 5-hydroxytryptamine" in its pharmacologic and chromatographic characteristics. "The in vitro ACTH-releasing activity was also observed in a fraction of Substance P of gut origin and possibly in extracts of brain cortex."

Clayton, G. W., Bell, W. R., Guillemin, R.: "Stimulation of ACTH-release in humans by non-pressor fraction from commercial extracts of posterior pituitary." *Proc. Soc. Exp. Biol. Med.* **96**: 777-779 (1957).

C45,822/57

Fortier, C., Ward, D. N.: "Limitations of the in vitro pituitary incubation system as an assay for ACTH-releasing activity." *Can. J. Biochem.* **36**: 111-118 (1958).

C48,445/58

The in vitro release of ACTH from rat pituitaries is not very specific, and may be obtained with various substances which merely produce passive leakage.

Garilhe, M. P. de, Gros, C., Chauvet, J., Fromageot, C., Mialhe-Voloss, C., Benoit, J.: "Nouvelles données concernant l'existence d'une hypophysostimuline à effet corticotrope" (New data related to the existence of a hypophyseal stimulant with a corticotrophic effect). *Biochim. Biophys. Acta* **29**: 603-611 (1958). C57,765/58

Saffran, M., Schally, A. V.: "An in vitro system for the study of the neural control of ACTH secretion." In: Curri, S. B. and Martini, L., *Pathophysiologia Diencephalica*, pp. 780-783. Wien: Springer-Verlag, 1958.

D94,108/58

In vitro studies on rat pituitaries revealed that "the release of ACTH is increased to a minor extent by epinephrine and norepinephrine. Hypothalamus, brain cortex, and posterior pituitary tissue have little, if any, influence by themselves, but in combination with norepinephrine, these tissues stimulate the release of ACTH. The greatest effect is exerted by the posterior lobe. The active material in the posterior lobe seems to be similar to, but distinct from, the beef posterior lobe principles, oxytocin and vasopressin."

Eik-Nes, K. B., Brizzee, K. R.: "Some aspects of corticotrophin secretion in the

trained dog. I. The presence of a corticotrophin releasing factor in the blood stream of dogs shortly after hypophysectomy." *Acta Endocrinol.* **29**: 219-223 (1958).

C59,055/58

In dogs the peripheral blood contains large amounts of CRF during the first week after hypophysectomy, presumably because the stress of survival after this operation stimulates its production.

Leeman, S. E., Munson, P. L.: "In vivo system for detection of the neural hormone responsible for ACTH secretion in stress." *Fed. Proc.* **17**: 387 (1958). C51,861/58

In rats, blockade of ACTH secretion by morphine is used as a basis for the bioassay of CRF.

Guillemin, R., Nichols, B., Lipscomb, H. S.: "Facteur hypothalamique de décharge de l'hormone corticotrope: activité in vivo chez l'animal avec lésion hypothalamique ou blocage pharmacologique" (The hypothalamic corticotrophic releasing factor: in vivo activity in animals with hypothalamic lesions or pharmacologic blockades). *C.R. Acad. Sci. (Paris)* **247**: 1662-1664 (1958).

C78,054/58

Schally, A. V., Saffran, M., Zimmermann, B.: "A corticotrophin-releasing factor: partial purification and amino acid composition." *Biochem. J.* **70**: 97-103 (1958).

C58,163/58

Royce, P. C., Sayers, G.: "Corticotropin releasing activity of a pepsin labile factor in the hypothalamus." *Proc. Soc. Exp. Biol. Med.* **98**: 677-680 (1958). C58,395/58

Diepen, R., Engelhardt, F., Christ, J.: "Neurosecretion as a neuronal process." In: Bogaert, L. van and Radermecker, J., *First International Congress of Neurological Sciences, Brussels, 1957. 4. Neuropathology*, pp. 165-174. London, New York and Paris: Pergamon Press, 1959. J12,761/59

Histologic studies suggesting neurosecretion in the supraoptic nuclei of various mammals (34 refs.).

Porter, J. C., Rumsfeld, H. W. Jr.: "Investigation of the release of ACTH." *Endocrinology* **64**: 942-947 (1959).

C69,490/59

In the venous blood of the pituitary stalk, CRF-active fractions could be isolated which stimulated ACTH secretion in hypophysectomized or cortisol-blocked rats. This activity "was not attributable to contamination with

nor-epinephrine, epinephrine, histamine, or serotonin."

Porter, J. C., Rumsfeld, H. W. Jr.: "Further study of an ACTH-releasing protein from hypophyseal portal vessel plasma." *Endocrinology* **64**: 948-954 (1959).

C69,491/59

In dogs, fractions of the plasma from hypophyseal portal vessels contain an ACTH-releasing factor, some of whose chemical properties are described.

Schally, A. V., Guillemin, R.: "Concentration of corticotropin releasing factor by chromatography on carboxymethylcellulose." *Proc. Soc. Exp. Biol. Med.* **100**: 138-139 (1959).
C63,526/59

McCann, S. M., Haberland, P.: "Relative abundance of vasopressin and corticotrophin-releasing factor in neurohypophysial extracts." *Proc. Soc. Exp. Biol. Med.* **102**: 319-325 (1959).
C77,949/59

Gros, C., Garilhe, M. P. de: "Obtention d'hypophyso-stimuline à effet corticotrope dépourvue de vasopressine par distribution à contre-courant" (Isolation of a hypophyseal stimulant with a corticotrophic effect, devoid of vasopressin, using countercurrent distribution). *C.R. Acad. Sci. (Paris)* **249**: 2234-2236 (1959).
J12,256/59

By use of countercurrent distribution, it was possible to isolate from pig posterior pituitaries a polypeptide with strong CRF and no vasopressor potency.

Saffran, M.: "Activation of ACTH release by neurohypophysial peptides." Symp. on Neurosecretion. First Annual Meeting Can. Fed. Biol. Soc., Kingston, June, 1958. *Can. J. Biochem. Physiol.* **37**: 319-329 (1959).
C63,550/59

Vasopressin, oxytocin and CRF can release ACTH from adenohypophyseal tissue in vitro. Presumably in rats, "the ability to promote the release of ACTH is a property shared by a family of substances, rather than a property of a unique neurohormone" (43 refs.).

Rochefort, G. J., Rosenberger, J., Saffran, M.: "Depletion of pituitary corticotrophin by various stresses and by neurohypophysial preparations." *J. Physiol.* **146**: 105-116 (1959).
C67,709/59

In rats, various stressors (sound, histamine, cold) differ in the intensity and speed with which they deplete the anterior or posterior pituitary of its ACTH content; hence

the differentiation between "neurogenic" and "systemic" stressors appears to be justified. CRF causes a prompt and sustained fall in the ACTH content of the anterior pituitary, with only a momentary dip at sixty minutes in the posterior lobe. Commercial and synthetic vasopressin preparations are less effective than CRF; hence the latter is presumably the physiologic releasing substance. Pretreatment with cortisol decreases but does not abolish the sensitivity of the anterior lobe to CRF.

Guillemin, R., Dear, W. E., Nichols, B. Jr., Lipscomb, H. S.: "ACTH releasing activity in vivo of a CRF preparation and lysine vasopressin." *Proc. Soc. Exp. Biol. Med.* **101**: 107-111 (1959) (14 refs.).
C68,936/59

Rumsfeld, H. W. Jr., Porter, J. C.: "ACTH-releasing activity in an acetone extract of beef 'hypothalamus'." *Arch. Biochem.* **82**: 473-476 (1959).
C73,258/59

Schally, A. V., Andersen, R. N., Lipscomb, H. S., Long, J. M., Guillemin, R.: "Evidence for the existence of two corticotrophin-releasing factors, α and β ." *Nature* **188**: 1192-1193 (1960).
C97,961/60

Chemical characterization of two distinct CRF types which can be separated by chromatography. "In view of the discrepancy in the specific activities and preliminary amino-acid composition of the two substances, one might propose that β -corticotrophin-releasing factor is the true chemical mediator for release of adrenocorticotropic hormone, whereas α -corticotrophin-releasing factor is an α -melanocyte stimulating hormone analogue, possibly a precursor in the biosynthesis of adrenocorticotropic hormone."

Guillemin, R., Schally, A. V., Andersen, R. N., Lipscomb, H. S., Long, J. M.: "Sur l'existence de deux types de substances à activité hypophysiotrope" (On the existence of two types of substances with hypophysiotropic activity). *C.R. Acad. Sci. (Paris)* **250**: 4462-4464 (1960).
J12,257/60

Chromatographic separation of α -CRF, which exhibits weak adrenocorticotropic activity in vivo and in vitro and resembles α -MTH both in its polypeptide composition and chromatographic behavior. β -CRF is a polypeptide more closely resembling vasopressin and is fifty to one hundred times more potent as a corticotrophic releasing factor than α -CRF.

Royce, P. C., Sayers, G.: "Purification of

hypothalamic corticotropin releasing factor." *Proc. Soc. Exp. Biol. Med.* **103**: 447-450 (1960). C84,048/60

Garilhe, M. P. de, Gros, C., Porath, J., Lindner, E. B.: "Further studies on corticotropin releasing factor (CRF); corticotropin releasing activity of synthetic peptides." *Experientia* **16**: 414-415 (1960).

C99,048/60

Vogt, M.: "The control of the secretion of corticosteroids." In: Clark, F. and Grant, J. K., *The Biosynthesis and Secretion of Adrenocortical Steroids* (Biochem. Soc. Symp. No. 18), pp. 85-95. Cambridge: Cambridge University Press, 1960.

E82,754/60

Review of the early history of CRF and the agents causing its production and discharge.

Eik-Nes, K. B., Brown, D. M., Brizzee, K. R., Smith, E. L.: "Partial purification and properties of a 'corticotropin influencing factor' (CIF) from human spinal fluid: an assay method for CIF in the trained dog." *Endocrinology* **69**: 411-421 (1961).

D10,602/61

In dogs, injection of CSF obtained from other dogs or from man into the carotid artery raised plasma 17-OHCS levels. The responsible agent appeared to be identical with CRF.

Garilhe, M. de: "Acquisitions récentes sur la biochimie du CRF" (Recent achievements in the biochemistry of CRF). In: Courrier, R. and Guillemin, R., *Etudes d'Endocrinologie. 2. Rapports entre le Complexe Hypothalamo-Hypophysaire et la Fonction Adréno-corticotrope*, pp. 317-331. Paris: Hermann, 1961.

J12,263/61

Guillemin, R.: "Critères nécessaires pour la caractérisation du facteur hypothalamique de décharge d'ACTH (Facteur ACTH-hypophysiotrope ou CRF)" (Essential criteria for the characterization of the hypothalamic ACTH-releasing factor [ACTH-hypophysiotrophic factor or CRF]). In: Courrier, R. and Guillemin, R., *Etudes d'Endocrinologie. 2. Rapports entre le Complexe Hypothalamo-Hypophysaire et la Fonction Adréno-corticotrope*, pp. 309-316. Paris: Hermann, 1961.

J12,262/61

Guillemin, R.: "Diabète insipide par lésion stéréotaxique de l'hypothalamus et fonction adréno-corticotrope. Rôle de la vasopressine dans la décharge de l'ACTH" (Diabetes in-

sipidus following stereotaxic lesion of the hypothalamus and adrenocorticotropic function. Role of vasopressin in the release of ACTH). In: Courrier, R. and Guillemin, R., *Etudes d'Endocrinologie. 2. Rapports entre le Complexe Hypothalamo-Hypophysaire et la Fonction Adréno-corticotrope*, pp. 285-297. Paris: Hermann, 1961 (27 refs.).

J12,261/61

Schally, A. V., Lipscomb, H. S., Guillemin, R.: "Isolation and amino acid sequence of α_2 -corticotropin-releasing factor (α_2 -CRF) from hog pituitary glands." *Endocrinology* **71**: 164-173 (1962).

D28,202/62

Brief review of the literature on three members of the family of CRF peptides: β -CRF (related to vasopressin), α_1 -CRF, and α_2 -CRF, both derivatives of MTH with regard to structure and physiologic activity. The isolation of α_2 -CRF is described in detail (42 refs.).

Arimura, A., Long, C. N. H.: "Effect of intracarotid injection of pitressin, pitocin, epinephrine and acetylcholine on ACTH release in rats." *Jap. J. Physiol.* **12**: 423-428 (1962).

D39,230/62

In rats, vasopressin (pitressin) was most active in causing ACTH release.

Schally, A. V., Lipscomb, H. S., Long, J. M., Dear, W. E., Guillemin, R.: "Chromatography and hormonal activities of dog hypothalamus." *Endocrinology* **70**: 478-480 (1962).

D21,865/62

Leeman, S. E., Glenister, D. W., Yates, F. E.: "Characterization of a calf hypothalamic extract with adrenocorticotropin-releasing properties: evidence for a central nervous system site for corticosteroid inhibition of adrenocorticotropin release." *Endocrinology* **70**: 249-262 (1962) (51 refs.).

D36,341/62

Guillemin, R., Schally, A. V., Lipscomb, H. S., Andersen, R. N., Long, J. M.: "On the presence in hog hypothalamus of β -corticotropin releasing factor, α - and β -melanocyte stimulating hormones, adrenocorticotropin, lysine-vasopressin and oxytocin." *Endocrinology* **70**: 471-477 (1962).

D21,864/62

Brodish, A., Long, C. N. H.: "ACTH-releasing hypothalamic neurohumor in peripheral blood." *Endocrinology* **71**: 298-306 (1962).

D29,046/62

In hypophysectomized, but not in intact rats, an ACTH-releasing factor could be demonstrated in peripheral blood even after

adrenalectomy or treatment with large doses of cortisol but not after lesions of the hypothalamus. "It is concluded that the ACTH-releasing substance observed in the peripheral circulation of hypophysectomized animals is indeed a specific hypothalamic neurohumor for the regulation of ACTH secretion from the anterior pituitary."

Schally, A. V., Guillemin, R.: "Isolation and chemical characterization of a β -CRF from pig posterior pituitary glands." *Proc. Soc. Exp. Biol. Med.* **112**: 1014-1017 (1963).
D66,021/63

Guillemin, R., Schally, A. V.: "Recent advances in the chemistry of neuroendocrine mediators originating in the central nervous system." In: Nalbandov, A. V., *Advances in Neuroendocrinology*, pp. 314-328. Urbana, Ill.: University of Illinois Press, 1963 (52 refs.).
J12,264/63

Yates, F. E., Yates, M. B., Marcus, R.: "Corticotropin-releasing activity of lysyl-8-vasopressin tested by direct pituitary micro-injection." *Program 46th Ann. Meeting Endocr. Soc.*, p. 164. San Francisco, 1964.
F71,529/64

Guillemin, R.: "Hypothalamic factors releasing pituitary hormones." *Rec. Prog. Horm. Res.* **20**: 89-121 (1964) (219 refs.).
E4,212/64

McCann, S. M., Schally, A. V., Nallar, R., Bowers, C. Y.: "Evidence for separate corticotrophin- and luteinizing hormone-releasing factors in hypothalamic extracts." *Proc. Soc. Exp. Biol. Med.* **117**: 435-438 (1964).
F25,188/64

Saffran, M.: "Discussion: hypothalamic factors releasing pituitary hormones." *Rec. Prog. Horm. Res.* **20**: 126 (1964).
E3,939/64

Brief summary of evidence indicating that CRF is not identical with vasopressin.

Vernikos-Danellis, J.: "Estimation of corticotropin-releasing activity of rat hypothalamus and neurohypophysis before and after stress." *Endocrinology* **75**: 514-520 (1964).
F22,529/64

The CRF activity of posterior lobe extract is thought to be largely accounted for by vasopressin and is not measurable after acute stress. The CRF activity appears to be concentrated in the ME, and increases rapidly after stress (surgery under ether).

Ganong, W. F., Wise, B. L., Shackleford, R., Boryczka, A. T., Zipf, B.: "Site at which α -ethyltryptamine acts to inhibit the secretion of ACTH." *Endocrinology* **76**: 526-530 (1965).
F33,025/65

In dogs, α -ethyltryptamine decreased 17-OHCS output after surgical stress, even if most of the CNS was removed except for "hypothalamic islands." However, direct stimulation of the ME produced 17-OHCS secretion which could not be blocked by α -ethyltryptamine. Perhaps the compound "may prevent stimulation of the CRF-secreting neurons by impulses in the incoming afferent fibers." Although α -ethyltryptamine is a MAO inhibitor, its blockage of ACTH secretion is so transient that it seems unlikely to be related to MAO inhibition. Besides, other MAO inhibitors do not share this effect.

Evans, J. S., Nikitovitch-Winer, M. B.: "Reactivation of hypophysial grafts by continuous perfusion with median eminence extracts (MEE)." *Fed. Proc.* **24**: 190 (1965).
F35,942/65

Bovine ME extracts, continuously infused through the renal artery in young hypophysectomized rats with pituitary autografts in the kidney, produced ovarian follicles with enlargement of the adrenal and thyroid. This work furnishes "direct evidence that the hypothalamic neurohumors act not only as 'releasing' factors but also have tropic effects on many other phases of adenohypophysial function."

Vernikos-Danellis, J.: "Effect of rat median eminence extracts on pituitary ACTH content in normal and adrenalectomized rats." *Endocrinology* **76**: 240-245 (1965).
F31,470/65

In rats a single intracarotid injection of ME extract increased the ACTH content of the pituitary. This response was particularly marked after adrenalectomy. "It is concluded that the close similarity in the pattern of the changes in pituitary ACTH content after stress or after the administration of median eminence extracts suggests that the median eminence plays an important role in bringing about the changes in ACTH synthesis and secretion caused by stress."

Dhariwal, A. P. S., Antunes-Rodrigues, J., Krulich, L., McCann, S. M.: "Separation of growth hormone-releasing factor (GHRF) from corticotrophin-releasing factor (CRF)." *Neuroendocrinology* **1**: 341-349 (1966).
G44,208/66

Harris, G. W., Reed, M., Fawcett, C. P.: "Hypothalamic releasing factor and the control of anterior pituitary function." *Br. Med. Bull.* **22**: 266-272 (1966). G41,014/66

Dhariwal, A. P. S., Antunes-Rodrigues, J., Reeser, F., Chowers, I., McCann, S. M.: "Purification of hypothalamic corticotrophin-releasing factor (CRF) of ovine origin." *Proc. Soc. Exp. Biol. Med.* **121**: 8-12 (1966). F61,356/66

Fraschini, F., Motta, M., Martini, L.: "Methods for the evaluation of hypothalamic hypophysiotropic principles." In: Mantegazza, P. and Piccinini, F., *Methods in Drug Evaluation* (Proc. Int. Symp., Milano, 1965), pp. 424-457. Amsterdam: North-Holland, 1966 (nearly 200 refs.).

J12,272/66

McCann, S. M., Dhariwal, A. P. S.: "Hypothalamic releasing factors and the neurovascular link between the brain and the anterior pituitary." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 1, pp. 261-296. New York and London: Academic Press, 1966. E6,487/66

Excellent review, wherein evidence indicating that the pituitary "is actually controlled by a new family of polypeptide neurohormones from the SME region is detailed. At present writing, it appears that the anterior lobe is controlled by six specific factors, one for each tropin secreted by the gland. Five of these factors cause the release of the tropin in question, while one, the PIF, inhibits release of prolactin. All of these factors appear to be small basic polypeptides dissimilar from the known neurohypophyseal hormones, vasopressin and oxytocin" (about 120 refs.).

Mess, B., Fraschini, F., Motta, M., Martini, L.: "The topography of the neurons synthesizing the hypothalamic releasing factors." In: Martini, L., Fraschini, F. et al., *Proceedings of the Second International Congress on Hormonal Steroids, Milan, 1966*. Amsterdam: Excerpta Medica, 1967.

J12,173/67

Purves, H. D., Sirett, N. E.: "Corticotrophin secretion by ectopic pituitary glands." *Endocrinology* **80**: 962-968 (1967).

F75,878/67

In hypophysectomized adult rats, five neonatal pituitaries implanted under the kidney capsule partially maintained adrenal weight, but the peripheral plasma corticosterone lev-

els were not significantly higher than in hypophysectomized controls. One hour after stress (ether, urethane, hemorrhage, restraint), significant elevations of peripheral plasma corticosterone were noted. The response to hemorrhage in the graft-bearing rats was inhibited by dexamethasone at very low dose levels ineffective in normal controls. Infusion of lysine vasopressin released corticotrophin from the grafts, but only at very high dose levels. "The results are ascribed to an accumulation of a physiological corticotrophin releasing factor in the peripheral circulation leading to a delayed release of corticotrophin from the grafts."

Arimura, A., Saito, T., Schally, A. V.: "Assays for corticotropin-releasing factor (CRF) using rats treated with morphine, chlorpromazine, dexamethasone and Nembutal." *Endocrinology* **81**: 235-245 (1967).

F87,059/67

Upon administration of CRF preparations from rat stalk ME, β -CRF, α -CRF and hypothalamic CRF, rats pretreated with chlorpromazine, morphine and Nembutal showed consistently greater rises in plasma corticosterone than those given dexamethasone, morphine and Nembutal. "This suggests a direct suppression of the CRF activity by dexamethasone." These and other observations also indicate that chlorpromazine + morphine + Nembutal-treated rats "have many advantages as a new assay preparation for CRF and can be used with greater ease and reliability."

Schally, A. V., Müller, E. E., Arimura, A., Bowers, C. Y., Saito, T., Redding, T. W., Sawano, S., Pizzolato, P.: "Releasing factors in human hypothalamic and neurohypophyseal extracts." *J. Clin. Endocrinol. Metab.* **27**: 755-762 (1967).

F80,601/67

Egdahl, R. H.: "Excitation and inhibition of ACTH secretion." In: James, V. H. T. and Landon, J., *Memoirs of the Society for Endocrinology*, No. 17, pp. 29-37. Cambridge: Cambridge University Press, 1968.

E7,496/68

Résumé of the author's numerous publications concerning the diverse stimuli of pituitary-adrenocortical secretion (drugs, extremes of temperature, nervous stimulation, oligemia and so on). "Although most examples of inhibition of ACTH secretion may be explained on the basis of nervous pathways, it is difficult to interpret adrenal cortical hypersecretion in dogs with isolated pituitaries

without suggesting the existence of a CNS hormone inhibitory to pituitary ACTH secretion."

Schally, A. V., Arimura, A., Bowers, C. Y., Kastin, A. J., Sawano, S., Redding, T. W.: "Hypothalamic neurohormones regulating anterior pituitary function." *Rec. Prog. Horm. Res.* **24**: 497-588 (1968) (about 250 refs.). E8,349/68

Doepfner, W.: "The influence of neurohypophysial polypeptides on adenohypophysial function." In: Eichler, O., Farah, A. et al., *Handbuch der Experimentellen Pharmakologie*, Vol. XXIII, pp. 625-654. Berlin, Heidelberg and New York: Springer-Verlag, 1968. E7,707/68

Handbook article on the influence of hypothalamic-releasing factors upon anterior pituitary function, with special reference to ACTH secretion during stress (several hundred refs.).

Hiroshige, T., Sato, T., Ohta, R., Itoh, S.: "Increase of corticotropin-releasing activity in the rat hypothalamus following noxious stimuli." *Jap. J. Physiol.* **19**: 866-875 (1969). G73,482/69

In both intact and adrenalectomized rats, various stressors (vasopressin, EP, histamine, ether, laparotomy, formalin, noise, light) increased the CRF activity of the ME, as demonstrated by an intrapituitary microinjection method. There was considerable circadian variation in their response. Adrenalectomy itself caused no change in hypothalamic CRF (25 refs.).

Hiroshige, T., Sakakura, M., Itoh, S.: "Physiological significance of hypothalamic CRF in the regulation of ACTH secretion." *Gunma Symp. Endocrinol.* **6**: 231-247 (1969). H22,288/69

In rats, various stressors produced an increase in the CRF content of the hypothalamus (intrapituitary microinjection assay technique), although no such result was obtained with adrenalectomy. This is possibly due to autoinhibition by endogenous ACTH, since pretreatment with ACTH blocks the rise in CRF induced by ether anesthesia.

Bergland, R. M., Torack, R. M.: "An electron microscopic study of the human infundibulum." *Z. Zellforsch. Mikrosk. Anat.* **99**: 1-12 (1969). G69,072/69

EM observations on the human infundibulum (obtained for biopsy during hypophysectomy) "support other evidence that two

types of neural control are involved in anterior pituitary regulation, but a more precise correlation between structure and function is not possible. The vascular bed of the neural infundibulum is characterized by blood vessels whose structure ranks them with venules."

Brodish, A.: "Effect of hypothalamic lesions on the time course of corticosterone secretion." *Neuroendocrinology* **5**: 33-47 (1969). H19,454/69

"Increased corticosterone secretion was not detected in rats with hypothalamic lesions during the 2 h period following laparotomy, unilateral adrenalectomy, or cold stress (2°C). However, such animals did exhibit elevated levels of corticosterone in the plasma 4 h after the onset of the stress." This delayed hypersecretion of corticosterone was prevented by hypophysectomy or dexamethasone blockade. Treatment with multiple stressors (ether, cold, laparotomy, unilateral adrenalectomy) accelerated the corticosterone response. Apparently, in lesioned animals with endogenous CRF deficiency, a transient increase in ACTH secretion can be obtained two to four hours after the onset of stress. However, a rapid release of ACTH is produced in the rats with hypothalamic lesions when blood from hypophysectomized donors (which presumably contains much CRF) is injected.

Wied, D. de, Witter, A., Versteeg, D. H. G., Mulder, A. H.: "Release of ACTH by substances of central nervous system origin." *Endocrinology* **85**: 561-569 (1969).

G75,450/69

In rats in which blockade of ACTH secretion was attempted with pentobarbital, atropine, chlorpromazine, morphine, dexamethasone or posterior lobe extirpation, the ACTH-releasing effects of prostaglandin E, angiotensin II, arginine vasopressin, carbachol and so on were found to be active under some conditions and inactive under other conditions. However, "the anterior pituitary in vitro was the only assay system in which the crude CRF was the sole material which effectively triggered the release of ACTH."

Dhariwal, A. P. S., Russell, S. M., McCann, S. M., Yates, F. E.: "Assay of corticotropin-releasing factors by injection into the anterior pituitary of intact rats." *Endocrinology* **84**: 544-556 (1969). H10,012/69

In the rat, CRF is more active in provok-

ing ACTH release when given into the adenohypophysis than when introduced into the ME after pretreatment with dexamethasone, Nembutal or morphine.

Mulder, A. H., Geuze, J. J., Wied, D. de: "Studies on the subcellular localization of corticotrophin releasing factor (CRF) and vasopressin in the median eminence of the rat." *Endocrinology* 87: 61-79 (1970).

H25,067/70

Gradient centrifugation and EM studies in rats "suggest that the major part of both CRF and vasopressin is localized in nerve endings and stored in granules within these endings. However, the different localization patterns in the subfractions containing the synaptosomes may indicate that production, transport and release of CRF and vasopressin take place in separate neurones within the hypothalamus" (37 refs.).

Burgus, R., Guillemin, R.: "Hypothalamic releasing factors." *Annu. Rev. Biochem.* 39: 499-526 (1970). H27,402/70

Review on all hypothalamic releasing factors with a section on CRF (143 refs.).

Marks, B. H., Hall, M. M., Bhattacharya, A. N.: "Psychopharmacological effects and pituitary-adrenal activity." *Prog. Brain Res.* 32: 57-70 (1970). J11,401/70

The mechanism of CRF release was studied in rats by a technique whose main characteristics are described as follows: "Basically, median eminence fragments were extracted with acid. The lyophilized and reconstituted extracts were then incubated with pituitary halves from normal female donor rats. The ACTH released into the medium was biologically assayed by measuring its effect on the adrenal corticosterone content of dexamethasone-blocked assay rats. Within a limited range, the ACTH released is proportional to the amount of CRF in the incubation medium." When directly added to the latter, even large amounts of monoamines did not produce ACTH secretion, and hence alterations in monoamine content of the hypothalamus by drugs should not influence the results of CRF measurements. ACTH secretion was greatly enhanced by chlorpromazine and intraperitoneal reserpine in vivo. At the same time the CRF content of the ventral hypothalamus decreased markedly under the influence of these two drugs. In rats, treatment with pargyline (a MAO inhibitor) before reserpine increased the brain content of catecholamine and 5-

HT, and reversed the behavioral effects of reserpine. At the same time, it markedly reduced the burst of ACTH secretion in response to acute stressors (ether, laparotomy). On the basis of these and other observations, it is proposed that, "in the rat, psychopharmacologic agents may initiate marked and persistent changes in the rate of CRF release by acting upon neural mechanisms in the brain which control this process. Those drugs which produce cholinergic effects or which block central adrenergic activity increase the rate of CRF secretion. Those drugs which augment adrenergic activity or which block central cholinergic processes reduce the rate of CRF secretion."

Mess, B., Zanisi, M., Tima, L.: "Site of production of releasing and inhibiting factors." In: Martini, L., Motta, M. et al., *The Hypothalamus*, pp. 259-276. New York and London: Academic Press, 1970. J12,267/70

Review on the production of various adenohypophyseal hormone-releasing or release-inhibiting factors, among which the following are discussed:

Hypothalamic Factors

- Corticotropin Releasing Factor¹
- Fractions of CRF²
- Thyrotropin Releasing Factor³
- Luteinizing Hormone Releasing Factor⁴
- Growth Hormone Releasing Factor⁵
- Follicle-Stimulating Hormone Releasing Factor⁶
- Melanocyte-Stimulating Hormone Releasing Factor⁷
- Prolactin Releasing Factor (pigeon)⁸
- Prolactin Inhibiting Factor (mammals)⁹
- Melanocyte-Stimulating Hormone Inhibiting Factor¹⁰
- Growth Hormone Inhibiting Factor¹¹

¹ Saffran et al. (1955)

² Guillemin et al. (1960); Schally et al. (1962); Schally et al. (1962)

³ Shibusawa et al. (1959)

⁴ McCann et al. (1960)

⁵ Franz et al. (1962)

⁶ Igarashi and McCann (1964)

⁷ Taleisnik and Orias (1965)

⁸ Kragt and Meites (1965)

⁹ Pasteels (1962)

¹⁰ Kastin (1965)

¹¹ Krulich et al. (1967)

(Reproduced from Martini, Motta et al., *The Hypothalamus* (1970), Table 1, p. 260, with permission of B. Mess et al. and Academic Press.)

There is good evidence that all of these factors originate in different but closely situated regions of the basal hypothalamus. However, "extrahypothalamic structures, belonging mainly to the limbic system (e. g. amygdala complex, habenular region, and hippocampus) or to the lower brain stem (e.g. reticular formation of the mesencephalon) might influence the rate of synthesis or release of these different hypothalamic mediators, either by direct or indirect neuronal connections with the hypophysiotropic area or by some indirect interglandular interplay."

Hiroshige, T., Sato, T.: "Postnatal development of circadian rhythm of corticotropin-releasing activity in the rat hypothalamus." *Endocrinol. Jap.* **17**: 1-6 (1970).

H27,251/70

In rats a circadian rhythm in plasma corticosterone, with a peak in the evening and a nadir in the morning, as well as concurrent circadian variations in the hypothalamic CRF content, become detectable only at about three weeks of age.

Meites, J. (ed.): *Hypophysiotropic Hormones of the Hypothalamus: Assay and Chemistry* (Proc. Workshop Conf., Tucson, Ariz., 1969), p. 338. Baltimore: Williams & Wilkins, 1970.

E10,577/70

Proceedings of a conference containing special sections written by outstanding experts on CRF and other chemical transmitters of impulses for adenohypophyseal activity during stress.

Hiroshige, T.: "Various stresses and ACTH releasing factor (CRF) of the hypothalamus." *Adv. Neurol. Sci. (Tokyo)* **14**: 178-184 (1970) (Japanese).

J24,252/70

Hiroshige, T., Sato, T.: "Circadian rhythm and stress-induced changes in hypothalamic content of corticotropin-releasing activity during postnatal development in the rat." *Endocrinology* **86**: 1184-1186 (1970).

H25,238/70

In rats, the development of a circadian rhythm in CRF activity becomes evident between the fourteenth and twenty-first day of postnatal life, whereas responsiveness to stressors is manifest by the seventh day. "The hypothalamic CRF may at least be one of the rate-limiting phases in the mechanism of stress nonresponsiveness during the first few days of postnatal life in the rat."

Hiroshige, T., Sato, T.: "Changes in hypothalamic content of corticotropin-releasing

activity following stress during neonatal maturation in the rat." *Neuroendocrinology* **7**: 257-270 (1971). H42,531/71

Even fetal hypothalamic tissue exhibited an immediate increment of CRF after stress, but the plasma corticosterone rise was delayed, perhaps because of immaturity of the portal vessels. "Since the pituitary glands of the 2-day-old neonates contained ACTH, to which their own adrenals were quite responsive, it is most likely that inability of CRF release from the hypothalamus may be a cause of non-responsiveness to stress during this specific period. Furthermore, since a fetal response to stress as well as a day-1 neonatal responsiveness was clearly observed, it is probable that the day-2 neonatal non-responsiveness is a result of the previous activity associated with delivery and not a developmental rate limitation as suggested by others."

Hiroshige, T., Sato, T., Abe, K.: "Dynamic changes in the hypothalamic content of corticotropin-releasing factor following noxious stimuli: delayed response in early neonates in comparison with biphasic response in adult rats." *Endocrinology* **89**: 1287-1294 (1971).

H48,432/71

Takebe, K., Kunita, H., Sakakura, M., Horiochi, Y., Mashimo, K.: "Suppressive effect of dexamethasone on the rise of CRF activity in the median eminence induced by stress." *Endocrinology* **89**: 1014-1019 (1971).

H47,039/71

In rats, dexamethasone blocks the stress-induced (surgery) rise in the CRF level of the ME and in the plasma corticosterone concentration. The pituitaries of dexamethasone-treated rats respond to ME extract in a normal manner. It is concluded that dexamethasone-induced inhibition acts mainly at or above the hypothalamic level.

Drzhevetskaia, I. A., Borodin, A. D.: "Corticotropin-releasing activity of rat hypothalamic extracts under stress conditions." *Patol. Fiziol. Éksp. Ter.* **15** Nos. 5-6: 42-45 (1971) (Russian).

J21,370/71

In rats, exposure to various stressors (ether, histamine, insulin) or uninephrectomy increased the CRF content of the hypothalamus during the alarm reaction, but this was followed by a decrease if the stress situation was prolonged.

Witorsch, R. J., Brodish, A.: "Evidence for acute ACTH release by extrahypotha-

lamic mechanisms." *Endocrinology* **90**: 1160-1167 (1972). H54,745/72

Following stress induced by laparotomy, ether or hemorrhage, the "rapid increases in plasma corticosterone in rats bearing ventral hypothalamic lesions, expanded hypothalamic lesions and pituitary islands provide evidence for the existence of extrahypothalamic pathways for acute ACTH release in rats."

Rhees, R. W., Abel, J. H. Jr., Frame, J. R.: "Effect of osmotic stress and hormone therapy on the hypothalamus of the duck (*Anas platyrhynchos*)."
Neuroendocrinology **10**: 1-22 (1972). H58,144/72

Péczely, P.: "Effect of ether stress on CRF-ACTH system of the domestic pigeon."
Acta Biol. Acad. Sci. Hung. **23**: 23-29 (1972). G99,695/72

"In 15 min after the stress, the CRF activity and the ACTH content of the pituitary gland decreased by 17 and 55 per cent, respectively, and the corticosterone production of the adrenals increased by 218 per cent."

Takebe, K., Sakakura, M.: "Circadian rhythm of CRF activity in the hypothalamus after stress."
Endocrinol. Jap. **19**: 567-570 (1972). J17,033/72

In intact, adrenalectomized, or hypophysectomized rats, the increment in the CRF content of the ME was greatest after ether stress at 08:00, and slightest at 18:30. The final poststress level was essentially the same, but the resting level was highest in the late afternoon. "Thus it is likely that the response of ACTH release to stimulus is not influenced by the diurnal rhythm of plasma corticoids or ACTH, but is related to other factors such as inherent neural sensitivity to stress."

Zarrow, M. X., Campbell, P. S., Denenberg, V. H.: "Handling in infancy: increased levels of the hypothalamic corticotropin releasing factor (CRF) following exposure to a novel situation."
Proc. Soc. Exp. Biol. Med. **141**: 356-358 (1972). H60,966/72

Observations on rats confirmed "previous findings that handled animals release less corticosterone than nonhandled animals when exposed to a novel environment.... A functionally different mechanism for release of CRF may exist as a result of infantile stimulation."

Seiden, G., Brodish, A.: "Persistence of a

diurnal rhythm in hypothalamic corticotrophin-releasing factor (CRF) in the absence of hormone feedback."
Endocrinology **90**: 1401-1403 (1972). H54,781/72

By use of an improved pituitary incubation method, "a diurnal rhythm of hypothalamic CRF activity in hypophysectomized rats was detected which parallels the rhythm found in intact rats. Absolute levels of hypothalamic CRF activity were higher in the hypophysectomized rats than in the intact rats at all times of the day tested." Although ACTH and/or corticoids influence the concentration of CRF, the diurnal rhythm of its activity is independent of hormonal feedback.

Nelson, D. H.: "Regulation of glucocorticoid release."
Am. J. Med. **53**: 590-594 (1972). G95,722/72

Résumé of the factors regulating glucocorticoid release during stress, with special emphasis upon the role of CRF.

Guillemin, R., Burgus, R.: "The hormones of the hypothalamus."
Sci. Am. **227**: 24-33 (1972). G95,674/72

Semipopular review on the releasing factors of the hypothalamus.

Hiroshige, T., Abe, K.: "Dynamics of activity of hypothalamic corticotropin releasing factor in the rat."
J. Physiol. Soc. Jap. **34**: 529-530 (1972). H79,788/72

In rats the circadian rhythm in hypothalamic CRF content (with a peak in the afternoon and a nadir in the morning) develops after two to three weeks of postnatal life, whereas responses to stress occur as early as the seventh day. The circadian rhythm persists in the absence of circulating corticosterone and hence appears to be dependent only upon nervous regulation, not upon negative feedback.

Lymangrover, J. R., Brodish, A.: "Tissue CRF: an extra-hypothalamic corticotrophin releasing factor (CRF) in the peripheral blood of stressed rats."
Neuroendocrinology **12**: 225-235 (1973). H67,204/73

In rats bearing extensive ventral hypothalamic lesions, extra-hypothalamic CRF activity was demonstrable in the blood.

Chowers, I., Siegel, R., Conforti, N., Feldman, S.: "Effect of acute neurogenic stress on hypothalamic corticotropin-releasing factor content."
Isr. J. Med. Sci. **9**: 1056-1058 (1973). H77,289/73

The stressor effect of sound (strong bell)

depletes the hypothalamic CRF considerably within four minutes, following a rapid initial rise. CRF was assayed by the in vitro pituitary incubation method.

Guillemin, R.: "Hypothalamic hormones: releasing and inhibiting factors." *Hosp. Pract.* November, 1973, pp. 111-120.

J13,316/73

Brief but excellent review of the history of CRF and other releasing factors, with illustrations and a description of present-day knowledge.

Hiroshige, T.: "CRF assay by intrapituitary injection through the parapharyngeal approach and its physiological validation." In: Brodish, A. and Redgate, E. S., *Brain-Pituitary-Adrenal Interrelationships*, pp. 57-78. Basel, München and New York: S Karger, 1973 (about 70 refs.). J19,024/73

Mess, B.: "Localization of production and mechanism of release of the releasing factors." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 54-72. Tokyo: Igaku Shoin, 1974. E10,860/74

Fortier, C.: "New frontiers in neuroendocrinology." In: Mogenson, G. J. and Calaresu, F. R., *Stevenson Memorial Volume on "The Limbic System,"* Chapter 13, pp. 2-24. Toronto: University of Toronto Press, 1974. J12,064/74

A review on the origin and nature of the various releasing factors, with special reference to a cAMP-dependent protein kinase in initiating the synthesis and discharge of adenohypophyseal hormones.

Brodish, A., Sakakura, M.: "Tissue-CRF: properties, secretion and action of a potent stimulator of the pituitary-adrenal system." *Fed. Proc.* 33: 206 (1974). H83,820/74

Tissue-CRF activity was detected in the blood of stressed rats (by infusion into rats with hypothalamic lesions), although it was relatively unstable at room temperature. It was also demonstrable in the plasma of hypophysectomized rats bearing hypothalamic lesions, and in these it increased for an even longer period after laparotomy.

Lymangrover, J. R., Brodish, A.: "Physiological regulation of tissue-CRF." *Neuroendocrinology* 13: 234-245 (1974).

H81,875/74

Intact rats generally show a transient but immediate discharge of ACTH after exposure to acute stress, with a return to

normal within two hours. This response, ascribed to CRF from the ME (ME-CRF), is usually not seen after hypothalamic lesions, but under certain conditions there is a delayed ACTH secretion two to four hours later due to tissue-CRF release from sites other than the hypothalamus. In rats with hypothalamic lesions, stressors (laparotomy, rapid injection of pooled plasma from heparinized ether-anesthetized donors) caused delayed ACTH secretion after two to eight hours. When ME-CRF or ACTH was administered at the time of exposure to the stressor, the delayed response was suppressed and plasma corticosterone remained near normal. In hypophysectomized, lesioned donor rats, laparotomy caused a delayed increase in the blood concentration of tissue-CRF, which could be suppressed by pretreatment with ACTH at the time of laparotomy. "Tissue-CRF may be released in conditions of severe stress when the hypothalamic-CRF mechanism is inadequate to provide the sustained elevated levels of pituitary-adrenal secretions in time of need."

Grant, G. F., Vale, W.: "Hypothalamic control of anterior pituitary hormone secretion. Characterized hypothalamic-hypophysiotropic peptides." *Curr. Top. Exp. Endocrinol.* 2: 37-72 (1974). J13,593/74

Review on the various hypothalamic-releasing and release-inhibiting factors in which CRF is barely mentioned (91 refs.).

Dallman, M. F., DeManincor, D., Shin-sako, J.: "Diminishing corticotrope capacity to release ACTH during sustained stimulation: the twenty-four hours after bilateral adrenalectomy in the rat." *Endocrinology* 95: 65-73 (1974). H88,113/74

Observations on rats given extracts of rat ME or hypothalamus at different intervals after bilateral adrenalectomy suggest that the triphasic curve in plasma ACTH normally seen after this operation is due to alterations in the capacity of the adenohypophysis to secrete ACTH during sustained stimulation of CRF. The findings agree with the assumption that CRF secretion increases a few minutes after adrenalectomy and remains high thereafter. However, following adrenalectomy or application of chronic stressors, the adenohypophysis has a transiently decreased capacity to release ACTH, despite the sustained rise in CRF secretion.

Csernus, V., Lengvári, I., Halász, B.: "Data on the localization of CRF-producing

neural elements." *Gen. Comp. Endocrinol.* **22:** 360 (1974). H83,188/74

In rats, adenohypophyseal tissue was implanted into different hypothalamic regions and then the pituitary was removed. ACTH secretion was estimated by plasma corticosterone levels and found to be raised only in those rats in which the implant was in contact with the ME. It is concluded that only the ME contains enough CRF to cause a significant ACTH secretion.

Cerebrospinal Fluid (CSF)

(See also our earlier stress monographs, p. xiii)

Myers, R. D., Sharpe, L. G.: "Cerebrospinal fluid production during temperature stress and feeding in the conscious monkey." *Experientia* **25:** 497-498 (1969).

H13,633/69

Various stressors increase CSF production.

Loon, G. R. van, Scapagnini, U., Cohen, R., Ganong, W. F.: "Effect of intraventricular administration of adrenergic drugs on the adrenal venous 17-hydroxycorticosteroid response to surgical stress in the dog." *Neuroendocrinology* **8:** 257-272 (1971).

H48,631/71

In dogs, intraventricular administration of several adrenergic drugs blocks 17-OHCS secretion in response to laparotomy. The same is true of the catecholamine precursor L-dopa and the MAO inhibitor α -ethyltryptamine. On the other hand, tyramine (which releases catecholamines from nerve endings) inhibits the 17-OHCS response when given intraventricularly but not when given systemically. "These data support our previously presented hypothesis that a central adrenergic neural system inhibits ACTH secretion in dogs."

Kendall, J. W., Jacobs, J. J., Kramer, R. M.: "Studies on the transport of hormones from the cerebrospinal fluid to hypothalamus and pituitary." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 342-349. Basel and New York: S Karger, 1972. E10,557/72

Studies in rats on the possible transport of hormones regulating adenohypophyseal function. "(1) CSF median eminence-pituitary transport was considered possible because radioactivity appeared in the median

eminence and pituitary promptly after injection of radioactive hormones into the ventricular system of rats. (2) The possibility of physiologically significant transport of TRH [thyrotrophin releasing hormone] in CSF was considered unlikely because TRH was no more effective in causing TSH secretion when administered in the lateral ventricle than in the saphenous vein of rats. (3) Previous studies of CSF transport of cortisol and thyroxin were reviewed and a general conclusion was made: in judging the significance of implantation experiments designed to localize sites of hormone effects in the brain, the possibility of transport of the hormone in CSF from the placement site to another receptor site must be considered."

Leonhardt, H., Eberhardt, H. G.: "Dye transport from the median eminence to the hypothalamic wall." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 335-341. Basel and New York: S Karger, 1972. E10,571/72

In rats, supravital dyes can pass from the blood vessels of the ME into the hypothalamic wall by way of the CSF. EM observations show that "the underlying tissue of the ependyma of the hypothalamic wall contains numerous large basement membranes which form a labyrinth of ramified extrusions. This labyrinth is also directed at the ventricle up to a distance of 1 μ ."

Diencephalon, Mesencephalon (Midbrain)

(See also our earlier stress monographs, p. xiii)

Hess, W. R.: *Functional Organization of the Diencephalon*, p. 40. New York: Grune & Stratton, 1957. E10,658/57

Newman, A. E., Redgate, E. S., Farrell, G.: "The effects of diencephalic-mesencephalic lesions on aldosterone and hydrocortisone secretion." *Endocrinology* **63:** 723-736 (1958). J12,363/58

In cats, destruction of the ventral diencephalon reduced, whereas transection of the midbrain reticular formation did not alter, aldosterone or cortisol secretion into the adrenal venous blood. An even greater reduction in aldosterone-cortisol levels was obtained by lesions in the reticular formation of the midbrain and caudal diencephalon. On the other hand, aldosterone secretion was

significantly increased without affecting cortisol release when the lesions extended into the rostral half of the pons.

Slusher, M. A., Critchlow, V.: "Effect of midbrain lesions on ovulation and adrenal response to stress in female rats." *Proc. Soc. Exp. Biol. Med.* **101**: 497-499 (1959).

C72,442/59

In female rats, coagulating lesions in the posterior portion of the midbrain and the level of rostral pons caused "increased corticosterone secretion into adrenal venous effluent in response to surgical stress. Lesions in posterior diencephalon and rostral midbrain structures resulted in depressed corticosterone secretion. Adrenal ascorbic acid response to stress was not correlated with corticosterone response. Ovulation was blocked in rats with brain lesions in any of these areas where concomitant mammillary peduncle damage was present."

Egdahl, R. H.: "The effect of brain removal, decortication and midbrain transection on adrenal cortical function in dogs." *1st Int. Congr. Endocrinology*, pp. 49-50. Copenhagen, 1960.

J12,258/60

Comparative studies on dogs with complete bilateral decortication, brain removal, spinal cord and midbrain transection. The high resting corticoid outputs after midbrain transection suggest that cerebral inhibition of some hindbrain factor-releasing area is effected through nervous, and not humoral, pathways. "Adrenal cortical responses to nerve stimulation are less than maximal in these animals, and this would seem to indicate that it is the hind brain center rather than the hypothalamic one which has been activated to result in ACTH release." [The brief abstract does not lend itself to critical evaluation (H.S.).]

Martini, L., Pecile, A., Saito, S., Tani, F.: "The effect of midbrain transection on ACTH release." *Endocrinology* **66**: 501-507 (1960).

C84,071/60

In rats, midbrain transection interferes with ACTH secretion during stress.

Suzuki, T., Romanoff, E. B., Koella, W. P., Levy, C. K.: "Effect of diencephalic stimuli on 17-hydroxycorticosteroid secretion in unanesthetized dogs." *Am. J. Physiol.* **198**: 1312-1314 (1960).

C90/173,60

In unanesthetized dogs, stimulation of the posterior hypothalamic or lower thalamic areas by implanted electrodes increases 17-OHCS secretion. Stimulation of the upper

posterior hypothalamic area or the area pre-optica causes only a slight rise in 17-OHCS release followed by a marked decrease to below normal. Stimulation of the capsula interna produces no change.

Endrőczi, E., Lissák, K.: "The role of the mesencephalon, diencephalon and archicortex in the activation and inhibition of the pituitary-adrenocortical system." *Acta Physiol. Acad. Sci. Hung.* **17**: 39-55 (1960).

C91,648/60

In cats and dogs, electric stimulation of the reticular formation and of the posterior hypothalamus caused changes in adrenocortical secretion similar to those elicited by chronic ACTH treatment. "Lesions of the septum affecting the afferent and efferent connections of the rhinencephalon considerably influenced the adrenocortical activity. As to the function of the archicortex, the existence of a modifying and inhibitory regulation was assumed, which manifests itself both in the behaviour of the animals and the activity of the pituitary-adrenocortical system."

Davis, J. O., Anderson, E., Carpenter, C. C. J., Ayers, C. R., Haymaker, W., Spence, W. T.: "Aldosterone and corticosterone secretion following midbrain transection." *Am. J. Physiol.* **200**: 437-443 (1961).

D2,868/61

In dogs, "complete midbrain transection does not interfere with the high rate of aldosterone secretion which occurs in response to acute blood loss or following caval constriction if venous pressure is maintained at the high control level."

Ahrén, C.: "Effects of diencephalic lesions on acute and chronic stress responses in male rabbits." *Acta Endocrinol. (Kbh.)* **41** Supp. 69: 1-92 (1962).

D38,126/62

Monograph on the effects of variously placed diencephalic lesions upon the stress response of rabbits given formalin subcutaneously. "The results indicate that the lymphopenic response was completely blocked by small, circumscribed lesions in the region of the dorsomedial and ventromedial nuclei as well as by lesions in the posterior border of the mammillary bodies and the region dorso-caudal thereto, whilst it remained unaffected by lesions in the premammillary area or in the anterior half of all the mammillary bodies. Lesions in the anterior preoptic area and posterior orbitofrontal cortex, in the ventro-caudal septum or in the anterior hypo-

lamic area dorsocaudal to the optic chiasm were associated with partial inhibition, and occasionally even with total blockage, of the lymphopenic response." The findings do not permit conclusions concerning any particular region which would represent a "center" of such stress responses in the limbic structures or mesencephalon.

Kendall, J. W. Jr., Allen, C., Greer, M. A.: "ACTH secretion in midbrain-transected rats." *Endocrinology* 77: 1091-1096 (1965). F58,070/65

In midbrain-transected rats, basal plasma corticosterone levels are high during the first two days postoperatively, and ether anesthesia induces them to rise even further. Dexamethasone suppresses plasma corticosterone in these animals as it does in normals. Apparently, both stimulatory and inhibitory influences can act on ACTH secretion after midbrain transection, and there is no evidence for a "tonic inhibitory neural center" in ACTH release.

Slusher, M. A., Hyde, J. E.: "Effect of diencephalic and midbrain stimulation on ACTH levels in unrestrained cats." *Am. J. Physiol.* 210: 103-108 (1966).

F59,593/66

In unrestrained cats with chronically implanted electrodes, "measurable ACTH was released 1-2 min after stimulation of sites in dorsal midbrain, or four of eight sites in diencephalon; 30 min later, levels were again below the minimum detectable. Inhibition of the pituitary-adrenal axis was demonstrated by paired stimulation of a potentially inhibitory site with a demonstrably facilitative one: diencephalically evoked release of ACTH was blocked by concurrent stimulation of sites in the ventral midbrain or the preoptic region."

Cross, B. A., Kitay, J. I.: "Unit activity in diencephalic islands." *Exp. Neurol.* 19: 316-330 (1967).

J11,315/67

Warburton, D. M.: "Modern biochemical concepts of anxiety. Implications for psychopharmacological treatment." *Int. Pharmacopsychiatry* 9: 189-205 (1974).

J21,388/74

In man, "corticosteroids produce agitation and enhance anxiety. It is proposed that anxiety results from the neurochemical changes induced by corticosteroids. Evidence was presented to show that the critical changes for anxiety are due to modifications

in serotonin pathways in the tegmental region of the midbrain."

Ependyma

(See also our earlier stress monographs, p. xiii, and cf. Median Eminence [ME], Tuber Cinereum)

Löfgren, F.: "New aspects of the hypothalamic control of the adenohypophysis." *Acta Morphol. Neerl. Scand.* 2: 220-229 (1959).

J12,061/59

In newborn rats the ependymal cells in the recessus infundibuli are "irregularly multilayered with a 'broken-up' appearance," and display interstices communicating with the recess which seem to carry colloid-like substances. Presumably they bear "secretory substances which are transported to the pars distalis via the cerebrospinal fluid and a glial-vascular chain."

Löfgren, F.: "The glial-vascular apparatus in the floor of the infundibular cavity. Further studies on the transport mechanism between the hypothalamus and the anterior pituitary." *Lunds Univ. Arsskrift* 57: 1-18 (1961).

D6,827/61

The peculiar type of glial and ependymal elements in the infundibular process might play a role in pituitary hormone secretion, as indicated by morphologic evidence.

Lévéque, T. F., Hofkin, G. A.: "Demonstration of an alcohol-chloroform insoluble, periodic acid-Schiff reactive substance in the hypothalamus of the rat." *Z. Zellforsch. Mikrosk. Anat.* 53: 185-191 (1961).

J12,876/61

"An alcohol-chloroform insoluble, periodic acid-Schiff reactive substance associated with the ependymal lining of the supraoptic and infundibular recesses was demonstrated in the hypothalamus of the white rat." This special ependyma is stratified, but contains long processes throughout the extent of the recess in which the PAS-reactive substance is present.

Vigh, B., Aros, B., Wenger, T., Koritsán-szky, S., Ceglédi, G.: "Ependymosecretion (ependymal neurosecretion). IV. The Golmori positive secretion of the hypothalamic ependyma of various vertebrates and its relation to the anterior lobe of the pituitary." *Acta Biol. Acad. Sci. Hung.* 13: 407-419 (1963).

J12,756/63

The Gomori-positive substance in certain regions of the ependyma in the third ventricle of various species represents an "ependymo-secretion" or "ependymal neurosecretion" and is probably "an important factor in the correlation between hypothalamus and anterior pituitary."

Kumar, T. C. A.: "Sexual differences in the ependyma lining the third ventricle in the area of the anterior hypothalamus of adult rhesus monkeys." *Z. Zellforsch. Mikrosk. Anat.* **90**: 28-36 (1968).

J12,543/68

Sexual differences in the tanycyte ependyma in contact with the ME furnish additional evidence supporting the view that these cells play an important role in the regulation of adenohypophyseal function.

Kumar, T. C. A.: "Modified ependymal cells in the ventral hypothalamus of the rhesus monkey and their possible role in the hypothalamic regulation of anterior pituitary function." *J. Endocrinol.* **41**: xvii-xviii (1968).

H2,338/68

Description of special ependymal cells lining the ventral hypothalamus which contain argyrophilic and PAS-positive granules and processes extending toward the ME. Their ultrastructure also suggests endocrine activity. They become degranulated after ovariectomy, this being prevented by estrogen treatment. These cells show morphologic changes related to sexual maturity and the menstrual cycle. "The observations made in this study suggest a possible role for these glandular cells in the hypothalamic regulation of anterior pituitary function."

Duvernoy, H., Koritke, J. G.: "Les vaisseaux sous-épendymaires du recessus hypophysaire" (Subependymal vessels of the hypophyseal recessus). *J. Hirnforsch.* **10**: 227-245 (1968).

J12,676/68

Extensive histologic studies on the subependymal origins of the hypothalamo-adeno-hypophyseal portal vessels in various mammals and birds. There exist numerous connections between the subependymal vessels and the cavity of the third ventricle from which they are separated only by a thin and often discontinuous ependymal membrane. "Such a structure will possibly allow exchanges between the blood of the hypophysis and the ventricular liquid which is continuously in motion in the third ventricle."

Knigge, K. M., Scott, D. E.: "Structure

and function of the median eminence." *Am. J. Anat.* **129**: 223-244 (1970).

G78,982/70

Mainly on the basis of ME studies, the authors question the view that all neurosecretory cells concerned with releasing factors are restricted to a small region of the basal hypothalamus and transport their products through axons ending in the contact zone of the ME. "Terminals of the arcuate-tuberoinfundibular system contain populations of clear and dense-core vesicles which have been associated with acetylcholine by morphological inference and some physiological data, with catecholamines by morphological and histochemical correlates, and with releasing hormones largely by physiological studies for which acceptable alternate hypotheses appear possible. The arcuate-tuberoinfundibular fibers contain significant dopaminergic fibers whose role in median eminence function requires elucidation. From morphological criteria, ependymal cells (tanycytes) appear to serve some role which functionally links cerebrospinal fluid of the third ventricle and blood of the primary pituitary portal plexus, this role may be the extraction and transport of some releasing hormones placed in the cerebrospinal fluid at sites distant from the median eminence."

Weindl, A., Joynt, R. J.: "The median eminence as a circumventricular organ." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 280-297. Basel and New York: S Karger, 1972.

E10,569/72

EM studies on the cat, monkey, rat and rabbit suggest that ependymal cells in the ME and organum vasculosum of the lamina terminalis and the area postrema have several unique cytologic features in common. In both, the nonciliated ependymal cells possess long basal processes which are rich in microfilaments and end in the peripheral basal lamina of the perivascular space. "Segregation of homogeneous material from the apical surface of ependymal cells and discharge into the ventricular fluid are seen in the organum vasculosum of the rabbit. Once this material has reached the ventricular fluid it may be dissolved, and carried to the infundibular recess. After reaching the pericellular environment of arcuate neurons through open gap junctions it may influence their activity."

Scott, D. E., Dudley, G. K., Gibbs, F. P., Brown, G. M.: "The mammalian median

eminence. A comparative and experimental model." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 35-49. Basel and New York: S Karger, 1972.
E10,565/72

Extensive studies in the cat, rat and monkey using transmission and scanning EM, cytochemistry and vascular perfusion with microfil to assess the function of the neuronal, ependymal and vascular constituents of the ME. The ME of "normal squirrel monkeys exhibited unusually large numbers of dense core vesicles (DCV). The DCV population was increased in rats having undergone bilateral adrenalectomy with subsequent dexamethasone administration. Intermediate range DCV, large osmophilic neurosecretory vesicles and junctional structures between the apical plasmalemma of ventricular ependyma were selectively opacified" with certain reagents, which suggests the presence of some basic amino acid residues. Dense inclusions in ependymal perivascular end-feet, as well as EM alterations in their ventricular apices, indicate the possibility of their participation in fundamental neuroendocrine events.

Bleier, R.: "Structural relationship of ependymal cells and their processes within the hypothalamus. Implications for functional localization." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 306-318. Basel and New York: S Karger, 1972.
E10,570/72

Observations on various mammals showed that ependymal cells extend numerous processes into cell groups within the hypothalamus, connecting with neurons and capillaries. "It is postulated that this ependymal system has a secretory and transport role for substances involved in adenohypophyseal regulation and that it forms a framework for the organization of adenohypophyseal functional localization within the hypothalamus."

Calas, A., Hartwig, H. G., Collin, J. P.: "Noradrenergic innervation of the median eminence. Microspectrofluorimetric and pharmacological study in the duck, *Anas platyrhynchos*." *Z. Zellforsch. Mikrosk. Anat.* 147: 491-504 (1974).
J13,342/74

Fluorescent microscopic demonstration of noradrenergic but not of dopaminergic fibers in the subependymal layer of the ME in the duck.

Fornix

(See also our earlier stress monographs, p. xiii)

Nauta, W. J. H.: "An experimental study of the fornix system in the rat." *J. Comp. Neurol.* 104: 247-271 (1956).
J12,752/56

Histologic studies tracing the course of the fornix system after hippocampal lesions in the rat.

Nakadate, G. M., Groot, J. de: "Fornix transection and adrenocortical function in rats." *Anat. Rec.* 145: 338 (1963).

J11,290/63

After complete bilateral transection of the fornix in rats, the circadian variations of corticosterone production disappeared.

Moberg, G. P., Scapagnini, U., Groot, J. de, Ganong, W. F.: "Effect of sectioning the fornix on diurnal fluctuation in plasma corticosterone levels in the rat." *Neuroendocrinology* 7: 11-15 (1971).
H36,762/71

In rats, sectioning of the fornix abolishes the circadian variations in plasma corticosterone by raising the lowest and decreasing the highest values during the day.

Scapagnini, U., Preziosi, P.: "Role of brain norepinephrine and serotonin in the tonic and phasic regulation of hypothalamic hypophyseal adrenal axis." *Arch. Int. Pharmacodyn Ther.* 196 Suppl.: 205-220 (1972).

H56,654/72

Résumé of the literature and the extensive experiments of the authors and their co-workers led to the following main conclusions: (1) There is an adrenergic system in the brain that inhibits ACTH secretion. Drugs that release active catecholamines from nerve endings block ACTH discharge if they can pass the blood-brain barrier or are injected directly into the third ventricle or ME. Stressors deplete brain NEP and increase ACTH secretion. Admittedly, the amount of drugs necessary for inhibition is large compared to the normal catecholamine levels present in the brain, and hence their action is of doubtful physiologic significance. They may act merely by constricting the portal vessels so that CRF cannot reach an adequate concentration in the adenohypophysis. Among the drugs used to explore the ACTH inhibitory adrenergic mechanism were: amphetamine, α -ethyltryptamine, L-dopa, tyramine, α -MT, guanethidine, FLA-63 (an inhibitor of dopamine- β -oxidase), L-threo-dihydroxy-phenyl-serine ("DOPS")

which selectively repletes NEP after depletion of NEP and dopamine by α -MT, phentolamine (an α -blocking agent) and so on. (2) 5-HT appears to regulate the circadian variations of ACTH secretion by the limbic system. Its concentration is particularly high in the raphé nuclei (containing the highest level of serotonergic cell bodies), particularly the amygdala and hippocampus, in which it shows circadian variations. Destruction of these nuclei abolishes circadian plasma corticosterone rhythm.

Lengvári, I., Halász, B.: "Evidence for a diurnal fluctuation in plasma corticosterone levels after fornix transection in the rat." *Neuroendocrinology* 11: 191-196 (1973).

H68,128/73

In rats, immediately after transection of the fornix, the circadian variations in plasma corticosterone disappeared, although they reappeared a few weeks after this operation. It is concluded that "contrary to the assumption of other authors, the fornix is not the key structure in the mediation of extrahypothalamic influences to the medial basal hypothalamus that are essential for the diurnal rhythm in plasma corticosterone levels."

Brown, G. M., Uhlir, I. V., Seggie, J., Schally, A. V., Kastin, A. J.: "Effect of septal lesions on plasma levels of MSH, corticosterone, GH and prolactin before and after exposure to novel environment: role of MSH in the septal syndrome." *Endocrinology* 94: 583-587 (1974). H86,300/74

In rats, septal lesions considerably altered hormonal reactions to various stressors, and concurrently there were pronounced behavioral changes. The literature on the "septal syndrome" is reviewed (26 refs.).

Habenula

(See also our earlier stress monographs, p. xiii)

Milne, R., Stern, P.: "Effect of reserpine on the stressogenic reactivity of habenular-pineal complex." *Anat. Rec.* 136: 243-244 (1958). C95,318/58

In hares, fear caused regressive changes in the internal nuclear habenular ganglion which could be prevented by reserpine. Allegedly, the "results show that the habenular-pineal complex has an important role in the

neuroendocrinology of the general adaptation syndrome."

Nielson, H. C., McIver, A. H.: "Cold stress and habenular lesion effects on rat behaviors." *J. Appl. Physiol.* 21: 655-660 (1966) (30 refs.). G37,781/66

Postnov, Y. V., Strakhov, E. V., Glukhovets, B. I., Gorkova, S. I.: "Hypothalamic neurosecretory nuclei and nucleus habenularis of epithalamus in essential hypertension." *Virchows Arch. [Pathol. Anat.]* 364: 275-283 (1974). H95,408/74

"In patients with essential hypertension, morphological signs of functional hypertrophy were observed in the nucleus habenularis of the epithalamus."

Hippocampus

(See also our earlier stress monographs, p. xiii, and cf. Limbic System)

Kim, C., Kim, C. U.: "Effect of partial hippocampal resection on stress mechanism in rats." *Am. J. Physiol.* 201: 337-340 (1961). D11,353/61

In rats with hippocampal lesions, the adrenal ascorbic acid depletion caused by acute stress was increased, and the rise after chronic stress diminished. Presumably, "the hippocampus exerts a sustained inhibitory influence upon the pituitary-adrenocortical mechanism."

Knigge, K. M.: "Adrenocortical response to stress in rats with lesions in hippocampus and amygdala." *Proc. Soc. Exp. Biol. Med.* 108: 18-21 (1961). D14,359/61

After lesions were placed in the amygdala, the rise in plasma free corticoid levels of rats exposed to the stress of restraint was greatly delayed but not prevented. Lesions in the hippocampus did not alter the chronologic pattern of this stress response, but the basal plasma free corticoid levels were above normal (29 refs.).

Knigge, K. M.: "Adrenocortical response to immobilization in rats with lesions in hippocampus and amygdala." *Fed. Proc.* 20: 185 (1961). D3,983/61

In dogs the resting free plasma corticosterone levels are increased after hippocampal lesions, while lesions in the amygdala depress

the rise in corticoid blood levels after immobilization.

Endrőczi, E., Lissák, K.: "Interrelations between palaeocortical activity and pituitary-adrenocortical function." *Acta Physiol. Acad. Sci. Hung.* **21**: 257-263 (1962).

J11,528/62

In cats, stimulation of the dorsal hippocampus at low frequencies inhibited ACTH release by painful stressors, whereas stimulation at high frequencies increased corticoid output.

Knigge, K. M., Hays, M.: "Evidence of inhibitory role of hippocampus in neural regulation of ACTH release." *Proc. Soc. Exp. Biol. Med.* **114**: 67-69 (1963).

E29,658/63

In rats, plasma corticoid levels rose after ether anesthesia and hemorrhage. Bilateral electrolytic lesions in the midbrain reticular formation or the amygdaloid nuclei suppressed or blocked this response. In such unresponsive animals, additional lesions in the hippocampus negated the block. It is concluded that the "hippocampus contributes an inhibitory component to the neural mechanisms regulating ACTH release."

Mandell, A. J., Chapman, L. F., Rand, R. W., Walter, R. D.: "Plasma corticosteroids: changes in concentration after stimulation of hippocampus and amygdala." *Science* **139**: 1212 (1963). D59,312/63

In patients in whom electrodes were implanted for the evaluation of psychomotor epilepsy, stimulation of the amygdala caused a rise in 17-OHCS, whereas hippocampal stimulation resulted in a decrease.

Liberson, W. T., Bernsohn, J., Wilson, A., Daly, V.: "Brain serotonin content and behavioral stress." *J. Neuropsychiatry* **5**: 363-365 (1964). D17,697/64

In guinea pigs, prolonged hypnosis training significantly decreased the 5-HT content of the cortex and hippocampus, and to a lesser degree, of the brain stem and cerebellum.

McEwen, B. S., Weiss, J. M., Schwartz, L. S.: "Retention of corticosterone by cell nuclei from brain regions of adrenalectomized rats." *Brain Res.* **17**: 471-482 (1970).

J12,015/70

In adrenalectomized rats, nuclear uptake of labeled corticosterone was highest in the

hippocampus, but was also demonstrable in the amygdala and cerebral cortex.

Dupont, A., Bastarache, E., Endrőczi, E., Fortier, C.: "Effect of hippocampal stimulation on the plasma thyrotropin (TSH) and corticosterone responses to acute cold exposure in the rat." *Can. J. Physiol. Pharmacol.* **50**: 364-367 (1972). H54,958/72

In rats, exposure to cold increases both plasma TTH and corticosterone concentration, but concurrent minor environmental stress (presence of observer) suppresses the TTH response and enhances the rise in corticosterone. Concurrent stimulation of the gyrus dentatus of the hippocampus by implanted electrodes restores the TTH response to cold and inhibits the rise in corticosterone. Presumably, "the concurrent stimulation of ACTH release and inhibition of TSH [TTH] secretion induced by nonspecific stress are possibly related to depressed hippocampal activity."

Viru, A., Allikmets, L., Körge, P., Laidna, A.: "Adrenocortical activity during prolonged exertions in rats with lesions in the hippocampus and amygdala." *Estonian Contr. Int. Biol. Program, Tartu, Rep. No. 4*, 145-154 (1973). H86,933/73

After prolonged swimming, the corticoid content of the blood and adrenals decreases in sham-operated and amygdalectomized, but not in hippocampectomized rats. Presumably, "during the prolonged muscular activity, the decrease of the adrenocortical activity is caused by the inhibitory influence from the hippocampus in the regulation of pituitary adrenocorticotropic function."

Yanase, M.: "A study on the role of brain for the establishment of adaptation to the repeated immobilization stress. II. A role of the limbic-midbrain system in the repeated immobilization stress." *J. Physiol. Soc. Jap.* **35**: 171-178 (1973) (Japanese). J17,716/73

In rabbits, ACTH release following repeated restraint diminished as a consequence of adaptation. This was not found after sectioning of the fornix. "Therefore, hippocampal inhibition of ACTH release is considered to correlate with the inhibition of ACTH release under the repeated stress, and hippocampus may play an important role in the establishment of adaptation to the stress."

Wilson, M., Critchlow, V.: "Effect of

fornix transection or hippocampectomy on rhythmic pituitary-adrenal function in the rat." *Neuroendocrinology* **13**: 29-40 (1974).

H81,373/74

In rats, ablation of the hippocampo-fornix system does not disturb the circadian rhythm of plasma corticosterone variations either under nonstress conditions or after ether stress. Dexamethasone produces normal suppression of corticosterone levels.

Kawakami, M., Terasawa, E., Arita, J.: "Effects of hippocampal ablation on stress-induced gonadotropin secretion: an observation of the sexual difference." *Endocrinol. Jap.* **21**: 289-296 (1974). H96,221/74

Various stressors increased FSH in females and in orchidectomized, folliculoid-pretreated males, but this effect was suppressed by hippocampal ablation. Serum LH was not altered by stressors in either sex. "Hippocampal ablation, however, brought about LH release in stressed females and abolished stress-induced increase in LH in orchidectomized estrogen primed males."

Zippel, U., Kolle, U., Gabriel, H.-J., Rüdiger, W.: "Das Entladungsverhalten hippocampaler Neurone unter dem Einfluss eines emotionell negativen bedingten Reizes" (Spike activity of the hippocampus during the influence of an emotionally negative conditioned stimulus). *Acta Biol. Med. Ger.* **32**: 643-649 (1974). J20,836/74

Observations on rats suggest that "emotionally positive stimuli produce an increase in the inhibitory responses in contrast to emotionally negative stimuli which predominantly provoke facilitatory reactions of hippocampal neurones."

Segal, M., Bloom, F. E.: "The action of norepinephrine in the rat hippocampus. I. Iontophoretic studies." *Brain Res.* **72**: 79-97 (1974). J12,390/74

"It is suggested that NE is a neurotransmitter candidate in the hippocampus and that it may act via the cyclic AMP system."

Segal, M., Bloom, F. E.: "The action of norepinephrine in the rat hippocampus. II. Activation of the input pathway." *Brain Res.* **72**: 99-114 (1974). J12,391/74

Baylé, J.-D., Bouillé, C.: "Activité corticosurrénalienne après lésion de l'hippocampe chez le pigeon" (The adrenal cortex function after lesion of the hippocampus in the pigeon). *Gen. Comp. Endocrinol.* **22**: 360-361 (1974). H83,189/74

Bilateral electrolytic lesions of the hippocampus in pigeons raise the basic plasma corticosterone level. The response to immobilization stress is only slightly reduced. Conversely, stimulation of the hippocampus diminishes plasma corticosterone.

Storm-Mathisen, J., Guldberg, H. C.: "5-hydroxytryptamine and noradrenaline in the hippocampal region: effect of transection of afferent pathways on endogenous levels, high affinity uptake and some transmitter-related enzymes." *J. Neurochem.* **22**: 793-803 (1974). J13,464/74

Hypothalamus and Thalamus

(See also our earlier stress monographs, p. xiii, and cf. Stalk, Portal Vessels)

Smith, P. E.: "The disabilities caused by hypophysectomy and their repair. The tuberal (hypothalamic) syndrome in the rat." *J.A.M.A.* **88**: 158-161 (1927).

2,779/27

In rats "a lesion of the hypothalamic region of the brain (tuber cinereum) gives rise to a syndrome which is distinct from that caused by pituitary ablation. This tuberal syndrome is characterized by extreme obesity and an atrophy of the genital system; neither the thyroids nor the suprarenal cortex atrophy."

Krieg, W. J. S.: "The hypothalamus of the albino rat." *J. Comp. Neurol.* **55**: 19-89 (1932). B26,941/32

Excellent description of seventeen nuclei that are subdivided and schematically reproduced to show their spatial relations (about 50 refs.).

Houssay, B. A., Biasotti, A., Sammartino, R.: "Modifications fonctionnelles de l'hypophyse après les lésions infundibulo-tubériennes chez le crapaud" (Functional changes of the hypophysis after lesions of the lobus infundibularis in toads). *C.R. Soc. Biol. (Paris)* **120**: 725-727 (1935). 56,016/35

In the toad the hypothalamus consists of a pars basalis, lamina terminalis and lobus infundibularis. The latter is attached to the hypophysis. Lesions of the lobus infundibularis cause circulatory arrest in the principal lobe of the hypophysis with increased absorption of MTH, darkening of the animal, and other hormonal derangements.

Ranson, S. W., Fisher, C., Ingram, W. R.: "Adiposity and diabetes mellitus in a monkey with hypothalamic lesions." *Endocrinology* **23**: 175-181 (1938). A17,002/38

In rhesus monkeys, hypothalamic lesions conducive to diabetes mellitus and adiposity were not associated with any detectable adrenal change.

Ranson, S. W., Magoun, H. W.: "The hypothalamus." *Ergeb. Physiol.* **41**: 56-163 (1939). A19,119/39

Monograph on the structure and function of the hypothalamus, with special reference to its anatomy, neural connections with other parts of the CNS, and the influence of hypothalamic lesions upon psychic disturbances, somnolence, pituitary function, adiposity, carbohydrate metabolism, diabetes insipidus and thermoregulation (approximately 300 refs.).

Scharrer, E., Scharrer, B.: "Secretory cells within the hypothalamus." *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **20**: 170-194 (1940). 78,342/40

Excellent and well-illustrated review of secretory neurons in the hypothalamus of various vertebrates.

Dankmeijer, J., Nauta, W. J. H.: "Studies on the hypothalamic region of the diencephalon. II. The magnocellular hypothalamic nuclei of the guinea-pig." *Acta Neur. Morphol.* **5**: 363-377 (1945). B61,953/45

Harris, G. W.: "Neural control of the pituitary gland." *Physiol. Rev.* **28**: 139-179 (1948). B26,619/48

A classic review on nervous factors controlling pituitary activity in which the author describes his first observations on the regulation of ACTH secretion by the hypothalamus during stress (450 refs.).

McDermott, W. V., Fry, E. G., Brobeck, J. R., Long, C. N. H.: "Release of adrenocorticotropic hormone by direct application of epinephrine to pituitary grafts." *Proc. Soc. Exp. Biol. Med.* **73**: 609-610 (1950). B48,233/50

"Homologous grafts of pituitary tissue to the anterior chamber of the eye of the hypophysectomized rat retain the ability to secrete ACTH, both spontaneously and in response to activation by epinephrine. The effect of epinephrine in releasing ACTH may be brought about by its direct application to anterior pituitary tissue."

Nowakowski, H.: "Infundibulum und Tu-

ber cinereum der Katze" (The infundibulum and the tuber cinereum in the cat). *Dtsch. Z. Nervenheik* **165**: 261-339 (1951).

B60,898/51

Detailed anatomic studies on the structure of the tuber and infundibulum of the cat, with special reference to its possible role in the regulation of adenohypophyseal secretion.

Porter, R. W.: "Alterations in electrical activity of the hypothalamus induced by stress stimuli." *Am. J. Physiol.* **169**: 629-637 (1952). B74,875/52

"In cats and monkeys, a marked increase in electrical activity, limited to the posterior hypothalamus, was induced by epinephrine and other stimuli, the stressful nature of which was indicated by a resulting eosinopenia. Minimal electrocortical changes also occurred, but hypothalamic discharge was uninfluenced by decortication or by transection of the lower brain stem. Considered generally, these results provide added support for participation of the brain in the pituitary-adrenal response to stress."

Hume, D. M.: "The relationship of the hypothalamus to the pituitary secretion of ACTH." In: Wolstenholme, G. E. W., *Ciba Found. Colloquia on Endocrinology*, Vol. 4, pp. 87-99. London: J & A Churchill, 1952. B76,068/52

Harris, G. W.: "The hypothalamus and regulation of ACTH secretion." In: Ralli, E. P., *Adrenal Cortex*, pp. 54-88. New York: Josiah Macy Jr., Foundation, 1952.

B70,924/52

Proceedings of a symposium in which the hypothalamic control of ACTH secretion was discussed by a number of specialists (36 refs.).

Bogdanove, E. M., Halmi, N. S.: "Effects of hypothalamic lesions and subsequent propylthiouracil treatment on pituitary structure and function in the rat." *Endocrinology* **53**: 274-292 (1953). B86,246/53

In rats with lesions in various parts of the hypothalamus, administration of propylthiouracil inhibited adrenal and/or thyroid enlargement, but the number of animals was small and adrenal size too variable to draw definite conclusions concerning the exact location of the various regulating centers.

Knoche, H.: "Ueber das Vorkommen eigenartiger Nervenfasern (Nodus-fasern) in Hypophyse und Zwischenhirn von Hund

und Mensch" (The occurrence of peculiar nerve fibers [nodulus fibers] in the hypophysis and the hypothalamus of the dog and man). *Acta Anat.* 18: 208-223 (1953).

B85,818/53

In the dog and man, "there are nervous 'nodulus fibres' in the tuber cinereum, the nucleus supraopticus, nucleus paraventricularis and in the neurohypophysis. The nerve fibres show nodules of different size or ring-like structures; they join the nerve cells of the tuber cinereum and they are continued into the peripheral part of the infundibulum." They are readily demonstrable with the silver impregnation (Gomori and Nissl) technique, but their functional significance is unknown.

Porter, R. W.: "I. Nervous system—Hormone interrelationships. The central nervous system and stress-induced eosinopenia." *Rec. Prog. Horm. Res.* 10: 1-18 (1954).

B98,592/54

In rhesus monkeys the nervous regulation of the pituitary-adrenocortical response to stress was demonstrated by the following observations: "1) Increased electrical activity was noted in the posterior hypothalamus on application of certain acute stress stimuli. 2) The integrity of the hypothalamus was essential for the production of stress-induced eosinopenia. 3) Electrical excitation of this region evoked a marked eosinopenia. It was concluded that although many regions of the brain can modify the eosinopenic response to an acute stress stimulus, the hypothalamus alone is essential for its manifestation."

Xuereb, G. P., Prichard, M. M. L., Daniel, P. M.: "The hypophysial portal system of vessels in man." *Q. J. Exp. Physiol.* 39: 219-230 (1954).

C5,988/54

Folkow, B., Euler, U. S. von: "Selective activation of noradrenaline and adrenaline producing cells in the cat's adrenal gland by hypothalamic stimulation." *Circ. Res.* 2: 191-195 (1954).

J12,802/54

In cats, stimulation of different parts of the hypothalamus may lead to secretion of either EP or NEP. Presumably, "the two hormones are secreted from different cells with separate innervation."

McCann, S. M., Sydnor, K. L.: "Blood and pituitary adrenocorticotrophin in adrenalectomized rats with hypothalamic lesions." *Proc. Soc. Exp. Biol. Med.* 87: 369-373 (1954).

E53,302/54

In adrenalectomized rats subjected to

stress (ether, hemorrhage), lesions of the ME inhibited ACTH secretion and also interrupted the supraopticohypophyseal tract (causing diabetes insipidus).

McCann, S. M., Brobeck, J. R.: "Evidence for a role of the supraopticohypophyseal system in regulation of adrenocorticotrophin secretion." *Proc. Soc. Exp. Biol. Med.* 87: 318-324 (1954).

J9,398/54

In rats, variously placed hypothalamic lesions which block ACTH secretion (as indicated by adrenal ascorbic acid depletion, adrenal weight, plasma ACTH) always destroy large areas of the supraopticohypophyseal tract and cause diabetes insipidus. Large doses of vasopressin stimulate ACTH secretion in these rats. "It appears likely, therefore, that destruction of the median eminence is not a necessary condition for blockade of the stress response and that destruction of a large percentage of the supraopticohypophyseal tract is the most constant feature in rats with effective lesions of the hypothalamus."

Hume, D. M., Nelson, D. H.: "Effect of hypothalamic lesions on blood ACTH levels and 17-hydroxycorticosteroid secretion following trauma in the dog." *J. Clin. Endocrinol. Metab.* 15: 839 (1955).

C7,110/55

Katsuki, S., Ikemoto, T., Shimada, H., Hagiwara, F., Kanai, J.: "The functional relationship between the hypothalamus and the anterior pituitary-adrenal system." *Endocrinol. Jap.* 2: 304-312 (1955).

C31,375/55

In cats, electric stimulation of the posterior hypothalamus caused an increase in the corticoid content of adrenal venous blood, whereas stimulation of the middle part of the hypothalamus resulted in considerable catecholamine secretion.

Bogdanove, E. M., Spirtos, B. N., Halmi, N. S.: "Further observations on pituitary structure and function in rats bearing hypothalamic lesions." *Endocrinology* 57: 302-315 (1955).

D78,841/55

Endrőczi, E., Mess, B.: "Einfluss von Hypothalamusläsionen auf die Funktion des Hypophysen-Nebennierenrinden-Systems" (Effect of hypothalamic lesions on the hypophyseal-adrenal system). *Endokrinologie* 33: 1-8 (1955).

C10,158/55

In rats the effects of stereotaxic lesions placed in various parts of the hypothalamus suggest that only lesions in the region of the tuber cinereum inhibit the increase in ACTH

secretion produced by EP or unilateral adrenalectomy (11 refs.).

Born, F.: "Neurosecretion in man under strain. I. A survey and a contribution." *Acta Psychiatr. Scand.* **30**: 65-76 (1955).

J25,483/55

The structure of the supraoptic nucleus is compared in controls and in patients who died of protracted psychic or somatic stress. Studies indicate that "both the character and the intensity of the terminal stress is determinative of the degree of vacuolization, resp. of the neurosecretory activity changes."

Anand, B. K., Dua, S.: "Hypothalamic involvement in the pituitary adreno-cortical response." *J. Physiol. (Lond.)* **127**: 153-156 (1955).

C6,203/55

In unanesthetized cats with permanently implanted electrodes, it was found that "after stimulating the medial part of the anterior and middle hypothalamic regions (anteromedial region of the median eminence of tuber cinereum), the average reduction in eosinophil count was 25% or more of the original level. It is therefore assumed that these hypothalamic regions are concerned with ACTH secretion."

Ganong, W. F., Fredrickson, D. S., Hume, D. M.: "The effect of hypothalamic lesions on thyroid function in the dog." *Endocrinology* **57**: 355-362 (1955).

C8,317/55

In dogs, hypothalamic lesions just above the anterior end of the ME produced thyroid atrophy that was not necessarily correlated with a deficient eosinopenic response to stress or gonadal atrophy. Apparently, the exact position of the lesion determines which trophic function is destroyed.

Cleghorn, R. A.: "The hypothalamic-endocrine system." *Psychosom. Med.* **17**: 367-376 (1955) (77 refs.).

D79,914/55

Noda, H., Sano, Y., Oki, S., Saito, O.: "Ueber den neurosekretorischen Tractus tuberohypophyseus. I. Seine Existenz beim Hunde (Beiträge zur vergleichenden Histologie des Hypothalamus-Hypophysensystems. 17. Mitteilung)" (The neurosecretory tractus tuberohypophyseus. I. Its existence in the dog [Comparative histology of the hypothalamic-hypophyseal system. 17th report]). *Arch. Histol. Jap.* **10**: 63-70 (1956) (Japanese, with German summary).

C27,048/56

Description of neurosecretory nerves in the eye that originate in the subependymal

part of the lateral wall of the third ventricle, mostly in the region of the nucleus infundibularis tuberis of Spatz. Their cell bodies are small and are somewhat less tingible with the Gomori system than are the nodular dilatations in their processes, which descend through the tuber towards the hypophysis. It is uncertain whether they reach the latter, but "they undoubtedly represent a neurosecretory pathway between the tuber cinereum and the pituitary region."

Endrőczi, E., Kovács, S., Lissák, K.: "Die Wirkung der Hypothalamusreizung auf das endokrine und somatische Verhalten" (Endocrine and somatic responses to hypothalamic stimulation). *Endocrinologie* **33**: 271-278 (1956).

C23,659/56

Electric stimulation of various regions of the hypothalamus or thalamus in the rat was tested for its ability to cause ACTH secretion. Purely motor reactions produced no endocrine response, and it was concluded that "affective loading" is indispensable for the mobilization of endocrine adaptive phenomena during the G.A.S. Adrenal demedullation did not prevent such responses.

Halász, B.: "Die Rückwirkung von Cortisonzufuhr auf den Bau der Nebennierenrinde nach Hypothalamusläsion" (Retroactive effects of cortisone on the structure of the adrenal cortex after hypothalamic lesions). *Acta Morphol. Acad. Sci. Hung.* **6**: 119-127 (1956).

J13,132/56

In rats, adrenocortical atrophy produced by cortisone is not prevented by lesions in the posterior tuberal nuclei, or by transection of the hypophyseal stalk. However, depletion of lipids in the zona fasciculata and reticularis, as seen in cortisone-treated intact rats, is blocked by lesions in the posterior tuberal region (22 refs.).

Gloor, P.: "Telencephalic influences upon the hypothalamus." In: Fields, W. S., Guillemin, R. et al., *Hypothalamic-Hypophysial Interrelationships. A Symposium*, pp. 74-113. Springfield, Ill.: Charles C Thomas, 1956.

C23,838/56

Saffran, M.: "Stress and the pituitary." (Symposium on Stress, Montreal, November 18, 1955). *Psychiatr. Res. Rep. APA* **7**: 1-9 (1957).

C46,633/57

Brief description of the earliest experiments concerning the hypothalamic regulation of ACTH secretion.

Schmid, R., Gonzalo, L., Blobel, R.,

Muschke, E., Tonutti, E.: "Über die hypothalamische Steuerung der ACTH-Abgabe aus der Hypophyse bei Diphtherie-Toxin-Vergiftung" (The hypothalamic regulation of ACTH release from the hypophysis in poisoning by diphtheria toxin). *Endocrinologie* **34**: 65-91 (1957). D74,892/57

In guinea pigs, selective destruction of anterior or posterior hypothalamic nuclei did not prevent the hemorrhagic necrosis of the adrenals normally produced by bacterial endotoxin. Lesions situated closer to the pituitary stalk did offer protection against this effect.

Endrőczi, E., Kovacs, S., Szalay, G.: "Einfluss von Hypothalamusläsionen auf die Entwicklung des Körpers und verschiedener Organe bei neugeborenen Tieren" (The influence of hypothalamic lesions on the somatic growth and development of various organs in newborn animals). *Endocrinologie* **34**: 168-175 (1957). C32,398/57

In newborn rats and dogs, electrocoagulation in the anterior hypothalamus greatly inhibits somatic growth but does not interfere markedly with the development of internal organs, including the thyroid and adrenals. Similar lesions in the posterior hypothalamus cause no change in somatic growth, but they do inhibit development of the adrenals, liver and kidney.

Slusher, M. A.: "Dissociation of adrenal ascorbic acid and corticosterone responses to stress in rats with hypothalamic lesions." *Endocrinology* **63**: 412-419 (1958).

C58,603/58

In rats, "lesions in the posterior and mid-central portions of the hypothalamus specifically inhibited corticosterone release without altering adrenal ascorbic acid response or the weights of target organs dependent upon the normal production of pituitary hormones. Similarly, lesions in the basal tuberal region inhibited adrenal ascorbic acid depletion without affecting corticosterone release in response to stress." Gross damage to the ME, basal tuberal region, and portal systems blocked both adrenal responses.

Mason, J. W.: "Plasma 17-hydroxycorticosteroid response to hypothalamic stimulation in the conscious rhesus monkey." *Endocrinology* **63**: 403-411 (1958).

C58,602/58

In conscious rhesus monkeys, stimulation of the hypothalamus by implanted electrodes caused a marked elevation of plasma 17-

OHCS, comparable to that obtained by intravenous ACTH. No similar changes were produced by stimulation of the putamen or anterior thalamus.

Hume, D. M.: "Hypothalamic localization for the control of various endocrine secretions." In: Jasper, H. H., Proctor, L. D. et al., *Reticular Formation of the Brain*, pp. 231-262. Boston: Little, Brown, 1958.

C78,257/58

A review of the literature and personal observations on dogs with well-localized electrolytic lesions "suggest that there are three separate zones in the hypothalamus for the control of TSH, ACTH, and GTH [gonadotrophic hormone] secretion. The TSH and ACTH areas overlap and are located in the anterior portion of the median eminence and the postoptic area. The location of the area for the control of the gonadotropic hormones is in the posterior limb of the stalk, completely separate from the area for ACTH and TSH control and well localized to this rather small zone in the hypothalamus" (13 refs.).

Bachrach, D., Kordon, C.: "Suppression de l'hypertrophie surrénalienne compensatrice à la suite de lésions hypothalamiques chez le rat" (Prevention of compensatory hypertrophy of the adrenal following hypothalamic lesions in the rat). *C.R. Acad. Sci. (Paris)* **247**: 2462-2464 (1958).

C90,729/58

In rats, only lesions in the anterior or central part of the basal hypothalamus prevent compensatory hypertrophy of the remaining adrenal following unilateral adrenalectomy.

Smelik, P. G.: "Modifying effect of hypothalamic lesions on the adrenal stress response." *Acta Endocrinol. (Kbh.)* **28** Supp. 38: 84 (1958).

C59,251/58

Destruction of the posterior hypothalamus ("sympathetic area") induces a pronounced adrenal ascorbic acid depletion, while lesions in the anterior hypothalamus ("parasympathetic area") inhibit this response, even after exposure to stress.

Koibuchi, E.: "The effects of hypothalamic lesions of the pituitary-adrenocortical system." *Endocrinol. Jap.* **5**: 89-98 (1958).

C57,340/58

In rats, lesions in the anterior hypothalamus and the anterior part of the medial hypothalamus caused atrophy of the hypophysis and adrenals. These changes were suppressed by vasopressin. "It seemed likely that the control center of ACTH release is found in

the anterior hypothalamus of the anterior part of the medial hypothalamus, and that vasopressin accelerates the release of ACTH."

Hume, D. M.: "The method of hypothalamic regulation of pituitary and adrenal secretion in response to trauma." *Pathophysiol. Diencephal.* 217-228 (1958).

J12,694/58

Daily, W. J. R., Ganong, W. F.: "The effect of ventral hypothalamic lesions on sodium and potassium metabolism in the dog." *Endocrinology* 62: 442-454 (1958).

C50,859/58

In dogs, ventral hypothalamic lesions produced diabetes insipidus with gonadal atrophy and/or inhibition of 17-OHCS secretion in response to surgical trauma. However, none of these animals showed abnormal sodium or potassium metabolism and all withstood salt restriction and salt load in a normal fashion.

Smelik, P. G.: "Autonomic Nervous Involvement in Stress-Induced ACTH Secretion." Thesis, University of Groningen, 1959.

C65,870/59

Doctoral dissertation on hypothalamo-pituitary interrelations. The evidence that CRF is identical with vasopressin is based mainly on the observations that the neurosecretory material mobilized into the portal vessels during stress is associated with a rise of plasma vasopressin, and that commercial vasopressin preparations cause ACTH discharge from the pituitary of cortisol-treated or hypophysectomized rats. However, the demonstration of such a parallelism is no proof of the identity of the two hormones. Furthermore, data are given to indicate that, contrary to the theory of Sayers and Sayers, adrenal stimulation during stress is not due to a drop in blood corticoid levels, and that the corticoid feedback mechanism is not necessarily exerted on both the hypothalamus and pituitary, as postulated by McCann. The author writes that McCann and his associates reported that "in rats bearing hypothalamic lesions which reduced the compensatory adrenal hypertrophy after unilateral adrenalectomy, a further inhibition of this hypertrophy could be obtained by daily administration of hydrocortisone. They assumed, therefore, that corticoids suppress both the release of the CRF and the excitability of the hypophysis itself. This evidence is not convincing, since their

hypothalamic lesions exerted only a partial inhibition of the compensatory adrenal hypertrophy, whereas in our experience median eminence lesions completely inhibit the hypertrophy of the remaining adrenal gland. It is likely that in McCann's experiments the production of the CRF was not entirely inhibited and that consequently hydrocortisone caused a further block of the CRF release."

Egdahl, R. H., Irons, G., Jackson, B. T.: "Pituitary ACTH release in dogs with removal of hypothalamus and higher CNS structures." *Fed Proc.* 18: 41 (1959).

J10,795/59

The authors' earlier experiments showed that removal of the brain down to the hypothalamus does not prevent the maximal release of ACTH following operative trauma. Now it has been demonstrated that if the hypothalamus is removed in addition to the cerebral cortex, hippocampus and thalamus (brain stem intact below the level of the inferior colliculus), the resting 17-OHCS values of adrenal venous blood are increased and will rise even higher after burns. [Histologic examination showed remnants of ME in at least some animals (H.S.).] It is concluded that the pituitary can be activated to secrete ACTH even in the absence of the hypothalamus and higher CNS structures. Dogs with these operations have high resting adrenal corticoid outputs which "could be due to the removal of high CNS inhibition of ACTH release from the pituitary. This would leave a pituitary remarkably sensitive to previously inhibited stimuli. It is possible that intact dogs with hypothalamic lesions fail to show adrenal cortical responses to trauma because of unopposed higher CNS inhibition of pituitary ACTH release."

Knigge, K. M., Penrod, C. H., Schindler, W. J.: "In vitro and in vivo adrenal corticosteroid secretion following stress." *Am. J. Physiol.* 196: 579-582 (1959).

C65,769/59

In rats, scalding or restraint produces an initial biphasic response in ACTH and corticosterone secretion in which the drop is not due to adrenal exhaustion since it occurs at the time when the pituitary contains approximately twice the normal amount of ACTH. "The low level of hormone secretion was replaced by very high levels by treatment of the stressed rat with reserpine or by placement of hypothalamic lesions. At a variable time after stress, corresponding to time of least corticosteroid secretion, there

appears to exist an inability of the pituitary to release ACTH, which may be due to cessation of the initial hypothalamic stimulation or to a neural mechanism which temporarily suppresses or inhibits the secretion of endogenous ACTH."

Kovács, S., Lissák, K., Endrőczi, E.: "Effect of the lesion of paraventricular nucleus on the function of the pituitary, thyroid, adrenal cortex and gonadal systems." *Acta Physiol. Acad. Sci. Hung.* **15**: 137-144 (1959). C72,311/59

In rats, lesions of the paraventricular nucleus decreased the corticoid content of the adrenals. This was interpreted as an indication of adrenal hyperactivity.

Winkler, G., Blobel, R., Tonutti, E.: "17-OH-Corticoidausscheidung bei Meerschweinchen mit Läsionen im mittleren Hypothalamus" (The effect of lesions in the middle region of the hypothalamus on 17-OH-corticoid excretion in guinea pigs). *Acta Neuroveg. (Wien)* **20**: 230-237 (1959). C76,659/59

Smelik, P. G., Bouman, P. R., Wied, D. de: "Influence of hypothalamic lesions on compensatory adrenal hypertrophy." *Acta Physiol. Pharmacol. Neerl.* **8**: 515 (1959). D91,593/59

In rats, destruction of the ME diminished the compensatory hypertrophy of the remaining adrenal following unilateral adrenalectomy. Extensive bilateral lesions in the anterior or posterior hypothalamus did not produce this effect.

Halász, B., Szentágothai, J.: "Histologischer Beweis einer nervösen Signalübermittlung von der Nebennierenrinde zum Hypothalamus" (Histologic evidence of nervous signals from the adrenal cortex to the hypothalamus). *Z. Zellforsch. Mikrosk. Anat.* **50**: 297-306 (1959). J13,010/59

In rats, exposure to stress (formalin) or ACTH causes shrinkage of the nucleus ventromedialis in the hypothalamus with concurrent adrenocortical hypertrophy. Cortisone, adrenalectomy or denervation of the adrenals has an inverse effect. Unilateral adrenalectomy induces nuclear swelling only in the contralateral nucleus ventromedialis. Presumably, the latter receives nervous signals from the contralateral adrenal cortex that may affect its function.

Harris, G. W.: "Central control of pituitary secretion." In: Magoun, H. W., *Hand-*

book of Physiology. Section I. Neurophysiology, Vol. 2, pp. 1007-1038. Washington, D.C.: American Physiological Society, 1960 (366 refs.). E7,322/60

Sayers, G.: "Hypothalamus and adenohypophysis: with special reference to corticotrophin release." *Acta Endocrinol. (Kbh.)* **50** Supp.: 25-31 (1960). C92,384/60

Dear, W. E., Guillemin, R.: "Adrenal sensitivity to ACTH as a function of time after hypothalamic lesion and after hypophsectomy." *Proc. Soc. Exp. Biol. Med.* **103**: 356-358 (1960). C81,326/60

After hypophsectomy or lesion of the ME, sensitivity to ACTH gradually decreases. Hence, it is desirable to use only animals recently operated on for the testing of CRF.

Moll, J.: "Localization of hypothalamic lesions inhibiting adrenal weight maintenance in the rat." *Acta Endocrinol. (Kbh.)* **34**: 19-26 (1960). C84,933/60

An attempt was made to find the center responsible for the maintenance of adrenal weight. Following lesions in the antero-basal and mid-basal hypothalamus the weights of both adrenals were subnormal. Compensatory adrenal hypertrophy was only slightly inhibited by the lesions. Lesions destroying the pituitary stalk and lesions in the median eminence, had no effect on adrenal weight."

D'Angelo, S. A.: "Hypothalamus and endocrine function in persistent estrous rats at low environmental temperature." *Am. J. Physiol.* **199**: 701-706 (1960). C94,846/60

In rats, preoptic and anterior hypothalamic lesions caused persistent estrus and pituitary hypertrophy. Serum TTH, thyroid histology and the ascorbic acid concentration in the adenohypophysis and adrenal remained normal. Exposure to cold caused ovarian atrophy, uterine involution, cessation of estrus and inhibition of the pituitary hypertrophy otherwise noted after the lesions. Despite adrenal enlargement, plasma corticosterone levels in the lesioned rats exposed to cold averaged less than one-third those of controls, and adrenal ascorbic acid concentration remained normal. Presumably, "hypothalamic lesions which permit adequate trophic hormone secretion at normal temperatures drastically curtail thyroidal and ovarian function and selectively limit adrenal responses in the cold."

Endrőczi, E.: "Contributions to the hypothalamic control of pituitary, ovarian and

adrenal cortical function." *Acta Physiol. Acad. Sci. Hung.* 18: 301-307 (1961).

E57,282/61

In rats, electrocoagulation of the anterior hypothalamic area, between the periventricular nucleus optic chiasma and infundibulum extending into the preoptic region, increased uterine weight and induced continuous estrus. ACTH secretion (corticoid level of adrenal venous blood) was augmented. The gonadal changes were enhanced by adrenalectomy but prevented by ovariectomy. It is concluded, "the adrenocortical reaction to the hypothalamic lesion is due to a primarily increased ovarian activity, and that adrenocortical secretion very probably lessens the gonadal changes appearing after hypothalamic lesion."

Ahrén, C.: "The effect of hypothalamic lesions on acute and chronic stress reaction." *Acta Pathol. Microbiol. Scand.* 51 Supp. 144: 145-149 (1961). B46,032/61

Summary of an oral presentation of experiments on rabbits given repeated injections of formaldehyde which indicate that "experimental animals with lesions in the premammillary posterior of the hypothalamus lose their ability to react with an adrenal hyperplasia during chronic stress, while experimental animals with lesions in the corpora mamillaria react with an accentuated adrenal hyperplasia." An acute alarm reaction causes intense lymphopenia within three hours, but this response is not prevented by lesions in the premammillary region or in the corpora mamillaria. "Judging by these partly preliminary results, it appears that different parts of the hypothalamus are engaged in on the one hand the chronic stress reaction and on the other hand the acute alarm reaction. It also appears probable that different parts of the hypothalamus are engaged in the development of the complete adaptation syndrome."

Moll, J., Wied, D. de, Kranendonk, G. H.: "Observations on the thyroid-adrenal relationship in rats with hypothalamic lesions." *Acta Endocrinol. (Kbh.)* 38: 330-340 (1961). D13,092/61

In rats, electrocoagulation of the hypothalamic area between the fornix and the paraventricular nuclei induces adrenal atrophy and decreases corticoid secretion without preventing the adrenal response to stressors.

Halász, B., Pupp, L., Uhlarik, S.: "Hypo-

physiotrophic area in the hypothalamus." *J. Endocrinol.* 25: 147-154 (1962).

D38,273/62

Adenohypophyseal tissue of thirty-day-old rats was transplanted into different regions of the hypothalamus of adult recipients. Grafts in the ventral hypothalamus retained a normal histologic appearance despite lack of contact with the ME. A "hypophysiotrophic" area was detected by the location of basophils in the graft and the maintenance of the target organs for anterior lobe hormones, except that the gonads sometimes underwent atrophy. Grafts in other sites did not maintain their structure or preserve the integrity of the target glands.

Saffran, M.: "Mechanisms of adrenocortical control." *Br. Med. Bull.* 18: 122-126 (1962).

D23,888/62

Review on the mechanism controlling corticoid secretion, especially during stress and under the influence of hypothalamic mediators.

Goldfien, A., Ganong, W. F.: "Adrenal medullary and adrenal cortical response to stimulation of diencephalon." *Am. J. Physiol.* 202: 205-211 (1962).

D20,306/62

In dogs, electric stimulation of sixty-six points in the hypothalamus and adjacent parts of the brain resulted in increased catecholamine and 17-OHCS secretion from certain regions, but the two responses were not necessarily correlated.

Brodish, A.: "Diffuse hypothalamic system for the regulation of ACTH secretion." *Endocrinology* 73: 727-735 (1963).

E35,524/63

In rats, plasma-corticosterone increases in response to ether stress were impeded "following placement of a small lesion in almost any region at the base of the hypothalamus between the optic chiasm and the mammillary bodies." Larger lesions produced even more severe, but never complete suppression of ACTH discharge. The results are interpreted as indicating that "the entire region of the ventral hypothalamus extending from the optic chiasm to the mammillary bodies is involved in ACTH secretion and that a diffuse hypothalamic nucleus or network exists for the control of ACTH secretion rather than a localized discrete center."

Kovács, K.: *Die Rolle des Hypothalamus-Adenohypophysen-Systems im Wasserhaushalt* (The role of the hypothalamo-adeno-hypophyseal system in water metabolism),

p. 237. Szeged, Hungary: University of Szeged, 1963. E2,963/63

Extensive review on the hypothalamus-adenohypophyseal system in the regulation of water metabolism and stress reactions (1477 refs.).

Fortier, C.: "Hypothalamic control of anterior pituitary." In: Euler, U.S. von and Heller, H., *Comparative Endocrinology. I. Glandular Hormones*, pp. 1-24. New York and London: Academic Press, 1963.

E3,687/63

Review on the hypothalamic regulation of all adenohypophyseal hormones, with only one section devoted to stress and ACTH (more than 200 refs.).

Snyder, J., D'Angelo, S. A.: "Hypothalamic stimulation and ascorbic acid content of endocrine glands of the albino rat." *Proc. Soc. Exp. Biol. Med.* **112**: 1-4 (1963).

D54,492/63

In rats, electric stimulation of the preoptic and anterior hypothalamic areas causes adrenal hypertrophy and corpus luteum formation.

Endrőczi, E., Lissák, K.: "Effect of hypothalamic and brain stem structure stimulation on pituitary-adrenocortical function." *Acta Physiol. Acad. Sci. Hung.* **24**: 67-77 (1963). E32,622/63

In cats with electrodes chronically implanted in different hypothalamic structures, "stimulation of the basal septum, antero-lateral hypothalamus and lateral hypothalamus inhibits adrenocortical secretion. No significant change resulted from the stimulation of the supraoptic and paraventricular nuclei. Secretion increased markedly in response to the stimulation of the posterior tuber, premammillary region, mesencephalic reticular formation, and ventral tegmentum. Stimulation of the dorsal tegmentum at the level of the superior colliculus caused inhibition."

D'Angelo, S. A., Snyder, J., Grodin, J. M.: "Electrical stimulation of the hypothalamus: simultaneous effects on the pituitary-adrenal and thyroid systems of the rat." *Endocrinology* **75**: 417-427 (1964). F20,067/64

In rats, the mere presence of electrodes in the medial ventral hypothalamus had no effect on TTH secretion, but it did cause adrenal enlargement and elevation of plasma corticosteroid levels. Excitation of the rostral or caudal hypothalamus induced further adrenal enlargement without substantial

change in other indices of adrenocortical activity. These and other observations "support the view that the portions of the hypothalamus involved in the regulation of TSH [TTH] and ACTH secretion are overlapping and diffuse rather than discrete."

Brodish, A.: "Role of the hypothalamus in the regulation of ACTH release." In: Bajusz, E. and Jasmin, G., *Major Problems in Neuroendocrinology*, pp. 177-195. Basel and New York: S Karger, 1964. E3,993/64

In rats, electrolytic lesions in the hypothalamus interfere with stress-induced ACTH release more by delaying than by preventing it. The duration of the delay largely depends upon the magnitude of the hypothalamic lesions. "Nevertheless these animals were capable of a delayed response which approached to within 90% of the secretion of hormone observed in normal rats" (32 refs.).

Cross, B. A.: "The hypothalamus in mammalian homeostasis." *Symp. Soc. Exp. Biol.* **18**: 157-193 (1964) (almost 100 refs.).

J13,138/64

Wied, D. de, Smelik, P., Moll, J., Bouman, P. R.: "On the mechanism of ACTH release." In: Bajusz, E. and Jasmin, G., *Major Problems in Neuroendocrinology*, pp. 156-176. Basel and New York: S Karger, 1964 (87 refs.). E3,992/64

Yoshio, H.: "Inhibitory effect of pre-optic stimulation on adrenal 17-hydroxycorticosteroid secretion rate in the cat." *Nature* **201**: 1334-1335 (1964). G10,717/64

Slusher, M. A.: "Effects of chronic hypothalamic lesions on diurnal and stress corticosteroid levels." *Am. J. Physiol.* **206**: 1161-1164 (1964). F10,922/64

In unanesthetized, unrestrained rats, "anterior hypothalamic lesions bilaterally destroying the periventricular zone and arcuate nuclei were associated with inhibition of the normal 5 PM rise but with normal rise in plasma corticosteroid levels in response to sound or to a 1-min electrical stimulation of the posterior diencephalon. Posterior tuber cinereum lesions were associated with normal 5 PM rise but with inhibition of response to sound. Response to ether stress was unaffected by any lesion."

Brodish, A.: "Delayed secretion of ACTH in rats with hypothalamic lesions." *Endocrinology* **74**: 28-34 (1964). F30,764/64

Experiments in rats with hypothalamic

lesions of various sizes and locations. Especially when large areas were destroyed the rapid stress-induced release of ACTH was prevented, but there remained a substantial delayed response in which the plasma corticosterone concentration "was almost 90% of that found in control rats." This was associated with ascorbic acid depletion.

Szentagothai, J.: "The parvicellular neurosecretory system." *Prog. Brain Res.* **5**: 135-146 (1964). J12,757/64

"A peculiar neuron system is demonstrated in the ventral part of the hypothalamus by the aid of the rapid Golgi technique in the dog and the cat. Its small cell bodies are situated in the arcuate (infundibular), and in the ventral part of the anterior periventricular nuclei, as well as in the medial part of the retrochiasmatic region." The axons of these cells can be traced to the proximal part of the pituitary, the ME, where they terminate in the zona palisadica of Martinez. This system corresponds exactly to the "hypophysiotrophic region" of Halász, which is where the CRF probably originates.

Eik-Nes, K. B., Brizzee, K. R.: "Concentration of tritium in brain tissue of dogs given [1,2-³H₂] cortisol intravenously." *Biochim. Biophys. Acta* **97**: 320-333 (1965). G26,963/65

In dogs given [1,2-³H₂] cortisol, the hypothalamus took up radioactivity with somewhat pronounced selectivity. "It is postulated that cortisol inhibition of the adrenal pituitary axis primarily occurs at a hypothalamic level." Considerable evidence in support of this view is quoted from the literature (27 refs.).

Mitro, A., Mikulaj, L.: "Karyometric changes in the hypothalamus of the male albino rat during adaptation to repeated stress. I. NN. ventromedialis, dorsomedialis and arcuatus." *Biológia* (Bratislava) **20**: 856-861 (1965) (Slovak). J24,460/65

Kruk, B., Sadowski, B.: "Influence of activation of the medial thalamus on the lymphopenic response in rabbits submitted to stress stimulation." *Acta Physiol. Pol.* **17**: 375-388 (1966). J23,710/66

Electrical stimulation of the medial thalamus frequently reduced the lymphopenic response of rabbits submitted to restraint-induced stress.

Pearl, J. M., Ritchie, W. P. Jr., Gilsdorf,

R. B., Delaney, J. P., Leonard, A. S.: "Hypothalamic stimulation and feline gastric mucosal cellular populations. Factors in the etiology of the stress ulcer." *J.A.M.A.* **195**: 281-284 (1966). F60,597/66

In cats, "low intensity stimulation of the anterior hypothalamus resulted in a marked hyperplasia of all gastric mucosal cellular elements within 48 to 72 hours. This was sustained until ulceration occurred producing a mixed picture of fibrosis and hyperplasia. If the vagus nerve was sectioned prior to stimulation, no hyperplasia was noted."

Benson, B.: "Urinary 17-hydroxycorticosteroid excretion in guinea-pigs with hypothalamic lesions." *Acta Endocrinol. (Kh.)* **53**: 369-381 (1966). F73,323/66

On the basis of selective electrolytic lesions and subsequent plasma ACTH and urinary 17-OHCS determinations, "it was postulated that in the guinea-pig the hypothalamic mechanisms in control of ACTH are to be found in the middle and anterior hypothalamus, in the neuropil associated with the ventromedian and dorsomedian nuclei."

Chowers, I., Hammel, H. T., Eisenman, J., Abrams, R. M., McCann, S. M.: "Comparison of effect of environmental and preoptic heating and pyrogen on plasma cortisol." *Am. J. Physiol.* **210**: 606-610 (1966). F62,277/66

Jacobsohn, D.: "The techniques and effects of hypophysectomy, pituitary stalk section and pituitary transplantation in experimental animals." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 1-21. London: Butterworths, 1966. E10,525/66

Harris, G. W., Donovan, B. T. (eds.): *The Pituitary Gland*, Vol. 1, p. 586; Vol. 2, p. 670, Vol. 3, p. 678. London: Butterworths, 1966. E10,524/66

A three-volume encyclopedia on the structure and function of the pituitary, with extensive sections on its role during stress, particularly in connection with the hypothalamus-adrenocortical system. Each chapter is written by a recognized specialist in the field (several hundred refs.).

Guillemin, R.: "The adenohypophysis and its hypothalamic control." *Annu. Rev. Physiol.* **29**: 313-348 (1967). F78,407/67

Review of the literature on hypothalamic neurohormones regulating pituitary function, with special reference to the discharge of ACTH during stress (143 refs.).

James, V. H. T., Landon, J.: *The Investigation of Hypothalamic-Pituitary-Adrenal Function*, p. 311. London: Memoirs of the Society for Endocrinology, No. 17. Cambridge University Press, 1968. E7,493/68

Proceedings of a symposium in which numerous participants discussed various aspects of the mechanism through which the hypothalamus-pituitary-adrenocortical system can be activated. Several sections deal specifically with the effects of stressors.

Duvernoy, H., Koritke, J. G.: "Les vaisseaux sous-épendymaires du recessus hypophysaire" (Subependymal vessels of the hypophyseal recessus). *J. Hirnforsch.* **10**: 227-245 (1968). J12,676/68

Extensive histologic studies on the subependymal origins of the hypothalamo-adenohypophyseal portal vessels in various mammals and birds. There exist numerous connections between the subependymal vessels and the cavity of the third ventricle from which they are separated only by a thin and often discontinuous ependymal membrane. "Such a structure will possibly allow exchanges between the blood of the hypophysis and the ventricular liquid which is continuously in motion in the third ventricle."

McCann, S. M., Porter, J. C.: "Hypothalamic pituitary stimulating and inhibiting hormones." *Physiol. Rev.* **49**: 240-284 (1969). H10,837/69

Critical review of evidence concerning the nature of the factors responsible for the release not only of ACTH but also of other anterior pituitary hormones (354 refs.).

Asfeldt, V. H., Buhl, J.: "Inhibitory effect of diphenylhydantoin on the feedback control of corticotrophin release." *Acta Endocrinol. (Kbh.)* **61**: 551-560 (1969). H15,117/69

Epileptic patients receiving diphenylhydantoin retain a normal circadian rhythm of ACTH release, but they respond poorly to the increase in ACTH normally produced by metyrapone or the suppression of ACTH secretion by dexamethasone, presumably as a result of deranged ACTH feedback controls.

Haymaker, W., Anderson, E., Nauta, W. J. H. (eds.): *The Hypothalamus*, p. 805. Springfield, Ill.: Charles C Thomas, 1969.

E10,578/69

Review on the hypothalamic control of adenohypophyseal activity, with special reference to ACTH secretion during stress.

Beyer, C., Sawyer, C. H.: "Hypothalamic unit activity related to control of the pituitary gland." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 255-287. New York, London and Toronto: Oxford University Press, 1969. E10,616/69

Harris, G. W., George, R.: "Neurohumoral control of the adenohypophysis and the regulation of the secretion of TSH, ACTH and growth hormone." In: Haymaker, W., Anderson E. et al., *The Hypothalamus*, pp. 326-388. Springfield, Ill.: Charles C Thomas, 1969 (514 refs.). J17,217/69

Fujita, T., Eguchi, Y., Morikawa, Y., Hashimoto, Y.: "Hypothalamic-hypophysial adrenal and thyroid systems: observations in fetal rats subjected to hypothalamic destruction, brain compression and hypervitaminosis A." *Anat. Rec.* **166**: 659-672 (1970).

G74,197/70

Observations suggest that "in the late period of fetal life in rats, the hypophysial-adrenal system is regulated largely by the hypothalamus," but the hypophyseal-thyroid system is not fully under its control.

Smelik, P. G.: "Integrated hypothalamic responses to stress." In: Martini, L., Motta, M. et al., *The Hypothalamus*, pp. 491-497. New York and London: Academic Press, 1970.

J12,268/70

Lawzewitsch, I. von, Sarrat, R.: "Das neurosekretorische Zwischenhirn-Hypophysensystem von Vögeln nach langer osmotischer Belastung" (The neurosecretory hypothalamo-hypophyseal system of birds after long-term osmotic stress). *Acta Anat. (Basel)* **77**: 521-539 (1970).

G84,461/70

It is concluded that "the hypothalamohypophyseal neurosecretory system of cocks under a chronic stress of a 0.3 m NaCl solution ad libitum, resulting in an exhaustion of the system, enters into a period of adaptation during which new neurosecretory material is stored by the cells of the nucleus. This adaptation could either result from the synthesizing ability of the neurosecretory cells being increased by a prolonged stress or from the decrease in hormonal demand due to functional changes in the periphery."

Grant, J. K., Hall, P. E.: "Laboratory investigation of the human hypothalamic-pituitary-adrenocortical system." *Scott. Med. J.* **16**: 157-167 (1971).

G83,953/71

Review on the results of laboratory investigations on human hypothalamic-pitu-

itary-adrenocortical reactions, especially to stress (about 50 refs.).

Choudhury, S. R.: "Response of the hypothalamic secretory neurons to trauma." *Acta Anat.* (Basel) **79**: 84-92 (1971).

G85,674/71

In rats, "surgical stress" causes a cyto-metrically detectable activation of the secretory neurons in the hypothalamus.

Stone, E. A.: "Hypothalamic norepinephrine after acute stress." *Brain Res.* **35**: 260-263 (1971).

H65,343/71

Machida, T.: "Luteinization of ovaries under stressful conditions in persistent-estrous rats bearing hypothalamic lesions." *Endocrinol. Jap.* **18**: 427-431 (1971).

H49,947/71

In rats bearing a croton oil granuloma pouch, persistent vaginal cornification and corpus luteum formation occurred if the medial preoptic area was destroyed. When both the medial preoptic area and the suprachiasmatic nuclei were destroyed, persistent estrus likewise developed, but without corpora lutea. These and other findings "suggest that the preoptic-suprachiasmatic region of the hypothalamus, especially the suprachiasmatic nuclei, is involved in luteinization of ovaries in persistent-estrous rats following exposure to stressful stimuli."

Carroll, B. J.: "The hypothalamic-pituitary-adrenal axis: functions, control mechanisms and methods of study." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Sect. 2, pp. 23-68. Springfield, Ill.: Charles C Thomas, 1972.

E10,503/72

Discussion of the literature on the clinical value of ACTH stimulation, metyrapone, pyrogen, vasopressin, insulin, hypoglycemia, and dexamethasone suppression tests, which help to clarify the neurohumoral mechanisms responsible for corticoid secretion.

Bouillé, C., Baylé, J.-D.: "Experimental studies on the adrenocorticotropic area in the pigeon hypothalamus." *Neuroendocrinology* **11**: 73-91 (1973).

H66,001/73

In pigeons, hypothalamic control of stress-induced adrenocortical activity was examined by means of hypothalamic lesions combined with hypophysectomy or pituitary autografts. "A well-defined adrenocorticotropic area is present in the posterior medial and lateral hypothalamic region. Destruction of the area leads to the same decrease of the plasma

corticosterone level as is seen after adeno-hypophysectomy and also prevents the progressive recovery of adrenocortical function after autografting. The adrenal cortical response to various stressful stimuli is suppressed after lesioning of this same area." It remains to be seen whether the residual adrenocortical responsiveness of hypophysectomized pigeons is due to partial autonomy of the gland or to some extrahypophyseal control system. In any case, corticotrophic activity is abolished by destruction of the regulating hypothalamic area, and hence the hypothesis of the functional autonomy of the pigeon adrenal "is invalidated."

Mamedov, A. M.: "Electronic computer data on functional connections and phase changes in stress rhythm of cortical and hypothalamic projection zones during formation of pain stress." *Dokl. Akad. Nauk SSSR* **213** No. 1: 242-245 (1973) (Russian).

J18,103/73

Experiments on rabbits.

Besser, M.: "The hypothalamus and pituitary gland." *Medicine* (Baltimore) **2**: 97-116 (1973).

J14,917/73

Bendikov, É. A., Basaeva, A. I.: "The use of DOPA in replacement therapy in disturbances of circulatory regulation during stress." *Biull. Èksp. Biol. Med.* **76** No. 12: 36-39 (1973) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **76**: 1414-1416 (1973).

J20,146/73

In cats, stress produced by injection of potassium chloride into the lateral ventricles caused depletion of NEP in the hypothalamus, with inhibition of sympathetic vaso-motor tone. These changes could be corrected by injection of DOPA.

Halász, B.: "Hypothalamic mechanisms controlling pituitary adrenocorticotropic hormone secretion." *Colloques Inst. Nat. Santé Recherche Méd.* **22**: 101-124 (1973).

J17,630/73

Excellent, concise review on hypothalamo-pituitary interrelationships.

Halász, B.: "Possible role of the hypothalamic-hypophysiotropic area in the control of rhythmic functions of the anterior pituitary." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 39-53. Tokyo: Igaku Shoin, 1974.

E10,859/74

Roudier, R.: "Etude des modifications neuro-sécrétoires hypothalamo-hypophysaires

en fonction de différents stress. Essai de correction par le méclofénoxate" (The influence of various stressors on hypothalamo-hypophyseal neurosecretory modifications. Attempt at correction by meclofenoxate). *Ann. Anesth. Fr.* **15**: 517-522 (1974).

J19,327/74

In rats, various stressors cause an immediate disappearance of Gomori granulations from the hypothalamus, with hemorrhagic lesions in the adrenals. Meclofenoxate (an analeptic drug) inhibits these changes and acts as an "antistress substance."

Hatotani, N. (ed.): *Psychoneuroendocrinology* (Workshop Conf. Int. Soc. Psychoneuroendocrinology, Miiken, 1973), p. 312. Basel, München and Paris: S Karger, 1974.

E10,797/74

Report on a symposium with the participation of numerous experts (predominantly Japanese). Special sections are devoted to "Stress and Biological Rhythm," and "Regulation of Hypothalamo-Pituitary Function."

Natelson, B. H., Smith, G. P., Stokes, P. E., Root, A. W.: "Plasma 17-hydroxycorticosteroids and growth hormone during defense reactions." *Am. J. Physiol.* **226**: 560-568 (1974).

H83,654/74

In rhesus monkeys, electric stimulation of the hypothalamus caused a rise in plasma 17-OHCS, especially during the initial excitement. Although increases were obtained after stimulation of various sites scattered throughout the anterior, tuberal and posterior parts of the lateral hypothalamus, plasma STH rose only when the posterior sites were stimulated. This pattern of a smaller hypothalamic area for STH than for ACTH release has also been observed in the rat, cat and squirrel monkey, and is probably a general principle of organization.

Lévéque, T. F.: "The endocrine hypothalamus: An historical review." *Can. J. Neurol. Sci.* **1**: 24-28 (1974).

J10,239/74

Excellent review of the development of our knowledge of hypothalamic functions from the earliest destruction experiments in 1901 up to the present time. It is concluded that "no matter how else one might classify the hypothalamus it has now gained the status of an 'endocrine organ.'"

Tagiev, S. K., Garibov, A. I.: "Histostructural changes of nuclei hypothalamus and thalamus at different stages of starvation." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 53-54. Baku, USSR, 1974

(Russian, with extensive English summary).

J17,537/74

Redgate, E. S., Szechtman, H., Fahringer, E. E.: "The effect of plasma cortisol concentration on the pituitary adrenal response elicited by electrical stimulation of the infundibular area of the awake unrestrained cat." *Horm. Res.* **5**: 173-181 (1974).

H86,890/74

In cats with bilateral electrodes implanted in the infundibular area, electric stimulation maximally elevated adrenal venous cortisol when the initial values were low, but either no change or a decrease occurred when the starting levels were high. No overt behavioral change accompanied the variations in cortisol production.

Krisch, B.: "Different populations of granules and their distribution in the hypothalamo-neurohypophysial tract of the rat under various experimental conditions. I. Neurohypophysis, nucleus supraopticus and nucleus paraventricularis." *Cell Tissue Res.* **151**: 117-140 (1974).

J16,399/74

Grizzle, W. E., Dallman, M. F., Schramm, L. P., Gann, D. S.: "Inhibitory and facilitatory hypothalamic areas mediating ACTH release in the cat." *Endocrinology* **95**: 1450-1461 (1974).

H94,164/74

Krasnovskaia, I. A.: "Changes in hypothalamo-hypophyseal neurosecretory system of rats under conditions of prolonged hypoxia." *Probl. Endokrinol.* **20** No. 2: 53-57 (1974) (Russian).

H92,515/74

In rats exposed to hypoxia, histologic evidence of decreased neurosecretion was noted in the paraventricular nucleus of the hypothalamus, presumably as a consequence of "training."

Ganong, W. F., Alpert, L. C., Lee, T. C.: "ACTH and the regulation of adrenocortical secretion." *N. Engl. J. Med.* **290**: 1006-1011 (1974).

H85,990/74

Excellent and very succinct review on factors regulating corticoid production. The neurohumoral mechanisms are summarized in Figure 13 (p. 978).

Aldosterone secretion occurs in the glomerulosa which, unlike the fasciculata and reticularis, undergoes no atrophy following glucocorticoid overdosage. However, aldosterone discharge by the glomerulosa is stimulated by angiotensin, and this effect is not prevented by corticoid-induced adrenocortical atrophy.

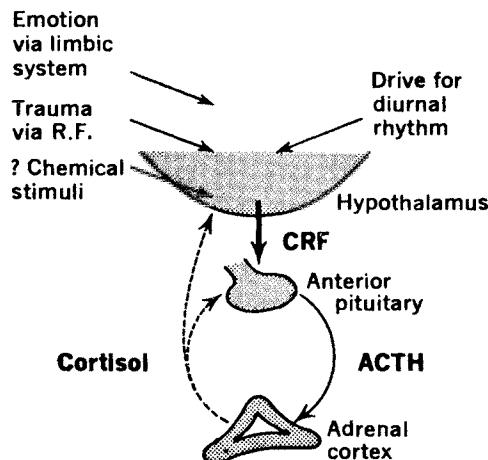


Figure 13. Diagram of current concepts of the control of ACTH secretion. The dashed arrows indicate inhibitory effects and the solid arrows stimulating effects. RF = reticular formation. (Reproduced from *Review of Medical Physiology* (6th ed., 1973), Fig. 20-21, p. 283, by permission of W. F. Ganong and Lange Medical Publications.)

Besser, G. M.: "Hypothalamus as an endocrine organ. I." *Br. Med. J.* August 31, 1974, pp. 560-564. H88,995/74

[Centrarchidae]. *Adv. Anat. Embryol. Cell Biol.* **48:** 1-82 (1974). J15,761/74

Mamedov, A. M.: "Computer data on relationships between projectional areas of the cortex and hypothalamus influenced by specific afferentation under emotional stresses." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 33-36. Baku, USSR, 1974 (Russian, with extensive English summary). [Species not mentioned (H.S.).] J17,531/74

Monograph on the hypothalamus-hypophyseal system of a teleost (*Centrarchidae*) with respect to its anatomy and function under normal conditions and after various hormone treatments or surgical interventions. Special attention is given to the identification of nerve centers and anterior pituitary cells responsible for the selective secretion of diverse adenohypophyseal hormones, as well as to changes in the pituitary during the annual reproductive cycle and its responsiveness to prolongation of the daily light period (about 160 refs.).

Bernardis, L. L.: "Localization of neuroendocrine functions within the hypothalamus." *Can. J. Neurol. Sci.* **1:** 29-39 (1974). J10,240/74

Mitro, A., Szetei, F., Kvethansky, R.: "Stress-induced changes of monoamine oxidase activity (MAO) in different areas of the rat hypothalamus" (abstracted). *Physiol. Bohemoslov.* **24:** 71-72 (1975). J22,935/75

Excellent concise review of contemporary thought concerning the localization of the sites where the various releasing factors of the hypothalamus are produced. Schematic drawings illustrate the conclusions.

Wüstenberg, P. W.: "Das Zwischenhirn-Hypophysensystem. Steuerungsmechanismen im endokrinen Regulatorium" (The hypothalamus-hypophyseal system. Endocrine regulation systems). *Z. Aerztl. Fortbild* **68:** 473-481 (1974) (29 refs.). J15,786/74

Simon, N., Reinboth, R.: "Adenohypophyse und Hypothalamus. Histophysiologische Untersuchungen bei *Lepomis* (Centrarchidae)" (Adenohypophysis and hypothalamus. Histophysiologic studies on the *Lepomis*). In dogs, removal of the brain down to the pons or preparation of "hypothalamic is-

Hypothalamic Deafferentation

(See also our earlier stress monographs, p. xiii)

Egdahl, R. H.: "Further studies on adrenal cortical function in dogs with isolated pituitaries." *Endocrinology* **71:** 926-935 (1962). D45,363/62

In dogs, removal of the brain down to the pons or preparation of "hypothalamic is-

lands," as well as ablation of the entire brain and spinal cord, initially depressed adrenocortical function and then elevated the resting secretion. Neither removal of the posterior pituitary nor abdominal evisceration altered this response.

Matsuda, K., Kendall, J. W. Jr., Duyck, C., Greer, M. A.: "Neural control of ACTH secretion: effect of acute decerebration in the rat." *Endocrinology* 72: 845-852 (1963).

D67,087/63

Removal of the cerebral cortex and subjacent brain rostral to the superior colliculus did not increase peripheral plasma corticosterone in the rat. Hence, it is doubtful that the pituitary is released from inhibition by this operation in this species, as has been reported for dogs. "The minimal amount of tissue permitting approximately normal pituitary-adrenocortical activation appeared to be the median eminence-stalk-pituitary complex."

Matsuda, K., Duyck, C., Kendall, J. W. Jr., Greer, M. A.: "Pathways by which traumatic stress and ether induce increased ACTH release in the rat." *Endocrinology* 74: 981-985 (1964).

F12,792/64

In rats, removal of all forebrain anterior to the superior colliculus, leaving an isolated ME, stalk and pituitary intact, still permits ACTH release (corticosterone in adrenal effluent in response to ether anesthesia) with or without traumatic stress (fracture of foreleg). However, after Nembutal anesthesia, traumatic stress is not active in this respect. Bone fracture distal to a section of the spinal cord of otherwise intact rats also fails to raise adrenocortical secretion under Nembutal but not under ether anesthesia. "Ether apparently directly stimulates the median eminence to cause increased ACTH release. Traumatic stress induces ACTH release through ascending neural pathways feeding into the hypothalamus through the dorsal mesencephalon."

Halász, B., Pupp, L.: "Hormone secretion of the anterior pituitary gland after physical interruption of all nervous pathways to the hypophysiotrophic area." *Endocrinology* 77: 553-562 (1965).

F49,818/65

Review of earlier studies which showed that in rats the transplanted pituitary maintains its structure and function only if placed in direct contact with the ME. To further elucidate this problem, "a small knife was designed, fixed on the electrode holder of a

stereotaxic instrument, and used to cut around the hypophysiotrophic area leaving the area in contact with the pituitary by means of the unbroken pituitary stalk." Adrenal weight was increased, and lipid distribution in the cortex indicated enhanced ACTH secretion, yet the corticosterone content of adrenal venous blood was not appreciably changed. Following deafferentation, the thyroid weight and structure, hypertrophy after methylthiouracil, and the appearance of the testes were maintained, but the ovaries decreased in size and showed histologic changes. Apparently the hypothalamus is largely autonomous in regulating pituitary activity, but is subject to control by afferent nervous stimuli.

Halász, B., Slusher, M. A., Gorski, R. A.: "Adrenocorticotrophic hormone secretion in rats after partial or total deafferentation of the medial basal hypothalamus." *Neuroendocrinology* 2: 43-55 (1967).

F81,329/67

In rats a few weeks after deafferentation of the medial basal hypothalamus by means of the Halász knife, plasma and adrenal corticosterone levels were greatly increased, except in the venous effluent. Unilateral adrenalectomy under ether further raised the corticosterone levels in these rats, and the remaining adrenal underwent compensatory hypertrophy. The circadian rhythm was abolished by total deafferentation or selective transection of the anterior pathways to the MBH but not by transection of the lateral, dorsal and posterior connections to it. Presumably, the anterior pathways convey afferent input for circadian variations. "It is concluded that ACTH secretion of the anterior pituitary is maintained by the MBH in the absence of neural input. For normal ACTH function, however, afferent impulses to the MBH are required."

Halász, B., Vernikos-Danellis, J., Gorski, R. A.: "Pituitary ACTH content in rats after partial or total interruption of neural afferents to the medial basal hypothalamus." *Endocrinology* 81: 921-924 (1967).

F89,131/67

"Complete deafferentation of the MBH resulted in a marked increase in pituitary ACTH content and a disappearance of the diurnal ACTH rhythm present in the sham-operated controls. Similar findings were obtained after the interruption of the anterior connections of the MBH, leaving all other afferents intact. The severance of the dorsal, lateral and posterior connections of the MBH

did not interfere with pituitary ACTH content, including the diurnal ACTH rhythm. It is concluded that the neural pathways reaching the MBH from anterior are essential for the maintenance of normal ACTH secretion."

Greer, M. A., Rockie, C.: "Inhibition by pentobarbital of ether-induced ACTH secretion in the rat." *Endocrinology* 83: 1247-1252 (1968). H5,714/68

In rats, ether anesthesia stimulated ACTH release, apparently acting through the ME. Pentobarbital anesthesia actually blocked this release, as indicated by plasma corticosterone levels. Rats with hypothalamic-pituitary islands (Halász knife) had high resting plasma corticosterone levels, which further increased after ether. Pentobarbital also blocked this response. Presumably, "pentobarbital acts on the basal hypothalamus to prevent ether from inducing ACTH release but does not prevent ACTH release following trauma."

Feldman, S., Conforti, N., Chowers, I., Davidson, J. M.: "Differential effects of hypothalamic deafferentation on responses to different stresses." *Isr. J. Med. Sci.* 4: 908-910 (1968). H3,150/68

Following deafferentation of the hypothalamus (Halász knife), both the normal concentration of plasma corticosterone of rats and its considerable increase after "ether stress" are unchanged. On the other hand, "audiogenic stress" appears to produce no evidence of ACTH discharge. "It might be possible to subdivide ACTH-releasing stimuli into 'systemic' or 'neurogenic' on the basis of whether or not they can activate the hypothalamo-pituitary unit in the absence of afferent nervous input to this area."

Palka, Y. S., Coyer, D. D., Critchlow, V.: "Hypothalamic deafferentation and adrenal function." *Fed. Proc.* 27: 217 (1968). H56/68

Following complete deafferentation of the hypothalamus, the circadian rhythm of corticosterone secretion was abolished in rats. The same result was obtained by blocking the anterior, but not the posterior, input into the MBH. The response to ether was not prevented even after total deafferentation, whereas the stimulating effect of immobilization and the suppression caused by dexamethasone were abolished.

Voloschin, L., Joseph, S. A., Knigge,

K. M.: "Endocrine function in male rats following complete and partial isolations of the hypothalamo-pituitary unit." *Neuroendocrinology* 3: 387-397 (1968). H5,991/68

In rats with total or partial deafferentation of the hypothalamus by a modified Halász knife, it was found that "a) the isolated hypothalamo-pituitary unit is capable of responding to ether stress, although at a submaximal level, b) differential effects may be obtained from animals with total isolations depending upon the amount of neural tissue included in the knife cut, c) some of the neural afferents which influence the ACTH-releasing principles of median eminence origin ascend from caudal regions of the CNS and in the hypothalamus traverse a path within 1 mm of the midline."

Joseph, S. A., Knigge, K. M., Voloschin, L.: "Effects of isolation of the hypothalamo-pituitary unit in newborn guinea pigs." *Neuroendocrinology* 4: 42-50 (1969).

H8,974/69

In newborn guinea pigs, deafferentation of the hypothalamus with a modified Halász knife showed that within about three months "growth and gonadal function were most seriously impaired; development of thyroid and adrenal function was unaffected in male animals and only moderately affected in females. The results indicate that those RF-producing neurones associated with growth hormone and the gonadotrophins may require afferent neural connections for their normal maturation, while RF-producing neurones associated with thyrotrophin and corticotrophin may develop normally in the isolated hypothalamo-pituitary unit."

Dunn, J., Critchlow, V.: "Feedback suppression of 'non-stress' pituitary-adrenal function in rats with forebrain removed." *Neuroendocrinology* 4: 296-308 (1969).

H14,759/69

In rats, forebrain removal or brain stem transection did not interfere with the suppression of corticoid secretion by dexamethasone, "suggesting that negative feedback acts in part directly on anterior pituitary." Rats with large hypothalamic islands had unusually high plasma corticosterone levels, whereas those with basal hypothalamic islands, pituitary islands, or brain stem transections maintained their blood corticoids within essentially normal limits.

Dunn, J., Critchlow, V.: "Pituitary-adrenal response to stress in rats with hypotha-

lamic islands." *Brain Res.* **16**: 395-403 (1969).
H9,631/69

Plasma corticosterone levels were determined in rats in which the mesencephalo-diencephalic junction was severed and graded amounts of forebrain removed, leaving either a hypothalamic island (HI), a basal hypothalamic island (BHI), or a pituitary island (PI). Sham-operated and intact animals served as controls. "Stress plasma samples were obtained 15 min following onset of 3-min ether or immobilization stress. Whereas BHI, sham-operated and intact rats had comparable 'non-stress' Cpd B [corticosterone] levels and showed significant stress responses, HI rats had higher 'non-stress' Cpd B levels and did not show stress responses. PI rats did not respond to stress but had 'non-stress' Cpd B levels comparable to those of controls. These results suggest that the isolated hypothalamo-pituitary unit responds to stress if 'non-stress' Cpd B levels are not elevated. The inability of PI rats to respond to stress implies that the hypothalamus and/or median eminence are essential to the stress response." Thus, hypothalamic deafferentation and forebrain removal indicate that hypothalamic regulation of ACTH secretion is largely independent of neural connections with other parts of the CNS. "This is not to say, however, that limbic, midbrain, and other neural structures do not influence pituitary-adrenal function in the intact animal." [Clearly, all theories suggesting that every stressor must travel to the hypothalamus-pituitary system by nervous pathways from the site of injury are no longer tenable (H.S.).]

Halász, B.: "Endocrine function of hypothalamic islands." In: Gual, C. and Ebling, F. J. G., *Progress in Endocrinology* (Proc. 3rd Int. Congr. Endocrinol., Mexico) *Int. Congr. Ser.* No. 184, pp. 508-514. Amsterdam and New York: Excerpta Medica, 1969.

J11,124/69

Detailed description of surgical techniques for complete or incomplete deafferentation of the hypothalamus-pituitary complex in the rat. A résumé of the many experiments performed with these techniques showed that there may be 2 levels of neural control of the anterior pituitary: "(1) One level seems to be represented by the medial basal hypothalamus (the hypophysiotrophic area). We assume that this hypothalamic region produces the releasing and inhibiting factors essential for the anterior lobe (releasing fac-

tors system). The area may be responsible by itself for maintaining the basal secretion of pituitary hormones and appears to be able to produce and release the 'hypophysiotrophic' substances in the absence of neural afferents. (2) The nervous structures located outside the medial basal hypothalamus and involved in the neural control of the anterior pituitary can be considered the second control level. This level consists of several structures (various hypothalamic areas outside the hypophysiotrophic area, limbic system, midbrain reticular formation, cortex, etc.). Our data suggest that the ovulatory mechanism is triggered, at least partly, by the preoptic area itself and that the neural afferents essential for the diurnal ACTH rhythm enter the hypophysiotrophic area from the anterior direction. The second control level probably does not act directly on the adenohypophysis, but exerts its influence via the medial basal hypothalamus (release regulating system)."

Halász, B.: "The endocrine effects of isolation of the hypothalamus from the rest of the brain." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 307-342. New York, London and Toronto: Oxford University Press, 1969.

J11,367/69

Excellent review of the effects of hypothalamic deafferentation, based mainly on the author's personal work. There appear to be "two levels in the neural control of the anterior pituitary. One level is in the medial basal hypothalamus. It seems likely that this region stores or produces the hypothalamic releasing and inhibiting substances that regulate anterior pituitary secretion. The area appears to be able to produce and release these substances in the absence of neural afferents, and is probably responsible by itself for the maintenance of the basal secretion of the anterior lobe hormones. The feedback action of the peripheral hormones and the action of some other substances appear to be exerted on this region. The other level is in neural structures located outside the medial basal hypothalamus. This level exerts stimulatory as well as inhibitory effects on the adenohypophysis, and probably acts via the medial basal hypothalamus. The ovulatory surge of LH from the anterior lobe is triggered, at least in part, from the preoptic area." In rats, complete deafferentation of the medial ventral hypothalamus does not interfere with the basal secretion of pituitary tropic hormones, and fails to cause atrophy of their

target organs. Compensatory hypertrophy of the adrenals develops after unilateral adrenalectomy; there is ACTH release after stress, and propylthiouracil elicits thyroid hypertrophy. Castration increases the LH content of the anterior lobe and causes formation of castration cells. Growth is only slightly retarded. However, such rats do not ovulate, and the diurnal rhythm of ACTH secretion is abolished.

Makara, G. B., Stark, E., Palkovits, M., Révész, T., Mihály, K.: "Afferent pathways of stressful stimuli: corticotrophin release after partial deafferentation of the medial basal hypothalamus." *J. Endocrinol.* **44**: 187-193 (1969). H15,202/69

Observations on rats after deafferentation of the MBH with the Halász knife led to the conclusion that "(a) noise and vibration, sham adrenalectomy and injection of 1% formalin trigger ACTH release through neural pathways arriving at the MBH from anterior, lateral and dorsal directions, (b) histamine or capsaicin releases ACTH partly through anterolateral neural afferents to the MBH. In contrast, the ACTH-releasing stimulus of bacterial endotoxin injection reaches the hypothalamo-hypophysial unit by humoral pathways and/or posterior nerve fibres."

Palka, Y., Coyer, D., Critchlow, V.: "Effects of isolation of medial basal hypothalamus on pituitary-adrenal and pituitary ovarian functions." *Neuroendocrinology* **5**: 333-349 (1969). H23,543/69

In rats, deafferentation of the medial basal hypothalamus with a modified Halász knife eliminated "the diurnal peak in non-stress plasma corticosterone levels. Such isolation was compatible with a normal response to 3-min ether stress; the response to immobilization stress was present, though significantly reduced." Dexamethasone given subcutaneously suppressed resting plasma corticosterone levels. On the other hand, isolated interruption of the anterior connections of this hypothalamic area did not measurably influence ACTH secretion under these conditions.

Feldman, S., Conforti, N., Chowers, I., Davidson, J. M.: "Pituitary-adrenal activation in rats with medial basal hypothalamic islands." *Acta Endocrinol. (Kbh.)* **63**: 405-414 (1970). H23,303/70

In rats with deafferentation of the hypothalamus (Halász knife), the increase in plasma corticosterone produced by ether remained unaffected, and that elicited by ether

plus venesection was only slightly inhibited. Conversely, the hypercorticism following auditory or optic stimulation was considerably diminished, and that following hypoxia and immobilization was totally unaffected. "It is concluded that (1) ACTH release following auditory, and to a somewhat lesser extent, optic stimulation depends on neural input to the basal medial hypothalamus and (2) the corticotrophic responses to ether, anoxia and immobilization may be mediated by humoral activation of the same region."

Makara, G. B., Stark, E., Palkovits, M.: "Afferent pathways of stressful stimuli: corticotrophin release after hypothalamic deafferentation." *J. Endocrinol.* **47**: 411-416 (1970). H29,802/70

In rats with complete deafferentation of the medial basal hypothalamus, capsaicin failed to increase plasma corticosterone levels, but *E. coli* endotoxin, histamine, insulin and formaldehyde continued to produce normal ACTH release. Histamine and insulin were effective in this respect, even in rats having only an ME-pituitary stalk island. Presumably, among the agents tested only capsaicin is totally dependent upon neural pathways for causing ACTH release.

Greer, M. A., Allen, C. F., Gibbs, F. P., Gullickson, C.: "Pathways at the hypothalamic level through which traumatic stress activates ACTH secretion." *Endocrinology* **86**: 1404-1409 (1970). H26,878/70

In rats, complete hypothalamic deafferentation (Halász knife) blocked the rise in plasma corticosterone normally caused by fracture of a leg on either side. Unilateral deafferentation significantly abolished this increase after contralateral, but not ipsilateral, leg break. The effect of contralateral leg fracture was also blocked by a one-sided anterior quarter section, but not by a posterior quarter section. Not even complete hypothalamic deafferentation suppressed the rise in plasma corticosterone following placement of a rubber band tourniquet on a single extremity. "The pathway via which a single leg break causes increased ACTH secretion is usually contralaterally distributed at the level of the basal hypothalamus as well as through the spinal cord to the pons. This pathway enters the anterior basal hypothalamus within 1 mm of the ventral brain surface. A rubber band tourniquet probably increases ACTH secretion through some pathway different from that followed by the stimulus of a leg break."

Stark, E., Makara, G. B., Palkovits, M., Mihály, K.: "Afferent pathways of stressful stimuli: their dependence on strength and the time elapsed after the onset of stimulation." *Acta Physiol. Acad. Sci. Hung.* **38**: 43-49 (1970). G81,960/70

Observations on rats with anterolateral deafferentation of the MBH and denervation of a hind limb show that the resulting plasma corticosterone elevations are variable. "A change in the intensity of a stressful stimulus can involve another pathway; with time, different pathways may be at work after exposure to some stressful stimuli but not to others."

Chowers, I., Conforti, N., Feldman, S.: "Effects of hypothalamic deafferentation on adrenocortical responses to cold stress." *Isr. J. Med. Sci.* **7**: 323-325 (1971).

H62,648/71

In rats, hypothalamic deafferentation (Halász knife) only partially inhibits corticoid production during cold-induced stress.

Halász, B., Schalch, D. S., Gorski, R. A.: "Growth hormone secretion in young rats after partial or total interruption of neural afferents to the medial basal hypothalamus." *Endocrinology* **89**: 198-203 (1971).

H43,027/71

In rats, hypothalamic deafferentation does not significantly affect STH secretion, even during stress.

Makara, G. B., Stark, E., Mészáros, T.: "Corticotrophin release induced by *E. coli* endotoxin after removal of the medial hypothalamus." *Endocrinology* **88**: 412-414 (1971).

H35,419/71

In rats, one day after division of the pituitary stalk or removal of the medial hypothalamus, intraperitoneal *E. coli* endotoxin produced a small but significant rise in plasma corticosterone. Presumably, "some of the pathways through which *E. coli* endotoxin releases corticotrophin bypass the medial hypothalamus."

Halász, B.: "Neural control of pituitary ACTH secretion under resting conditions." *Acta Med. Acad. Sci. Hung.* **29**: 71-76 (1972).

J10,354/72

Brief review on the neural control of ACTH secretion under resting conditions. The MBH elaborates CRF, but receives stimuli from external areas such as the limbic system, mesencephalon, and so on. Some of these regions presumably stimulate, while others inhibit, ACTH production (35 refs.).

Feldman, S., Conforti, N., Chowers, I.: "Effects of partial hypothalamic deafferentations on adrenocortical responses." *Acta Endocrinol. (Kbh.)* **69**: 526-530 (1972).

H52,370/72

In rats with anterior hypothalamic deafferentation, only ACTH secretion remained unchanged under the stress of ether, light and noise, while in those with anterolateral and posterolateral deafferentation the response to ether was normal, but the response to photic and acoustic stimulation was significantly inhibited. Presumably, "the transmission of impulses in the medial forebrain bundle and possibly posterior sensory inputs to the hypothalamus play an important role in the adrenocortical responses following neurogenic stimulation."

Ondo, J. G., Kitay, J. I.: "Effects of dexamethasone and stressful stimuli on hypothalamic electrical activity in rats with diencephalic islands." *Neuroendocrinology* **9**: 215-227 (1972).

H56,043/72

In rats with diencephalic islands (Cross and Kitay technique), dexamethasone was shown to have a direct effect on the neurons of the isolated basal hypothalamus. However, vasopressin and histamine, which have an inverse influence on ACTH secretion, similarly inhibited the firing of hypothalamic neurons. Thus, "a simple explanation relating neuronal firing rate and the mechanisms involved in the control of ACTH secretion is obviously not possible." The literature on the effect of various hormones on hypothalamic neurons is reviewed.

Bouillé, C., Herbuté, S., Baylé, J.-D.: "Modulatory influences of central nervous structures on pituitary-adrenocortical activity: effect of chronic deafferentation of the hypothalamus in the pigeon." *J. Physiol. (Paris)* **66**: 437-446 (1973).

J9,213/73

In Carneau pigeons, deafferentation of the hypothalamus with a modification of the Halász knife suppressed the usual circadian variations in plasma corticosterone levels. Responses to ether stress were reduced but not abolished.

Vermes, I., Molnár, D., Telegdy, G.: "Hypothalamic serotonin content and pituitary-adrenal function following hypothalamic deafferentation." *Acta Physiol. Acad. Sci. Hung.* **43**: 239-245 (1973).

J12,931/73

In rats, partial or total deafferentation of the hypothalamus decreases the adrenal response to "ether stress" and concurrently di-

minishes hypothalamic 5-HT concentration. The findings support the concept that "serotonin plays an inhibitory role in the function of the hypothalamo-pituitary-adrenal axis, and indicate that serotonergic fibres are reaching the hypothalamus from the anterior and antero-superior parts."

McCann, S. M., Ajika, K., Fawcett, C. P., Hefco, E., Illner, P., Negro-Vilar, A., Orias, R., Watson, J. T., Krulich, L.: "Hypothalamic control of the adenohypophyseal response to stress by releasing and inhibiting neurohormones." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 67-77. Bratislava: Slovak Academy of Sciences, 1973. E10,458/73

Mainly on the basis of plasma hormone determinations and observations in rats whose hypothalamus-pituitary system was isolated with the Halász knife, the authors were led to the conclusion that "following the application of a stressful stimulus, afferent impulses are probably generated which pass to the brainstem and thence to the hypothalamus where they influence release of the various releasing and inhibiting hormones which control the AP [anterior pituitary]. We would postulate that the afferent pathways are similar for all AP hormones and that the differential patterns of release are brought about by specific intrahypothalamic mechanisms. Consistent with this hypothesis is the differential localization of the various releasing and inhibiting factors in the hypothalamus." Even transfer from the stock room to the laboratory sufficed to cause a dramatic increase in the rats' serum STH and LH values within less than one hour.

Collu, R., Jéquier, J. C., Letarte, J., Leboeuf, F., Ducharme, J. R.: "Effect of stress and hypothalamic deafferentation on the secretion of growth hormone in the rat." *Neuroendocrinology* 11: 183-190 (1973). H68,127/73

Ether and auditory stressors were equally effective in diminishing plasma STH (radioimmunoassay) in controls and in frontally deafferented rats. Ether also inhibited STH secretion in completely deafferented animals, whereas auditory stress was ineffective. α -MT pretreatment blocked the effect of ether after complete deafferentation. These and other data "seem to indicate that ether stress is transmitted through a humoral, dopaminergic pathway, while auditory stress follows a nervous pathway." [The many ob-

servations suggesting increased STH secretion during stress are not discussed (H.S.).]

Feldman, S., Conforti, N., Chowers, I.: "Effect of dexamethasone on adrenocortical responses in intact and hypothalamically deafferented rats" (abstracted). *Isr. J. Med. Sci.* 10: 572 (1974). H89,689/74

Inhibition of ACTH secretion by dexamethasone is more pronounced in intact than in hypothalamically deafferented rats. Apparently, the negative feedback of corticoids is exerted at the hypothalamic level, but extrahypothalamic structures also participate in it.

Vermesh, I., Ryzhenkov, V. E.: "Functional condition of the hypophysis-adrenal system in rats with deafferentated hypothalamus; the action of dexamethasone and nialamide." *Probl. Endokrinol. (Mosk.)* 20 No. 3: 67-70 (1974) (Russian). H92,315/74

In rats with a completely deafferented MBH, the basal plasma corticosterone level rose; this elevation could be inhibited by dexamethasone or nialamide. "At the same time suppression of corticosterone secretion in stress [restraint] by nialamide was stronger in comparison with dexamethasone. Nialamide potentiated the depressive action of dexamethasone on the basal corticosterone secretion, but not under stress."

Allen, C. F., Allen, J. P., Greer, M. A.: "Anterolateral hypothalamic deafferentation prevents compensatory hypersecretion of ACTH following adrenalectomy in the rat." *Proc. Soc. Exp. Biol. Med.* 146: 840-843 (1974). H89,021/74

"Complete or anterolateral, but not anterior, basal hypothalamic deafferentation prevented the increased basal secretion of ACTH in chronically adrenalectomized rats. ACTH secretion in response to ether stress was at least as great in the deafferented, adrenalectomized rats as in intact controls." Presumably, extrahypothalamic influences entering the basal hypothalamus are necessary to achieve high basal ACTH secretion when plasma glucocorticoids are depressed.

Conforti, N., Feldman, S., Chowers, I.: "Adrenal function in heat-exposed hypothalamically-disconnected rats." *Isr. J. Med. Sci.* 10: 291 (1974). H86,881/74

In rats with hypothalamic deafferentation (Halász knife), corticosterone release following exposure to heat was diminished, but was nevertheless demonstrable following repeated exposure. These and other observations led

to the conclusion that CRF discharge following exposure to heat depends upon direct connections between peripheral heat receptors mediated by afferent pathways and systemic influences.

Krulich, L., Hefco, E., Aschenbrenner, J. E.: "Mechanism of the effects of hypothalamic deafferentation on prolactin secretion in the rat." *Endocrinology* **96**: 107-118 (1975).

H98,036/75

Insula of Reil

(See also our earlier stress monographs, p. xiii)

Misra, D. K.: "Insula and adrenocortical function." *Calcutta Med. J.* **69**: 96-107 (1972). H79,786/72

In dogs, unilateral or bilateral stimulation of the insula of Reil raised the 17-OHCS content of adrenal venous blood. No significant change was noted after lesions of the same region, but burn stress enhanced the response. Presumably, the insula, through nervous connections with the hypothalamus across subcortical areas, can activate the hypothalamo-pituitary-adrenal axis.

Limbic System

(See also our earlier stress monographs, p. xiii, and cf. various specifically-named parts of the limbic system)

Mason, J. W.: "Visceral functions of the nervous system." *Annu. Rev. Physiol.* **21**: 353-380 (1959). J11,142/59

Review on the role of the CNS in visceral functions, particularly endocrine regulation. A special section deals with the effect of emotional factors upon the limbic system, the hypothalamus and the reticular formation (219 refs.).

Okinaka, S., Ibayashi, H., Motohashi, K., Fujita, T., Ohsawa, N., Murakawa, S.: "Regulation of the pituitary-adrenocortical function through the limbic system." *Neurol. Med. Chir. (Tokyo)* **2**: 110-115 (1960).

D82,582/60

In dogs, adrenal venous 17-OHCS and blood ACTH were determined after electric stimulation of the posterior orbital surface, amygdaloid nuclear complex, hippocampus

and midbrain reticular formation. It was concluded that "the stimulation of the posterior orbital surface, the amygdaloid nuclear complex, and possibly the midbrain reticular formation especially its caudal portion facilitated the pituitary adrenocortical function transiently, while the stimulation of the hippocampal formation appeared to give a prolonged suppression."

Nauta, W. J. H.: "Limbic system and hypothalamus: anatomical aspects." *Physiol. Rev.* **40** Supp. 4: 102-104 (1960).

J11,497/60

The "limbic forebrain structures" are described as consisting "in part of a relatively primordial cortex (hippocampus, piriform lobe, gyrus forniciatus, caudal orbitofrontal cortex), partly also of subcortical structures (septal region, amygdaloid complex). Together, these structures are arranged in an almost complete ring around the hilus of the cerebral hemisphere, Broca's grand lobe limbique."

Okinaka, S., Ibayashi, H., Motohashi, K., Fujita, T., Yoshida, S., Ohsawa, N.: "Effect of electrical stimulation of the limbic system on pituitary-adrenocortical function: posterior orbital surface." *Endocrinology* **67**: 319-324 (1960).

J12,153/60

"The role of limbic system structures in the regulation of ACTH secretion."

Mason, J. W., Nauta, W. J. H., Brady, J. V., Robinson, J. A., Sachar, E. J.: "The role of limbic system structures in the regulation of ACTH secretion." *Acta Neuroveg. (Wien)* **23**: 4-14 (1961). E94,848/61

In conscious monkeys, electric stimulation of the amygdala causes pronounced rises in plasma 17-OHCS that are followed by a depression if the stimulus continues for several hours. Stimulation of the distal tip of the hippocampus causes a slight acute elevation, followed by a pronounced and prolonged depression, of 17-OHCS levels. Bilateral amygdalectomy diminishes the acute rise in 17-OHCS normally elicited by conditioned avoidance sessions. "These experiments indicate an important modulatory role for limbic structures in the regulation of endocrine functions."

Okinaka, S.: "Die Regulation der Hypophysen-Nebennierenfunktion durch das Limbic-System und den Mittelhirnanteil der Formatio reticularis" (The role of the limbic system and the midbrain portion of the re-

ticular formation in regulating hypophyseal-adrenal function). *Acta Neurolog. (Wien)* **23**: 15-20 (1962). J11,476/62

In dogs, "stimulation of the posterior orbital surface, the prepyriformic region, transitory area between pyriformic lobe and olfactory tract, resulted in a prompt and pronounced elevation of both 17-OHCS and ACTH content, which returned to the pre-stimulation level 30 minutes later. No such increase was demonstrated upon stimulation of the anterior sylvian gyrus. Stimulation of amygdaloid nuclear complex resulted in a similar elevation of 17-OHCS and ACTH content. Stimulation of hippocampal formation, however, resulted in a decrease of 17-OHCS and ACTH for 30 minutes. The role of posterior orbital surface and the amygdaloid nuclear complex thus appears to be facilitating, while that of hippocampal formation seems to be inhibitory, on the pituitary-adrenal system."

Rubin, R. T., Mandell, A. J., Crandall, P. H.: "Corticosteroid responses to limbic stimulation in man: localization of stimulus sites." *Science* **153**: 767-768 (1966).

F68,624/66

"Corticosteroids in human plasma and urine increase after amygdala stimulation, and plasma corticosteroids decrease after hippocampus stimulation. Five subjects underwent unilateral temporal lobectomy, and histopathologic localization of electrode sites was attempted. Localization was successful for six sites: three in basolateral amygdala and three in hippocampus."

Eleftheriou, B. E., Zolovick, A. J., Pearse, R.: "Effect of amygdaloid lesions on pituitary-adrenal axis in the deer mouse." *Proc. Soc. Exp. Biol. Med.* **122**: 1259-1262 (1966).

F72,633/66

In the deer mouse, lesions in the medial amygdaloid complex increased plasma ACTH and corticosterone levels within twelve hours, presumably by eliminating an inhibitory effect.

Usher, D. R., Kasper, P., Birmingham, M. K.: "Comparison of pituitary-adrenal function in rats lesioned in different areas of the limbic system and hypothalamus." *Neuroendocrinology* **2**: 157-174 (1967).

F88,389/67

Rats exposed to intermittent air blasts develop thymus involution and a pronounced increase in plasma corticosterone and pituitary ACTH levels. Lesions in various loca-

tions of the limbic system and hypothalamus can block these effects independently of each other, indicating that different mechanisms are involved in their production.

McEwen, B. S., Weiss, J. M., Schwartz, L. S.: "Uptake of corticosterone by rat brain and its concentration by certain limbic structures." *Brain Res.* **16**: 227-241 (1969) (35 refs.). J11,765/69

Redgate, E. S.: "ACTH release evoked by electrical stimulation of brain stem and limbic system sites in the cat: the absence of ACTH release upon infundibular area stimulation." *Endocrinology* **86**: 806-823 (1970).

H23,415/70

In cats, "plasma ACTH levels rose promptly after stimulation at sites in the amygdaloid septal complex matching the rapidity of the response to hemorrhage or sciatic nerve stimulation. In contrast, after stimulation at sites in the medullary reticular formation, medial midbrain structures, lemniscal systems, or posterior lateral hypothalamus, the rise in plasma ACTH concentration was consistently delayed for 5-10 min, providing the basis for the suggestion that there are at least 2 different neural systems within the brain of the cat participating in ACTH release." These and related observations indicate "that central nervous system mediated ACTH release is accomplished not by a single system with unified action but by separate subsystems endowed with sufficient independence to produce prompt responses and delayed responses" (71 refs.).

Schadé, J. P.: "The limbic system and the pituitary-adrenal axis." *Prog. Brain Res.* **32**: 2-11 (1970).

J11,296/70

McEwen, B. S., Weiss, J. M., Schwartz, L. S.: "Retention of corticosterone by cell nuclei from brain regions of adrenalectomized rats." *Brain Res.* **17**: 471-482 (1970).

J12,015/70

In adrenalectomized rats, nuclear uptake of labeled corticosterone was highest in the hippocampus, but was also demonstrable in the amygdala and cerebral cortex.

Kawakami, M., Kimura, F., Ishida, S., Yanase, M.: "Changes in the activity of the limbic-hypothalamic neural pathways under the repeated immobilization stress." *Endocrinol. Jap.* **18**: 469-476 (1971).

H52,611/71

In restrained rabbits, "both the hippo-

campally and the amygdaloidly evoked potentials in the medial basal tuberal region revealed decreases in their amplitudes."

Oniani, T. N.: "The electroencephalographic, vegetative and behavioral effects of electrical stimulation of the limbic structures." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 39-43. Baku, USSR, 1974 (Russian, with extensive English summary). J17,533/74

Bouillé, C., Baylé, J.-D.: "Effects of limbic stimulations or lesions on basal and stress-induced hypothalamic-pituitary-adrenocortical activity in the pigeon." *Neuroendocrinology* 13: 264-277 (1974).

H81,878/74

It is generally believed that the amygdala facilitates, whereas the hippocampus depresses, ACTH-releasing activity by the hypothalamus. The archistriatum is claimed to constitute the avian homologue of the amygdaloid complex of mammals. Hence, experiments were performed in the conscious pigeon by electric stimulation (implanted electrodes) and bilateral electrolytic lesions. Hippocampal stimulation or lesions induced either a marked drop or rise in plasma corticosterone, whereas archistriate stimulation increased it. Diurnal variations in corticoid levels were suppressed after hippocampal lesions, but stress-induced (restraint) responses were only slightly reduced. In the pigeon the hippocampus appears to inhibit the modulatory system of ACTH activity, whereas the archistriatum (like the amygdala of mammals) antagonizes this effect.

Simonov, P. V.: "Functions of limbic structures according to the information theory of emotions." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 43-46. Baku, USSR, 1974 (Russian, with extensive English summary). J17,534/74

Gasanov, G. G.: "Emotions, visceral functions and limbic system." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 10-15. Baku, USSR, 1974 (Russian, with extensive English summary). J17,523/74

Koikegami, H.: "Anatomical considerations of modulatory effects of the limbic and paralimbic structures upon the hypothalamic hormonal or autonomic function." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp 1-38. Tokyo: Igaku Shoin, 1974.

E10,858/74

Endrőczi, E.: "Circadian rhythm in the

pituitary-adrenal function; limbic clock and its influence by nervous and humoral factors." In: Kawakami, M., *Biological Rhythms in Neuroendocrine Activity*, pp. 281-292. Tokyo: Igaku Shoin, 1974.

E10,875/74

Delapaz, R. L., Dickman, S. R., Grosser, B. I.: "Effects of stress on rat brain adenosine 3',5'-monophosphate in vivo." *Brain Res.* 85: 171-175 (1975).

J20,677/75

Observations showing "a relationship between stress and increases in the level of cAMP in several regions of the rat brain. A marked rise is seen in the septum after stress from electric shock or restraint. Smaller increases are seen in hippocampus and brain stem in animals stressed by electric shock. These changes in septum and hippocampus are of interest since these regions are components of the limbic system and, therefore, might be involved in the mediation of emotional responses during stress."

Median Eminence (ME), Tuber Cinereum

(See also our earlier stress monographs, p. xiii, and cf. Ependyma.)

Hume, D. M.: "The neuro-endocrine response to injury: present status of the problem." *Ann. Surg.* 138: 548-557 (1953).

B89,126/53

Review of the literature and personal observations show that stimulation of the ME in the dog causes a release of ACTH with eosinopenia. Following trauma, the ACTH discharge appears to be mediated through this center, although nerve impulses from the injured area are essential for initiating the response (36 refs.).

Halász, B., Szöllössy, L.: "Einfluss peripherischer Denervation auf den hypothalamischen Kernvergrößerungseffekt der Zona Fasciculata der Nebennierenrinde" (The influence of peripheral denervation on the hypothalamic enlargement effect of nuclei in the fasciculata of the adrenal). *Acta Morphol. Acad. Sci. Hung.* 3: 1-9 (1953).

B88,339/53

In rats, lesions in the tuber cinereum cause enlargement of the nuclei in the fasciculata of the adrenal. This effect is blocked by transection of the preganglionic and sensory nerves of the adrenal; in fact, after such

denervation, tuber lesions diminish nuclear volume in the same region of the adrenal.

McCann, S. M.: "Effect of hypothalamic lesions on the adrenal cortical response to stress in the rat." *Am. J. Physiol.* **175**: 13-20 (1953). B87,327/53

McCann, S. M., Laqueur, G. L., Schreiner, L. H., Rosemberg, E., Anderson, E., Rioch, D. M.: "Effect of hypothalamic lesions on stress induced eosinopenia in the cat." *Fed. Proc.* **12**: 95 (1953). B78,603/53

In cats with lesions in the hypothalamus or pituitary stalk, EP and laparotomy failed to produce the usual eosinopenic reaction.

Ganong, W. F., Hume, D. M.: "Absence of stress-induced and 'compensatory' adrenal hypertrophy in dogs with hypothalamic lesions." *Endocrinology* **55**: 474-483 (1954).

B98,714/54

In dogs, hypothalamic lesions prevent adrenal enlargement following exposure to stressors (trauma) or unilateradrenalectomy, but only if they destroy the ME.

Török, B.: "Lebendbeobachtung des Hypophysenkreislaufes an Hunden" (In vivo observations on hypophyseal circulation in dogs). *Acta Morphol. Acad. Sci. Hung.* **4**: 83-89 (1954). C2,052/54

In dogs and cats, hypophyseal circulation was observed in vivo by use of vital dyes. "Under physiologic conditions—despite rich anastomoses—blood flow is strictly unilateral in the symmetrical halves of the Pars tuberalis → Eminentia medialis → hypophyseal stalk → anterior lobe vascular systems."

Ganong, W. F., Hume, D. M.: "Effect of hypothalamic lesions on steroid-induced atrophy of adrenal cortex in the dog." *Proc. Soc. Exp. Biol. Med.* **88**: 528-533 (1955).

C4,554/55

In unilaterally adrenalectomized dogs in which the ME is destroyed, the remaining adrenal does not undergo atrophy unless the animals are treated with large doses of cortisol. Hypothalamic lesions outside the ME do not have this effect. Apparently, "an intact median eminence is necessary for the increase in ACTH secretion in response to stress, but not for the decrease that follows steroid injection."

Laqueur, G. L., McCann, S. M., Schreiner, L. H., Rosemberg, E., Rioch, D. M., Anderson, E.: "Alterations of adrenal cortical and

ovarian activity following hypothalamic lesions." *Endocrinology* **57**: 44-54 (1955).

C6,334/55

In cats exposed to stressors (EP, laparotomy), suprachiasmatic or posterior hypothalamic lesions failed to interfere with the normal eosinopenia and the secretion of corticoids. Cats with lesions in the ME and adjacent hypothalamus showed very little response to stressful stimuli, and the eosinopenia after laparotomy was slight. Yet reactivity was not completely abolished, and the animals developed diabetes insipidus.

Fulford, B. D., McCann, S. M.: "Suppression of adrenal compensatory hypertrophy by hypothalamic lesions." *Proc. Soc. Exp. Biol. Med.* **90**: 78-80 (1955). C9,816/55

In unilaterally adrenalectomized rats, destruction of the supraopticohypophyseal tract in the rostral portion of the ME prevented compensatory hypertrophy of the remaining suprarenal and produced diabetes insipidus.

Greer, M. A., Erwin, H. L.: "Evidence of separate hypothalamic centers controlling corticotropin and thyrotropin secretion by the pituitary." *Endocrinology* **58**: 665-670 (1956).

C14,624/56

In rats, destruction of the ME "sometimes" inhibited amphenone-induced adrenal hypertrophy, whereas posterior hypothalamic lesions did not significantly affect ACTH secretion but did suppress TTH production. Presumably, the centers for ACTH and TTH secretion are distinct, and the format is limited to the ME.

George, R., Way, E. L.: "The hypothalamus as an intermediary for pituitary-adrenal activation by aspirin." *J. Pharmacol. Exp. Ther.* **119**: 310-316 (1957).

C34,580/57

In rats, lesions of the ME completely blocked adrenal ascorbic acid depletion following treatment with large doses of acetylsalicylic acid.

Knigge, K. M.: "Inhibitor component in the neural control of ACTH release." *Anat. Rec.* **130**: 326 (1958).

J13,015/58

Brief abstract reporting experiments which show that stress (kind of stressor not indicated) causes a biphasic pattern of ACTH secretion in the rat. During the first one to two hours, there occurs an elevated discharge of ACTH, which is followed by a fall to about one-fifth the normal level at twelve

to eighteen hours after stress. The drop in hormone secretion is not due to secretory exhaustion of the adrenals, since the latter still respond normally when incubated with ACTH in vitro, and the ACTH content of the pituitary is up to twice normal at twelve hours after stress. Presumably, "there exists an inability of the pituitary to release ACTH because of the activity of a neural inhibitor mechanism." Lesions placed in the ME area, or treatment with reserpine two hours after stress, interfere with this pituitary inhibition and result in "adrenal secretion 12 hours after stress which is greater than that observed at any time in the untreated, stressed animal."

Royce, P. C., Sayers, G.: "Extrapituitary interaction between Pitressin and ACTH." *Proc. Soc. Expt. Biol. Med.* **98**: 70-74 (1958).

C54,346/58

Natural vasopressin depletes adrenal ascorbic acid in hypophysectomized rats and potentiates the corresponding action of ACTH, even after destruction of the ME. "Only part of this effect can be explained by release of ACTH from the pituitary since Pitressin will also deplete adrenal ascorbic acid in a lesioned rat which has been decapitated."

Fortier, C., Groot, J. de: "Release and synthesis of ACTH following electrolytic destruction of the median eminence in the rat." *21st Int. Congr. Physiol. Sci.*, p. 96. Buenos Aires, 1959.

J12,865/59

Metuzals, J.: "The structure of the hypothalamic final common path to the adenohypophysis in the cat. The periventricular area of the nucleus arcuatus and the eminentia mediana." *J. Comp. Neurol.* **113**: 103-137 (1959).

C82,320/59

Detailed histologic investigation of the paraventricular area of the nucleus arcuatus and the ME in the cat. The final common pathway to the adenohypophysis is complex, yet it appears to be constructed "(a) of neurons, which extend into the adenohypophysis and terminate probably among the gland cells, and (b) of neurons, which terminate in the external layer of the eminentia and establish contact with the gland cells of the adenohypophysis through the hypophysial portal vessels."

Smelik, P. G., Bouman, P. R., Wied, D. de: "The effect of hypothalamic lesions on compensatory adrenal hypertrophy in

rats." *Acta Endocrinol. (Kbh.)* **31**: 451-456 (1959).

C71,164/59

In unilaterally adrenalectomized rats, coagulation of the posterior part of the ME inhibited compensatory hypertrophy, whether the stalk was intact or not. Stalk lesions alone exerted such an effect only during the first four days. Comparable lesions in the anterior and posterior hypothalamus were ineffective in this respect.

Ganong, W. F.: "Adrenal-hypophyseal interrelations." In: Gorbman, A., *Comparative Endocrinology*, pp. 187-201. New York: John Wiley & Sons, 1959.

D2,002/59

A review of the literature and personal observations suggest that there is a "basal" ACTH secretion independent of the ME and probably of the entire hypothalamus, since no one has been able to produce adrenal atrophy by hypothalamic lesions in any location. Only ACTH secretion in response to stressors is mediated through the hypothalamus by a pathway unaffected by corticoids. A second factor "modulating the amount of pituitary secretion" is the blood corticoid level, which acts merely "as a damping, or braking, mechanism on the coarse fluctuations initiated by the neuroendocrine mechanism."

Moll, J., Vogel, T.: "Observations on the effect of lesions in the pituitary stalk and median eminence on the zonation of the adrenal cortex." *Acta Endocrinol. (Kbh.)* **31**: 568-572 (1959).

C71,929/59

In rats, lesions of the pituitary stalk and ME not only block compensatory adrenal hypertrophy but characteristically alter the zonation of the remaining adrenal.

D'Angelo, S. A.: "Thyroid hormone administration and ovarian and adrenal activity in rats bearing hypothalamic lesions." *Endocrinology* **64**: 685-702 (1959).

C68,037/59

In rats with bilaterally, symmetrical electrolytic lesions in the arcuate nucleus and ME, there was ovarian atrophy, reduced thyroid function and hypothalamic obesity, but such lesions had no consistent effect on adrenal morphology. Administration of T_4 and T_3 failed to reverse the gonadal atrophy, but nevertheless it caused adrenal hypertrophy, as it did in intact controls. Such a differential response was also found in rats made severely hypothyroidic by propylthiouracil prior to hypothalamic destruction. Adrenal cortical acti-

vation was also seen in rats with hypothalamic diabetes insipidus and in chronically starved rats with marked hypothalamic deficit. It is presumable that "ACTH secretion can be enhanced by chronic stress despite arcuate-median eminence lesions and that some aspects of thyroovarian interaction may be mediated through a hypothalamic-hypophyseal component."

McCann, S. M., Haberland, P.: "Further studies on the regulation of pituitary ACTH in rats with hypothalamic lesions." *Endocrinology* **66**: 217-221 (1960). J12,283/60

In rats, recent and old lesions in the ME block the ascorbic acid depletion of the adrenals that normally occurs after unilateral adrenalectomy. Such lesions induce adrenal atrophy in the presence of normal-sized testes. The adrenal ascorbic acid depletion in rats with atrophic adrenals is variable, and only some of these animals have diabetes insipidus. The pituitary ACTH falls only some time after the ME lesions.

Krieger, D. T., Wagman, I. H.: "Hypothalamic lesions and adrenal function in the cat." *Acta Endocrinol. (Kbh.)* **38**: 88-98 (1961). D10,468/61

Cats with bilateral electrolytic lesions of the ME had a low basal blood corticoid level and failed to respond to exogenous or stress-induced ACTH stimulation. Yet the adrenals were enlarged and rich in lipids. "The surprising finding was that these animals with M. E. lesions also did not respond to exogenously administered ACTH." It is assumed that "a lesion of the median eminence depresses adrenal cortical function by interference with release of steroid from the adrenal and not by inducing adrenal atrophy."

Ganong, W. F., Nolan, A. M., Dowdy, A., Luetscher, J. A.: "The effect of hypothalamic lesions on adrenal secretion of cortisol, corticosterone, 11-desoxycortisol and aldosterone." *Endocrinology* **68**: 169-170 (1961). C98,309/61

The output of cortisol, corticosterone, 11-desoxycortisol and aldosterone in the adrenal venous blood of dogs was depressed following destruction of the ME but was unaffected by lesions elsewhere in the hypothalamus.

Wied, D. de: "Effect of hypothalamic lesions and hypophysectomy on corticoid production in vitro and on adrenal weight in rats." *Acta Endocrinol. (Kbh.)* **37**: 279-287 (1961). D5,783/61

In rats with lesions in the ME, stress (ether) inhibited adrenal corticoidogenesis, as tested subsequently in vitro. Vasopressin stimulated corticoidogenesis of the adrenals in such rats. The weight of the adrenals decreased more rapidly after hypophysectomy than after ME lesions. The adrenal hypertrophy usually observed some time after placement of ME lesions did not occur in the present series. Following unilateral adrenalectomy, compensatory hypertrophy of the contralateral adrenal was prevented both by hypophysectomy and by ME lesions.

Miller, R. A.: "Hypertrophic adrenals and their response to stress after lesions in the median eminence of totally hypophysectomized pigeons." *Acta Endocrinol. (Kbh.)* **37**: 565-576 (1961). D80,692/61

In pigeons, hypophysectomy causes adrenal atrophy, but the interrenal tissue hypertrophies during stress elicited by formaldehyde or insulin, even in the absence of the pituitary. Very large lesions in the ME and ventral hypothalamus cause adrenal hypertrophy rather than atrophy, even after total hypophysectomy. They also react to formaldehyde. "It appears that the interrenal tissue of the pigeon responds to a humoral stimulus not of hypophyseal origin in the absence of the hypophyseal-hypothalamic system."

Barry, J., Cotte, G.: "Etude préliminaire, au microscope électronique, de l'éminence médiane du cobaye" (Preliminary electron-microscopic study of the median eminence in the guinea pig.) *Z. Zellforsch. Mikrosk. Anat.* **53**: 714-724 (1961) (about 60 refs.). J12,738/61

Saba, G. C., Saba, P., Marescotti, V.: "Diencephalic lesions and corticosterone production." *Int. Congr. on Hormonal Steroids*, Milan, *Int. Congr. Ser. No. 51*, p. 160. Amsterdam and New York: Excerpta Medica, 1962. J13,136/62

In rats the corticosterone level in the adrenal venous blood diminishes after lesions in the ME but does not after damage to other formations in the hypothalamus.

Kennedy, G. C., Lipscomb, H. S., Hague, P.: "Plasma corticosterone in rats with experimental diabetes insipidus." *J. Endocrinol.* **27**: 345-353 (1963). E35,990/63

In rats, electrolytic lesions in the ME produced diabetes insipidus and variable changes in plasma corticosterone under resting conditions and ether anesthesia.

However, the changes in corticoid levels were not clearly correlated with the severity of the polyuria.

Davidson, J. M., Feldman, S.: "Cerebral involvement in the inhibition of ACTH secretion by hydrocortisone." *Endocrinology* **72**: 936-946 (1963). D67,102/63

In rats, single cortisol implants in the ME and the anteromedial hypothalamus abolished the compensatory adrenal hypertrophy normally produced by unilateral adrenalectomy. Similar implants in the lateral basal hypothalamus elicited only partial inhibition, and implants in the pituitary itself were virtually ineffective. "The hypothalamus rather than the pituitary should be regarded as the primary locus of feedback inhibition of ACTH by hydrocortisone."

Kobayashi, T., Kobayashi, T., Yamamoto, K., Inatomi, M.: "Electron microscopic observation on the hypothalamo-hypophyseal system in the rat. I. The ultrafine structure of the contact region between the external layer of the infundibulum and Pars tuberalis of the anterior pituitary." *Endocrinol. Jap.* **10**: 69-80 (1963). D66,269/63

Halász, B., Pupp, L., Uhlarik, S.: "Changes in the pituitary-target gland system following electrolytic lesions of the median eminence and hypophyseal stalk in male rats." *Acta Morphol. Acad. Sci. Hung.* **12**: 23-31 (1963). D7,234/63

In the rat, "after lesions in the anterior part of the median eminence, thyroid atrophy develops which is considered to be of neurogenic nature.—After lesions in the posterior median eminence or the hypophyseal stalk the pituitary is always reduced in weight and depending on the degree of the lesion a gonadal, or gonadal and thyroid, or in the most severe cases, gonadal, thyroid, and adrenal atrophy develops. Three weeks after a posterior median eminence or stalk lesion no isolated thyroid or adrenal atrophy has been observed.—The isolated adrenal atrophy occasionally observed after a median eminence lesion is explained on the basis of the time factor of the atrophy, which develops much quicker in the adrenal than, especially, in the male gonad."

Vernikos-Danellis, J.: "Quantitative changes in corticotropin releasing activity of rat hypothalamus and neurohypophysis after stress." *Program 45th Meet. Endocrinol. Soc.*, pp. 28-29. New York, 1963.

E20,839/63

In rats the ME is particularly rich in CRF, and adrenalectomy further elevates it. Ether anesthesia in adrenalectomized rats causes an additional rise within 1.25 minutes. The CRF activity of hypothalamic tissue outside the ME is comparatively low. "It is concluded that the median eminence is the major source of CRF and that it responds to stress in a manner that parallels changes in pituitary ACTH."

Krieger, D. T., Krieger, H. P.: "The effects of intrahypothalamic injection of drugs on ACTH release in the cat." Proc. 2nd Int. Congr. Endocrinol., London, 1964, Part 1. *Int. Congr. Ser. No. 83*, pp. 640-645. Amsterdam and New York: Excerpta Medica, 1964.

F48,895/64

In cats, implantation of cholinergic or adrenergic drugs (5-HT or GABA) in the ME and various adjacent regions shows that different neurons of the hypothalamus are selectively sensitive to diverse substances, and that the same drug applied to different sites produces different results, especially as regards ACTH release. It is suggested that not neurons but synapses are stimulated.

Fortier, C., Groot, J. de: "Residual synthesis and release of ACTH following electrolytic destruction of the median eminence in the rat." In: Bajusz, E. and Jasmin, G., *Major Problems in Neuroendocrinology*, pp. 203-219. Basel and New York: S Karger, 1964.

E3,995/64

In rats, immediately following electrolytic destruction of the ME, there is a temporary increase in plasma ACTH that is probably initiated during the stress of the operation. Plasma corticosterone then falls and stabilizes at a subnormal level, probably owing to the disappearance of CRF and to adenohypophyseal ischemia (yet its level remains somewhat above that of hypophysectomized animals). The adenohypophyseal weight is decreased, yet following the transitory fall, its ACTH content rises above normal within one week, subsequently dropping to subnormal levels. Eventually, "the synchronized rates of synthesis and release are interpreted as evidence that residual corticotrophic activity is compatible with the exclusion of hypothalamic influence presumably achieved by complete destruction of the bulbus of the Median Eminence" (20 refs.).

Fortier, C., Groot, J. de: "Effect of localized destruction of the ventral hypothalamus on the adrenocorticotrophic responses to sur-

gical trauma and to hypocorticoidism in the rat." In: Bajusz, E. and Jasmin, G., *Major Problems in Neuroendocrinology*, pp. 220-229. Basel and New York: S Karger, 1964.

E3,996/64

In rats, stimulation of ACTH secretion by unilateral or bilateral adrenalectomy was suppressed following electrolytic destruction of the bulbous portion of the ME or of premammillary and mammillary structures. It is concluded that the hypothalamus plays an essential role in the mediation of ACTH secretion during stress and hypocorticoidism.

Fuxe, K.: "Cellular localization of monoamines in the median eminence and the infundibular stem of some mammals." *Z. Zellforsch. Mikrosk. Anat.* **61**: 710-724 (1964).

G2,752/64

In various mammals the ME is particularly rich in fluorescence microscopy-demonstrable monoamines, especially in the terminal parts of nonsympathetic nerve fibers that converge upon the portal system. "The findings indicate that primary catecholamines are released to the primary plexus of the hypophyseal portal system and thus transported to the anterior lobe. These amines may consequently act as neuro-humoral transmitters for the regulation of the activity of the anterior pituitary.—No direct adrenergic innervation of the cells in the pars tuberalis and anterior lobe was found. The portal vessels in the pars tuberalis receive a very sparse adrenergic innervation, and the vessels in the anterior lobe receive no or very few adrenergic nerves."

Röhlich, P., Vigh, B., Teichmann, I., Aros, B.: "Electron microscopy of the median eminence of the rat." *Acta Biol. Acad. Sci. Hung.* **15**: 431-457 (1965).

J12,740/65

EM studies of the ependymal cells in the region of the ME suggest that they may have a secretory function (30 refs.).

Duffy, P. E., Menefee, M.: "Electron microscopic observations of neurosecretory granules, nerve and glial fibers, and blood vessels in the median eminence of the rabbit." *Am. J. Anat.* **117**: 251-286 (1965).

G34,613/65

Mazzuca, M.: "Structure fine de l'éminence médiane du cobaye" (Fine structure of the median eminence of guinea pigs). *J. Microsc. (Paris)* **4**: 225-238 (1965) (53 refs.).

J12,741/65

Vernikos-Danellis, J.: "Effect of stress,

adrenalectomy, hypophysectomy and hydrocortisone on the corticotropin-releasing activity of rat median eminence." *Endocrinology* **76**: 122-126 (1965).

G32,998/65

In rats, the CRF content of the ME begins rising five days after adrenalectomy and reaches a peak after twenty days. Hypophysectomy does not influence it, whereas the stress of ether anesthesia markedly increases the ACTH-releasing activity within less than two minutes in normal, adrenalectomized or hypophysectomized rats. Cortisol drastically reduces CRF activity and prevents the rise caused by stress. "It is suggested that the close parallelism between the changes occurring in the median eminence and pituitary under these conditions indicates that CRF may regulate pituitary ACTH synthesis."

D'Angelo, S. A., Young, R.: "Chronic lesions and ACTH: effects of thyroid hormones and electrical stimulation." *Am. J. Physiol.* **210**: 795-800 (1966).

F63,559/66

In rats with chronic ME lesions, T₃ and T₄ increased adrenal weight without correcting pituitary and ovarian atrophy, decreased adrenal and ovarian ascorbic acid contents, and elevated plasma and adrenal corticoids. Electric stimulation of the anterior hypothalamus in intact rats caused ACTH release, and this was blocked by ME lesions. Basal ACTH secretion following destruction of the ME remains appreciable and can be enhanced by hyperthyroidism. Presumably, "neural stimuli from the rostral hypothalamus mediate their effects on ACTH release via the median eminence; and augmentation of ACTH secretion in severe hyperthyroidism involves a non-neural, humoral metabolic pathway."

Rinne, U. K., Arstila, A. U.: "Ultrastructure of the neurovascular link between the hypothalamus and anterior pituitary gland in the median eminence of the rat." *Neuroendocrinology* **1**: 214-227 (1965-66).

F68,590/65-66

Rinne, U. K.: "Ultrastructure of the median eminence of the rat." *Z. Zellforsch. Mikrosk. Anat.* **74**: 98-122 (1966).

G41,473/66

Porter, J. C., Dhariwal, A. P. S., McCann, S. M.: "Response of the anterior pituitary-adrenocortical axis to purified CRF." *Endocrinology* **80**: 679-688 (1967).

F81,565/67

Various experiments suggest that the inability of rats with lesions in the ME to

respond to stressors by an increased discharge of ACTH (as evidenced by corticosterone blood levels) results from failure "to secrete CRF and is not due to deficiencies in pituitary blood flow, that the activity of the pituitary-adrenocortical system varies directly with CRF output, and that CRF is involved in the minute-to-minute regulation of ACTH secretion" (25 refs.).

Akmayev, I. G., Réthelyi, M., Majorossy, K.: "Changes induced by adrenalectomy in nerve endings of the hypothalamic median eminence (Zona palisadica) in the albino rat." *Acta Biol. Acad. Sci. Hung.* **18**: 187-200 (1967). G48,945/67

Description of the structural changes produced by adrenalectomy in the ME of the rat. These probably reflect an increased discharge of CRF.

Monroe, B. G.: "A comparative study of the ultrastructure of the median eminence, infundibular stem and neural lobe of the hypophysis of the rat." *Z. Zellforsch. Mikrosk. Anat.* **76**: 405-432 (1967).

G44,280/67

Kobayashi, T., Kobayashi, T., Yamamoto, K., Kaibara, M., Ajika, K.: "Electron microscopic observation on the hypothalamo-hypophyseal system in the rat. III. Effect of reserpine treatment on the axonal inclusions in the median eminence." *Endocrinol. Jap.* **15**: 321-335 (1968). H4,331/68

In rats, EM studies of the ME revealed an increase in electron-dense large granules (thought to be carriers of neurohypophyseal hormones) and a decrease in small granules (presumably carriers of catecholamines) after reserpine treatment.

Porter, J. C.: "Site of corticotropin-releasing factor (CRF) releasing elements: effect of lesions on ACTH release and adenohypophyseal blood flow." *Endocrinology* **84**: 1398-1403 (1969). H13,663/69

In rats, electrolytic lesions in the pituitary stalk and ME completely suppressed ACTH release after surgical trauma throughout the seventy-minute-period of observation, whereas lesions in the anterior ME slowed the rate of ACTH discharge only temporarily. Apparently the CRF-secreting elements are located in the pituitary stalk and/or near its junction with the ME (27 refs.).

Chan, L. T., Wied, D. de, Saffran, M.: "Comparison of assays for corticotrophin-

releasing activity." *Endocrinology* **84**: 967-972 (1969). H11,041/69

In rats with electrolytic lesions in the ME, three assay methods for CRF in vivo and in vitro were tested following vasopressin injection.

Kobayashi, H., Matsui, T.: "Fine structure of the median eminence and its functional significance." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 3-46. New York, London and Toronto: Oxford University Press, 1969. E10,612/69

Rodríguez, E. M.: "Ependymal specializations. I. Fine structure of the neural (internal) region of the toad median eminence, with particular reference to the connections between the ependymal cells and the subependymal capillary loops." *Z. Zellforsch. Mikrosk. Anat.* **102**: 153-171 (1969).

G72,035/69

In toads, an anatomic arrangement connecting the specialized ependymal cells of the ME with the long loops of the primary plexus in the pituitary-hypophyseal system "makes the possibility of an interrelationship between the cerebrospinal fluid and the portal blood very considerable." Earlier literature concerning such specialized ependymal cells is extensively reviewed.

Voitkevich, A. A., Dedov, I. I.: "Neurovascular contacts of the median eminence of the neurohypophysis." *Dokl. Akad. Nauk SSSR* **186**: 373-376 (1969) (English trans. of Russian original). J13,889/69

Réthelyi, M., Halász, B.: "Origin of the nerve endings in the surface zone of the median eminence of the rat hypothalamus." *Exp. Brain Res.* **11**: 145-158 (1970).

J10,894/70

In rats, various hypothalamic areas were partially or totally separated from the brain by means of a stereotactically manipulated bayonet-shaped knife, and the zona palisadica was examined for degeneration of axon terminals under the EM. It was found that "the nerve terminals in the zona palisadica arise exclusively from neurons in the medial basal hypothalamus, and that fibers of other origin do not terminate in this zone. The present observations support the assumption that the hypothalamic releasing (and inhibiting) factors are produced by, and the neural control of the anterior pituitary is exercised over a short final neuronal link, localized in the medial basal hypothalamus." These findings again confirm that the zona palisadica of the

ME and the proximal part of the pituitary stalk play key roles in the neurohumoral control of the adenohypophysis.

Brown, G. M., Schalch, D. S., Reichlin, S.: "Hypothalamic mediation of growth hormone and adrenal stress response in the squirrel monkey." *Endocrinology* **89**: 694-703 (1971). H45,128/71

In squirrel monkeys the stress of emotional excitement (chair restraint, capture) increases plasma STH and corticoid levels, but the two changes do not run parallel. The STH response to capture and ether was blocked by small lesions either in the anterior or posterior ME, while the adrenal responses to capture and chair restraint were blocked by lesions in the posterior ME. The STH responses to ether were enhanced by midline optic chiasm lesions. However, great individual variations interfered with the precise evaluation of these data.

Takebe, K., Kunita, H., Sakakura, M., Horiuchi, Y., Mashimo, K.: "Suppressive effect of dexamethasone on the rise of CRF activity in the median eminence induced by stress." *Endocrinology* **89**: 1014-1019 (1971). H47,039/71

In rats, dexamethasone blocked stress-induced (surgery) rises in the CRF level of the ME and in the plasma corticosterone concentration. The pituitaries of dexamethasone-treated rats responded to ME extract in a normal manner. It is concluded that dexamethasone-induced inhibition acts mainly at or above the hypothalamic level.

Fink, G., Smith, G. C.: "Ultrastructural features of the developing hypothalamo-hypophysial axis in the rat. A correlative study." *Z. Zellforsch. Mikrosk. Anat.* **119**: 208-226 (1971). G85,999/71

EM studies on the fetal ME of the rat. The finding that "the development of granular vesicles precedes that of agranular vesicles is discussed with reference to the times at which neurosecretory materials and monoamines become detectable in the region."

Knigge, K. M., Scott, D. E., Weindl, A. (eds.): *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, p. 368. Basel and New York: S Karger, 1972.

E10,204/72

Proceedings of a congress dealing with all aspects of the ME, including its embryonic development, histology, ultrastructure, the various agents that influence it, and its prob-

able function as a neuroendocrine organ in different species (numerous refs.).

Halász, B., Kosaras, B., Lengvári, I.: "Ontogenesis of the neurovascular link between the hypothalamus and the anterior pituitary in the rat." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 27-34. Basel and New York: S Karger, 1972. J17,773/72

Monroe, B. C., Newman, B. L., Schapiro, S.: "Ultrastructure of the median eminence of neonatal and adult rats." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 7-26. Basel and New York: S Karger, 1972. J17,772/72

Knigge, K. M., Silverman, A. J.: "Transport capacity of the median eminence." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 350-363. Basel and New York: S Karger, 1972.

E10,558/72

Studies using various techniques in the mink and rat suggest that the ME is dynamically active and controls several aspects of hormonal feedback. Both *in vivo* and *in vitro*, it exhibits a high metabolic activity and a great capacity to accumulate thyroxine injected into the CSF, and then to release it into the portal circulation, whence it is transmitted to the adenohypophysis. TTH and dopamine significantly affect thyroxine uptake.

Dedov, I. I.: "Median eminence of neurohypophysis under extreme conditions." *Dokl. Akad. Nauk SSSR* **204**: 1503-1506 (1972) (Russian). Engl. trans.: *Proc. Acad. Sci. USSR, Biol. Sci.* **204**: 298-301 (1972).

J20,136/72

EM changes in the rat hypophysis following exposure to various stressors or metyrapone.

Smith, G. C., Helme, R. D.: "Ultrastructural and fluorescence histochemical studies on the effects of 6-hydroxydopamine on the rat median eminence." *Cell Tissue Res.* **152**: 493-512 (1974). J18,969/74

In the ME of the rat, regeneration of catecholamine-containing neurons is almost complete within three weeks after treatment with intravenous 6-hydroxydopamine. [This fact should be remembered in studies on the role of the ME in stress reactions (H.S.).]

Watkins, W. B., Schwabedal, P., Bock, R.: "Immunohistochemical demonstration of a CRF-associated neurophysin in the external zone of the rat median eminence." *Cell Tissue Res.* **152**: 411-421 (1974). J18,966/74

"In normal rats, 'Gomori-positive' substances and neurophysin were confined to the internal zone of the median eminence. After adrenalectomy, however, 'Gomori-positive' granules and a neurophysin-like protein also became apparent in the external zone. Their amount increases, if the animals are treated with DOCA from the 15th to the 21st day after the operation. The distribution of the neurophysin-like protein in the external zone is similar to that of the 'Gomori-positive' granules." The latter are regarded as morphologic correlates of CRF. Since they cross-react with neurophysin antiserum, the name "CRF-neurophysin" is proposed.

Gouget, A., Duvernoy, J., Bugnon, C.: "Recherches sur la participation du tractus infundibulaire dopaminergique dans le fonctionnement de l'axe corticotrope" (Investigation on the participation of the dopaminergic infundibular tract in the activity of the corticotrophic axis). *Bull. Assoc. Anat. (Nancy)* **58**: 315-322 (1974). J17,278/74

By use of the Falck-Hillarp histochemical fluorescence method, an important decrease in monoamines was demonstrated fifteen days after adrenalectomy in the ME of the rat. This decrease indicates a diminution of dopamine in the terminals of the infundibular tract. "A kinetic study of the rate of MA [monoamine] depletion in control and adrenalectomized rats, treated by α -MT, confirms an accelerated turnover and an important discharge of DA with CRF release in the portal vessels."

Dunn, J., Arimura, A.: "Serum growth hormone levels following ablation of medial basal hypothalamus." *Neuroendocrinology* **15**: 189-199 (1974). H91,993/74

In rats with large medial hypothalamic lesions, STH secretion after "ether stress" was impaired but not abolished. (The destruction was accomplished by a modified Halász knife with a cross bar which interrupted the vascular supply from the ventral surface of the brain.) Perhaps the simultaneous elimination of stimulation and inhibition by neural impulses largely compensated for the effect upon STH release. "The pituitary somatotrophs appear capable of autonomous secretion."

Schwabedal, P. E.: "Influence of stress on the amount of 'Gomori-positive' granules in the outer layer of the median eminence of bilaterally adrenalectomized rats." *J. Neural. Transm.* **35**: 217-231 (1974). J17,427/74

In rats, various stressors (formaldehyde, histamine, endotoxins) diminish the number of "Gomori-positive" granules in the ME, reflecting the release of CRF.

Knigge, K. M., Silverman, A. J.: "Anatomy of the endocrine hypothalamus." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7, Endocrinology*, Vol. IV, Part 1, pp. 1-32. Washington, D. C.: American Physiological Society, 1974.

E10,721/74

Excellent review on the fine structure of the hypothalamus, with a special section on the catecholamine content of the ME during stress.

Medulla Oblongata, Pons, Locus Coeruleus

(See also our earlier stress monographs, p. xiii)

Gibbs, F. P.: "Area of pons necessary for traumatic stress-induced ACTH release under pentobarbital anesthesia." *Am. J. Physiol.* **217**: 84-88 (1969). H14,557/69

From observations on rats with lesions in the pons produced under pentobarbital anesthesia and tibial fractures ten days later, it was concluded that "there is an area in the pontine reticular formation which facilitates the traumatic stress-induced release of ACTH..." Only lesions in the pontine reticular formation block ACTH significantly, although destruction of other areas also causes slight inhibition.

Belova, T. I., Bunkina, L. S.: "Catecholamines of the oral region of the brain stem under normal conditions and during rapidly developing stress. (Histochemical investigation)." *Biull. Èksp. Biol. Med.* **70**: No. 12: 93-96 (1970) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **70**: 1438-1441 (1970).

J21,614/70

In mice, the stress of asphyxia changed the histochemical distribution of catecholamines in the "locus coeruleus; substantia nigra; grisea centralis, and adjacent ventrolateral portions of the mesencephalic reticular formation; the region of the raphé; ganglion interpedunculare, together with regions lying laterally to it."

Bubenik, G., Monnier, M.: "Nuclear size variations in cells of the locus ceruleus during sleep, arousal and stress." *Exp. Neurol.* **35:** 1-12 (1972). G90,134/72

Korf, J., Aghajanian, G. K., Roth, R. H.: "Increased turnover of norepinephrine in the rat cerebral cortex during stress: role of the locus coeruleus." *Neuropharmacology* **12:** 933-938 (1973). J21,582/73

"The noradrenergic nerve terminals in the rat cerebral cortex are mainly supplied by norepinephrine-containing neurones originating in the locus coeruleus." Stress increases the turnover of NEP in this location. Apparently, "the locus coeruleus plays an important role in mediating the effect of stress on the metabolism of norepinephrine in the cerebral cortex."

Roussel, B., Cure, M., Renaud, B., Valatx, J.-L.: "Hypertrophie surrénalienne après lésion des neurones catécholaminergiques pontiques, chez le Rat" (Adrenal hypertrophy after lesion of the catecholaminergic pontine neurons in the rat). *C.R. Acad. Sci. [D]* (Paris) **277:** 1897-1900 (1973).

J28,455/73

In rats, destruction of the locus coeruleus and subcoeruleus causes temporary hyperplasia of the fasciculata in the adrenal cortex. This is of interest since the noradrenergic neurons with hypothalamic projections are located in the locus coeruleus, and destruction of this center suppresses the blocking effect of NEP on hypothalamic or pituitary inhibitors.

Ögren, S. O., Fuxe, K.: "Learning, brain noradrenaline and the pituitary-adrenal axis." *Med. Biol.* **52:** 399-405 (1974).

J24,846/74

In rats, the NEP pathways to the forebrain were destroyed by the injection of 6-hydroxy-dopamine (6-OH-DA) into the coeruleo-cortico (dorsal) bundle without significantly impairing retention of the conditioned avoidance response (CAR). However, when 6-OH-DA lesions were combined with adrenalectomy, "there was a marked reduction of the retention of CAR and a complete failure to relearn the CAR."

Peripheral Nerves

(See also our earlier stress monographs, p. xiii)

Cannon, W. B.: "The stimulation of adre-

nal secretion by emotional excitement." *Proc. Am. Phil. Soc.* **1:** 226-227 (1911).

35,529/11

Cannon, W. B.: "The emergency function of the adrenal medulla in pain and the major emotions." *Am. J. Physiol.* **33:** 356-372 (1914). 57,873/14

Review of the earliest animal experiments showing that fear, rage, asphyxia and pain cause the discharge of EP from the adrenal medulla, and that this response is mediated through the splanchnic nerves. Direct stimulation of the latter exerts the same effect. The resulting glycogenolysis and increase in blood sugar furnish energy. At the same time, blood circulation is improved. Stimulation of the splanchnics also hastens blood coagulation and thereby protects against bleeding in the event of injury. All these changes are "directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve."

Rydin, H., Verney, E. B.: "The inhibition of water-diuresis by emotional stress and by muscular exercise." *Q. J. Exp. Physiol.* **27:** 343-374 (1938). A14,575/38

In dogs, emotional excitement and muscular exercise inhibit diuresis. This response is unaltered by transection of the renal nerves, by extirpation of one adrenal and denervation of the other, or by decentralization of the whole abdominal sympathetic system with ablation of ganglia L2 to S1 inclusive. The course of this inhibition is matched by vasopressin. "The post-pituitary equivalent of this stress in terms of the standard powder is of the order of 1 µg."

Vogt, M.: "Cortical lipids of the normal and denervated suprarenal gland under conditions of stress." *J. Physiol. (Lond.)* **106:** 394-404 (1947). B26,537/47

In rats and cats, repeated injections of EP cause conspicuous degranulation of the adrenal cortical cells, which is ascribed to stress and cannot be prevented by adrenal denervation.

Gordon, M. L.: "An evaluation of afferent nervous impulses in the adrenal cortical response to trauma." *Endocrinology* **47:** 347-350 (1950). B48,953/50

In adrenal-demedullated rats, adrenal ascorbic acid discharge following fracture or a mild burn to the leg was diminished by denervation of the injured extremity. This was not the case after severe scalding.

Ray, B. S., Console, A. D.: "Bodily adjustments in man during stress in the absence of most visceral afferents and sympathetic nervous system regulation." In: Wolff, H. G., Wolf, S. G. Jr., et al., *Life Stress and Bodily Disease*, pp. 114-120. Baltimore: Williams & Wilkins, 1950. B51,898/50

"Total sympathectomy in man imposes great limitations on his response to stress of all types but at the same time protects him from certain destructive effects of emotional stress."

Hume, D. M., Nelson, D. H.: "Adrenal cortical function in surgical shock." *Surg. Forum* 5: 568-575 (1954). E40,942/54

In dogs, increased 17-OHCS output into the adrenal blood under the influence of trauma or hemorrhage does not depend upon the integrity of the nerves supplying the adrenal medulla.

Greer, M. A.: "Studies on the influence of the central nervous system on anterior pituitary function." *Rec. Prog. Horm. Res.* 13: 67-98 (1957). C38,181/57

Brodie, D. A., Hanson, H. M.: "A study of the factors involved in the production of gastric ulcers by the restraint technique." *Gastroenterology* 38: 353-360 (1960). C87,271/60

Bilateral subdiaphragmatic vagotomy did not significantly reduce the incidence of restraint ulcers in the rat.

Menguy, R.: "Effects of restraint stress on gastric secretion in the rat." *Am. J. Dig. Dis.* 5: 911-916 (1960). C93,988/60

"Previously vagotomized rats were partially protected from stress [restraint] ulcers whereas hypophysectomy or adrenalectomy were without effect" (13 refs.).

Nauta, W. J. H.: "Central nervous organization and the endocrine motor system." In: Nalbandov, A. V., *Advances in Neuroendocrinology*, pp. 5-21. Urbana, Ill.: University of Illinois Press, 1963. J12,286/63

Review on the influence of various nervous structures (hypothalamus, limbic forebrain, limbic system-midbrain circuit) on behavior, "vital feelings," "behavioral attitude" (angry, anxious, predatory or relaxed), as well as on the response to stressors (traumatic injuries, hypoxia), especially in relation to hormonal regulation (43 refs.).

Colehour, J. K., Graybiel, A.: "Excretion of 17-hydroxycorticosteroids, catechol amines, and uropepsin in the urine of normal persons

and deaf subjects with bilateral vestibular defects following acrobatic flight stress." *Aerosp. Med.* 35: 370-373 (1964).

G11,705/64

Deaf persons with vestibular defects accompanying experienced pilots on acrobatic flights failed to show the usual increase in corticoids and catecholamines, presumably because their appropriate sensory organs in the inner ear were not functional.

Lissák, K., Endrőczi, E.: *The Neuroendocrine Control of Adaptation*, p. 180. Oxford, New York and Paris: Pergamon Press, 1965.

E6,042/65

Slightly updated English version of a book originally published in German, briefly summarizing all aspects of hormonal and nervous influences during adaptation and correlating the work of I. P. Pavlov and W. B. Cannon with the nonspecific adaptive processes characteristic of the G.A.S.

Djahanguiri, B., Sadeghi, D., Hemmati, S.: "Système orthosympathique et ulcères gastriques expérimentaux" (The orthosympathetic system and experimental gastric ulcers). *Arch. Int. Pharmacodyn. Ther.* 173: 154-161 (1968). F99,278/68

In rats, cold increases the ulcerogenic effect of restraint, whereas α -adrenergic blocking agents prevent it.

Saito, A.: "Autoadaptation mechanism of the human body." *Tohoku J. Exp. Med.* 102: 289-312 (1970). H36,779/70

Review of the literature and theoretical considerations on the relationship between the G.A.S. and the vegetative nervous system, with special reference to Japanese publications (39 refs.).

Shum, A., Johnson, G. E., Flattery, K. V.: "Catecholamine and metabolite excretion in cold-stressed immunosympathectomized rats." *Am. J. Physiol.* 221: 64-68 (1971).

H41,823/71

Immunosympathectomy did not prevent the increase in NEP secretion produced in the rat by exposure to cold. However, when compared with untreated littermates, the immunosympathectomized rats excreted slightly less NEP and normetanephrine, and considerably less 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). "It is postulated that a decreased sympathetic reserve in these animals caused a higher percentage of norepinephrine synthesized to be secreted as such, causing the lower MHPG excretion."

Van-Toller, C., Tarpy, R. M.: "Effect of cold stress on the performance of immunosympathectomized mice." *Physiol. Behav.* **8**: 515-517 (1972). G90,601/72

The results of escape-avoidance behavior in immunosympathectomized mice confined in a cold chamber "question previous generalizations concerning the role of the peripheral sympathetic nervous system in aversively motivated behavior."

Bushman, J. A.: "Investigation of the behaviour of the autonomic nervous system under stress." *Proc. R. Soc. Med.* **66**: 477-478 (1973). J19,550/73

O'Boyle, A., Gannon, D., Hingerty, D.: "Sympatho-adrenal response to stress." *J. Ir. Med. Assoc.* **66**: 699-704 (1973).

J10,153/73

Review of the sympathoadrenal participation in stress, with personal observations "on cardiac infarct patients, normal and toxæmic pregnant subjects and on subjects undergoing various forms of athletic stress."

Delft, A. M. L. van, Nyakas, C., Kaplanski, J., Tilders, F. J. H.: "The effect of 6-hydroxydopamine administration to neonatal rats on some endocrine and behavioral parameters." *Arch. Int. Pharmacodyn. Ther.* **206**: 403-404 (1973). H82,629/73

Depletion of catecholamines in the rat brain, achieved by 6-hydroxydopamine, caused severe anorexia with impairment of growth and delayed vaginal opening, but curiously the stressor activity of the pituitary-adrenal system did not appear to be significantly affected. "Adrenal weights were normal when expressed per 100 g body weight. Diurnal peak and trough activities of adrenocortical activity as determined by measuring both plasma corticosterone levels and corticoid production of excised adrenal tissue in vitro were comparable to the activities found in control rats. Also the response of the pituitary-adrenal system when animals were exposed to strange environment or ether stress was completely within the normal range. These findings raise serious doubts with regard to the theory of the existence of a noradrenergic inhibitory system acting on pituitary-adrenal regulatory processes in the brain."

Dobkin, A. B., Pieloch, P. A.: "The metabolic effects of neuroleptanesthesia." *Int. Anesthesiol. Clin.* **11**: 155-169 (1973).

J9,286/73

Brief résumé of the literature and per-

sonal observations on the metabolic changes associated with anesthesia, particularly neuroleptanesthesia, in man. The changes in blood sugar, plasma cortisol, catecholamines, and so on were clearly characteristic of systemic stress. Furthermore, in the case of concurrent surgical interventions, "balanced anesthesia, with or without the neuroleptic component, does not block the stress response. Associated rises in blood sugar, plasma cortisol, and catecholamines during anesthesia and surgery appear to be well documented" (31 refs.).

Leduc, J.: "Effet de la sympathectomie chez le rat exposé au froid" (Effect of sympathectomy on rats exposed to cold). *Ann. ACFAS* **40**: 128 (1973). H87,897/73

6-Hydroxydopamine, which causes a "chemical sympathectomy," greatly diminishes resistance to cold. There is a marked rise in urinary EP but not NEP. Apparently, the adrenal medulla can largely compensate for the loss of sympathetic nerve activity.

Orlandi, F., Serra, D.: "La risposta ipotalamo-ipofisaria all'elettrostimolazione del nervo olfattivo" (Hypothalamo-hypophyseal reaction to electric stimulation of the olfactory nerve). *Folia Endocrinol. (Roma)* **26**: 441-446 (1973). H83,463/73

In man, direct electric stimulation of the nasal mucosa elicits rapid increases in plasma cortisol with other manifestations of stress, presumably because the olfactory nerve is directly connected with the CRF-producing hypothalamic centers.

Valdman, A. V.: "Functional and neurochemical analysis of visceral reactions related to emotional stress." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 56-59. Baku, USSR, 1974 (Russian, with extensive English summary). J17,539/74

Vedyayev, F. P.: "Emotional stress condition models and their visceral manifestations." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 62-67. Baku, USSR, 1974 (Russian, with extensive English summary). J17,541/74

Schumpelick, V., Paschen, U.: "Vergleich der protektiven Wirkung von Diazepam und Vagotomie auf das Stressulkus der Ratte" (Comparison of the protective activity of diazepam and vagotomy on stress ulcers in rats). *Arzneim. Forsch.* **24**: 176-179 (1974). H82,750/74

In rats, stress ulcers produced by restraint

can be partially prevented by diazepam pre-treatment or vagotomy, but combined application of both agents offers the best protection. "This fact demonstrates a different mode of action. The antiulcerative effect of diazepam is explained by its direct action on the vegetative regulation centres in the hypothalamic and limbic system, leading to a partial inhibition of the vagally controlled HCl-pepsin component and the splanchnic nerve dependent vascular factor of ulcerogenesis as well."

Carson, V. G., Wenzel, B. M.: "Tele-metered heart rates of immunosympathectomized and/or adrenal-medullectomized mice during behavioral tasks." *J. Comp. Physiol. Psychol.* **87**: 449-457 (1974). J16,524/74

Schumpelick, V., Kauffmann-Mackh, G.: "Der Einfluss des N. Vagus auf die Ulkusentstehung bei portokavaler Anastomose der Ratte" (The influence of the vagus nerve on ulcer formation in rats with portacaval anastomosis). *Brun's Beitr. Klin. Chir.* **221**: 239-246 (1974). J13,241/74

In rats with portacaval anastomosis, multiple ulcers occurred following pylorus ligation because of vagal stimulation. This was largely inhibited by vagotomy, which also diminished the quantity and acidity of the gastric juice (32 refs.).

Reticular Formation, Reticular Activating System

(See also our earlier stress monographs, p. xiii)

Nauta, W. J. H., Kuypers, H. G. J. M.: "Some ascending pathways in the brain stem reticular formation." In: Jasper, H. H., Proctor, L. D. et al., *Reticular Formation of the Brain*, pp. 3-30. Boston: Little, Brown, 1958. J12,282/58

Detailed and well-illustrated review concerning the morphology of the brain stem reticular formation in cats, emphasizing that "long and short ascending projections to the medial region of the caudal midbrain could constitute pathways capable of activating endocrine and autonomic mechanisms such as those involved in the stress response."

Harris, G. W.: "The reticular formation, stress and endocrine activity." In: Jasper, H. H., Proctor, L. D. et al., *Reticular Forma-*

tion of the Brain, pp. 207-221. Boston: Little, Brown, 1958. C78,255/58

Review of the literature showing that stressors, especially those causing increased EP, vasopressin and ACTH secretion, as well as decreased TTH secretion, probably act through the reticular activating system, which is closely related to, and has many characteristics in common with, the hypothalamus-hypophyseal system (57 refs.).

Royce, P. C., Sayers, G.: "Blood ACTH: effects of ether, pentobarbital, epinephrine and pain." *Endocrinology* **63**: 794-800 (1958). C61,941/58

In rats, painful stimuli markedly elevate blood ACTH within a few minutes. "Ether first excites, then inhibits ACTH release. Pentobarbital exhibits only a depressant action. The excitatory action of ether is blocked by decerebration and by destruction of the median eminence area of the hypothalamus. The excitatory action of epinephrine is manifest in the decerebrate but not in the median eminence lesioned rat. Since ether and pentobarbital depress the brain stem reticular system, it is reasonable to speculate that the action of these two agents in inhibiting ACTH release involves this multisynaptic conduction system."

Feldman, S., Heide, C. S. van der, Porter, R. W.: "Evoked potentials in the hypothalamus." *Am. J. Physiol.* **196**: 1163-1167 (1959). C70,825/59

Following electric stimulation of the sciatic nerve in cats, "the hypothalamic evoked potentials had a very prolonged recovery time on double stimulation, were sensitive to pentobarbital even to a greater degree than the evoked potentials in the midbrain reticular formation, and were abolished by high frequency stimulation of the midbrain reticular formation. The long latency potentials in the hypothalamus were similar to those evoked in the midbrain reticular formation, while the short latency potentials had properties similar to those of the lemniscal potentials. This fact suggested that the short latency potentials signaled the arrival of impulses from lemniscal collaterals."

Mazzone, R., Sozio, N., Padolecchia, N.: "Effetti della sensibilizzazione colinergica sulla sindrome reattiva allo 'stress'" (Effect of cholinergic sensitization on the syndrome reactive to "stress"). *Boll. Soc. Ital. Biol. Sper.* **36**: 157-159 (1960). J23,135/60

Cholinergic drugs increase reactivity to

pain-induced stress in the rabbit. These and other experiments with eserine and atropine suggest that the stress reaction develops in a zone sensitive to acetylcholine but not to atropine, and thus furnishes indirect evidence of the role of this reticular formation in the organization of defense mechanisms.

Welch, B. L.: "Psychophysiological response to the mean level of environmental stimulation: A theory of environmental integration." *Proc. Symp. Medical Aspects of Stress in the Military Climate*, pp. 39-99 (1965). G41,327/65

Review on the relationship between stress and the Mean Level of Environmental Stimulation (MLES). Detailed survey of the literature and personal observations on the effects of isolation with sensory deprivation or crowding on nonspecific responsiveness. Particular attention is given to the influence of the Ascending Reticular Activating System (ARAS) upon the hypothalamus and through it upon ACTH, glucocorticoid and catecholamine discharges. The numerous feedbacks in several mechanisms involved in arousal and relaxation are critically analyzed (205 refs.).

Kuntsevich, M. V.: "The effect of reticular formation of the mesencephalon on the hormone formation in the adrenal cortex in stress." *Probl. Endokrinol.* **13** No. 2: 61-64 (1967) (Russian). F78,769/67

In rats with electrolytic lesions in the reticular formation of the mesencephalon, the stress of surgical trauma failed to stimulate corticoid production.

Taylor, A. N.: "The role of the reticular activating system in the regulation of ACTH secretion." *Brain Res.* **13**: 234-246 (1969). H27,699/69

In cats, electric stimulation of the pontine and mesencephalic reticular formations caused "sustained cortical arousal, pupillary dilatation and a humorally mediated pressor response resulted in facilitation or inhibition of ACTH release commencing within 5 min after a 30-sec stimulation, reaching a maximum or minimum at 15 min and lasting 30-40 min. The direction of the ACTH response was dependent upon prestimulation levels of cortisol secretion. When these were low, facilitatory responses occurred, when high, inhibition or no change was observed" (28 refs.).

Cooper, C. J.: "Anatomical and physiological mechanisms of arousal, with special ref-

erence to the effects of exercise." *Ergonomics* **16**: 601-609 (1973). J8,261/73

Evidence suggesting that the stressor effect of exercise is at least partially mediated through an activation of the reticular formation.

Rhinencephalon (Archicortex)

(See also our earlier stress monographs, p. xiii)

Endrőczi, E., Lissák, K., Szép, C., Tígyi, A.: "Examinations of the pituitary-adrenocortical-thyroid system after ablation of neocortical and rhinencephalic structures." *Acta Physiol. Acad. Sci. Hung.* **6**: 19-31 (1954). C5,574/54

Working with cats, the authors "did not succeed in demonstrating an essential change in the adrenocortical function of animals with neocortical operation." In cats displaying a rage response, there was considerable exhaustion of lipid granules in the fasciculata, whereas the normally low lipid content of the reticularis tended to be increased. Blood corticoid levels also rose.

Slusher, M. A., Hyde, J. E.: "Inhibition of adrenal corticosteroid release by brain stem stimulation in cats." *Endocrinology* **68**: 773-782 (1961). D4,925/61

Review of the earliest literature on the enhancement or inhibition of ACTH secretion by stimulation or destruction of various parts of the CNS. In the present experiments, cats prepared as "encéphale isolés" exhibited a rapid decrease in adrenal venous corticoids following stimulation of the ventral midbrain tegmentum. Stimulation of the posterior diencephalon induced an increase, decrease, or no significant change in various cats. "An interrelationship between midbrain and diencephalic areas concerned with the regulation of ACTH release appears evident on the basis of reversals in corticosteroid levels in response to combined stimulation."

Endrőczi, E., Lissák, K.: "The role of rhinencephalon in the activation of the hypophyseoadrenocortico-gonad system and in the formation of emotional and sexual behavior" *Probl. Endokrinol. Gormonoter.* **7** No. 4: 18-26 (1961) (Russian, 34 refs.). D10,122/61

Septum

(See also our earlier stress monographs, p. xiii)

Usher, D. R., Ling, G. M., MacConaill, M.: "Some endocrine and behavioural effects of chlordiazepoxide in septal-lesioned rats." *Int. J. Clin. Pharmacol.* **1**: 191-196 (1968).

G64,766/68

Rats with septal lesions developed a typical behavioral pattern, the "septal syndrome," with enhanced ACTH synthesis, but diminished release of this hormone during stress. "Chlordiazepoxide reduced the hyper-reactivity of septal-lesioned rats, but had no effect on endocrine organ weights; the reduction of hyper-reactivity was more marked in the stressed animals. Lesioned rats had larger adenohypophyses than sham-operated animals. The weight of this gland was reduced in all stressed animals, whether sham-operated or lesioned. It is postulated that mild stress and chlordiazepoxide both contribute to a diminished hyper-reactivity of rats with septal lesions."

Kozlovskaya, M. M., Valdman, A. V.: "Behavioral and EEG reactions evoked by stimulation of the medial and lateral septal zones of the brain in the rabbit." *Zh. Vyssh. Nerv. Deyat.* **20**: 1022-1030 (1970) (Russian).
J21,849/70

Endrőczi, E., Nyakas, C.: "Effect of septal lesion on exploratory activity, passive avoidance learning and pituitary-adrenal function in the rat." *Acta Physiol. Acad. Sci. Hung.* **39**: 351-360 (1971). G87,966/71

"A possible role of the cessation of hippocampal-hypothalamic connections, on the one hand, and a selective corticosterone accumulation by the hippocampus, on the other hand, as events involved in behavioural changes after rostral septal lesion, are discussed."

Golda, V., Stránský, Z., Petr, R., Herink, J., Záková, Z.: "Brain serotonin in stressed, adrenalectomized and septal rats." *Activ. Nerv. Sup. (Praha)* **14**: 215-217 (1972).
J20,547/72

Brown, G. M., Uhlir, I. V., Seggie, J., Schally, A. V., Kastin, A. J.: "Effect of septal lesions on plasma levels of MSH, corticosterone, GH and prolactin before and after exposure to novel environment: role of MSH in the septal syndrome." *Endocrinology* **94**: 583-587 (1974). H86,300/74

In rats, septal lesions considerably altered hormonal reactions to various stressors, and concurrently there were pronounced behavioral changes. The literature on the "septal syndrome" is reviewed (26 refs.).

Usher, D. R., Lieblich, I., Siegel, R. A.: "Pituitary-adrenal function after small and large lesions in the lateral septal area in food-deprived rats." *Neuroendocrinology* **16**: 156-164 (1974). H98,364/74

Ladisch, W.: "Stress und Serotoninstoffwechsel in verschiedenen Arealen des Zentralnervensystems der Ratte" (Stress affecting the serotonin metabolism in different regions of the central nervous system in the rat). *Arzneim. Forsch.* **24**: 1025-1027 (1974).
H88,829/74

In rats, electric footshock caused a pronounced increase in 5-HIAA in the raphé and septum, whereas 5-HT concentrations rose mainly in the septum, thalamus and hypothalamus. In general, "septum and raphé appeared to be the regions whose 5-HT metabolism was mostly changed by the stress of electric footshock."

Seggie, J., Uhlir, I., Brown, G. M.: "Adrenal stress responses following septal lesions in the rat." *Neuroendocrinology* **16**: 225-236 (1974). H98,370/74

Uhlir, I., Seggie, J., Brown, G. M.: "The effect of septal lesions on the threshold of adrenal stress response." *Neuroendocrinology* **14**: 351-355 (1974). H89,268/74

In rats with septal lesions, "baseline corticosterone values were unaltered, plasma corticosterone concentrations in lesioned animals were elevated in response to stimuli that did not produce a corresponding elevation in sham-lesioned and unlesioned animals. Neither baseline nor stress levels of prolactin were affected by septal lesions at the times studied. It is concluded that a septal lesion lowers the stimulation threshold for activation of the pituitary adrenal axis and is suggested that corticosterone and prolactin stress responses are under different neural control."

Seggie, J., Shaw, B., Uhlir, I., Brown, G. M.: "Baseline 24-hour plasma corticosterone rhythm in normal, sham-operated and septally-lesioned rats." *Neuroendocrinology* **15**: 51-61 (1974). H89,697/74

In rats the circadian rhythm of plasma corticosterone is elevated after damage to

the septum under ordinary conditions, but not under rigorously controlled environmental isolation excluding any disturbing stressor stimuli. "Thus, the hypothesis is borne out that although the baseline adrenal function is normal in septally-lesioned rats, adrenal responses to stimulation are enhanced."

Kelsey, J. E.: "Role of pituitary-adrenocortical system in mediating avoidance behavior of rats with septal lesions." *J. Comp. Physiol. Psychol.* **88**: 271-280 (1975).

J20,817/75

through the interior of the stalk to the tuberal region."

Collin, R.: "Les fondements morphologiques de la notion de neurocrinie hypophysaire. Etat actuel de la question" (Morphologic basis of the notion of the hypophyseal "neurocrinie." Present state of the subject). *Ann. Physiol. Physicochim. Biol.* **10**: 953-962 (1934). 29,038/34

On the basis of purely morphologic observations, colloid granules in the pituitary are regarded as carriers of hormonal products that are microscopically detectable manifestations of secretions. Colloid can be formed in all parts of the gland, and appears to be discharged into the general circulation (hemocrinie), the CSF, (hydrencéphalocrinie), the tuber cinereum after traversing the neurohypophysis infundibulum (neurocrinie) and the hypophyseal portal vessels (hémoneurocrinie). The author still supports the view that the circulation through the portal vessels flows from the pituitary to the hypothalamus.

Westman, A., Jacobsohn, D.: "Endokrinologische Untersuchungen an Ratten mit durchtrenntem Hypophysenstiel. 5. Mitteilg. Verhalten des Wachstums, der Nebennieren und der Schilddrüsen" (Endocrinologic studies in rats with transection of the pituitary stalk. 5. Studies on somatic growth, adrenals, and thyroid). *Acta Pathol. Microbiol. Scand.* **15**: 435-444 (1938).

A17,898/38

In rats, transection of the pituitary stalk inhibits somatic growth and causes histologic evidence of thyroid inactivity, but the adrenals are not atrophic and fail to show the characteristic sudanophobe zone seen after hypophysectomy.

Uotila, U. U.: "On the role of the pituitary stalk in the regulation of the anterior pituitary, with special reference to the thyrotropic hormone." *Endocrinology* **25**: 605-614 (1939). A19,997/39

In rats, after transection of the pituitary stalk [without any measures to prevent vascular regeneration] the adrenal and thyroid structures remain essentially normal, but upon exposure to cold the adrenals show a typical hypertrophy of the alarm reaction, whereas the usual stimulation of the thyroid does not occur.

Green, J. D., Harris, G. W.: "The neurovascular link between the neurohypophysis

Stalk, Portal Vessels

(See also our earlier stress monographs, p. xiii, and cf. Hypothalamus and Thalamus)

Pietsch, K.: "Aufbau und Entwicklung der Pars tuberalis des menschlichen Hirnanhangs in ihren Beziehungen zu den übrigen Hypophysenteilen" (Anatomy and development of the human hypophyseal pars tuberalis, and its relationship to the other parts of the hypophysis). *Z. Mikrosk. Anat. Forsch.* **22**: 227-258 (1930). 5,087/30

Anatomic studies on the human pituitary indicate that the veins and capillaries of the anterior lobe and pars tuberalis carry blood upwards into the tuber cinereum, and that the histologically visible colloid they contain may represent a secretion of the glandular parts, "a secretory stream of the anterior lobe towards the hypothalamic centers."

Popa, G. T., Fielding, U.: "Hypophysio-portal vessels and their colloid accompaniment." *J. Anat.* **67**: 227-232 (1933).

29,759/33

After a brief résumé of earlier data on venous vessels in the pituitary stalk, personal observations on man are reported which suggest that the pituitary stalk and tuber region contain colloid in their vessels. This "colloid—whatever it may be—is formed in the pituitary and not in the brain, so that its association with the vessels may be taken as indicating that the direction of the flow is certainly hypophysio-hypothalamic." The authors discredit the earlier findings of Karl Pietsch who, on the basis of very similar observations, concluded that "the veins and the capillaries of the pars tuberalis are derived from the adenohypophysis.... They partly abut into the sinus circulatorius but most of them I see progressing

and adenohypophysis." *J. Endocrinol.* **5**: 136-146 (1947). B1,426/47

In the rabbit, monkey and man, nervous connections between the neuro- and adenohypophysis are scanty. Vascular connections are prominent in the rat, guinea pig, rabbit, dog and man, particularly between the capillary loops of the ME, infundibular stem and the hypophyseal portal vessels. These vessels are well supplied with nerve fibers. "It is suggested that the central nervous system regulates the activity of the adenohypophysis by means of a humoral relay through the hypophyseal portal vessels."

Green, J. D.: "Vessels and nerves of amphibian hypophyses. A study of the living circulation and of the histology of the hypophyseal vessels and nerves." *Anat. Rec.* **99**: 21-53 (1947). B4,690/47

Detailed description of the hypophyseal portal system in the bullfrog and *Ambystoma*.

Harris, G. W.: "The blood vessels of the rabbit's pituitary gland, and the significance of the pars and zona tuberalis." *J. Anat.* **81**: 343-351 (1947). B35,058/47

Merényi, D.: "Angioarchitektur der Katzenhypophyse. Morphologische Grundlagen zur experimentellen Forschung über das hypophyseo-diencephale System" (Angioarchitecture of the hypophysis in cats. Morphologic baseline for experimental investigations of the hypophyseal-diencephalic system). *Virchows Arch. [Pathol. Anat.]* **315**: 534-547 (1948). B27,100/48

Ink preparation injections indicate that in the cat the anterior lobe receives no arterial blood and is supplied only by the portal vessels descending from the pars tuberalis and the stalk. Consequently, transection of the stalk causes pituitary necrosis; hence this species is unsuitable for studies concerning results of severing the pituitary from the hypothalamus.

Green, J. D., Harris, G. W.: "Observation of the hypophyseal-portal vessels of the living rat." *J. Physiol. (Lond.)* **108**: 359-361 (1949). B32,936/49

A technique for the observation of hypophyseal-portal vessels in the living rat shows that the direction of the blood flow is from the ME to the pars distalis.

Harris, G. W.: "Regeneration of the hypophyseal portal vessels." *Nature* **163**: 70 (1949). B71,852/49

Cheng, C. P., Sayers, G., Goodman, L. S., Swinyard, C. A.: "Discharge of adrenocorticotropic hormone in the absence of neural connections between the pituitary and hypothalamus." *Am. J. Physiol.* **158**: 45-50 (1949). B38,333/49

In rats, pituitary stalk transection does not interfere with the normal adrenocortical response. "It is therefore concluded that the prompt release of adrenocorticotropic hormone from the adenohypophysis in response to stress is not dependent upon neural connections between the hypothalamus and the anterior pituitary." The authors are careful to point out that their findings "do not rule out the possibility that a neurohumor, arising in the hypothalamus and passing to the adenohypophysis via a hypophyseal portal system, mediates the release of ACTH in response to the application of stress."

Harris, G. W., Johnson, R. T.: "Regeneration of the hypophyseal portal vessels, after section of the hypophyseal stalk, in the monkey (*Macacus rhesus*)."*Nature* **165**: 819 (1950). B71,853/50

Harris, G. W.: "Oestrous rhythm. Pseudopregnancy and the pituitary stalk in the rat." *J. Physiol. (Lond.)* **111**: 347-360 (1950).

B54,599/50

In rats, sectioning of the pituitary stalk is followed by regeneration of the hypophyseal portal vessels and fails to cause manifest pituitary deficiency, unless foreign bodies (usually paper plates) are placed between the cut ends of the stalk to prevent the formation of such vascular connections.

Xuereb, G. P., Prichard, M. M. L., Daniel, P. M.: "The hypophyseal portal system of vessels in man." *Q. J. Exp. Physiol.* **39**: 219-230 (1954). C5,988/54

Harris, G. W.: "The function of the pituitary stalk." *Bull. Johns Hopkins Hosp.* **97**: 358-375 (1955). C18,503/55

Worthington, W. C. Jr.: "Some observations on the hypophyseal portal system in the living mouse." *Bull. Johns Hopkins Hosp.* **97**: 343-357 (1955) (28 refs.).

J12,052/55

Engelhardt, F.: "Über die Angioarchitektonik der hypophysär-hypothalamischen Systeme" (Angioarchitecture of the hypophyseal-hypothalamic system). *Acta Neuroveg. (Wien)* **13**: 129-170 (1956) (several hundred refs.). C16,881/56

Brettschneider, H.: "Ueber die Innervation der Spezialgefässe des Infundibulum" (The innervation of blood vessels in the infundibulum). *Z. Mikrosk Anat. Forsch.* **62**: 30-39 (1956). C18,499/56

Histologic studies on the nerves of the blood vessels in the infundibulum and stalk of the dog and horse. Claims that the adenohypophysis receives nerve fibers from the hypothalamus have not been confirmed.

Porter, J. C., Jones, J. C.: "Effect of plasma from hypophyseal-portal vessel blood on adrenal ascorbic acid." *Endocrinology* **58**: 62-67 (1956). J11,918/56

Plasma obtained from the hypophyseal-portal veins of hypophysectomized dogs decreased the adrenal ascorbic acid content in cortisol-overdosed, but not in hypophysectomized rats. These observations suggest that blood from the hypophyseal portal vessels contains a substance(s) which accelerates the release of ACTH from the anterior lobe. These observations further suggest that a block in the response of the rat to the stress of unilateral adrenalectomy occurs at some site other than the anterior lobe, perhaps the hypothalamus."

Donovan, B. T., Harris, G. W.: "The effect of pituitary stalk section on light-induced oestrus in the ferret." *J. Physiol. (Lond.)* **131**: 102-114 (1956).

J6,721/56

In the ferret—as in most other species examined—simple section of the pituitary stalk is followed by regeneration of the vessels, as a result of which the initially suppressed, light-induced estrus response reappears. Permanent separation of the hypophysis from the hypothalamus by interposition of waxed paper between the cut ends of the stalk abolishes light-induced estrus and causes a decrease in thyroid and adrenal weight.

Fortier, C., Harris, G. W., McDonald, I. R.: "The effect of pituitary stalk section on the adrenocortical response to stress in the rabbit." *J. Physiol. (Lond.)* **136**: 344-363 (1957). C33,587/57

In rabbits the pituitary stalk was sectioned, and a waxed-paper plate was inserted between the cut ends. This operation, followed "by little or no regeneration of the portal vessels, reduced or abolished the lymphopenic response to restraint and exposure to cold, but exerted little effect on the response to injection of adrenaline or laparotomy or on the adrenal ascorbic acid deple-

tion following unilateral adrenalectomy. These findings support the view that environmental stimuli may be divided into two types: those that affect ACTH secretion solely by an action through the central nervous system, and those that act also by affecting the composition of the blood in the systemic circulation."

Daniel, P. M., Prichard, M. M. L.: "The vascular arrangements of the pituitary gland of the sheep." *Q. J. Exp. Physiol.* **42**: 237-248 (1957). C37,349/57

Koibuchi, E., Fukuda, M.: "Pituitary reaction following the stalk section." *Endocrinol. Jap.* **5**: 11-20 (1958). C54,411/58

Even after transection of the pituitary stalk, burns or laparotomy caused some increase in corticoid secretion, perhaps because "the humoral stimulator could be transported into the anterior pituitary via the systemic circulation."

Duvernoy, A.: "Contribution à l'Étude de la Vascularization de l'Hypophyse" (Contribution to the study of hypophyseal vascularization). Thesis, University of Paris, 1958.

J12,867/58

Doctoral thesis on the structure of the hypothalamus-pituitary vascular connections.

Daniel, P. M., Prichard, M. M. L.: "The effects of pituitary stalk section in the goat." *Am. J. Pathol.* **34**: 433-469 (1958).

C54,157/58

In goats, insertion of a wax plate between the cut ends of the pituitary stalk led to massive infarction of the anterior lobe, but certain areas always survived and underwent regeneration with mitotic proliferation. The posterior lobe became atrophic and showed certain histologic signs of degeneration. The pars intermedia underwent hypertrophy (44 refs.).

Holmes, R. L., Hughes, E. B., Zuckerman, S.: "Section of the pituitary stalk in monkeys." *J. Endocrinol.* **18**: 305-318 (1959). C69,542/59

In rhesus monkeys, pituitary stalk section with interposition of polythene film between the cut ends caused diabetes insipidus and posterior lobe atrophy but no significant adrenal involution.

Clegg, M. T., Ganong, W. F.: "The effect of hypothalamic lesions on ovarian function in the ewe." *Endocrinology* **67**: 179-186 (1960). J12,312/60

In ewes, stereotaxic lesions placed in various parts of the hypothalamus interfered selectively with diverse manifestations of adenohypophyseal activity. In two animals with stalk lesions, peripheral 17-OHCS failed to rise after stress (laparotomy), but in none of the animals was there any significant adenohypophyseal atrophy.

Worthington, W. C. Jr.: "Vascular responses in the pituitary stalk." *Endocrinology* **66**: 19-31 (1960). C79,623/60

Description of the portal blood flow of the pituitary in normal mice and their response to barbiturates, morphine, hemorrhage and burns. Changes in anterior lobe function may depend largely upon variations in blood flow (43 refs.).

Martinez, P. M.: "The Structure of the Pituitary Stalk and the Innervation of the Neurohypophysis in the Cat," p. 158. Thesis, University of Leiden, 1960. G35,942/60

Doctoral thesis on the embryology and microscopy of the cat hypophysis, with special emphasis upon the infundibulum, the neurohypophysis, the ME, and the ependymal lining of the pituitary recess (about 200 refs.).

Zhdanov, D. A., Akhmayev, I. G., Sapin, M. P.: "To the solution of some controversial problems of functional anatomy of blood circulation in hypophysis." *Arkh. Anat. Gistol. Embriol.* **40**: 35-49 (1961) (Russian). D50,633/61

Detailed studies on the vascular supply of the pituitary, with special reference to the portal vessels.

Kovács, K., Dávid, M. A., László, F. A.: "Adrenocortical function in rats after lesion of the pituitary stalk." *J. Endocrinol.* **25**: 9-18 (1962). D32,342/62

In rats in which electrolytic destruction of the pituitary stalk caused diabetes insipidus, the histologic structure of the adrenals was essentially unchanged. Operative stress and uniadrenalectomy elicited no adrenal ascorbic acid depletion, whereas ACTH administration did. The corticosterone content of adrenal venous blood was slightly decreased, but aldosterone secretion remained unchanged. Large doses of corticosterone continued to cause compensatory atrophy.

Adams, J. H., Daniel, P. M., Prichard, M. M. L., Schurr, P. H.: "The volume of the infarct in pars distalis of a human pituitary gland, 30 hr. after transection of the pitu-

itary stalk." *J. Physiol. (Lond.)* **166**: 39-41 (1963). D65,372/63

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "The effect of stalk section on the volume of the pituitary gland of the sheep." *Acta Endocrinol. (Kbh.)* **43** Supp. 81: 1-27 (1963). E25,464/63

In sheep the pituitary stalk was transected, a plate being inserted between the cut ends to prevent vascular regeneration. Comparatively small areas of the adenohypophysis escaped infarction, and the infundibular process decreased in volume. The location of the infarcted areas is attributed to differential distribution of the stalk vessel.

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "Volume of the infarct in the anterior lobe of the monkey's pituitary gland shortly after stalk section." *Nature* **198**: 1205-1206 (1963). D69,623/63

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "Transection of the pituitary stalk in the goat, and its effect on the volume of the pituitary gland." *J. Pathol. Bacteriol.* **87**: 1-14 (1964). G2,581/64

In goats, a nonirritant plate was inserted between the cut ends of the pituitary stalk. This caused massive infarcts in the pars distalis with no substantial regeneration. The infundibular process became extremely small, whereas the pars intermedia underwent hypertrophy.

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "Distribution of hypophysial portal blood in the anterior lobe of the pituitary gland." *Endocrinology* **75**: 120-126 (1964). F15,507/64

Studies in goats, rats and sheep indicate that partial transection of the pituitary stalk causes circumscribed lesions in the adenohypophysis because the portal vessels running down the stalk vascularize specific, limited areas. The neurovascular link between the hypothalamus and pars distalis may include many pathways, each with circumscribed areas of origin and termination. "Thus, individual groups of anterior lobe cells of similar function could receive specific neurohumors produced by particular groups of hypothalamic nerve cells."

Török, B.: "Structure of the vascular connections of the hypothalamo-hypophysial region." *Acta Anat. (Basel)* **59**: 84-99 (1964). G27,505/64

Extensive review of the literature and per-

sonal observations on cats and dogs concerning the portal circulation between the hypothalamus and pituitary.

Dávid, M. A., Csernay, L., László, F. A., Kovács, K.: "The importance of the hypothalamo-hypophyseal connections in the function of the pituitary-adrenocortical axis. Hypophyseal blood flow after destruction of the pituitary stalk." Proc. 2nd. Int. Congr. Endocrinol., London, 1964, Part 1, *Int. Congr. Ser. No. 83*, pp. 530-537. Amsterdam and New York: Excerpta Medica, 1964.

F48,879/64

Dávid, M. A., Csernay, L., László, F. A., Kovács, K.: "Hypophysial blood flow in rats after destruction of the pituitary stalk." *Endocrinology* **77**: 183-187 (1965).

F46,723/65

Zukoski, C. F., Ney, R. L.: "ACTH secretion after pituitary stalk section in the dog." *Am. J. Physiol.* **211**: 851-854 (1966).

F70,429/66

In dogs, transection of the pituitary stalk was followed by the insertion of aluminum foil to prevent regeneration of vessels. Baseline peripheral and adrenal venous 17-OHCS levels, as well as the rise in adrenal venous 17-OHCS after ACTH administration and laparotomy, remained normal. In most animals, 17-OHCS production after metyrapone infusion was increased.

Worthington, W. C. Jr.: "Blood samples from the pituitary stalk of the rat: method of collection and factors determining volume." *Nature* **210**: 710-712 (1966). F67,488/66

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "Observations on the portal circulation of the pituitary gland." *Neuroendocrinology* **1**: 193-213 (1966).

F68,589/66

The portal circulation of the pituitary was studied by use of injected preparations and through experiments in which lesions were made in the pituitary stalk to arrest part of the blood flow to the gland. In man, monkeys, sheep and goats, the "pars distalis" derives its sole blood supply from the hypophysial portal vessels, of which there are two main groups. The long portal vessels run down the stalk and supply the greater part of pars distalis (e.g., up to 90% of the lobe in man). The territory supplied by an individual long portal vessel is strictly circumscribed, the cells in a given area of pars distalis being supplied always by the

same portal vessel. The short portal vessels are situated at a lower level than the long ones, and supply a relatively small area along the dorsal border of the lobe. The primary capillary beds which supply these two groups of portal vessels both lie in the neurohypophysis, but at different levels." At their distal end the individual portal vessels are probably distributed to small specific areas of anterior lobe cells comparable to the arrangement at their proximal end. Thus, "an individual portal vessel would convey blood containing neurohumors derived from a specific group of hypothalamic cells to an area of pars distalis which is especially rich in certain types of epithelial cell." The situation in man is illustrated in Figure 14 (p. 1008).

Adams, J. H., Daniel, P. M., Prichard, M. M. L.: "The long-term effect of transection of the pituitary stalk on the volume of the pituitary gland of the adult goat." *Acta Endocrinol. (Kbh.)* **51**: 377-390 (1966).

F65,157/66

In goats, transection of the pituitary stalk with prevention of anastomosis formation by a resin plate caused atrophy of the anterior lobe and infundibular process, whereas the intermediate lobe underwent substantial hypertrophy.

Jacobsohn, D.: "The techniques and effects of hypophysectomy, pituitary stalk section and pituitary transplantation in experimental animals." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 1-21. London: Butterworths, 1966.

E10,525/66

Schurr, P. H.: "Techniques and effects of hypophysectomy, pituitary stalk section and pituitary transplantation in man." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 22-48. London: Butterworths, 1966.

E10,526/66

László, F. A., Wied, D. de: "Pituitary-adrenal system in rats bearing lesions in the pituitary stalk." *Endocrinology* **79**: 547-553 (1966) (25 refs.). F70,589/66

Porter, J. C., Smith, K. R.: "Collection of hypophysial stalk blood in rats." *Endocrinology* **81**: 1182-1185 (1967). F89,884/67

Lasierra, J.: "Aportaciones a la distribución vascular y topografía neurosecretora en la superficie de contacto hipofisaria, así como vascularizaciones viscerales concomitantes en relación con estados experimentales

de alarma" (On the vascular distribution and neurosecretory topography in the contact surface of the hypophysis, as well as concomitant visceral vascularizations in relation to experimental states of the alarm reaction). *An. Anat.* **17**: 485-536 (1968). J11,399/68

Changes in the portal vessels of the pituitary characteristic of the alarm reaction produced by diphtheria toxin in cats (about 100 refs.).

Duvernoy, H., Koritke, J. G.: "Les vaisseaux sous-épendymaires du recessus hypophysaire" (Subependymal vessels of the hypophyseal recessus). *J. Hirnforsch.* **10**: 227-245 (1968). J12,676/68

Extensive histologic studies on the subependymal origins of the hypothalamo-adenohypophyseal portal vessels in various mammals and birds. There exist numerous connections between the subependymal vessels and the cavity of the third ventricle from which they are separated only by a thin and often discontinuous ependymal membrane. "Such a structure will possibly allow exchanges between the blood of the hypophysis and the ventricular liquid which is continuously in motion in the third ventricle."

Kendall, J. W., Roth, J. G.: "Adrenocortical function in monkeys after forebrain removal or pituitary stalk section." *Endocrinology* **84**: 686-691 (1969) (19 refs.).

H10,034/69

Porter, J. C., Mical, R. S., Tippit, P. R., Drane, J. W.: "Effect of selective surgical interruption of the anterior pituitary's blood supply on ACTH release." *Endocrinology* **86**: 590-599 (1970). H22,214/70

Observations on surgically stressed rats with various interventions in the stalk region. Sham operations failed to affect the maximal rises in corticosterone discharge. "Removal of the pituitary greatly suppressed the secretion of corticosterone. Posterior lobectomy or transection of the portal vessels in the upper stalk had no apparent effect on ACTH release. This finding was interpreted to mean that the posterior pituitary and post-chiasmatic eminence are not obligatory sources of CRF." These and other observations "indicate that CRF comes from the stalk, post-peduncular eminence and/or the cerebrospinal fluid," after entering the portal blood via the post-peduncular and/or pituitary stalk capillaries (42 refs.).

Duvernoy, H.: "The vascular architecture of the median eminence." In: Knigge, K. M.,

Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 79-108. Basel and New York: S Karger, 1972. E10,566/72

Studies on birds and various mammals, including man, showed that the ME "is vascularized by the primary plexus of the hypophysial portal system consisting of a surface network (Mantel-plexus) and a deep network which is made up of the long capillary loops and the subependymal plexus." The primary plexus drains into the adenohypophysis, and certain regions of the ME probably bring blood more or less specifically to some areas of the adenohypophysis. The primary plexus is closely connected with the ventricular cavity, the posterior lobe and the adjacent tuberal vessels.

Halász, B., Kosaras, B., Lengvári, I.: "Ontogenesis of the neurovascular link between the hypothalamus and the anterior pituitary in the rat." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 27-34. Basel and New York: S Karger, 1972. J17,773/72

Spinal Cord

(See also our earlier stress monographs, p. xiii)

Selye, H., MacLean, A.: "Prevention of gastric ulcer formation during the alarm reaction." *Am. J. Dig. Dis.* **11**: 319-322 (1944). A75,010/44

In rats the gastric ulcers produced by transection of the spinal cord at C7 "may be prevented by the prophylactic administration of various food substances, aluminum hydroxide gel and especially by comparatively small doses of dextrose. Dextrose is effective when given either per os or intravenously. It prevents gastric ulcer formation even in doses insufficient to raise the glucose content of the blood above the normal level for the duration of the experiment. The prophylactic effect of dextrose is non-specific in the sense that the compound prevents the formation of gastric ulcers by a variety of widely different damaging agents such as formaldehyde injections, exposure to cold or spinal cord transection."

Andersson, E., Bates, R. W., Hawthorne, E., Haymaker, W., Knowlton, K., Rioch, D. McK., Spence, W. T., Wilson, H.: "The

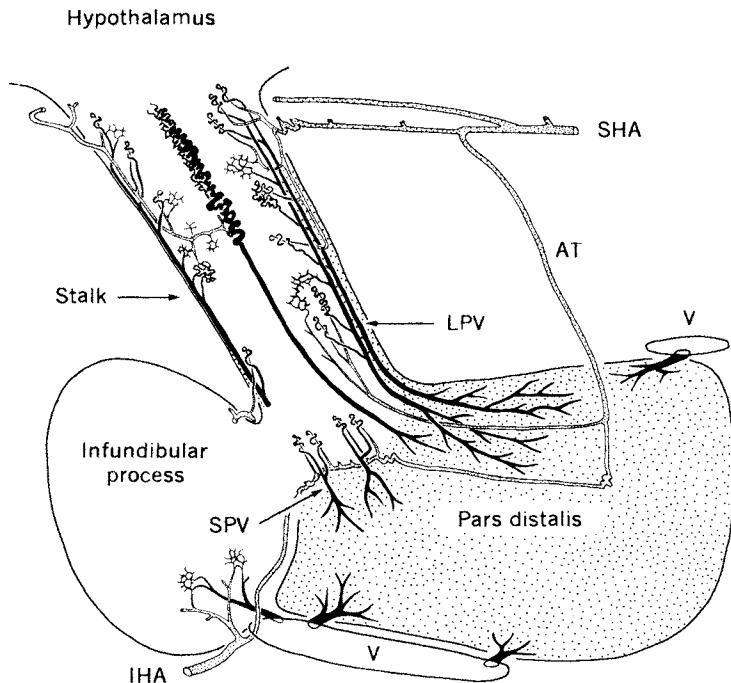


Figure 14. Human pituitary gland, in the sagittal plane, showing the main features of its blood supply. Note in particular the long portal vessels (LPV) and the short portal vessels (SPV) which between them provide the sole blood supply to pars distalis. The artery of the trabecula (AT) runs through pars distalis without supplying the parenchymal cells. In the operation of pituitary stalk section the aim is to transect the stalk just below the arrow to LPV. The median eminence, where the stalk joins the hypothalamus, is ill-defined in man and is not shown here. (Reproduced from *Neuroendocrinology* 1 (1966) by permission of J. H. Adams *et al.* and S. Karger.)

effects of midbrain and spinal cord transection on endocrine and metabolic functions with postulation of a midbrain hypothalamic-pituitary activating system." *Rec. Prog. Horm. Res.* 13: 21-59 (1957). C38,180/57

Egdahl, R. H.: "The differential response of the adrenal cortex and medulla to bacterial endotoxin." *J. Clin. Invest.* 38: 1120-1125 (1959). G33,275/59

In dogs, spinal cord transection at C7 abolishes adrenal medullary discharge by large doses of bacterial endotoxin, but febrile, hypotensive and adrenal cortical responses remain intact. "Epinephrine release is not necessary for the febrile and adrenocortical stimulating effects of endotoxin."

Redgate, E. S.: "Spinal cord and adrenocorticotropic release." *Proc. Soc. Exp. Biol. Med.* 105: 528-531 (1960).

C98,192/60

After spinal cord transection at T₂ in rats,

the adrenal ascorbic acid levels drop, but following recovery, the rats respond to ACTH as do twenty-four-hour hypophysectomized rats, so that ascorbic acid depletion of the adrenals can be employed as an indicator of endogenous ACTH secretion. Intact rats show equivalent ACTH release following electric shock to the fore- or hindpaws, whereas cord-sectioned rats respond only to forepaw stimulation with an ACTH discharge. "The results indicate that intact neural paths in the spinal cord are essential for mediation of ACTH release following hindpaw electrical stimulation."

Redgate, E. S.: "Spinal cord and ACTH release in adrenalectomized rats." *Fed. Proc.* 20: 185 (1961). D3,987/61

Purves, H. D., Sirett, N. E.: "Time course for corticotrophin release from ectopic pituitary grafts." *Endocrinology* 83: 1377-1380 (1968). H5,737/68

In rats a rubber band tightly applied to the hind leg stimulates ACTH release, which is inhibited by spinal cord transection. When five neonatal pituitaries are transplanted under the kidney of hypophysectomized rats, stimulation of ACTH secretion is diminished but not abolished.

Gibbs, F. P.: "Central nervous system lesions that block release of ACTH caused by traumatic stress." *Am. J. Physiol.* **217**: 78-83 (1969). H14,556/69

In rats, spinal cord and medulla oblongata hemisections blocked the increase in plasma corticosterone normally produced by contralateral, but not by ipsilateral, tibial fractures. Radio-frequency lesions placed almost anywhere in the brain stem abolished all fracture-induced ACTH releases within forty-eight hours. When the response was tested after ten days or more, unilateral lesions in the pontine reticular formation blocked the ACTH discharge much more after contralateral than after ipsilateral fractures. The lesions that abolished ACTH release during pentobarbital anesthesia were ineffective in unanesthetized controls. Presumably, "a nervous pathway mediating the traumatic stress-induced release of ACTH ascends to the pons on the side contralateral to the traumatized area." However, since Halász has shown that hypothalamic "deafferentation" does not prevent traumatic stress-induced ACTH secretion, there must be a mechanism other than a direct neural pathway from the pons to the basal hypothalamus.

Makara, G. B., Stark, E., Mihály, K.: "Corticotrophin release induced by traumatic stress in rats with unilateral spinal cord lesion." *Acta Physiol. Acad. Sci. Hung.* **38**: 199-203 (1970). G82,668/70

In rats, hemisection of the cervical spinal cord inhibits the ACTH-releasing effect of contralateral leg fracture, showing that the pathways conveying ACTH releasing information cross the midline.

Allen, J. P., Allen, C. F., Greer, M. A.: "Spinal cord pathways involved in tourniquet stimulation of ACTH secretion." *Neuroendocrinology* **13**: 246-254 (1974). H81,876/74

In adult male pentobarbital-anesthetized rats, a rise in plasma corticosterone twenty minutes after initiation of stress (hind leg tourniquet, bone fractures) indicated ACTH release. "Neither stressor stimulated ACTH

secretion in rats with complete cord transection between L₁ and T₂. Hemisection between L₁ and T₁₀ did not consistently block ACTH secretion following ipsilateral or contralateral tourniquet or leg break, but hemisection above T₁₀ blocked the effect of only the contralateral stressors. Complete cord transection above T₂ was associated with elevated 'basal' plasma immunoreactive ACTH and corticosterone concentrations in unanesthetized rats." These elevations could be partially suppressed by dexamethasone. It is concluded that tourniquet and bone fracture stimulate ACTH secretion through spinal pathways which are not consistently localized between L₁ and T₁₀ but are contralateral to the damaged extremity above T₁₀.

Cosgrove, D. O., Jenkins, J. S.: "The effects of epidural anesthesia on the pituitary-adrenal response to surgery." *Clin. Sci. Molec. Med.* **46**: 403-407 (1974).

J10,530/74

In women undergoing pelvic surgery under epidural anesthesia, cortisol secretion was very low compared to levels in others operated on under general anesthesia. Despite this deficient cortisol discharge, surgery was not impeded. The observations may be interpreted as indicating that "these pathways travel solely, through the spinal cord," and hence are blocked by epidural anesthesia.

Nervous vs. Systemic Stressors

(See also our earlier stress monographs, p. xiii)

Fortier, C.: "Studies on the control of ACTH release by means of hypophyseal transplants." In: Wolstenholme, G. E. W., *Ciba Foundation Colloquia on Endocrinology*, Vol. 4, pp. 124-136. London: J & A Churchill, 1952. B58,855/52

Observations on hypophysectomized rats with intraocular pituitary transplants led to the distinction between systemic (EP, cold, histamine) and neurotropic (sound, immobilization) stressors. The former do, whereas the latter do not, cause eosinopenia after severance of all connections between the hypothalamus and pituitary.

Guillemin, R., Fortier, C.: "Role of histamine in the hypothalamo-hypophyseal re-

sponse to stress." *Trans. N.Y. Acad. Sci.* **15**: 138-140 (1953). C80,534/53

In rats pretreated with Phenergan and exposed to various "neurotropic" (sound, restraint) or "systemic" (cold, histamine) stressors, only histamine became incapable of causing adrenal ascorbic acid discharge. "These results do not support the view that histamine may be an important factor and, in no way, an indispensable link in hypothalamo-pituitary alteration due to neurotropic stress." They also show that histamine cannot be the only humoral agent responsible for pituitary stimulation during stress.

Harris, G. W.: "The reciprocal relationship between the thyroid and adrenocortical responses to stress." In: Wolstenholme, G. E. W. and Cameron, M. P., *Ciba Foundation Colloquia on Endocrinology*, Vol. 8, pp. 531-550. London: J & A Churchill, 1955.

C3,662/55

In rabbits, transection of the pituitary stalk, with steps taken to prevent vascular regeneration, decreases the activity of the thyroid, adrenal cortex and ovaries; it also markedly reduces the effect of nervous and emotional stressors on the thyroid and adrenal cortex. On the other hand, the same intervention has little influence upon adrenocortical and thyroid responses to surgical trauma or large doses of EP. These findings are interpreted as evidence supporting the view that neurogenic and "systemic" stressors affect the pituitary through distinct mechanisms.

Mialhe-Voloss, C.: "Importance relative de l'antéhypophyse et de la posthypophyse dans les agressions systémiques et neurotropes" (Relative importance of anterior and posterior pituitary lobe in systemic and neurotropic stress). *Ann. Endocrinol.* (Paris) **17**: 104-110 (1956). C18,994/56

Fortier, C., Harris, G. W., McDonald, I. R.: "The effect of pituitary stalk section on the adrenocortical response to stress in the rabbit." *J. Physiol.* (Lond.) **136**: 344-363 (1957). C33,587/57

In rabbits the pituitary stalk was sectioned, and a waxed-paper plate was inserted between the cut ends. This operation, followed "by little or no regeneration of the portal vessels, reduced or abolished the lymphopenic response to restraint and exposure to cold, but exerted little effect on the response to injection of adrenaline or laparotomy or on the adrenal ascorbic acid deple-

tion following unilateral adrenalectomy. These findings support the view that environmental stimuli may be divided into two types: those that affect ACTH secretion solely by an action through the central nervous system, and those that act also by affecting the composition of the blood in the systemic circulation."

Nowell, N. W.: "Studies in the activation and inhibition of adrenocorticotropic secretion." *Endocrinology* **64**: 191-201 (1959).

C63,783/59

In neurohypophysectomized rats, adrenal ascorbic acid depletion could be produced by cold, hypertonic saline, and bell-ringing. A distinction is made between ascorbic acid factor (AAF) and adrenal weight factor (AWF) as two variants of ACTH. The neurohypophysis participates in the release of AAF, which is regulated by separate nerve centers in the hypothalamus. Enucleated adrenals regenerate under the influence of AWF, which is believed not to depend upon hypothalamic centers. "The neurohypophysis is involved in the release of ACTH/AAF in response to systemic stresses but not to emotional ones."

Smelik, P. G.: "The role of the posterior lobe of the pituitary gland in the corticotrophic response to acute stress." *Acta Physiol. Pharmacol. Neerl.* **9**: 125-126 (1960).

C89,917/60

In neurohypophysectomized rats, certain types of stressors no longer produce adrenal ascorbic acid discharge. It is suggested that "emotional stimuli activate the adrenal cortex only in the presence of the posterior lobe, but that somatic stimuli act as normally when the posterior lobe has been removed."

Giuliani, G., Martini, L., Pecile, A.: "Midbrain section and release of ACTH following stress." *Acta Endocrinol.* (Kbh.) Supp. 51: 37 (1960).

C93,249/60

In hypophysectomized rats with pituitary grafts in the anterior chamber of the eye, most stressors (ether anesthesia, anoxia, abdominal surgery, EP, acetylcholine, histamine, formalin, insulin, salicylate) and even unilateral adrenalectomy, failed to increase ACTH release (adrenal ascorbic acid tests), whereas vasopressin and hypertonic sodium chloride solutions remained highly effective. The same was true after cortisol treatment or midbrain section, although in the latter case not only vasopressin and hypertonic sodium chloride but also formalin, insulin,

salicylate and histamine retained their activity. Apparently, the pathways of mediation differ for the various stressors, but among the agents tested, only vasopressin acts directly upon the anterior lobe. [The brief abstract of an oral communication does not lend itself to evaluation (H.S.).]

Wied, D. de: "The significance of the antidiuretic hormone in the release mechanism of corticotropin." *Endocrinology* **68**: 956-970 (1961). D7,440/61

In rats, posterior lobe extirpation greatly reduces the antidiuretic response to hemorrhage, histamine or painful stimuli. Exposure of these animals to "systemic stress" (hemorrhage, histamine, nicotine) causes increases in plasma free corticosterone as great as those in sham-operated controls. However, "neurogenic stressors" (strange environment, sound, pain) become significantly less effective, although the adrenal is enlarged after posterior lobectomy. These and other observations led the authors to the conclusion that "the antidiuretic hormone is involved in the corticotrophic effect of neurogenic stimuli."

Matsuda, K., Duyck, C., Kendall, J. W. Jr., Greer, M. A.: "Pathways by which traumatic stress and ether induce increased ACTH release in the rat." *Endocrinology* **74**: 981-985 (1964). F12,792/64

In rats, removal of all forebrain anterior to the superior colliculus, leaving an isolated ME, stalk, and pituitary intact, still permits ACTH release (corticosterone in adrenal effluent) in response to ether anesthesia with or without additional traumatic stress (fracture of foreleg). However, after Nembutal anesthesia, traumatic stress is no longer active in this respect. Bone fracture distal to a section of the spinal cord in otherwise intact rats also fails to raise adrenocortical secretion under Nembutal but not under ether anesthesia. "Ether apparently directly stimulates the median eminence to cause increased ACTH release. Traumatic stress induces ACTH release through ascending neural pathways feeding to the hypothalamus through the dorsal mesencephalon."

Zarrow, M. X., Denenberg, V. H., Haltmeyer, G. C., Brumaghin, J. T.: "Plasma and adrenal corticosterone levels following exposure of the two-day-old rat to various stressors." *Proc. Soc. Exp. Biol. Med.* **125**: 113-116 (1967). F80,161/67

Even in two-day-old rats of both sexes,

ACTH, histamine, electroshock, heat and cold increased the plasma and adrenal corticosterone levels. Only tight ligature above the knee joint was ineffective in this age group, perhaps because (as Fortier suggested) neural stressors (pain) act through a different pathway. Presumably, the pituitary-adrenal axis is operative in the two-day-old rat, but "the neural component in the system is not active as yet." Contradictions in the earlier literature on the responsiveness of the neonatal pituitary are analyzed.

Feldman, S., Conforti, N., Chowers, I., Davidson, J. M.: "Differential effects of hypothalamic deafferentation on responses to different stresses." *Isr. J. Med. Sci.* **4**: 908-910 (1968). H3,150/68

Following deafferentation of the hypothalamus (Halász knife), both the normal concentration of plasma corticosterone of rats and its considerable increase after "ether stress" are unchanged. On the other hand, "audiogenic stress" appears to cause no such evidence of ACTH discharge. "It might be possible to subdivide ACTH-releasing stimuli into 'systemic' or 'neurogenic' on the basis of whether or not they can activate the hypothalamo-pituitary unit in the absence of afferent nervous input to this area."

Stark, E., Fachet, J., Makara, G. B., Mihály, K.: "An attempt to explain differences in the hypophyseal-adrenocortical response to repeated stressful stimuli by their dependence on differences in pathways." *Acta Med. Acad. Sci. Hung.* **25**: 251-260 (1968). G63,921/68

In rats, "certain non-specific stimuli that raise the plasma corticosterone level when administered on a single occasion fail to raise it when administered repeatedly whereas others raise it independently of the number of administrations. It is suggested that stressor agents reach the CRF-secreting hypothalamic cells by different pathways, and that the CRF-activating mechanism of some stressors does adapt itself to repeated stimuli, that of others does not."

Lutz, B., Koch, B., Mialhe, C.: "Libération des hormones antidiurétique et corticotrope au cours de différents types d'agression chez le rat" (Release of antidiuretic and corticotrophic hormones during different types of stress in rats). *Horm. Metab. Res.* **1**: 213-217 (1969). H18,220/69

In rats a neurotropic stressor (sound) causes a simultaneous discharge of ACTH

and vasopressin, whereas systemic stressors (ether, histamine) result in a release of vasopressin followed by that of ACTH.

Stark, E.: "Regulation of ACTH secretion in stressful conditions. The nature of afferent pathways involved in stress-induced ACTH secretion." *Acta Med. Acad. Sci. Hung.* **29**: 77-88 (1972). J10,355/72

A review of the literature and personal observations indicate that in rats, certain stressors stimulate CRF-ACTH release via neurons in the medial basal hypothalamus, whereas others act even after destruction of these neurons. "Enhanced ACTH release induced by endotoxin can be observed in animals deprived of the hypothalamus, even if the hypophyseal stalk has been transected weeks earlier. In this case the neurohypophysis does not come into consideration as a source of CRF or ACTH" (36 refs.).

Briaud, B.: "Réponse corticosurrénalienne aux agressions neurotropes et systémiques après injection de corticostéroïdes" (Adrenocortical response to neurotropic and systemic stress after corticosteroid injection). *J. Physiol. (Paris)* **66**: 259-270 (1973).

J7,439/73

In rats, about twice as much corticosterone or dexamethasone is needed to inhibit the adrenal response to systemic (ether) than to neurogenic (sound) stress of equal intensity.

Collu, R., Jéquier, J. C., Letarte, J., Leboeuf, F., Ducharme, J. R.: "Effect of stress and hypothalamic deafferentation on the secretion of growth hormone in the rat." *Neuroendocrinology* **11**: 183-190 (1973).

H68,127/73

Ether and auditory stressors were equally effective in diminishing plasma STH (radioimmunoassay) in controls and in frontally deafferented rats. Ether also inhibited STH secretion in completely deafferented animals, whereas auditory stress was ineffective. α -MT pretreatment blocked the effect of ether after complete deafferentation. These and other data "seem to indicate that ether stress is transmitted through a humoral, dopaminergic pathway, while auditory stress follows a nervous pathway." [The many observations suggesting increased STH secretion during stress are not discussed (H.S.).]

Allen, J. P., Allen, C. F.: "Role of the

amygdaloid complexes in the stress-induced release of ACTH in the rat." *Neuroendocrinology* **15**: 220-230 (1974). H91,996/74

Plasma corticosterone determinations in the rat "suggest that the amygdalae facilitate rather than directly transmit neurogenic stress-induced signals (leg break) but not signals from systemic stresses (ether)." However, "bilateral paired amygdaloid lesions blocked the effect of the leg break but not of ether or tourniquet. Bilateral paired lesions between the lateral hypothalamic area and the amygdalae also blocked the effect of the leg break but not ether or tourniquet, whereas bilateral lesions in the anterior portion of the striae terminali did not block the leg-break effect."

Stark, E., Makara, G. B., Marton, J., Palkovits, M.: "ACTH release in rats after removal of the medial hypothalamus." *Neuroendocrinology* **13**: 224-233 (1974).

H81,874/74

In rats, after ablation of the medial hypothalamus, "*E. Coli* endotoxin or a large dose of formaldehyde induced a significant increase in ACTH release, whereas either sham-adrenalectomy under ether anesthesia or a small dose of formaldehyde did not." Both resting and stress-induced discharges of ACTH could be inhibited by dexamethasone, even in the absence of the medial hypothalamus. Presumably pathways through which endotoxin and formaldehyde can release ACTH may bypass the hypothalamus, and the feedback action of the glucocorticoid is effective outside the hypothalamus.

Allen, J. P., Allen, C. F.: "The effect of dimethyl sulfoxide on hypothalamic pituitary-adrenal functions in the rat." *Ann. N.Y. Acad. Sci.* **243**: 325-336 (1975).

H98,565/75

Experimental observations suggesting that dimethyl sulfoxide (DMSO) acts either directly on the hypothalamic-anterior pituitary complex to cause secretion of ACTH (presumably through the release of CRF) or that it potentiates the effect of circulating ACTH on the adrenal cortex to stimulate the secretion of corticosterone. DMSO is ineffective whereas it significantly raises plasma corticosterone in adrenalectomized or deafferented animals.

HORMONAL MECHANISMS

All the mechanisms that regulate the responses of the body during stress are so closely interrelated and interdependent that here—as in virtually all other sections of this book—it is highly artificial and arbitrary to subdivide observations into separate categories. However, no other procedure is possible if this book is to be a practically useful source of information in which key references are presented in an easily retrievable manner. Hence, at least the majority of the most pertinent data concerning any one subject are listed under a particular heading, preferably that most closely related to the subject of the publication. Obviously, it would lead to an enormously wasteful number of repetitions if every publication were discussed under each heading upon which it might have some bearing. Thus, for example, the neurohormonal and the hormonal mechanisms of corticoid discharge following application of a painful stimulus to a leg could have been mentioned at each point of the nervous system through which the evocative stimulus travels (from the peripheral nerves to the hypothalamus), and then again under CRF and the portal vessels of the hypothalamohypophyseal system, under hormonal mechanisms in relation to the adenohypophysis and the adrenal cortex, or even the various ACTH- and corticoid-feedback mechanisms that modulate such a response. Indeed, even this classification would not be exhaustive.

I felt that the arbitrariness in my classification should be admitted and explained clearly at the outset, but I will not repeat it although it is applicable to each subheading in the following sections.

A general outline of my classification will help the reader determine what sections he should consult to find data of special interest in connection with his problem, as long as he realizes that all data pertinent to it will rarely, if ever, be listed under any one caption.

As a guide for such searches of the literature, it is useful to enumerate here the subheadings used, be they separate anatomic structures, individual hormones or special regulating mechanisms:

Anterior Lobe of the Hypophysis

Hypophysectomy

Anterior Lobe Transplantation

ACTH

ACTH Feedback

Extra-adrenal Actions of ACTH

Not Glucocorticoid-like Actions of ACTH

Not Stress-like Actions of ACTH

Somatotrophic Hormone (STH, GH)

Somatostatin, Somatomedin, Somantin

Thyrotrophic Hormone (TTH, TSH)

Luteotropic Hormone (LTH, Prolactin)

Middle (Intermediate) Lobe of the Hypophysis

Melanotropic Hormone (MTH, MSH)

Posterior (Neural) Lobe of the Hypophysis

Vasopressin, Antidiuretic Hormone (ADH), Oxytocin

Adrenals

Epinephrine, Norepinephrine (EP, NEP)

Dopamine

- Corticoids
- Corticoid Feedback
- Corticoid "Utilization"
- Transcortin
- The Shift in Adenohypophyseal Activity
- Syntoxic and Catatoxic Hormones
- Other Hormones and Hormone-like Substances
 - Thyroid
 - Gonads
 - Pineal
 - Thymicolumphatic Apparatus and Bursa
 - 5-HT
 - Histamine
 - Acetylcholine
 - Prostaglandins
 - GABA
 - Varia

Much additional evidence concerning the participation of hormones in stress reactions will be found in Chapter III, Characteristic Manifestations of Stress, in the subsection devoted to Hormones and Hormone-like Substances. In fact, it is somewhat arbitrary whether the observation of a change in the metabolism of a hormone is merely described as a characteristic of the stress reaction, or as a fact that illustrates its participation in the mechanism of stress responses.

ANTERIOR LOBE OF THE HYPOPHYSIS

The anterior lobe, or adenohypophysis, acting under the influence of hypothalamic neurohormones, plays a central role in the regulation of hormonal adaptation to non-specific demands. The most important activity of the anterior pituitary during stress is the secretion of ACTH, which stimulates corticoid production. This response is controlled mainly through two negative biofeedback mechanisms: both ACTH itself and the corticoids secreted under its influence act back upon the adenohypophysis, and tend to diminish excessive secretion of ACTH.

It is noteworthy that ACTH also has direct extra-adrenal actions and effects, which are not duplicated either by glucocorticoids or by exposure to stress. The literature supporting these views will be presented in separate sections entitled, Extra-adrenal Actions of ACTH, Not Glucocorticoid-like Actions of ACTH, and Not Stress-like Actions of ACTH.

In addition, there is strong evidence that stress is associated with characteristic changes in the secretion of STH (probably related to somatostatin, somatomedin and somantin), TTH and LTH. Stress is also manifested by variations in the production of other gonadotropic hormones, particularly FSH and LH (See Chapter III, Characteristic Manifestations of Stress). There is no convincing reason to believe that these are of special importance for defense against acute stressors, although they undoubtedly modify the development of sex organs and sexual behavior during chronic stress.

The role of the pituitary in the G.A.S. was the first major subject of investigation immediately after the discovery of this syndrome. The most useful techniques proved to be: (1) Hypophysectomy (which showed that, in the absence of the anterior lobe, stressors can no longer increase corticoid production). (2) Anterior lobe transplantation in ortho- or heterotopic positions (which showed that unless contact with the ME and reestablishment of the portal circulation are possible, the adenohypophyseal tissue responds to stressors with little if any ACTH discharge). (3) Injection of increasingly purified anterior pituitary hormones into intact or hypophysectomized animals (which helped to identify the role played by each of these substances during stress).

By the use of ^{86}Rb it has been possible to measure blood flow through various organs in the rat. It was noted that under the influence of "ether stress" the blood flow increased within a few minutes in the adenohypophysis and even more in the thyroid. Adrenalectomy did not affect the stress-induced rise in blood flow in the pituitary but blocked it in the thyroid. Curiously, the blood flow in the ME remained unchanged under all these experimental conditions.

Generalities

(See also our earlier stress monographs, p. xiii)

Mikulaj, L., Mitro, A.: "Endocrine functions during adaptation to stress." *Adv. Exp. Med. Biol.* **33**: 631-638 (1972) (64 refs.).
J23,810/72

Anterior Lobe

(See also our earlier stress monographs, p. xiii)

Green, J. D.: "The comparative anatomy of the hypophysis, with special reference to its blood supply and innervation." *Am. J. Anat.* **88**: 225-311 (1951) (about 200 refs.).
B75,878/51

Orr, W. H.: *Hormones, Health and Happiness*, p. 322. New York: Macmillan, 1954.
B97,161/54

Popular description of the role of endocrine glands in disease, with a special chapter on the alarm reaction.

Goldman, H.: "Effect of acute stress on the pituitary gland: endocrine gland blood flow." *Endocrinology* **72**: 588-591 (1963).
D60,687/63

In rats, the blood flow through the pituitary, adrenal, thyroid and ME was determined using ^{86}Rb . Under the influence of

"ether stress," blood flow was increased within a few minutes in the adenohypophysis and even more in the thyroid. Stress after adrenalectomy caused a marked rise in the blood flow of both the anterior and posterior pituitary but not of the thyroid. The blood flow in the ME remained unchanged under all these experimental conditions.

Onodera, H., Moroharu, T., Okada, F. et al.: "Effect of emotional stress in acute medication experiments—with special reference to the diencephalo-hypophyse-adrenal system." *Clin. Endocrinol. (Tokyo)* **16**: 962-966 (1968) (Japanese).
J22,434/68

Sternieri, E., Mucci, P., Bertolini, A.: "Incorporazione di l-aminoacidi- ^{14}C nell'ipofisi del ratto in seguito a stress chirurgico" (Incorporation of ^{14}C l-aminoacids into the rat pituitary following surgical stress). *Boll. Soc. Ital. Biol. Sper.* **45**: 423-425 (1969).
G70,599/69

Hypophysectomy

One of the first stress-related experiments, performed in 1936 immediately after the discovery of the stress syndrome, was designed to establish whether any characteristic manifestations of the G.A.S. would be abolished by hypophysectomy. It was found that in the rat, adrenocortical enlargement with acute loss of lipids and thymicolympathic atrophy produced by a variety of stressors (surgical trauma, cold, restraint, fasting, atropine, morphine, formaldehyde, EP) were invariably blocked after ablation of the pituitary. However, the thymus involution was more completely abolished by adrenalectomy than by hypophysectomy. Curiously, the lymphopenia produced by stressors (for example, EP) is also more completely abolished by adrenalectomy than by hypophysectomy. These findings suggested that the adrenal cortex may not be exclusively under pituitary control, but the mechanism of this extrahypophyseal action has not yet been fully clarified. Since hypophysectomized animals also proved to be extraordinarily susceptible to the lethal effects of stressors, it was concluded that adrenal stimulation and other manifestations of the alarm reaction "enable the organism to meet critical situations more efficiently."

One clue concerning the possible mechanism of an extrahypophyseal corticoid release was found in the observation that hypothalamic stimulation increases adrenal blood flow and arterial pressure, and after hypophysectomy there is a positive correlation between corticoid release and stimulation of blood flow. Presumably, adrenal blood flow is one of the factors of extrahypophyseal corticoid mobilization.

Hypophysectomy

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction," characterized by adrenocortical enlargement with acute loss of lipids, thymicolympathic atrophy, and loss of body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and, to a lesser extent, hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug" but greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and the other manifestations of the alarm reaction "enable the organism to meet critical situations more efficiently."

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937).

38,798/37

Hypophysectomy lessens the accidental involution of the thymus and adrenalectomy inhibits it completely, but both these operations greatly diminish resistance to all stressors examined. Thyroidectomy and ovariectomy do not considerably interfere with the thymicolympathic involution and splenic atrophy characteristic of the formalin-induced alarm reaction, nor do they significantly increase mortality.

Hungerford, G. F.: "Effect of epinephrine in decreasing number of circulating mononuclear leucocytes in the rat." *Proc. Soc. Exp. Biol. Med.* **70**: 356-358 (1949).

B31,654/49

EP decreases the number of circulating mononuclear leukocytes in intact or adreno-demedullated rats; however, it does not do so after complete adrenalectomy and does so only slightly after hypophysectomy.

Bertelli, A., Martini, L.: "Caduta dell'acido ascorbico surrenalico in animali trattati con ormoni postipofisari—Nota 3^a" (Adrenal as-

corbic acid depletion in animals treated with post-hypophyseal hormones—Note 3). *Atti Soc. Lomb. Sci. Med. Biol.* 7: 430–432 (1952). B77,331/52

In intact rats, both oxytocin and vasopressin cause adrenal ascorbic acid depletion, but since this response is inhibited by hypophysectomy it must be ascribed to a discharge of pituitary ACTH.

Applezeig, M. H., Baudry, F. D.: "The pituitary-adrenocortical system in avoidance learning." *Psychol. Rep.* 1: 417–420 (1955).

D78,108/55

In rats, hypophysectomy "did interfere with the acquisition of avoidance responses, and sham-restoration of the system by exogenous administration of ACTH appeared to improve conditioning somewhat."

Long, C. N. H., Bonnycastle, M. F. M.: "The rate of discharge of adrenocorticotropic hormone as determined by timed hypophysectomy in the rat." *Can. J. Biochem.* 35: 929–933 (1957).

C43,178/57

Bonfils, S., Dubrasquet, M., Potet, F., Lamblin, A.: "Influence de l'hypophysectomie sur l'ulcère expérimental de contrainte. Test de la pente de restriction" (Influence of hypophysectomy on experimental restraint ulcers. The test of graded restriction). *C.R. Soc. Biol. (Paris)* 155: 1928–1930 (1961).

D21,555/61

Hypophysectomy actually increases the incidence of restraint ulcers in the rat.

Skebelskaia, I. B., Bagramian, E. R.: "Reaction of the thyroid gland of hypophysectomized rats to stress." *Probl. Endokrinol. Gormonoter.* 8 No. 6: 27–30 (1962) (Russian).

D47,086/62

Schurr, P. H.: "Techniques and effects of hypophysectomy, pituitary stalk section and pituitary transplantation in man." In: Har-

ris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 22–48. London: Butterworths, 1966.

E10,526/66

Jacobsohn, D.: "The techniques and effects of hypophysectomy, pituitary stalk section and pituitary transplantation in experimental animals." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 1–21. London: Butterworths, 1966. E10,525/66

Kováč, A. G. B., Monos, E., Koltay, E., Desrius, A.: "Effect of hypothalamic stimulation on adrenal blood flow and glucocorticoid release prior to and after acute hypophysectomy." *Acta Physiol. Acad. Sci. Hung.* 38: 205–216 (1970).

G82,669/70

In rats, hypothalamic stimulation increased adrenal blood flow and arterial pressure. There was no correlation of corticoid release and blood flow upon stimulation before hypophysectomy, while after hypophysectomy, a positive correlation of the responses was noted, with an increase in corticoid discharge. "It is concluded that adrenal blood flow is one of the factors of extra-hypophyseal corticoid mobilization. Their coordination is probably organized at the hypothalamic level." To explain corticoid release after hypophysectomy, mobilization of extrahypophyseal ACTH depots may also be considered, but this would not be detectable in the presence of the pituitary with its much more effective power of ACTH discharge.

Camarda, R., D'Alessandro, F., Guarneri, R., Bonavita, V.: "Stress and brain nicotinamide adenine dinucleotides in normal and hypophysectomized rats." *Acta Neurol. (Napoli)* 26: 501–510 (1971).

J20,829/71

In rats, restraint or injection of saline modifies NAD, NADH, NADP and NADPH levels in the brain. Hypophysectomy prevents these changes.

Anterior Lobe Transplantation

It was shown as early as 1941 that adenohypophyseal transplants in the sella, unlike those placed in the anterior chamber of the eye, stimulated adrenal growth in the hypophysectomized rat. In 1949, it was shown furthermore that homotransplantation of anterior pituitary tissue in the anterior chamber of the eye still permitted the discharge of adrenal ascorbic acid in hypophysectomized rats exposed to surgical trauma or cold. It was concluded that at least certain stressors can stimulate ACTH release through pathways other than direct connections between the pituitary and hypothalamus.

Similar findings were reported for hypophysectomized rats bearing intraocular or intrasplenic adenohypophyseal grafts following treatment with histamine, while sound and immobilization failed to elicit ACTH discharge when the hypothalamus-hypophyseal pathways were interrupted.

Subsequently, the classic experiments of G. W. Harris (1952) showed that in rats adenohypophyseal homografts placed under the ME maintain estrus, pregnancy, lactation, as well as a normal ovarian, adrenal and thyroid structure. Similar grafts located under the temporal lobe had no such effects. It was concluded that presumably "the secretion of anterior pituitary hormones is under hypothalamic control, mediated by the hypophysial portal vessels." These and other observations led Fortier (1952) to distinguish between systemic (EP, cold, histamine) and neurotropic (sound, immobilization) stressors, only the former being capable of producing ACTH discharge after severance of all connections between the hypothalamus and the pituitary.

Vasopressin failed to cause ACTH release in hypophysectomized rats unless they carried ocular adenohypophyseal homotransplants. These observations were considered to be "consistent with the hypothesis that the posterior pituitary hormones act as humoral transmitting agents which, released by the hypothalamus into the hypophysial portal system, can activate the anterior pituitary to discharge ACTH." According to these observations, even heterotopic adenohypophyseal grafts can be activated by vasopressin.

In rats with homologous adenohypophyseal grafts in the anterior chamber of the eye, ACTH secretion also occurred after unilateral adrenalectomy.

Fetal pituitaries implanted into the eye of hypophysectomized rats remained viable and developed highly differentiated chromophobes but only few sparsely granulated acidophils and beta cells. These glands were also capable of a moderate ACTH discharge during acute stress.

In another series of hypophysectomized rats with pituitary grafts in the anterior chamber of the eye, acetylcholine, histamine, 5-HT, oxytocin and EP failed to cause ACTH release, whereas vasopressin was active when directly applied to the grafts. In glucocorticoid-blocked rats, vasopressin and oxytocin also elicited an ACTH discharge when given intravenously. It was postulated that perhaps posterior pituitary principles could act as physiologic regulators of ACTH output.

In hypophysectomized weanling rats bearing four pituitary transplants under the kidney capsule, somatic growth continued although at a slow rate, and the thyroids and gonads were partially maintained. Presumably, "in rats, somatotropin production and release are not completely dependent upon an intact hypothalamic-pituitary system." However, in other experiments on hypophysectomized rats with pituitary grafts in the eye, STH and gonadotropic activity ceased, but some ACTH and TTH secretion continued despite severance of all connections with the ME.

Amphenone causes adrenal enlargement in rats with adenohypophyseal grafts under the kidney capsule. This drug stimulates the adrenal by suppressing corticoid production; hence, the grafts apparently maintain their sensitivity to the corticoid feedback mechanism.

In thirty-day-old rats with adenohypophyseal transplants in the ventral hypothalamus, the normal structure of the anterior lobe was maintained, but grafts in other sites became undifferentiated.

In another series of hypophysectomized rats with pituitary homotransplants under the kidney capsule, ether, histamine and unilateral adrenalectomy failed to cause

ACTH discharge, although the grafts contained approximately normal amounts of ACTH. Presumably, it is the release of ACTH that depends upon direct contact with the hypothalamus. The adrenals were slightly heavier in transplant-bearing rats, possibly owing to a factor (other than ACTH) secreted by the graft.

In hypophysectomized rats with pituitary autotransplants under the kidney capsule, chronic CRF treatment maintained the synthesis of ACTH and permitted the graft to release ACTH when acutely stimulated by CRF. No such effect was obtained with vasopressin or α -MTH.

In the absence of stress, heterotopic pituitary homotransplants failed to support ACTH secretion at a level significantly above that in hypophysectomized controls. Yet in rats with intraocular homografts of adenohypophysis, the transplants retain their normal EM structure.

On the other hand, the MTH activity of heterotopic pituitary homotransplants drops considerably in hypophysectomized weanling rats, although the ACTH content remains normal.

In hypophysectomized rats with adenohypophyseal grafts in contact with the ME, thyroid and adrenal structure was well maintained, and even compensatory hypertrophy following uniadrenalectomy and goiter after methylthiouracil treatment were evident. Contact with the ME was not necessary for preservation of gonadotropic hormone secretion.

In young hypophysectomized rats with pituitary autografts in the kidney, continuous infusion of bovine ME extracts through the renal artery caused enlargement of the adrenals, thyroids and ovaries. These findings are taken as "direct evidence that the hypothalamic neurohumors act not only as 'releasing' factors but also have trophic effects on many other phases of adenohypophyseal functions."

Pituitary autografts under the kidney rapidly dedifferentiated and lost their function in rats, but resumed their normal structure as well as their adrenotropic and thyrotropic effect upon continuous infusion of ovine ME extracts. This again shows that the latter are not only releasing factors but also have trophic effects.

Hypophysectomized rats with transplants (under the renal capsule) of ten pituitaries from very young donors maintained nearly normal adrenal weights and plasma corticosterone levels. The grafts showed histologic evidence of anterior and intermediate lobe tissue growth. Dexamethasone suppressed corticosterone secretion in these animals, indicating that contiguity of the adenohypophysis with the ME is not necessary for corticoid feedback activity.

LTH secretion and lactation increase in rats after pituitary stalk transection as well as following hypophysectomy with heterotopic pituitary transplants.

In hypophysectomized adult rats bearing five neonatal pituitaries under the kidney capsule, adrenal weight and plasma corticosterone levels were not significantly different from those after hypophysectomy alone, but one hour following severe stress (for example, thiouracil, hemorrhage, restraint) significant elevations of plasma corticosterone occurred. The response to hemorrhage was inhibited by dexamethasone in graft-bearing rats, and lysine vasopressin released ACTH but only at very high dose levels. Apparently, such heterotopic grafts can store ACTH, and even release it, but only under the influence of very strong stimuli; furthermore, the corticoid feedback mechanism does not require the integrity of hypothalamus-hypophyseal connections.

Transplantation of ACTH-producing pituitary tumors decreased the weight and ACTH content of the pituitary in rats. Plasma ACTH rose slowly despite a considerable reduction in pituitary ACTH. At this time, stress still increased plasma ACTH,

but did not do so after hypophysectomy. Tumor implantation before adrenalectomy prevented the usual rise in plasma ACTH, possibly through the "short loop feedback" effect of ACTH from the tumor.

In rats with multiple adenohypophyseal homografts in the kidneys, plasma corticosterone levels rose after removal of the cerebral cortex. This effect was diminished by subsequent extirpation of the entire forebrain, as long as hypothalamic islands remained intact. Stalk and ME injections into graft-bearing hypophysectomized rats raised the plasma corticosterone levels, presumably because a neurohumor of hypothalamic origin passed into the general circulation.

Perhaps the most important facts learned from experiments with adenohypophyseal grafts are that they maintain their structure best, and are most effective in secreting ACTH, if placed in direct contact with the ME so that vascular connections with the latter may be reestablished. Heterotopic adenohypophyseal grafts are much less effective, but if they are numerous, and especially if they are derived from neonatal rats, they do take and can secrete ACTH under the influence of severe stressors. Such heterotopic grafts are also sensitive to corticoid feedback, since their ACTH-secreting power is inhibited by dexamethasone. Removal of the forebrain, excepting a hypothalamic island, increases plasma corticosterone in graft-bearing hypophysectomized rats. These also respond normally with ACTH release to stalk or ME extract injections.

Anterior Lobe Transplantation

(See also our earlier stress monographs, p. xiii)

Cutuly, E.: "Autoplastic grafting of the anterior pituitary in male rats." *Anat. Rec.* **80** Supp. 1: 83-97 (1941). A36,421/41

Autoplastic adenohypophyseal transplants were made in rats, either in the anterior chamber of the eye or in the sella. "Only sellar grafts were adrenotropic, and neither ocular nor sellar grafts caused any detectable activation of the thyroid gland." Earlier literature on pituitary transplants is reviewed (21 refs.).

Fortier, C., Selye, H.: "Adrenocorticotrophic effect of stress after severance of the hypothalamo-hypophyseal pathways." *Am. J. Physiol.* **159**: 433-439 (1949).

B37,371/49

In rats the hypothalamus-hypophyseal connections were severed in one experiment by partial hypophysectomy, and in another through anterior lobe homotransplantation into the anterior chamber of the eye following hypophysectomy. After these interventions, surgical trauma and cold still produced significant adrenal ascorbic acid discharge. Presumably, ACTH release by these stres-

sors is not exclusively mediated through nervous pathways.

Cheng, C.-P., Sayers, G., Goodman, L. S., Swinyard, C. A.: "Discharge of adrenocorticotrophic hormone from transplanted pituitary tissue." *Am. J. Physiol.* **159**: 426-432 (1949). B45,616/49

In hypophysectomized rats, intraocular and intrasplenic grafts of adenohypophyseal tissue promptly discharge ACTH in response to "histamine stress," but the amount of hormone release is subnormal. "The results have been interpreted to mean that neural or vascular connections between the hypothalamus and the anterior pituitary are not essential for the immediate discharge of ACTH in acute stress."

Schweizer, M., Long, M. E.: "The effect of intra-ocular grafts of anterior pituitary on the thyroid gland of hypophysectomized guinea pigs." *Endocrinology* **47**: 454-457 (1950). B53,919/50

A limited number of hypophysectomized animals with intraocular adenohypophyseal grafts showed partial maintenance of the adrenal cortex and very slight thyrotropic activity.

Schweizer, M., Long, M. E.: "Partial maintenance of the adrenal cortex by an-

terior pituitary grafts in fed and starved guinea pigs." *Endocrinology* **46**: 191-206 (1950). B47,455/50

In hypophysectomized guinea pigs, intraocular homografts of the adenohypophysis partially maintained the structure of the adrenal glands.

Fortier, C.: "Dual control of adrenocorticotrophic release." *Endocrinology* **49**: 782-788 (1951). B61,227/51

Following homotransplantation of the anterior pituitary into the anterior chamber of the eye, EP, cold and histamine still caused definite eosinopenia, while sound and immobilization failed to do so. "These results suggest a dual regulation of ACTH release, one purely humoral, in response to systemic stimuli, the other probably neuro-humoral, mediated by the hypothalamo-hypophysial neurovascular pathways, and coming into play under the influence of nervous and emotional stimuli."

Harris, G. W., Jacobsohn, D.: "Functional grafts of the anterior pituitary gland." *Proc. R. Soc. Lond. [Biol.]* **139**: 263-276 (1952).

B82,095/52

In hypophysectomized adult rats with adenohypophyseal homografts from a closely related species placed under the ME, pituitary functions were well maintained as indicated by estrus, pregnancy, lactation, and ovarian, adrenal and thyroid structure. Grafts under the temporal lobe had no such effects, because they did not establish vascular connections with the portal circulation of the ME. Grafts from immature donors in adult recipients showed hastened development. "These results offer strong support to the view that the secretion of anterior pituitary hormones is under hypothalamic control, mediated by the hypophysial portal vessels."

Harris, G. W., Jacobsohn, D.: "Functional hypophyseal grafts." In: Wolstenholme, G. E. W., *Ciba Foundation Colloquia on Endocrinology*, Vol. 4, pp. 115-119. London: J & A Churchill, 1952. B76,071/52

In hypophysectomized rats, hypophyseal homotransplants under the temporal lobe of the brain or the anterior chamber of the eye show good vascularization but do not maintain adrenal trophic function. Similar transplants under the ME are very effective in this respect because they form vascular connections with the hypophysial portal system.

Fortier, C.: "Studies on the control of ACTH release by means of hypophyseal

transplants." In: Wolstenholme, G. E. W., *Ciba Foundation Colloquia on Endocrinology*, Vol. 4, pp. 124-136. London: J & A Churchill, 1952. B58,855/52

Observations on hypophysectomized rats with intraocular pituitary transplants led to the distinction between systemic (EP, cold, histamine) and neurotropic (sound, immobilization) stressors. The former do, whereas the latter do not, cause eosinopenia after severance of all connections between the hypothalamus and the pituitary.

Martini, L., Poli, A. de: "Neurohumoral control of the release of adrenocorticotrophic hormone." *J. Endocrinol.* **13**: 229-234 (1956). C15,162/56

In hypophysectomized rats, injection of posterior pituitary hormones failed to cause the usual eosinopenia and adrenal ascorbic acid depletion. However, hypophysectomized rats with ocular adenohypophyseal homotransplants from adult rats responded to both intraperitoneal and intraocular injections of posterior pituitary hormones with eosinopenia and adrenal ascorbic acid depletion. "These results are consistent with the hypothesis that the posterior pituitary hormones act as humoral transmitting agents which, released by the hypothalamus into the hypophysial portal system, can activate the anterior pituitary to discharge ACTH."

Siperstein, E. R., Greer, M. A.: "Observations on the morphology and histochemistry of the mouse pituitary implanted in the anterior eye chamber." *J. Natl. Cancer Inst.* **17**: 569-599 (1956) (35 refs.).

J12,751/56

Fry, E. G., Long, C. N. H.: "The function of ocular and kidney transplants of pituitary tissue in the hypophysectomized rat." *20th Int. Congr. Physiol.*, pp. 307-308. Brussels, 1956.

C23,385/56

In rats, homologous anterior pituitary transplants in the anterior chamber of the eye took, whether the donors were infantile or adult. The gonads, thyroids and adrenals were maintained, and under the "stress of unilateral adrenalectomy," ACTH secretion occurred, as indicated by adrenal ascorbic acid depletion. Transplants under the renal capsule appeared to be less effective, yet they supported growth and reproduction after hypophysectomy. [This brief abstract gives no details and is difficult to evaluate (H.S.).]

Goldberg, R. C., Knobil, E.: "Structure and function of intraocular hypophyseal

grafts in the hypophysectomized male rat." *Endocrinology* **61**: 742-752 (1957).

C44,867/57

Fetal pituitaries implanted in the anterior chamber of the eye of hypophysectomized rats remain viable and develop into highly differentiated adenohypophyseal tissue, which consists mainly of chromophobes but also contains sparsely granulated acidophils and β -cells. The somatic growth of implant-bearing hypophysectomized rats is slightly above that of controls. "Evidence of slight secretion of ACTH by the implants was obtained from studies of adrenal weight and depletion of adrenal cholesterol following acute stress."

Nikitovitch-Winer, M., Everett, J. W.: "Functional restitution of pituitary grafts retransplanted from kidney to median eminence." *Endocrinology* **63**: 916-930 (1958).

J12,364/58

In rats, pituitaries autografted on the kidney lose the power to maintain ovaries, adrenals and thyroids, but when retransplanted under the ME, they regain their ability to maintain these glands. This is true with respect to the secretion of ACTH, TTH, FSH and LH.

Timmer, R. F., Sanders, A. E., Rennels, E. G.: "Evidence for limited ACTH secretion by pituitary autografts in the renal capsule of the rat." *Tex. Rep. Biol. Med.* **17**: 632-636 (1959).

D97,005/59

Casentini, S., Poli, A. de, Hukovic, S., Martini, L.: "Studies on the control of corticotrophin release." *Endocrinology* **64**: 483-493 (1959).

J10,796/59

In hypophysectomized rats with pituitary grafts in the anterior chamber of the eye, acetylcholine, histamine, 5-HT, oxytocin and EP failed to elicit an ACTH discharge (ascorbic acid depletion test), whereas vasopressin was active when applied directly to the grafted pituitary. In glucocorticoid-blocked rats, vasopressin, oxytocin and lysine-vasopressin caused ACTH release when given intravenously. It is noteworthy that in intact rats, EP, NEP, acetylcholine, histamine, 5-HT, vasopressin, oxytocin, lysine-vasopressin and synthetic oxytocin are all effective in this respect. Possibly, "posterior pituitary principles could play a role in the physiological regulation of ACTH output."

Nikitovich-Winer, M., Everett, J. W.: "Histocytologic changes in grafts of rat pituitary on the kidney and upon re-transplantation under the diencephalon." *Endocrinology* **65**: 357-368 (1959).

J12,755/59

Hertz, R.: "Growth in the hypophysectomized rat sustained by pituitary grafts." *Endocrinology* **65**: 926-931 (1959).

C78,359/59

Hypophysectomized weanling rats bearing four pituitary transplants under the kidney capsule continue to grow at about two-thirds the normal rate, and their thyroids and gonads are also partially maintained. "It is concluded that, in the rat, somatotropin production and release are not completely dependent upon an intact hypothalamic-pituitary system."

Martini, L., Poli, A. de, Pecile, A., Saito, S., Tani, F.: "Functional and morphological observations on the rat pituitary grafted into the anterior chamber of the eye." *J. Endocrinol.* **19**: 164-172 (1959).

C77,283/59

In hypophysectomized rats with pituitary grafts in the anterior chamber of the eye, STH and gonadotropic activity vanished, but some ACTH and TTH secretion continued despite severance of all connections with the ME. It is contended that "vasopressin may be the hypothalamic neurohumor involved in ACTH secretion, and that the ACTH-releasing activity of Guillemin's fraction D may be accounted for by its vasopressin content."

Hertz, R.: "Gonadotropin and adrenocorticotropin from rat pituitary homografts as manifested by host response to chorionic gonadotropin and amphenone." *Endocrinology* **66**: 842-844 (1960).

C87,506/60

In hypophysectomized rats bearing four adenohypophyseal grafts under the renal capsule, amphenone causes adrenal enlargement which is lacking in hypophysectomized controls. "Since the adrenomegalic response to amphenone is mediated through suppression of corticoid production by the rat adrenal, these pituitary grafts apparently also maintain a degree of reciprocal functional relationship with the adrenal cortex."

Yoshida, S., Sayers, G.: "ACTH in pituitary grafts." *Fed. Proc.* **20**: 183 (1961).

D3,973/61

In hypophysectomized rats with pituitary autografts under the kidney capsule or hypothalamus, vasopressin increased blood ACTH, whereas DOC suppressed it. [The brief abstract does not lend itself to critical evaluation (H.S.).]

Dávid, M. A., Horváth, I. W., Kovács, K.:

"Über die Nebennierenrindenfunktion von Ratten mit transplantiert Adenohypophyse" (The function of the adrenal cortex in rats bearing adenohypophyseal transplants). *Acta Med. Acad. Sci. Hung.* **17**: 239-246 (1961).

C60,008/61

In hypophysectomized rats with pituitary autotransplants in the anterior chamber of the eye, the adrenal atrophy elicited by removal of the hypophysis was not affected under basic conditions, but ACTH caused considerable adrenal ascorbic acid depletion.

Kovács, K.: "Histological alterations in the rat pituitary transplanted to the eye." *J. Endocrinol.* **23**: 109-117 (1961).

D13,068/61

Smith, P. E.: "Postponed homotransplants of the hypophysis into the region of the median eminence in hypophysectomized male rats." *Endocrinology* **68**: 130-143 (1961).

C98,302/61

In hypophysectomized rats with pituitary homotransplants placed under the ME, "there were pronounced gains in body weights, activation of the thyroids, structural repair of the adrenals and the reproductive organs, and fertility."

Halász, B., Pupp, L., Uhlarik, S.: "Hypophysiotrophic area in the hypothalamus." *J. Endocrinol.* **25**: 147-154 (1962).

D38,273/62

Adenohypophyseal tissue of thirty-day-old rats was transplanted into different regions of the hypothalamus of adult recipients. Grafts in the ventral hypothalamus retained a normal histologic appearance despite lack of any contact with the ME. A "hypophysiotrophic" area was detected by the location of basophils in the graft and the maintenance of the target organs for anterior lobe hormones, except that the gonads sometimes underwent atrophy. Grafts in other sites did not maintain their structure or preserve the integrity of the target glands.

Foster, R. Jr., Rothchild, I.: "On the secretion of corticotrophin by the homotransplanted pituitary gland in the rat." *Acta Endocrinol. (Kbh.)* **39**: 371-384 (1962).

D20,802/62

In hypophysectomized rats with pituitary homotransplants under the kidney capsule, ether anesthesia, histamine or unilateral adrenalectomy failed to cause adrenal ascorbic acid depletion, although the grafts contained approximately normal amounts of ACTH. ACTH release presumably depends upon di-

rect contact with the CNS. "The possibility that the slightly heavier adrenals in the transplant bearing animals might be due to a non-ACTH factor secreted by the transplant was also considered."

Critchlow, V., Lipscomb, H. S., Guillemin, R.: "Effect of CRF on maintenance of the adrenocorticotrophic function of anterior pituitary grafts." *J. Endocrinol.* **25**: 465-472 (1963).

D55,920/63

In rats with their own adenohypophysis transplanted under the kidney capsule, "prolonged administration of CRF has maintained synthesis of ACTH by the transplanted pituitary as well as its ability to release ACTH when acutely stimulated by CRF. These results were not duplicated by the administration of lysin-vasopressin or α -MSH in conditions identical to the ones used for studying CRF, and using doses equivalent to the vasopressor and melanophoretic activities of this particular preparation of CRF."

Greer, M. A., Kendall, J. W. Jr., Duyck, C.: "Failure of heterotopic rat pituitary transplants to maintain adrenocortical secretion." *Endocrinology* **72**: 499-501 (1963).

D57,894/63

"Heterotopic pituitary homotransplants [under the renal capsule or into the anterior chamber of the eye] were found incapable of supporting corticosterone secretion at a level significantly above that of hypophysectomized controls. There was no augmented adrenocortical secretion in response to traumatic stress."

Petrovic, A., Porte, A., Stoeckel, M. E., Heusner, A.: "Caractères ultrastructuraux de l'homogreffe adénohypophysaire intraoculaire chez le rat normal" (Ultrastructural characteristics of intraocular adenohypophyseal homografts in normal rats). *C.R. Soc. Biol. (Paris)* **157**: 368-370 (1963).

D69,080/63

In rats, intraocular homografts of adenohypophysis essentially retain their normal EM structure (14 refs.).

Purves, H. D., Sirett, N. E.: "Corticotrophin secretion by ectopic pituitary glands." *Proc. Univ. Otago Med. Sch. (Otago, N.Z.)* **41**: 3-5 (1963).

J12,878/63

In hypophysectomized rats with five neonatal pituitaries grafted under the kidney capsule, ACTH secretion is negligible under basal conditions but rises considerably in re-

sponse to various stressors and lysine-vasopressin.

Kastin, A. J., Ross, G. T.: "Melanocyte-stimulating hormone (MSH) and ACTH activities of pituitary homografts in albino rats." *Endocrinology* **75**: 187-191 (1964).

F17,785/64

Weanling hypophysectomized rats with renal capsular pituitary homografts from donors of the same age showed a considerable loss of MSH activity in the transplants, but loss of ACTH was much less evident.

Mialhe-Voloss, C., Koch, B.: "Bilan corticostérone-corticotrophine: application à l'étude de la greffe hypophysaire chez le rat" (Corticosterone-corticotropin balance: application to the study of hypophyseal grafts in rats). *Ann. Endocrinol. (Paris)* **25**: 305-310 (1964).

F15,473/64

In rats with renal homotransplants of adenohypophysis, the pituitary contains virtually normal amounts of ACTH, but this is not released or is insufficiently released, even during stress produced by histamine injection.

Virág, S., Kovács, K., Tiboldi, T., Hódi, M., Julesz, M.: "The electron-microscopic structure of the pituitary transplanted into the anterior chamber of the eye." *Acta Physiol. Acad. Sci. Hung.* **26** Supp.: 49 (1965).

J12,760/65

Halász, B., Pupp, L., Uhlarik, S., Tima, L.: "Further studies on the hormone secretion of the anterior pituitary transplanted into the hypophysiotrophic area of the rat hypothalamus." *Endocrinology* **77**: 343-355 (1965).

F46,916/65

In hypophysectomized rats with anterior lobe transplants, restoration of the target glands depended entirely on the location of the grafts. The structure of the thyroid and adrenals was best preserved after transplantation in contact with the ME; in these rats even compensatory hypertrophy following unilateral adrenalectomy, as well as goiter subsequent to methylthiouracil, were evident. Contact with the ME was not necessary for preservation of gonadotropic hormone secretion. Grafts placed in distant brain regions or under the renal capsule were ineffective.

Flament-Durand, J.: "Observations on pituitary transplants into the hypothalamus of the rat." *Endocrinology* **77**: 446-454 (1965).

F49,804/65

Pituitaries of ten-day-old rats were im-

planted into the hypothalamus of adult rats. Grafts located in the hypophysiotropic region contained numerous basophils. This was particularly striking in the case of grafts attached to the arcuate nuclei, which took the appearance of castration cells after hypophysectomy or castration. The effects of grafts in different locations on other target glands are also described.

Evans, J. S., Nikitovitch-Winer, M. B.: "Reactivation of hypophysial grafts by continuous perfusion with median eminence extracts (MEE)." *Fed. Proc.* **24**: 190 (1965).

F35,942/65

Bovine ME extracts, continuously infused through the renal artery in young hypophysectomized rats with pituitary autografts in the kidney, elicited ovarian follicles, with enlargement of the adrenal and thyroid. This work furnishes "direct evidence that the hypothalamic neurohumors act not only as 'releasing' factors but also have tropic effects on many other phases of adenohypophysial function."

Schalch, D. S., Reichlin, S.: "Plasma growth hormone concentration in the rat determined by radioimmunoassay: influence of sex, pregnancy, lactation, anesthesia, hypophysectomy and extrasellar pituitary transplants." *Endocrinology* **79**: 275-280 (1966).

F69,338/66

In rats, plasma STH levels become undetectable after hypophysectomy, and intraocular pituitary transplants fail to raise them. Brief periods of ether anesthesia depress STH levels only in male rats.

Schurr, P. H.: "Techniques and effects of hypophysectomy, pituitary stalk section and pituitary transplantation in man." In: Harris, G. W. and Donovan, B. T., *The Pituitary Gland*, Vol. 2, pp. 22-48. London: Butterworths, 1966.

E10,526/66

Gittes, R. F., Kastin, A. J.: "Effects of increasing numbers of pituitary transplants in hypophysectomized rats." *Endocrinology* **78**: 1023-1031 (1966).

F66,264/66

Intrastrain intramuscular pituitary transplants in weanling rats showed no homograft reactions and maintained body growth as well as the development of target organs. These effects were proportional to the number of pituitaries implanted, and with the grafting of thirty glands, they actually exceeded the norm. Presumably, ectopic pituitaries produce only small amounts of hormones, "but the aggregate output of 10 or

30 such glands brought about somatotropic, gonadotropic and mammatrophic changes not previously reported in hypophysectomized female rats bearing ectopic pituitary transplants."

Kendall, J. W., Allen, C.: "Brain-dependent ACTH secretion from multiple heterotopic pituitaries." *Proc. Soc. Exp. Biol. Med.* **122**: 335-337 (1966). F67,274/66

In hypophysectomized rats, heterotransplants of adult rat pituitary do not take well, and single grafts from even immature rats produce too little ACTH to maintain adrenal weight and function. However, in hypophysectomized rats with multiple pituitary transplants from two- to three-week-old donors, adrenal weights and corticosterone discharge remain essentially normal. "Removal of the entire forebrain, but not decortication, in these animals reduced corticosterone secretion nearly to values found in hypophysectomized control animals. These results indicate that heterotopic pituitary ACTH secretion is dependent on some subcortical portion of the forebrain."

Kendall, J. W., Stott, A. K., Allen, C., Greer, M. A.: "Evidence for ACTH secretion and ACTH suppressibility in hypophysectomized rats with multiple heterotopic pituitaries." *Endocrinology* **78**: 533-537 (1966). F62,883/66

Rats hypophysectomized five weeks after transplantation under their renal capsules of ten pituitaries from ten- to twenty-day-old donors maintained nearly normal adrenal weights as well as plasma and adrenal corticosterone levels. At autopsy, there was evidence of anterior and intermediate lobe tissue growth. "Suppression of corticosterone secretion by dexamethasone was similar in both transplanted and intact animals, indicating that contiguity of the pituitary with the hypothalamic median eminence is not essential for the suppression of ACTH secretion by corticosteroids."

Nikitovitch-Winer, M. B., Evans, J. E., Kiracofe, G. H.: "Hypophysiotropic effect of hypothalamic humoral factors." 2nd Int. Congr. on Hormonal Steroids, Milan, 1966, *Int. Congr. Ser. No. 111*, p. 95. Amsterdam and New York: Excerpta Medica, 1966. J13,140/66

In rats, pituitary autografts under the kidney capsule rapidly showed dedifferentiation and loss of functional activity. Continuous infusion of ovine ME extracts through the

renal artery for six to thirty-eight days caused adrenal and thyroid stimulation, whereas in the controls these organs became completely atrophic.

Ahmad, N., Lyons, W. R.: "Lactation in pituitary-autografted rats." *Endocrinology* **78**: 837-844 (1966). F63,825/66

Review of the literature and personal observations indicating that severance of the connections between the hypothalamus and adenohypophysis increases LTH secretion and lactation. This has been observed after stalk section, as well as following heterotopic pituitary transplantation after hypophysec-tomy (25 refs.).

Ducommun, S., Guillemin, R.: "Maintenance of normal morphology in adenohypophyseal transplants by topical administration of hypothalamic extracts with a simple method for transplantation in a pneumodermal pouch." *Proc. Soc. Exp. Biol. Med.* **122**: 1251-1255 (1966). F72,632/66

Purves, H. D., Sirett, N. E.: "Corticotrophin secretion by ectopic pituitary glands." *Endocrinology* **80**: 962-968 (1967). F75,878/67

In hypophysectomized adult rats, five neonatal pituitaries implanted under the kidney capsule partially maintained adrenal weight, but the peripheral plasma corticosterone levels were not significantly higher than in hypophysectomized controls. One hour after stress (ether, urethane, hemorrhage, restraint), significant elevations of peripheral plasma corticosterone were noted. The response to hemorrhage in the graft-bearing rats was inhibited by dexamethasone at very low dose levels, which were ineffective in normal controls. Infusion of lysine-vasopressin released corticotropin from the grafts, but only at very high dose levels. "The results are ascribed to an accumulation of a physiological corticotrophin releasing factor in the peripheral circulation leading to a delayed release of corticotrophin from the grafts."

Vernikos-Danellis, J., Trigg, L. N.: "Feedback mechanisms regulating pituitary ACTH secretion in rats bearing transplantable pituitary tumors." *Endocrinology* **80**: 345-350 (1967). F77,039/67

In rats bearing ACTH-producing pituitary tumors (MtT-F₄), there was a direct relationship between the increase in adrenal weight and the decrease in anterior pituitary weight and pituitary ACTH content. Plasma

ACTH remained near normal until about the sixth week after implantation, when blood corticosterone levels rose despite an 80 percent reduction in pituitary ACTH. At this time, stress (laparotomy under ether) doubled the plasma ACTH level, but this increase was abolished by hypophysectomy. Tumor implantation one day prior to adrenalectomy prevented the increase in plasma ACTH that occurred three weeks after the operation. Apparently, "in the absence of corticoids, an extrapituitary source of ACTH may inhibit adenohypophysial ACTH synthesis and secretion." ["Short loop feedback"] (H.S.)]

Yoshimura, F., Harumiya, K., Ishikawa, H., Ohtsuka, Y.: "Differentiation of isolated chromophobes into acidophils or basophils when transplanted into the hypophysiotrophic area of hypothalamus." *Endocrinol. Jap.* **16**: 531-540 (1969). H24,086/69

Sirett, N. E., Kendall, J. W.: "Hypothalamic control of ACTH release from ectopic pituitary glands." *Endocrinology* **85**: 784-788 (1969). H17,162/69

In rats with multiple adenohypophyseal homografts in their kidneys, plasma corticosterone levels were increased following the removal of the cerebral cortex, and this effect was diminished by subsequent extirpation of the entire forebrain. After removal of all the forebrain except a hypothalamic island, plasma corticosterone levels were 108 percent of the initial value. Stalk- and ME-extract injections into such graft-bearing

ing, hypophysectomized rats raised plasma corticosterone within thirty to sixty minutes. Presumably, "ACTH release from ectopic pituitaries is primarily dependent on a neurohumor of hypothalamic origin passing into the general circulation."

Peng, M. T., Pi, W. P., Wu, C. I.: "Growth hormone secretion by pituitary grafts under the median eminence or renal capsule." *Endocrinology* **85**: 360-365 (1969).

H15,826/69

As indicated by the growth of hypophysectomized rats, it is suggested that "the anterior pituitary transplanted under the median eminence can synthesize and secrete adequate growth hormone, although slightly less than in normal rats; and that the anterior pituitary transplanted underneath the renal capsule can also synthesize and secrete growth hormone as well as the graft placed under the median eminence if thyroxine is given daily."

Csernus, V., Lengvári, I., Halász, B.: "Data on the localization of CRF-producing neural elements." *Gen. Comp. Endocrinol.* **22**: 360 (1974). H83,188/74

Adenohypophyseal tissue was implanted in different hypothalamic regions of rats, and then the pituitary was removed. ACTH secretion was estimated by plasma corticosterone levels and was found to be raised only in those rats in which the implant was in contact with the ME. It is concluded that only the ME contains enough CRF to cause a significant ACTH discharge.

ACTH

In rats, an ACTH discharge occurs almost immediately after exposure to a stressor, since adrenalectomy performed ten minutes following an EP injection does not prevent stress eosinopenia.

In man, plasma corticoid concentrations during severe stress may exceed those obtained by maximal doses of exogenous ACTH. Nevertheless, even when plasma corticoids are already greatly elevated under the influence of stress, additional ACTH treatment can cause a further increment. Presumably, factors other than adrenal secretion may play an important part in the elevation of blood corticoid levels during stress.

Curiously, the ACTH content of the posterior lobe is very high in some species, occasionally equalling that of the adenohypophysis. In vitro, the rat adrenal can liberate corticosterone and aldosterone under the influence of anterior or posterior hypophyseal ACTH.

It has been claimed that in anxious patients, the plasma contains a "precortico-

trophin or adrenal weight-maintenance factor (AWMF)" in concentrations exceeding the ordinary ACTH, described as "ascorbic acid depletion factor (AADF)." The adrenal weight factor (also designated as AWF) is allegedly involved in the regeneration of enucleated adrenals under the influence of separate hypothalamic centers, whereas the neurohypophysis is involved in the discharge of the ascorbic acid factor (AAF) in response to systemic, but not emotional, stressors. Investigators have not pursued this type of research much further, and it is still uncertain whether ascorbic acid discharge and adrenal regeneration are actually regulated by two chemically distinct types of ACTH. However, these effects of ACTH upon the adrenal may be dissociated. For example, in hypophysectomized rats, ACTH causes an almost immediate rise in adrenal vein corticosterone and ascorbic acid content, but the latter soon falls below the initial values, while the former continues to rise. The weight increase also outlasts the effect of ACTH upon corticoid secretion.

Single unit action potentials, measured after deposition of minute amounts of dexamethasone in the immediate extracellular environment of individual cells, showed that steroid-sensitive neurons exist in the cortex, dorsal hypothalamus and thalamus. These were also sensitive to microelectrophoretically-applied NEP and acetylcholine. The predominant action of the former was inhibition, that of the latter, stimulation. In the adenohypophysis, ACTH-producing cells can be identified with peroxidase-labelled antibody, by special stains and by EM characteristics. However, all these techniques still require perfection.

Undoubtedly, ACTH stimulates the adrenal cortex most frequently to secrete glucocorticoids. There is good evidence that the hormone also enhances mineralocorticoid secretion, although perhaps mainly through increased production of steroids other than aldosterone.

ACTH

(See also our earlier stress monographs, p. xiii)

Love, W. D.: "Failure of adrenalectomy immediately following stress to prevent eosinopenia in rats." *Proc. Soc. Exp. Biol. Med.* **75**: 639-641 (1950). B54,242/50

In rats, adrenalectomy ten minutes after EP injection does not prevent stress eosinopenia. Apparently, ACTH and corticoid discharge occurs almost immediately following application of the stressor.

Tyler, F. H., Sandberg, A. A., Eik-Nes, K.: "Adrenal cortical reserve and its relation to stress." *J. Clin. Invest.* **32**: 608 (1953). B82,998/53

In man, plasma 17-OHCS concentrations during severe stress may exceed those obtainable by maximal doses of exogenous ACTH. Nevertheless, in such cases when plasma steroids are already greatly elevated, additional ACTH treatment can cause a further increment. "These findings suggest that factors other than adrenal secretion may

play an important role in the production of elevated steroid levels."

Sayers, G.: "Factors influencing the level of ACTH in blood." In: Wolstenholme, G. E. W. and Millar, E. C. P., *Ciba Foundation Colloquia on Endocrinology*, Vol. 11, pp. 138-149. London: J & A Churchill, 1957. C42,020/57

Review and personal observations on the stressors causing increased ACTH secretion and test techniques for its bioassay in the blood.

Mialhe-Voloss, C.: "Posthypophyse et activité corticotrope" (The posterior lobe of the hypophysis and corticotrophic activity). *Acta Endocrinol.* **28** Supp. 35: 1-96 (1958). C52,008/58

The ACTH content of the posterior lobe is essentially the same as that of the anterior pituitary in cattle. Somewhat smaller concentrations of ACTH are also present in the posterior lobe of the duck and rat. Their corticotrophic activity is not due to MTH (about 250 refs.).

Mialhe-Voloss, C., Baulieu, E. E.: "Étude qualitative des corticostéroïdes libérés par la surrénale du rat in vitro sous l'influence des hormones corticotropes antéhypophysaire et posthypophysaire" (Qualitative study on corticosteroids released by the rat adrenal in vitro, under the influence of corticotrophic hormones from the anterior and posterior lobes of the hypophysis). *C.R. Acad. Sci. (Paris)* **346**: 639-642 (1958). D1,182/58

In vitro, the rat adrenal, as such or after addition of anterior or posterior hypophyseal ACTH, liberates corticosterone and aldosterone. Under these conditions, ACTH extracted from the anterior or posterior lobe is equally effective in stimulating more corticosterone and aldosterone secretion.

Nowell, N. W.: "Studies in the activation and inhibition of adrenocorticotrophin secretion." *Endocrinology* **64**: 191-201 (1959).

C63,783/59

In neurohypophysectomized rats, adrenal ascorbic acid depletion could be produced by cold, hypertonic saline and bell-ringing. A distinction is made between ascorbic acid factor (AAF) and adrenal weight factor (AWF) as two variants of ACTH. The neurohypophysis participates in the release of AAF, which is regulated by separate nerve centers in the hypothalamus. Enucleated adrenals regenerate under the influence of AWF, which is believed not to depend upon hypothalamic centers. "The neurohypophysis is involved in the release of ACTH/AAF in response to systemic stresses but not to emotional ones."

Persky, H., Maroc, J., Conrad, E., Breejen, A. D.: "Blood corticotropin and adrenal weight-maintenance factor levels of anxious patients and normal subjects." *Psychosom. Med.* **21**: 379-386 (1959). D2,894/59

In anxious hypercorticoid patients, the plasma level of "precorticotropin or adrenal weight-maintenance factor (AWMF)" is more significantly increased than that of the classic ACTH or ascorbic acid depletion factor (AADF).

Lipscomb, H. S., Nelson, D. H.: "Dynamic changes in ascorbic acid and corticosteroids in adrenal vein blood after ACTH." *Endocrinology* **66**: 144-146 (1960). J12,365/60

In hypophysectomized rats, the ascorbic acid and corticosterone levels of adrenal vein blood rise immediately after small doses of ACTH, but then corticosterone continues to

increase, whereas ascorbic acid falls below pre-ACTH values.

Liddle, G. W., Island, D., Meador, C. K.: "Normal and abnormal regulation of corticotropin secretion in man." *Rec. Prog. Horm. Res.* **18**: 125-153 (1962).

D25,344/62

Review on the factors regulating ACTH secretion during stress and its bioassay in the blood (53 refs.).

Vernikos-Danellis, J.: "Effect of acute stress on the pituitary gland: Changes in blood and pituitary ACTH concentrations." *Endocrinology* **72**: 574-581 (1963).

D60,685/63

Observations on blood and pituitary ACTH in rats exposed to surgical trauma "suggested that the ability of the adenohypophysis to release ACTH after stress is independent of the prestress pituitary concentration but rather depends on the ability of the gland to synthesize 'new' ACTH rapidly."

Holzbauer, M.: "The part played by ACTH in determining the rate of aldosterone secretion during operative stress." *J. Physiol. (Lond.)* **172**: 138-149 (1964).

D17,639/64

In dogs, ACTH increases not only glucocorticoid but to some extent also aldosterone secretion. Both these corticoids are produced at a subnormal level after hypophysectomy.

Ducommun, P., Ducommun, S., Jobin, M., Kraicer, J., Mialhe, P., Mialhe-Voloss, C., Fortier, C.: "Synthèse et libération d'ACTH à la suite d'une agression aiguë chez le rat surrénalectomisé" (Synthesis and liberation of ACTH following acute stress in the adrenalectomized rat). *Schweiz. Med. Wochenschr.* **94**: 892-893 (1964).

G17,137/64

In adrenalectomized rats, laparotomy raised the blood ACTH level within five minutes but contrary to earlier claims, no increase in pituitary ACTH could be detected during the first ten minutes. Presumably, ACTH synthesis does not predominate. The subsequent fall in both pituitary and blood ACTH is ascribed to the fact that the synthesis of the hormone is more markedly inhibited than its release during the later stages of the stress response.

Porter, J. C., Klaiber, M. S.: "Relationship of input of ACTH to secretion of corticoste-

rone in rats." *Am. J. Physiol.* **207**: 789-792 (1964). F22,653/64

Porter, J. C., Klaiber, M. S.: "Corticosterone secretion in rats as a function of ACTH input and adrenal blood flow." *Am. J. Physiol.* **209**: 811-814 (1965). F52,837/65

Wied, D. de: "Effects of peptide hormones on behavior." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 97-140. New York, London and Toronto: Oxford University Press, 1969. E10,614/69

Review of the effects exerted by ACTH, vasopressin and MTH upon behavior.

Steiner, F. A., Ruf, K., Akert, K.: "Steroid-sensitive neurones in rat brain: anatomical localization and responses to neurohumours and ACTH." *Brain Res.* **12**: 74-85 (1969). H28,002/69

Microelectrophoresis allows deposition of minute amounts of soluble compounds in the immediate extracellular environment of single cells in the CNS, and permits direct monitoring of the local response by recording single unit action potentials. In rats, it has been shown with this technique that dexamethasone-sensitive cells can be identified accurately and localized in the hypothalamus and midbrain, scattered over wide areas. The large majority of these cells are clearly inhibited, but some are activated. No steroid-sensitive neurons were found in the cortex, dorsal hypothalamus or thalamus. The steroid-sensitive neurons were responsive to microelectrophoretically-applied NEP and acetylcholine. The predominant action of the former was inhibition, that of the latter was stimulation. ACTH activated the steroid-sensitive neurons. Presumably, "specific nerve cells in the hypothalamus and midbrain are sensitive to both hormonal and humoural factors and involved in negative and positive feedback actions of the hormones."

Nakayama, I., Nickerson, P. A., Skelton, F. R.: "An ultrastructural study of the adrenocorticotrophic hormone-secreting cell in the rat adenohypophysis during adrenal cortical regeneration." *Lab. Invest.* **21**: 169-178 (1969). G70,537/69

Baker, B. L., Pek, S., Midgley, A. R. Jr., Gersten, B. E.: "Identification of the corticotropin cell in rat hypophyses with peroxidase-labeled antibody." *Anat. Rec.* **166**: 557-567 (1970). G74,700/70

"Corticotropin cells were stellate and possessed processes that ended on the walls of

sinusoids. Corticotropin cells composed a small percentage of the total cell population, and were distributed throughout the gland except that they were less common posteriorly, superiorly, and immediately alongside the pars intermedia. Alteration in size of corticotropin cells was related directly to change in corticotropin content of the gland as effected by differing physiological conditions."

Nakane, P. K.: "Classifications of anterior pituitary cell types with immunoenzyme histochemistry." *J. Histochem. Cytochem.* **18**: 9-20 (1970). G72,551/70

With the peroxidase-labeled antibody method, it was possible to localize the adenohypophyseal cells responsible for the secretion of ACTH, STH, FSH, LH and LTH (28 refs.).

Siperstein, E. R., Miller, K. J.: "Further cytophysiologic evidence for the identity of the cells that produce adrenocorticotrophic hormone." *Endocrinology* **86**: 451-486 (1970). H22,201/70

EM studies of the pituitaries of cortisol-treated intact or adrenalectomized rats led to the conclusion that the so-called "adrenalectomy cells" are the site of ACTH secretion and that these can also be identified in intact animals by their characteristic ultrastructure.

Hodges, J. R., Mitchley, S.: "Effect of prolonged treatment with tetracosactrin on hypothalamo-pituitary-adrenal function in the rat." *Br. J. Pharmacol.* **43**: 804-813 (1971). G87,789/71

Prolonged treatment with tetracosactrin (synthetic ACTH) increases the size of the adrenal cortex and its sensitivity to ACTH, while suppressing the circadian rhythm of, and the stress-induced rise in, endogenous ACTH production.

Kolanowski, J., Salvador, G., Crabbé, J.: "Influence de l'agression chirurgicale sur la sensibilité du cortex surrénal à la corticotropine exogène" (Influence of surgical stress on adrenocortical sensitivity to exogenous corticotropin). *Ann. Endocrinol. (Paris)* **33**: 211-215 (1972). H57,788/72

Following surgical stress, the plasma cortisol increase produced by a standard dose of ACTH is augmented.

Lantos, C. P., Dahl, V., Cordero-Funes, J. R., Nicola, A. F. de: "A correlation study between adrenal function and the duration of sustained ACTH treatments in the rat."

Acta Physiol. Lat. Am. **23**: 277-287 (1973).

J9,058/73

In rats, chronic experiments with natural and synthetic ACTH preparations showed that both tropins, especially β^{1-24} corticotropin, provoke alterations in some adrenal parameters. The synthetic peptide demonstrated a marked dissociation between its trophic and secretion-stimulating properties, and natural ACTH decreased aldosterone/corticosterone ratios. Changes in adrenocortical responsiveness may partly account for the triphasic nature of the G.A.S.

Péczely, P., Szokoly, P. M.: "The effect of acute and chronic stimulation on ACTH cell of the pigeon's adenohypophysis." *Gen. Comp. Endocrinol.* **22**: 367 (1974).

H83,210/74

In pigeons, acute insulin hypoglycemia and fourteen-day treatment with metyrapone were studied in connection with their effect upon the epsilon cells (which were light red by Herland's stain). "Insulin stress causes a strong hypertrophy of the ACTH cells. The endoplasmic reticulum shows an extreme hyperplasia, and the quantity of the secretion granules and the ACTH content of the pars distalis decrease. Metyrapone treatment causes hypertrophy and hyperplasia of the ACTH cells. The quantity of the endoplasmic reticulum increases; the cisternae are dilated, and they form vesicles. A great number of secretory granules appear, mainly on the periphery of the cells. The ACTH content of the pars distalis increases." These findings agree with the assumption that the epsilon cells of birds are the source of ACTH, and that acute stimulation and chronic stimulation lead to different EM changes.

Pratt, J. H., Melby, J. C.: "Alterations in aldosterone metabolism induced by adreno-

corticotropin (ACTH)." *Program Amer. Soc. Clin. Invest.*, 66th Ann. Meeting, p. 62a. Atlantic City, N.J., 1974. H88,771/74

In man, "repository ACTH injected every 12 h for 6 days induced a five-fold increment in the aldosterone secretion rate and a four-fold increment in urinary tetrahydroaldosterone excretion by day 6, whereas plasma concentrations of aldosterone did not change significantly." It appears that increased mineralocorticoid activity after ACTH is due almost exclusively to the enhanced production of nonaldosterone mineralocorticoids. Probably, "the augmented metabolic clearance rate for aldosterone after ACTH stimulation can to an extent regulate aldosterone activity and may be a mechanism for escape from aldosterone effect."

Schulster, D.: "Adrenocorticotrophic hormone and the control of adrenal corticosteroidogenesis." *Adv. Steroid Biochem. Pharmacol.* **4**: 233-295 (1974). J15,156/74

Review of the intimate enzymatic mechanisms regulating the secretion of corticoids under the influence of ACTH (about 160 refs.).

Miller, L. H., Kastin, A. J., Sandman, C. A., Fink, M., Veen, W. J. van: "Polypeptide influences on attention, memory and anxiety in man." *Pharmacol. Biochem. Behav.* **2**: 663-668 (1974). J18,229/74

In man, ACTH_{1-24} had no effect on the mental activities examined, but ACTH_{4-10} "served to improve visual memory, decrease anxiety, reinstitute a previously habituated alpha blocking response in the occipital EEG, and generally influence the occipital EEG toward a pattern consistent with increased attention. The results were taken to suggest a direct polypeptide influence on CNS attentional mechanisms."

ACTH Feedback

The fact that a rise in the corticoid level of the blood inhibits further ACTH secretion has long been known, and will be discussed in another section. However, in addition to this "long-loop" biofeedback, there exists a "short-loop," self-regulating mechanism in which ACTH itself acts back upon the pituitary (either directly or through suppression of CRF secretion), to inhibit the continued production of corticotropin once its release has been initiated.

Thus, it was found that in adrenalectomized rats, exogenous ACTH reduces the ACTH content and weight of the hypophysis, and that homotransplants of adenohy-

pophyseal tissue in the hypothalamus of the rat causes adrenocortical atrophy as a consequence of decreased ACTH secretion.

Some investigators reported that ACTH increases, whereas cortisone decreases, the ACTH content of the rat pituitary, but during exposure to a standardized stressor, exogenous ACTH blocks the usual ACTH release from the hypophysis. Presumably, this is why the hormone accumulates in the gland when large amounts of it are suddenly administered.

In rats after adrenalectomy, the pituitary ACTH concentration rapidly increases, but at least two weeks are required to establish a stable balance in which both the content and the secretion of hypophyseal ACTH are high.

Implantation of solid ACTH into the ME of the rat depresses blood corticosterone levels, whereas similar implants in the cerebral cortex or pituitary are ineffective. In adrenalectomized rats given ACTH, nucleolar changes in the hypothalamic neurons also suggest a short-loop feedback mechanism. Several observations imply that the receptors for this negative biofeedback are in the ME.

Injection of ACTH into hypophysectomized-adrenalectomized rats reduces hypothalamic CRF, and it is presumably through this effect that the short-loop feedback inhibits ACTH secretion.

The suppression of ACTH discharge by exogenous ACTH during stress is a typical extra-adrenal action of the hormone.

ACTH Feedback

(See also our earlier stress monographs, p. xiii)

Gemzell, C. A., Heijkenskjöld, F.: "Effect of corticotrophin on the content of corticotrophin in the pituitary glands of adrenalectomized rats." *Acta Endocrinol.* **24:** 249-254 (1957). C41,922/57

In adrenalectomized rats, long-acting ACTH reduced the ACTH content and the weight of the pituitary.

Halász, B., Szentágothai, J.: "Über die unmittelbare Rückwirkung einer vom Hypophysenvorderlappen erzeugten Substanz auf den Hypothalamus" (The immediate retroactive effect on the hypothalamus of a substance produced in the adenohypophysis). *Acta Physiol. Acad. Sci. Hung. Supp.* **14:** 6 (1958). J12,874/58

Homotransplants of adenohypophyseal tissue into the hypothalamus of rats cause adrenocortical atrophy as a consequence of decreased ACTH production. Presumably, ACTH itself can act back on the adenohypophysis to inhibit ACTH secretion.

Kitay, J. I., Holub, D. A., Jailer, J. W.: "Hormonal regulation of pituitary adrenocorticotropicin." *Proc. Soc. Exp. Biol. Med.* **97:** 165-169 (1958). C47,220/58

As judged by in vitro bioassays, "ACTH administration and adrenalectomy both resulted in a striking increase in pituitary ACTH content. Epinephrine and cortisone administration were both followed by significant depletion of pituitary ACTH."

Kitay, J. I., Holub, D. A., Jailer, J. W.: "Extra-adrenal action of exogenous ACTH; inhibition of pituitary ACTH secretion." *Fed. Proc.* **17:** 87 (1958). C51,673/58

In adrenalectomized rats, exogenous ACTH increases, whereas cortisone decreases, the ACTH content of the pituitary. During exposure to a standardized stressor, exogenous ACTH inhibits the usual ACTH release from the adenohypophysis. Presumably, that is why the hormone accumulates in the gland when it is exogenously administered.

Hodges, J. R., Vernikos, J.: "Influence of circulating adrenocorticotrophin on the pituitary adrenocorticotrophic response to stress in the adrenalectomized rat." *Nature* **182:** 725 (1958). C61,601/58

In rats, adrenalectomy first increases the ACTH content of the pituitary, but at least two weeks are required before it adapts itself to secrete and maintain a great excess of this hormone. Tests performed at various intervals during this time showed that the

greatest increase in circulating ACTH occurred in rats with the lowest initial blood levels, and apparently the high serum level of ACTH inhibits its own secretion through an "auto-feedback" mechanism.

Kitay, J. I., Holub, D. A., Jailer, J. W.: "Inhibition of pituitary ACTH release: an extra-adrenal action of exogenous ACTH." *Endocrinology* **64**: 475-482 (1959).

C66,580/59

The stress-induced (scalding) ACTH depletion of the pituitary in adrenalectomized rats is inhibited by pretreatment with ACTH, which also blocks the fall in adrenal ascorbic acid during ether anesthesia in intact rats. Presumably, exogenous ACTH can inhibit the production of endogenous ACTH, which is an additional extraadrenal action of this hormone.

Halász, B., Szentágothai, J.: "Control of adrenocorticotrophic function by direct influence of pituitary substance on the hypothalamus." *Acta Morphol. Acad. Sci. Hung.* **9**: 251-261 (1960).

D15,080/60

Homotransplantation of adenohypophyseal tissue into the infundibular recess of the rat causes involution of the fasciculata of the adrenals. Transplantation of other tissues into the same location or homotransplantation of pituitary into other parts of the hypothalamus have an inverse effect. "The possibility of an automatic self-control of adrenocorticotrophic function by a direct hormonal feedback action from the pituitary on the hypothalamus is discussed on the basis of the results."

Stark, E., Fachet, J., Mihály, K.: "Pituitary and adrenal responsiveness in rats after prolonged treatment with ACTH." *Can. J. Biochem. Physiol.* **41**: 1771-1777 (1963).

E22,584/63

Following several daily ACTH injections, rats become increasingly sensitive to the corticosterone-discharging effect of this hormone. Reduced adrenal stimulation during the stage of resistance of the G.A.S. cannot be ascribed, therefore, to a diminished sensitivity to this hormone, but presumably results from decreased ACTH secretion. After prolonged ACTH treatment, the release of endogenous ACTH by stress (formalin) is also reduced.

Porter, J. C., Klaiber, M. S.: "Relationship of input of ACTH to secretion of corti-

costerone in rats." *Am. J. Physiol.* **207**: 789-792 (1964). F22,653/64

Dávid, M. A., Fraschini, F., Motta, M., Martini, L.: "Short' feedback loops and the control of pituitary function." *Program 47th Meeting Endocrinol. Soc.*, p. 27. New York, 1965. F39,943/65

In rats, implantation of solid ACTH into the ME depresses blood corticosterone levels, whereas similar implants in the cerebral cortex or the pituitary are ineffective, as are implants of LH or FSH in the ME. Thus, in addition to the receptors sensitive to corticoids, control of pituitary function may also be achieved through "short feedback loops," in which the signals are given by anterior pituitary hormones.

Vernikos-Danellis, J., Anderson, E., Trigg, L., Dickinson, J.: "Feedback mechanisms regulating ACTH secretion." *Program 47th Meeting Endocrinol. Soc.*, p. 27. New York, 1965. F39,944/65

In rats bearing ACTH-producing tumors, "inhibition of ACTH secretion by maximal endogenous levels of corticoids is slow to develop and even under conditions when such high levels persist for a considerable length of time the response to stress is not completely prevented. Furthermore, in the absence of corticoids an extra-pituitary source of ACTH may inhibit adenohypophysial ACTH synthesis and secretion."

Motta, M., Mangili, G., Martini, L.: "A 'short' feedback loop in the control of ACTH secretion." *Endocrinology* **77**: 392-395 (1965). F46,923/65

In the rat, permanent implants of synthetic ACTH into the ME depressed blood corticosterone, "suggesting that a 'short' feedback loop might link synthesis and/or release of ACTH to pre-existing levels of the hormone."

Ifft, J. D.: "Further evidence on an 'internal' feedback from the adenohypophysis to the hypothalamus." *Neuroendocrinology* **1**: 350-357 (1965-66). G44,209/65-66

In adrenalectomized rats given ACTH, nucleolar changes in the hypothalamic neurons suggest a short feedback mechanism.

Szentágothai, J., Flerkó, B., Mess, B., Halász, B.: *Hypothalamic Control of the Anterior Pituitary. An Experimental-Morphological Study*, p. 399. Budapest: Akadémiai Kiadó, 1968. E7,567/68

Extensive monograph critically discussing personal experiments and the literature on

hypothalamic control of various anterior pituitary hormones, with a brief chapter (22 pages) dealing with ACTH secretion during stress. "It seems very probable that the hypothalamus is responsible for the maintenance of basal ACTH secretion as well as for the pituitary ACTH response to stress. The hypothalamic influence on the pituitary might be mediated by CRF produced by the hypophysiotrophic area. The hypophysiotrophic area seems to be able to produce and release this substance in the absence of nervous connexions but for the preservation of normal ACTH secretion neural afferents to the area are required. These afferents might come from various hypothalamic and extrahypothalamic (limbic system, reticular formation, etc.) structures and are excitatory as well as inhibitory in character which probably do not affect directly pituitary ACTH secretion but might act through the hypophysiotrophic area by modulating the synthesis and release of CRF. ACTH secretion is also influenced by blood corticoid levels and there is some indication that ACTH itself might play some role in controlling pituitary ACTH function. Although the question of the site of corticoid and ACTH action is not settled as yet, it could be assumed that this action is also mediated—at least partly—through the hypothalamus." There is some evidence in favor of the "short-circuit feedback" influencing various anterior pituitary hormones, including ACTH, through direct inhibition of the hypothalamus. For example, ACTH implants in the ME significantly depress blood corticosterone levels, but the "short feedback" may not always be direct in the anatomic sense, that is, conveyed over a particular vascular link permitting the reverse flow through the portal vessels of the pituitary. It may also act through the systemic circulation (several thousand refs.).

Motta, M., Fraschini, F., Martini, L.: "Short' feedback mechanisms in the control of anterior pituitary function." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 211-253. New York, Lon-

don and Toronto: Oxford University Press, 1969.

E10,615/69

Motta, M., Sterescu, N., Piva, F., Martini, L.: "The participation of 'short' feedback mechanisms in the control of ACTH and TSH secretion." *Acta Neurol. Belg.* **69**: 501-507 (1969).

G70,812/69

Review of the literature and personal observations on rats indicate that "ACTH secretion can be automatically controlled through a 'short' feedback mechanism, whose receptors are located in the median eminence (ME) of the hypothalamus. The 'short' feedback control of ACTH secretion appears to be of the 'negative' (inhibiting) type. TSH [TTH] secretion may also be automatically regulated by circulating levels of TSH."

Stark, E., Ács, Z., Szalay, K. S.: "Further studies on the hypophyseal-adrenocortical response to various stressing procedures in ACTH-treated rats." *Acta Physiol. Acad. Sci. Hung.* **36**: 55-61 (1969).

G74,546/69

In rats, some but not all stressors fail to increase ACTH secretion after a five-day treatment with ACTH.

Seiden, G., Brodish, A.: "Physiological evidence for 'short-loop' feedback effects of ACTH on hypothalamic CRF." *Neuroendocrinology* **8**: 154-164 (1971).

H47,192/71

In long-term hypophysectomized rats (one to six weeks), CRF rises to three or four times its normal level, but no significant increase is seen two to four days after hypophysectomy. CRF activity in the hypothalamus of chronically adrenalectomized rats is half that found in normals, but the elevated hypothalamic CRF levels in hypophysectomized rats are not altered by subsequent adrenalectomy. Injection of ACTH into hypophysectomized, adrenalectomized rats reduces hypothalamic CRF to one-eighth the levels in similarly operated controls. "These results suggest a direct action of ACTH on the hypothalamus, and provide evidence for a 'short-loop' feedback system between ACTH and CRF."

Extra-adrenal Actions of ACTH

At first it was thought that ACTH acts only by stimulating the secretion of corticoids. The first demonstration of a direct "nonadrenal-mediated" action of ACTH was the finding that it stimulates the preputial glands in adrenalectomized-ovariectomized rats. From this, it was "concluded that ACTH possesses actions which are not

mediated through either the adrenals or the gonads and which do not even depend upon the simultaneous presence in the body of adrenal or gonadal hormones." Subsequently, this effect was confirmed with highly purified ACTH in doses insufficient to cause significant thymolysis.

Another early, pertinent observation was that, in adrenalectomized-orchidectomized rats, the thymolytic effect of cortisone and other glucocorticoids is considerably enhanced by simultaneous treatment with ACTH. The latter, however, has no direct effect upon the thymus, as evidenced by the absence of the thymolytic action after adrenalectomy in otherwise untreated rats.

The previously described "short-loop" feedback action of ACTH, through which the hormone inhibits its own excessive secretion, may also be regarded as an extra-adrenal action. The same is true of the recently-discovered neuropsychologic actions of ACTH.

Extra-adrenal Actions of ACTH

(See also our earlier stress monographs, p. xiii)

Jacot, B., Selye, H.: "A non-adrenal-mediated action of ACTH on the preputial glands." *Proc. Soc. Exp. Biol. Med.* **78**: 46-48 (1951). B59,872/51

First demonstration of a direct, "non-adrenal-mediated" action of ACTH on the preputial glands of adrenalectomized, ovariectomized rats. "It is concluded that ACTH possesses actions which are not mediated through either the adrenals or the gonads and which do not even depend upon the simultaneous presence in the body of adrenal or gonadal hormones."

Jacot, B., Selye, H.: "On extra-adrenal actions of adreno-corticotrophic preparations." *Endocrinology* **50**: 254-258 (1952). B62,775/52

Even a considerably purified preparation of ACTH stimulates the growth of the preputial glands in female adrenalectomized and ovariectomized rats. This effect is detectable at a dose that does not cause significant thymolysis.

Selye, H., Jacot, B.: "On the effect of various steroids upon the extra-adrenal thymolytic action of ACTH." *Acta Endocrinol. (Kbh.)* **9**: 333-336 (1952). B62,780/52

In adrenalectomized and orchidectomized rats, the thymolytic effect of cortisone is greatly enhanced by simultaneous administration of ACTH, which has no such action under similar conditions if given in combination with DOC or estradiol. Apparently, the thymolytic action of cortisone is enhanced

(conditioned) by ACTH, which has no direct effect on the thymus by itself.

Hess, M., Rennels, E. G., Finerty, J. C.: "Response of preputial and adrenal glands of hypophysectomized rats to ACTH." *Endocrinology* **52**: 223-227 (1953). D41,911/53

In rats, ACTH has a direct effect upon the preputial glands, increasing their weight and depleting them of ascorbic acid. After hypophysectomy the response of the adrenal and preputial glands remains normal. It is noteworthy that although there is no demonstrable relationship between the adrenal cortex and preputial glands, their reaction to ACTH is essentially the same.

Engel, F. L.: "Extra-adrenal actions of adrenocorticotropin." *Vitam. Horm.* **19**: 189-227 (1961). E5,711/61

Review on all the extra-adrenal actions of ACTH (about 200 refs.).

Yip, S. Y., Freinkel, R. K.: "The direct effect of ACTH on the rat preputial gland." *J. Invest. Dermatol.* **43**: 389-393 (1964). F25,543/64

Confirmation of earlier reports that ACTH stimulates the growth of the preputial glands in adrenalectomized, castrated rats. This direct effect of ACTH has also been confirmed *in vitro* by the enhancement of lipogenesis upon addition of ACTH (13 refs.).

Deckx, R., Moor, P. de, Denef, C., Raus, J.: "Effect of adrenalectomy, sham operation or ACTH on the cortisol metabolizing enzymes of rat liver homogenate." *Metabolism* **14**: 264-270 (1965). F32,028/65

In female rats, the direct effect of ACTH on the metabolism of cortisol by liver homogenate differs from that of stress. These circumstances may explain the many apparent contradictions concerning the effect of stress upon the overall rate of corticoid metabolism (21 refs.).

Wied, D. de: "Effects of peptide hormones on behavior." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 97-140. New York, London and Toronto: Oxford University Press, 1969.

E10,614/69

Review of the effects exerted by ACTH, vasopressin and MTH upon behavior.

Berliner, D. L., Keller, N., Dougherty, T. F.: "Mediated and directed effects of ACTH and corticosteroids in stress." In: Bajusz, E., *Physiology and Pathology of Adaptation Mechanisms: Neural-Neuroendocrine-Humoral*, pp. 204-213. Oxford, London and Edinburgh: Pergamon Press, 1969.

E8,170/69

Review of numerous publications reporting extra-adrenal actions of ACTH which undoubtedly play an important role in the pathogenesis of the G.A.S. (45 refs.).

Non-Glucocorticoid-like Actions of ACTH

The preputial gland-stimulating effect of exogenous ACTH, which we just discussed, is not duplicated by either endogenous or exogenous glucocorticoids.

Furthermore, by using the granuloma pouch technique, it was shown in the rat that exogenous ACTH suppresses inflammation and causes thymicolymphatic atrophy only at dose levels insufficient to induce general catabolism with loss of body weight. Certain testoids inhibit the catabolic effects of heavy ACTH overdosage, but not those of cortisol; conversely, under suitable conditions, DOC can suppress the catabolic effects of cortisol but not those of ACTH.

There is also some evidence that ACTH increases, whereas glucocorticoids decrease, fear-motivated behavior and arousal in the rat.

Not Glucocorticoid-like Actions of ACTH

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Selective alteration of certain ACTH and glucocorticoid effects by androstan derivatives." *Metabolism* 4: 403-415 (1955).

C2,007/55

By use of the granuloma pouch technique, it was found that "only ACTH preparations can suppress inflammation and cause thymicolymphatic involution at dose-levels which do not suffice to induce any pronounced catabolism in the rat. MAD and allied testoids suppress the catabolic effects of ACTH but not those of cortisol, while DCA suppresses

the catabolic effects of cortisol but does not prevent those of ACTH."

Weiss, J. M., McEwen, B. S., Silva, M. T. A., Kalkut, M. F.: "Pituitary-adrenal influences on fear responding." *Science* 163: 197-199 (1969).

H5,347/69

In passive avoidance situations, hypophysectomized rats show less, and adrenalectomized rats more, fear than normals. This may be due to the fact that the hypophysectomized rat lacks ACTH, which increases arousal, whereas adrenalectomized rats have enhanced ACTH production. Presumably, ACTH and glucocorticoids have opposite effects on the regulation of fear-motivated behavior.

Non-Stress-like Actions of ACTH

It is interesting that some of the actions of ACTH are not duplicated by stress, even when the latter obviously elicits an overproduction of this hormone. Thus, as we saw before, the preputial glands are stimulated by ACTH but not by stress, even

under conditions where stress greatly increases endogenous ACTH secretion. It is difficult to explain this peculiar phenomenon unless we assume that during stress a number of factors specifically inhibit certain actions of ACTH.

Non-Stress-like Actions of ACTH

(See also our earlier stress monographs, p. xiii)

Deckx, R., Moor, P. de, Denef, C., Raus, J.: "Effect of adrenalectomy, sham operation or ACTH on the cortisol metabolizing enzymes of rat liver homogenate." *Metabolism* **14**: 264-270 (1965). F32,028/65

In female rats, the direct effect of ACTH on the metabolism of cortisol by liver homogenate differs from that of stress. These circumstances may explain the many apparent contradictions concerning the effect of

stress upon the overall rate of corticoid metabolism (21 refs.).

Vecsei, P., Kessler, H.: "In vivo conversion of corticosterone into aldosterone in rats treated with ACTH or submitted to stress." *Experientia* **26** 1015-1016 (1970).

H31,555/70

Studies on the in vivo conversion of corticosterone to aldosterone in rat adrenals revealed a diminution after ACTH pretreatment, but not upon chronic exposure to stressors. It is concluded that the adrenocortical effect of stress is not mediated exclusively through ACTH secretion.

Somatotrophic Hormone (STH, GH)

The effect of stress upon STH secretion is dependent upon a number of complex factors that condition this response, through concurrent changes in the secretion of STH-releasing factor or the metabolism of STH. When indirect indicators are used, alterations in the responsiveness of peripheral tissues to this hormone further condition STH activity.

In rats, starvation reduces the synthesis of STH-releasing factor by the hypothalamus, thus indirectly decreasing STH secretion. EP, NEP and dopamine injected into the lateral ventricles depleted pituitary STH, whereas several other neurohormones tested did not share this effect. Hence, STH secretion has been considered to be controlled by catecholamines.

The tibia cartilage test indicates that many but not all stressors increase plasma STH. Presumably, catecholamines and hypothalamic STH-releasing factor act as mediators, but the sensitivity of the peripheral target organs must also be taken into account.

According to other investigators, radioimmunoassayable STH concentrations in the plasma of rats are suppressed by various stressors as well as by dexamethasone, even after adrenalectomy. These findings, if confirmed, suggest that STH secretion is subject to corticoid feedback, and that stress can inhibit the release of this hormone independently of adrenocortical activation.

NEP and dopamine at doses known to deplete pituitary STH in rats caused disappearance of STH-releasing factor from the hypothalamus and its appearance in the plasma of hypophysectomized rats but not of intact controls. In the intact rats, very small doses of intraventricular NEP depleted pituitary STH activity. This catecholamine appears to be the normal synaptic transmitter for the discharge of STH-releasing factor from neurosecretory neurons. Electrolytic lesions in discrete hypothalamic areas reduced pituitary and plasma radioimmunoassayable STH and impaired somatic

growth. Hypothalamic STH-releasing neurohormone has been purified, isolated and synthesized. It represents a straight-chain acidic decapeptide.

There is also some evidence suggesting the existence of an inhibitory hypothalamic factor. Serum STH is greatly increased in man following injection of L-dopa (a dopamine precursor) whereas antiadrenergic drugs depress the STH level. Several observations suggest that STH is subject to "short-loop" feedback, through which it blocks its own secretion.

In rats with large medial hypothalamic lesions, STH secretion during stress is impaired but not abolished. Presumably, in the absence of both stimulatory and inhibitory neural impulses, the pituitary somatotrophs are capable of autonomous secretion.

In children, exhausting bicycle exercise caused a simultaneous increase in plasma STH and cortisol, indicating that the two hormones can be discharged concurrently.

Somatostatin (STH-RIF, SRIF). Somatostatin is the STH release-inhibiting hormone. It is a peptide, presumably secreted by the ME, that impedes STH secretion not only under resting conditions, but also when it is augmented by exercise, insulin, arginine, NEP injected into the ventromedial nucleus, and electric stimulation of the amygdala or ventromedial nucleus. It appears to act directly on the adenohypophyseal somatotrophs. This conclusion agrees with the finding that intravenous synthetic somatostatin inhibits the STH discharge usually produced by stimulation of the hypothalamic ventromedial and basolateral amygdaloid nuclei. This tetradecapeptide is now available in synthetic form for clinical use. It decreases plasma insulin, glucose and LTH concentrations but raises FFA.

Somatomedin. This factor was previously described as the sulfation factor. It is intimately related to STH secretion, but its possible role in stress reactions has not been clarified. In fact, there may exist several types of somatomedins.

Somantin. This substance appears to be a product of the breakdown of STH. The STH molecule has at least two, perhaps three distinct parts, each eliciting different effects. The tail portion of the molecule, called somantin, inhibits insulin and can produce transient diabetes in partially pancreatectomized rats. Its name is an abbreviation of "somatotrophin antagonist of insulin." The head part has an opposite effect and has correspondingly been called cataglykin. The middle portion of STH between somantin and cataglykin may correspond to somatomedin. The role of these factors in stress has not yet been clarified.

Somatotropic Hormone (STH, GH)

(See also our earlier stress monographs, p. xiii)

Lundin, M., Schelin, U., Pellegrini, G., Mellgren, J.: "Plasma cell production in the adaptation syndrome." *Acta Pathol. Microbiol. Scand.* **35**: 339-356 (1954).

C9,986/54

In rats, various types of stressors eliciting a typical G.A.S. cause plasma cell proliferation that has been ascribed to increased production of STH.

Halász, B.: "Neural control of growth hormone secretion." Proc. 2nd Int. Congr. Endocrinol., London, 1964. *Int. Congr. Ser. No. 83*, pp. 517-521. Amsterdam and New York: Excerpta Medica, 1965. F48,877/64

Meites, J., Fiel, N. J.: "Effect of starvation on hypothalamic content of 'somatotropin releasing factor' and pituitary growth hormone content." *Endocrinology* **77**: 455-460 (1965). F49,805/65

In rats, starvation reduces the synthesis and release of STH-RF by the hypothalamus,

which results in a decreased STH discharge from the adenohypophysis.

Müller, E. E., dal Pra, P., Pecile, A.: "Influence of brain neurohumors injected into the lateral ventricle of the rat on growth hormone release." *Endocrinology* **83**: 893-896 (1968).

H3,581/68

In rats, EP, NEP and dopamine injected into the lateral ventricle induced depletion of pituitary STH, whereas 5-HT, acetylcholine, vasopressin and oxytocin did not share this STH-releasing effect. Presumably, adrenergic mediators participate in the neurohumoral control of STH secretion.

Müller, E. E., Pecile, A.: "Studies on the neural control of growth hormone secretion." In: Pecile, A. and Müller, E. E., *Growth Hormone*, pp. 253-266. Amsterdam and New York: Excerpta Medica, 1968.

E8,299/68

Observations on rats show that many but not all stressors increase plasma STH (tibia test). Although many similarities in the control of ACTH and STH are apparent, a different threshold of stimulation and/or diverse nervous pathways relaying impulses to the CNS might be the cause of dissociation between their control mechanisms. Stimuli releasing STH act via the hypothalamus, and catecholamines may be considered as mediators of STH-RF.

Wakabayashi, I., Arimura, A., Schally, A. V.: "Effect of adrenocortical hormones on plasma radioimmunoassayable growth hormone (RIA-GH) in rats." *Physiologist* **13**: 332 (1970).

H27,784/70

In rats, radioimmunoassayable STH concentrations in plasma are suppressed by various stressors, as well as by dexamethasone, even after adrenalectomy. Apparently, the stress-induced changes in plasma STH are independent of adrenocortical activation.

Müller, E. E., Pecile, A., Felici, M., Coccochi, D.: "Norepinephrine and dopamine injection into lateral brain ventricle of the rat and growth hormone-releasing activity in the hypothalamus and plasma." *Endocrinology* **86**: 1376-1382 (1970).

H26,874/70

In rats, NEP and dopamine (at doses known to deplete pituitary STH) caused the disappearance of STH-RF activity in the hypothalamus and its appearance in the plasma of hypophysectomized rats but not of intact controls. 5-HT was ineffective in this respect. In intact rats, intravenous NEP diminished pituitary STH activity in very small doses. The hypothalamic site for STH discharge by

catecholamines suggests that NEP is the synaptic transmitter that releases STH-RF from its neurosecretory neurons. This factor can be assayed by pituitary STH depletion following intracarotid injection of hypothalamic extracts or plasma.

Takahashi, K., Daughaday, W. H., Kipnis, D. M.: "Regulation of immunoreactive growth hormone secretion in male rats." *Endocrinology* **88**: 909-917 (1971).

H37,347/71

Plasma immunoreactive STH rose more in gentled rats than in nongentled controls, whereas plasma corticosterone levels were less elevated. In both gentled and nongentled rats, pentobarbital anesthesia caused a significant rise in plasma STH and a corresponding decrease in plasma corticosterone. Ether, hypertonic glucose, 2-deoxyglucose, insulin and EP elicited a marked suppression of plasma STH and an increase in plasma corticosterone, effects which were partly or totally blocked by pentobarbital anesthesia.

Müller, E. E.: "Nervous control of growth hormone secretion." *Neuroendocrinology* **11**: 338-369 (1973).

H71,999/73

Review on the neural control of STH secretion in mammals. Electrolytic lesions in discrete hypothalamic areas reduced pituitary and plasma radioimmunoassayable STH, impaired somatic growth, and diminished STH discharge in response to insulin but not after electric stimulation of brain areas. Hypothalamic STH secretion seems to be governed by an STH-releasing neuropeptide that has been purified, isolated and synthesized, and which represents a straight-chain acidic decapeptide. There is also some proof of an inhibitory hypothalamic factor whose function in STH discharge is not yet clear. STH-RF decreases in the hypothalamus and increases in the plasma when STH secretion is enhanced. Catecholamines play a significant role in the neurohormonal control of STH discharge. Serum STH is greatly increased in man following ingestion of L-dopa (a precursor of dopamine), whereas chlorpromazine, an antiadrenergic drug, depresses the STH level. During deep sleep, STH secretion in man is apparently independent of alterations in brain catecholamine turnover, but like other anterior pituitary hormones, STH is subject to a feedback on itself, which decreases its own discharge (about 150 refs.).

Massara, F., Camanni, F., Molinatti,

G. M.: "Liberazione di ormone somatotropo in seguito a stimolazione alfa-adrenergica nell'uomo" (Somatotropic hormone secretion following α -adrenergic stimulation in man). *Folia Endocrinol.* (Roma) **26**: 476-482 (1973). H83,466/73

Observations in man suggest that stimulation of α -adrenergic receptors excites CNS centers to cause STH secretion.

Winter, J. S. D.: "The metabolic response to exercise and exhaustion in normal and growth-hormone-deficient children." *Can. J. Physiol. Pharmacol.* **52**: 575-582 (1974).

H87,451/74

Exhausting bicycle exercise caused a rise in the STH and cortisol but a fall in the insulin content of the plasma in normal people.

Dunn, J., Arimura, A.: "Serum growth hormone levels following ablation of medial basal hypothalamus." *Neuroendocrinology* **15**: 189-199 (1974). H91,993/74

In rats with large medial hypothalamic lesions, STH secretion after "ether stress" was impaired but not abolished. (The destruction was accomplished by a modified Halász knife with a cross bar which interrupted the vascular supply from the ventral surface of the brain.) Perhaps the simultaneous elimination of stimulation and inhibition by neural impulses largely compensated the effect upon STH release. "The pituitary somatotrophs appear capable of autonomous secretion."

Somatostatin (STH-RIF, SRIF). Vale, W., Brazeau, P., Rivier, C., Rivier, J., Grant, G., Burgus, R., Guillemain, R.: "Biological activities of somatostatin" (abstracted). *Program 55th Ann. Meeting Endocrinol. Soc.*, p. A-118. Chicago, 1973. H73,038/73

Pelletier, G., Labrie, F., Arimura, A., Schally, A. V.: "Electron microscopic immunohistochemical localization of growth hormone-release inhibiting hormone (somatostatin) in the rat median eminence." *Am. J. Anat.* **140**: 445-450 (1974). J14,151/74

Dubois, M. P., Barry, J., Leonardelli, J.: "Mise en évidence par immunofluorescence et répartition de la somatostatine (SRIF) dans l'éminence médiane des vertébrés (mammifères, oiseaux, amphibiens, poissons)" (Immunofluorescence and distribution of somatostatin [SRIF] in the median eminence of vertebrates [mammals, birds, amphibia, fish]). *C.R. Acad. Sci. (Paris)* **279**: 1899-1902 (1974). J21,296/74

Koerker, D. J., Ruch, W., Chideckel, E.,

Palmer, J., Goodner, C. J., Ensinck, J., Gale, C. C.: "Somatostatin: hypothalamic inhibitor of the endocrine pancreas." *Science* **184**: 482-484 (1974). H85,690/74

Description of somatostatin, a hypothalamic peptide that impedes STH release. In fasted baboons, arginine-stimulated secretion of insulin and glucagon is also inhibited by somatostatin.

"Growth-hormone release-inhibiting hormone." *Lancet* June 8, 1974, pp. 1148-1150. H87,156/74

Brief review of contemporary knowledge on somatostatin. It inhibits STH secretion not only under ordinary conditions, but also when it is augmented by "various stimuli including exercise, insulin-induced hypoglycaemia, sleep, arginine, levodopa, morphine, pentobarbitone, noradrenaline injected into the ventromedial nucleus of the hypothalamus, and electrical stimulation of the amygdala or ventromedial nucleus." Apparently it acts directly on the somatotroph cells of the adenohypophysis (16 refs.).

Brazeau, P., Rivier, J., Vale, W., Guillemain, R.: "Inhibition of growth hormone secretion in the rat by synthetic somatostatin." *Endocrinology* **94**: 184-187 (1974).

H80,841/74

Synthetic somatostatin lowers the circulating level of immunoreactive STH in "gentled" rats; it also prevents or inhibits the rise in plasma STH induced by administration of pentobarbital. In chronic experiments, it decreases the rate of somatic growth.

Martin, J. B.: "Inhibitory effect of somatostatin (SRIF) on the release of growth hormone (GH) induced in the rat by electrical stimulation." *Endocrinology* **94**: 497-502 (1974). H86,286/74

Synthetic somatostatin (SRIF), given intravenously before stimulation of the hypothalamic ventromedial and basolateral amygdaloid nuclei, completely inhibits the usual STH discharge. Apparently, SRIF prevents STH release induced by stimulation of either of these brain regions, suggesting that the site of blockade is in the pituitary itself.

Yen, S. S. C., Siler, T. M., Vane, G. W. de: "Effect of somatostatin in patients with acromegaly. Suppression of growth hormone, prolactin, insulin and glucose levels." *N. Engl. J. Med.* **290**: 935-938 (1974).

H85,536/74

Somatostatin, a hypothalamic polypeptide, suppresses STH secretion in various tissues

in man. This STH-inhibiting factor is a tetradecapeptide which is now available in synthetic form for clinical use. It increases plasma FFA, decreases plasma insulin, glucose and LTH, and depresses STH secretion, not only in acromegaly, but also after exercise, sleep or treatment with arginine, L-dopa, hypoglycemic agents, and so on. It has not yet been shown to play a definite role in the G.A.S. (25 refs.).

Smythe, G. A., Lazarus, L.: "Suppression of human growth hormone secretion by melatonin and cyproheptadine." *J. Clin. Invest.* **54**: 116-121 (1974). H87,405/74

In the rat as in man, STH secretion (stimulated by serotoninergic pathways) can be inhibited by treatment with 5-HT antagonists such as cyproheptadine, and the pineal gland hormone, melatonin. [In this respect, these compounds resemble the actions of somatostatin (H.S.).]

Somatomedin. Hall, K., Wyk, J. J. van: "Somatomedin." *Curr. Top. Exp. Endocrinol.* **2**: 155-178 (1974). J13,597/74

Review on somatomedin, previously known as the "sulfation factor" (about 200 refs.).

Job, J.-C., Rappaport, R.: "Somatomedines et croissance" (Somatomedins and growth). *Arch. Fr. Pédiatr.* **31**: 333-337 (1974). J12,952/74

Review of the literature suggesting that there are several types of somatomedins. [Their possible participation in stress is not discussed, but they are obviously involved in the associated STH secretion (H.S.).]

Somantin. Vargas, L., Bronfman, M., Kawada, M. E.: "Stress, insulin antagonist and transient diabetes mellitus in the rat." *Horm. Metab. Res.* **6**: 275-280 (1974).

H90,727/74

In rats the diabetogenic activity of STH may depend upon an α_2 -glycoprotein that appears in the blood after exposure to various stressors or administration of STH. This substance inhibits insulin and produces transient diabetes in partially pancreatectomized rats. It may be related to somantin, which is the "tail" residue after splitting the STH molecule at the 166 amino acid site. It received its name as an abbreviation of "somatotrophin antagonist of insulin" and has insulin antagonistic properties in vitro. The "head" portion of the STH molecule exerts an opposite effect and has been called "cataglykin" (from the Greek *kata* and *glykos*). In themselves, neither somantin nor cataglykin have STH activity. The intermediate part of the molecule between cataglykin and somantin may be identical with somatomedin. The relationship between somantin and somatostatin is not discussed, although the two substances appear to be closely connected.

Thyrotrophic Hormone (TTH, TSH)

That stress can either increase or decrease thyroid activity, depending upon conditioning circumstances, has already been mentioned in other sections of this volume, for example, in the sections on Hormones and Hormone-like Substances (under Stressors and Conditioning Agents), Thyroid (under Morphologic Changes) and Diseases of Adaptation; it will again be discussed later in this section on Hormonal Mechanisms (under Hormones and Hormone-like Substances: Thyroid).

Here it will suffice to point out that cold increases both plasma TTH and corticosterone levels in the rat, but concurrent exposure to other stressors may suppress the TTH response selectively and enhance corticoid secretion. It has been postulated that contemporaneous stimulation of ACTH and inhibition of TTH secretion during stress are related to depressed hippocampal activity.

Thyrotrophic Hormone (TTH, TSH)

(See also our earlier stress monographs, p. xiii)

Dupont, A., Endrőczi, E., Fortier, C.: "Relationship of pituitary-thyroid and pituitary-adrenocortical activities to conditioned be-

haviour in the rat." In: Ford, D. H., *Influence of Hormones on the Nervous System* (Proc. Int. Soc. Psychoneuroendocr., Brooklyn, N.Y., 1970), pp. 451-462. Basel, München and Paris: S Karger, 1971 (25 refs.).

J12,174/71

Dupont, A., Bastarache, E., Endrőczi, E., Fortier, C.: "Effect of hippocampal stimulation on the plasma thyrotropin (TSH) and corticosterone responses to acute cold exposure in the rat." *Can. J. Physiol. Pharmacol.* **50**: 364-367 (1972). H54,958/72

In rats, exposure to cold increases both plasma TTH and corticosterone, but concurrent minor environmental stress (presence of an observer) suppresses the TTH response and enhances the rise in corticosterone. Concurrent stimulation of the gyrus dentatus of the hippocampus by implanted electrodes restores the TTH response to cold and inhibits the rise in corticosterone. "The concurrent stimulation of ACTH release and inhibition of TSH secretion induced by nonspecific

stress are possibly related to depressed hippocampal activity."

Leppäluoto, J., Ranta, T., Lybeck, H., Varis, R.: "Effect of TRH, and short-term exposure to experimental stress or cold on the serum immunoassayable TSH concentration in the rat." *Acta Physiol. Scand.* **90**: 640-644 (1974). J13,381/74

Various acute stressors temporarily raise plasma TTH levels, but this is followed by a lasting and pronounced decrease. Only cold causes a specific increase in plasma TTH activity. "The inhibition of TSH [TTH] secretion in response to stress refutes the hypothesis that stressful stimuli activate the thyroid gland."

Luteotrophic Hormone (LTH, Prolactin)

The effect of stress upon LTH production has been discussed under Chemical Changes (Hormones and Hormone-like Substances). Like the release of STH, it is subject to so many conditioning factors that accurate generalizations are difficult to formulate.

In rats, various stressors reduce the LTH content of the pituitary. This effect is generally prevented by Nembutal or acid bovine stalk-ME extracts.

Several findings suggest that a hypothalamic inhibitory factor for LTH secretion exists and that its suppression during stress enhances LTH secretion.

Luteotrophic Hormone (LTH, Prolactin)

(See also our earlier stress monographs, p. xiii)

Grosvenor, C. E., McCann, S. M., Nallar, R.: "Inhibition of nursing-induced and stress-induced fall in pituitary prolactin concentration in lactating rats by injection of acid extracts of bovine hypothalamus." *Endocrinology* **76**: 883-889 (1965).

F39,155/65

In rats, nursing and exposure to various stressors reduce the LTH content of the pituitary. Nembutal prevents the fall in LTH after laparotomy and bleeding. Acid extracts of bovine stalk-ME inhibit the fall in pituitary LTH following the combined stimuli of nursing and stress. There may exist "a hypothalamic inhibitory factor in the normal regulation of prolactin release in response to nursing or stress."

MIDDLE (INTERMEDIATE) LOBE OF THE HYPOPHYSIS Melanotrophic Hormone (MTH, MSH)

MTH secretion during stress has been discussed in the section on the Chemical Changes (under Hormones and Hormone-like Substances). It should be kept in mind, however, that MTH is not the only hormone of the intermediate lobe, since the latter is also extremely rich in ACTH.

In rats, one month after adrenalectomy, the ACTH content of the adenohypophysis

increases considerably whereas that of the intermediate lobe remains unchanged. Chronic treatment with cortisol decreases the ACTH concentration in the adeno-hypophysis but not in the pars intermedia. The role of the middle lobe in the metabolism of ACTH is still not clear, but in any event, the production, storage and discharge of ACTH is largely independent of MTH biogenesis and secretion.

**Middle (Intermediate) Lobe of the Hypophysis
Melanotrophic Hormone (MTH, MSH)**

(See also our earlier stress monographs, p. xiii)

Wied, D. de: "Effects of peptide hormones on behavior." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 97-140. New York, London and Toronto: Oxford University Press, 1969.

E10,614/69

Review of the effects exerted by ACTH, vasopressin and MTH upon behavior.

Gosbee, J. L., Kraicer, J., Kastin, A. J., Schally, A. V.: "Functional relationship between the pars intermedia and ACTH secretion in the rat." *Endocrinology* 86: 560-567 (1970).

H22,210/70

In rats, autoradiographic studies (thymidine-³H incorporation) showed that only one cell type, restricted to the pars intermedia, responded to altered ACTH secretion with an increase in the label index after adrenalectomy and a decrease after cortisol. Since no changes in plasma or hypophyseal MTH content were found, "it is concluded that there is a functional relationship between the pars

intermedia and ACTH secretion" (29 refs.).

Kraicer, J., Gosbee, J. L., Bencosme, S. A.: "Pars intermedia and pars distalis: two sites of ACTH production in the rat hypophysis." *Neuroendocrinology* 11: 156-176 (1973). H68,125/73

In rats "the concentration of ACTH in the pars intermedia is considerably greater than that in the pars distalis. At 1 month after adrenalectomy, the ACTH concentration in the pars distalis increased 3-fold, while that in the pars intermedia remained unchanged. Following chronic administration of cortisol, the ACTH concentration in the pars distalis fell to 27% of the control, while the fall in ACTH concentration in the pars intermedia was not significant.... Although a relation between the pars intermedia and ACTH is established, this relation is different from that between the pars distalis and ACTH."

Stratton, L. O., Kastin, A. J.: "Avoidance learning at two levels of shock in rats receiving MSH." *Horm. Behav.* 5: 149-155 (1974). J13,633/74

Experiments on rats suggest that MTH may facilitate learning at low but not at high levels of electric shock, which induces stress in a shuttle box.

POSTERIOR (NEURAL) LOBE OF THE HYPOPHYSIS

Data concerning the secretion of posterior lobe hormones have been reviewed in part under Characteristic Manifestations of Stress (Chemical Changes).

Transection of the supraoptico-hypophyseal tract causes atrophy of the posterior lobe and diabetes insipidus in the dog. It also inhibits the stress-induced release of vasopressin.

Both vasopressin and oxytocin injected into the CSF elicit an ACTH discharge, while EP and various stressors inhibit diuresis owing to hypersecretion of vasopressin concurrently with ACTH discharge.

In rats, neurohypophysectomy does not change the adrenal ascorbic acid-depleting effect of ether anesthesia or unilateral adrenalectomy, but partially inhibits these consequences of an ACTH discharge elicited by cold, emotional arousal or EP. It was postulated that psychic stressors act on the ACTH present in the posterior lobe by the

mediation of endogenous EP, whereas neither the posterior lobe nor EP is involved in the corresponding effect of somatic stress. The antidiuretic response to hemorrhage, histamine and painful stimuli is also reduced by posterior lobe extirpation. Vasopressin appears to be involved in the corticotrophic effect of neurogenic stimuli, since posterior lobectomized rats respond to "systemic stressors" (hemorrhage, histamine, nicotine) with a normal increase in plasma-free corticosterone. Conversely, those exposed to "neurogenic stressors" (strange environment, sound, pain) show a decreased response, despite the adrenal enlargement caused by posterior lobectomy.

However, recent investigations suggest that truly selective removal of the posterior and intermediate lobes does not significantly alter normal adenohypophyseal activity during stress.

Posterior (Neural) Lobe of the Hypophysis

(See also our earlier stress monographs, p. xiii)

O'Connor, W. J.: "The effect of section of the supraopticohypophyseal tracts on the inhibition of water-diuresis by emotional stress." *Q. J. Exp. Physiol.* **33**: 149-161 (1946). B36,165/46

In dogs, section of the supraopticohypophyseal tract caused atrophy of the neurohypophysis and diabetes insipidus. In addition, the amount of vasopressin released during emotional stress was greatly reduced and the slow type of inhibition of water-diuresis was almost abolished. In this respect, there was no significant difference between animals with posterior pituitary extirpation and those subjected to tract section.

Martini, L.: "Nuove osservazioni sulla regolazione ormonale della ipofisi anteriore ad opera della ipofisi posteriore: e deduzioni anche sul piano terapeutico" (New observations on hormonal regulation of the anterior hypophysis by the posterior lobe: also, deductions in the therapeutic field). *Clin. Ter.* **7**: 189-206 (1954). C569/54

A review and personal observations on the importance of posterior lobe hormones in the regulation of ACTH secretion. Both vasopressin and oxytocin, injected intravenously or into the CSF, elicit an ACTH discharge, whereas EP and various stressors inhibit diuresis (a sign of vasopressin hypersecretion) with a concurrent ACTH release. Both these phenomena are detectable only in the presence of the pituitary (164 refs.).

Green, J. D.: "Neural pathways to the hypophysis." In: Fields, W. S., Guillemin, R. et al., *Hypothalamic-Hypophysial Interrelationships. A Symposium*, pp. 3-14. Springfield, Ill.: Charles C Thomas, 1956.

tionships. A Symposium, pp. 3-14. Springfield, Ill.: Charles C Thomas, 1956.

C23,833/56

Nowell, N. W.: "Studies in the activation and inhibition of adrenocorticotrophin secretion." *Endocrinology* **64**: 191-201 (1959).

C63,783/59

In neurohypophysectomized rats, adrenal ascorbic acid depletion could be produced by cold, hypertonic saline and bell-ringing. A distinction is made between ascorbic acid factor (AAF) and adrenal weight factor (AWF) as two variants of ACTH. The neurohypophysis participates in the release of AAF, which is regulated by separate nerve centers in the hypothalamus. Enucleated adrenals regenerate under the influence of AWF, which is believed not to depend upon hypothalamic centers. "The neurohypophysis is involved in the release of ACTH/AAF in response to systemic stresses but not to emotional ones."

Smelik, P. G.: "Mechanism of hypophysial response to psychic stress." *Acta Endocrinol. (Kbh.)* **33**: 437-443 (1960). C81,900/60

In rats, neurohypophysectomy does not change the adrenal ascorbic acid-depleting effect of ether anesthesia or unilateral adrenalectomy, but it does partially inhibit the effect of exposure to cold, and it abolishes the effect of emotional disturbance or EP. Presumably, "psychic stress stimuli act on the corticotrophin present in the posterior lobe of the hypophysis by the mediation of endogenous adrenaline, whereas in the case of somatic stress neither the posterior lobe nor adrenaline is involved."

Smelik, P. G.: "The role of the posterior lobe of the pituitary gland in the corticotrophic response to acute stress." *Acta*

Physiol. Pharmacol. Neerl. **9:** 125-126 (1960). C89,917/60

In neurohypophysectomized rats, certain types of stressors no longer produce adrenal ascorbic acid discharge. It is suggested that "emotional stimuli activate the adrenal cortex only in the presence of the posterior lobe, but that somatic stimuli act as normally when the posterior lobe has been removed."

Wied, D. de: "The significance of the antidiuretic hormone in the release mechanism of corticotropin." *Endocrinology* **68:** 956-970 (1961). D7,440/61

In rats, posterior lobe extirpation greatly reduces the antidiuretic response to hemorrhage, histamine or painful stimuli. Exposure of these animals to "systemic stress" (hemorrhage, histamine, nicotine) increases plasma free corticosterone as much as in sham-operated controls. However, "neurogenic stressors" (strange environment, sound, pain) become significantly less effective, although the adrenal is enlarged after posterior lobectomy. These and other observations led the author to conclude that "the

antidiuretic hormone is involved in the corticotrophic effect of neurogenic stimuli."

Smelik, P. G., Gaarenstroom, J. H., Konijnendijk, W., Wied, D. de: "Evaluation of the role of the posterior lobe of the hypophysis in the reflex secretion of corticotrophin." *Acta Physiol. Pharmacol. Neerl.* **11:** 20-33 (1962). D32,829/62

Itoh, S.: "L'importanza della neuroipofisi nel risponso da stress" (Importance of the neurohypophysis in the stress response). *Minerva Med.* **56:** 1438-1439 (1965).

G30,806/55

Miller, R. E., Yueh-Chien, H., Wiley, M. K., Hewitt, R.: "Anterior hypophysial function in the posterior-hypophysectomized rat: normal regulation of the adrenal system." *Neuroendocrinology* **14:** 233-250 (1974). H86,430/74

Removal of the posterior and intermediate lobes did not alter normal anterior pituitary function in rats, whether at rest or following application of various stressors.

Vasopressin, Antidiuretic Hormone (ADH), Oxytocin

It has been established beyond reasonable doubt that the antidiuretic hormone (ADH) of the posterior lobe is identical with vasopressin. Various stressors decrease the antidiuretic activity of the pituitary and hypothalamus in the rat, especially during the alarm reaction phase of the G.A.S. Large doses of vasopressin stimulate ACTH secretion even in rats with diabetes insipidus induced by transection of the supraopticohypophyseal tract. It was felt, therefore, that the latter is intimately connected with a discharge of ACTH.

There was much debate about the possibility that vasopressin might be identical with or at least closely related to CRF, but this view has now been almost unanimously abandoned. The CRF activity of early vasopressin preparations was usually due to contamination with CRF. Of course, in the presence of the pituitary, large doses of vasopressin or even of oxytocin can produce an ACTH discharge by acting as stressors. This response is inhibited by hypophysectomy, but is demonstrable even in rats with ocular adenohypophyseal homotransplants. In this event, the posterior lobe hormones are particularly effective when applied topically to the graft; hence, it was concluded that they can act also as neurohumoral transmitters, even though they are less active in this respect than CRF.

In any event, vasopressin release may occur in man without an associated ACTH discharge and vice versa, indicating that endogenous vasopressin is not an indispensable ACTH-releasing factor.

In dogs, injection of minute doses of vasopressin into the third ventricle produced marked rises in the 17-OHCS level of adrenal venous blood, but the same amounts

administered intravenously were ineffective. Oxytocin had no such effect given by either route.

Synthetic arginine vasopressin stimulates ACTH secretion in rats, even after administration of large doses of cortisol, which prevent the typical response to stressors. This is another important point in favor of the hypothesis that vasopressin itself does have some direct ACTH-discharging properties. However, curiously, in dogs, direct arterial perfusion of the adrenal with synthetic lysine vasopressin stimulated cortisol secretion, evidently through some local action independent of the hypophysis. Like effects were obtained with several other synthetic vasopressin derivatives, but in this arrangement, pressor and ACTH activity were independent of each other. On the other hand, similar polypeptides (such as oxytocin), insulin, glucagon, EP and NEP did not cause cortisol secretion, whereas ACTH also raised aldosterone production when perfused through the adrenals of hypophysectomized dogs. Yet a detailed review of the literature published up to the time of these investigations led the author to conclude, "it seems justified to relegate the ADH theory of ACTH release to the emeritus role."

It is characteristic of the confusion in this domain that only a few years later it was found that ACTH-producing pituitary tumors, as well as various types of synthetic or natural vasopressin, were all active in causing ACTH release in proportion to their pressor activity. Hence it was postulated that "vasopressin is the ACTH-releasing hormone" and that even synthetic lysine-vasopressin has "CRF-like" effects. ACTH discharge was elicited by injections of minute amounts of vasopressin into the artery supplying an ACTH-secreting pituitary graft in the hind leg of a rat, whereas 1,500 times this amount of vasopressin given intravenously had no effect. Again it was concluded that "vasopressin may be the ACTH-releasing neurohumor."

In rats, vasopressin placed directly upon the ME after dexamethasone pretreatment produced pronounced ACTH release, but was less active when injected into the adenohypophysis. It was assumed that vasopressin acts directly on the hypothalamus to cause a discharge of endogenous CRF.

In rats with hereditary hypothalamic diabetes insipidus owing to a lack of vasopressin, various stressors raised plasma corticosterone but to a lesser extent than in normal controls. The CRF activity of the ME and the pituitary ACTH concentration were essentially normal in this strain of rats. Hence, it was assumed that although vasopressin is not identical with CRF, "it may play a small role in adrenal cortical response to stress."

In vasopressin-deficient rats with diabetes insipidus, in which stress causes a definite but subnormal increase in plasma corticosterone, in vitro observations suggest that the adrenal glands themselves are relatively insensitive to ACTH. Perhaps the presence of vasopressin during early life may permanently influence adrenal sensitivity.

In rats with the neurohypophysis removed but the adenohypophysis and portal circulation intact, there was no detectable vasopressin in the plasma after stress, despite the high concentration of CRF. Conversely, when the adenohypophysis was removed and the neurohypophysis left intact, there occurred a rise in plasma vasopressin after stress, but no detectable increase in CRF.

In patients with diabetes insipidus, the circadian variations in plasma cortisol are normal. These findings "do not support the view that under physiological conditions vasopressin would be the neurohumoral regulator of ACTH secretion."

In monkeys and in man, synthetic lysine-vasopressin occasionally produced not only corticoid but also STH discharges, although this effect may have been nonspecific.

**Vasopressin, Antidiuretic Hormone
(ADH), Oxytocin**

(See also our earlier stress monographs, p. xiii)

Nagareda, C. S., Gaunt, R.: "Functional relationship between the adrenal cortex and posterior pituitary." *Endocrinology* 48: 560-567 (1951). B59,637/51

Only in large doses did vasopressin deplete the rat adrenal of ascorbic acid. Large water loads had the same effect.

Kovács, K., Bachrach, D.: "Hypothalamus and water metabolism. Studies on the antidiuretic substance of the hypothalamus and hypophysis." *Acta Med. Scand.* 141: 137-152 (1951). B69,790/51

In rats the hypothalamus contains an antidiuretic substance apparently identical with vasopressin. Various stressors (formaldehyde, hypertonic sodium chloride), as well as adrenalectomy, diminish the antidiuretic activity of the pituitary and hypothalamus. This decrease "following the shock phase of the alarm reaction suggests that, besides the anterior lobe of the pituitary, this system too, takes an active part in defence against non-specific damage" (121 refs.).

McCann, S. M., Brobeck, J. R.: "Evidence for a role of the supraopticohypophyseal system in regulation of adrenocorticotrophin secretion." *Proc. Soc. Exp. Biol. Med.* 87: 318-324 (1954). J9,398/54

In rats, variously placed hypothalamic lesions which block ACTH secretion (as judged by adrenal ascorbic acid depletion, adrenal weight and plasma ACTH) always destroy large areas of the supraopticohypophyseal tract and cause diabetes insipidus. Large doses of vasopressin stimulate ACTH secretion in these rats. "It appears likely, therefore, that destruction of the median eminence is not a necessary condition for blockade of the stress response and that destruction of a large percentage of the supraopticohypophyseal tract is the most constant feature in rats with effective lesions of the hypothalamus."

Mirsky, I. A., Stein, M., Paulisch, G.: "The secretion of an antidiuretic substance into the circulation of rats exposed to noxious stimuli." *Endocrinology* 54: 491-505 (1954). B93,139/54

Mirsky, I. A., Stein, M., Paulisch, G.: "The secretion of an antidiuretic substance into the circulation of adrenalectomized and

hypophsectomized rats exposed to noxious stimuli." *Endocrinology* 55: 28-39 (1954).

B95,024/54

"Exposure of adrenalectomized and hypophsectomized rats to noxious stimuli results in a marked increase in the antidiuretic activity of the plasma. Exposure of cortisone-treated hydrated, hypophsectomized rats to such stimuli results in an antidiuresis. Consequently, neither the adrenal gland nor the hypophysis is the source of the factor responsible for the increased antidiuretic activity of the plasma of animals exposed to noxious stimuli."

Mirsky, I. A.: "Secretion of antidiuretic hormone in response to noxious stimuli." *Arch. Neurol. Psychiatry* 73: 135-137 (1955). C4,174/55

"The same stimuli which can initiate the sequence of events described by Selye as the 'alarm reaction' elicit also an antidiuretic response." The latter has been shown to result from an increase in the vasopressin concentration of the plasma.

Arimura, A.: "The effect of posterior-pituitary hormone on the release of ACTH." *Jap. J. Physiol.* 5: 37-44 (1955).

C6,604/55

Although large doses of vasopressin cause adrenal ascorbic acid depletion in the rat, pretreatment with small doses actually prevents the release of ACTH provoked by EP, histamine or cold.

Guillemin, R., Hearn, W. R.: "ACTH release by 'in vitro' pituitary. Effect of pitressin and purified arginine-vasopressin." *Proc. Soc. Exp. Biol. Med.* 89: 365-367 (1955).

C7,404/55

In a modified tissue culture procedure, rat adenohypophysis increased ACTH release, whereas purified arginine-vasopressin was ineffective. The activity of commercial vasopressin preparations "is attributed to a contaminant of vasopressin of probable hypothalamic origin."

Shibusawa, K., Saito, S., Fukuda, M., Kawai, T., Yoshimura, F.: "On the role of the hypothalamic-neurohypophyseal neurosecretion in the liberation of the adenohypophyseal hormones." *Endocrinol. Jap.* 2: 47-56 (1955). J12,732/55

In various species, vasopressin injection augments ACTH secretion; this hormone "is believed to be the prominent stimulator for the liberation of the pituitary adrenocortical hormone." Yet its release during stress is

said to follow ACTH discharge. [The quaint English used by the authors makes the interpretation of their data difficult (H.S.).]

Martini, L., Morpurgo, C.: "Neurohumoral control of the release of adrenocorticotrophic hormone." *Nature* **175**: 1127-1128 (1955). C7,998/55

Antidiuretic and oxytocic preparations from the posterior pituitary may produce ACTH release upon intravenous injection in intact dogs and rats. Allegedly, these preparations also cause a discharge of TTH and LTH. In rats, vasopressin decreases adrenal cholesterol, but only in the presence of the pituitary. "This demonstrates that cholesterol depletion after injection of posterior pituitary hormones is not due to contamination of the materials injected with adrenocorticotrophic hormone."

Martini, L., Poli, A. de: "Neurohumoral control of the release of adrenocorticotrophic hormone." *J. Endocrinol.* **13**: 229-234 (1956). C15,162/56

In hypophysectomized rats, injection of posterior pituitary hormones failed to cause the usual eosinopenia and adrenal ascorbic acid depletion. However, hypophysectomized rats with ocular adenohypophyseal homotransplants from adult rats responded to both intraperitoneal and intraocular injection of posterior pituitary hormones with eosinopenia and adrenal ascorbic acid depletion. "These results are consistent with the hypothesis that the posterior pituitary hormones act as humoral transmitting agents which, released by the hypothalamus into the hypophysial portal system, can activate the anterior pituitary to discharge ACTH."

Sayers, G.: "Discharge of ACTH from the adenohypophysis of the adrenalectomized rat." *Fed. Proc.* **15**: 162 (1956).

C16,643/56

Even in adrenalectomized rats, stress (ether), vasopressin and EP cause ACTH release. Although synthetic vasopressin is just as effective as the natural product, the results are compatible with the view, but do not prove, that vasopressin is the ACTH-releasing factor.

McCann, S. M.: "The ACTH-releasing activity of extracts of the posterior lobe of the pituitary *in vivo*." *Endocrinology* **60**: 664-676 (1957). F27,982/57

Observations on rats support the hypothesis that vasopressin "may be the neuro-

humor responsible for eliciting ACTH discharge" (32 refs.).

McDonald, R. K., Wagner, H. N., Weise, V. K.: "Relationship between endogenous antidiuretic hormone activity and ACTH release in man." *Proc. Soc. Exp. Biol. Med.* **96**: 652-655 (1957). C45,835/57

In man, vasopressin release may occur without ACTH secretion, and vice versa, under the influence of various stimuli. Presumably, endogenous vasopressin does not act as an ACTH-releasing factor.

Mialhe-Voloss, C.: "Posthypophyse et activité corticotrope" (The hypophyseal posterior lobe and corticotropic activity). *Acta Endocrinol.* **28** Supp. 35: 1-96 (1958).

C52,008/58

Review on posterior pituitary hormones as regulators of ACTH secretion (about 250 refs.).

Wied, D. de, Bouman, P. R., Smelik, P. G.: "The effect of a lipide extract from the posterior hypothalamus and of pitressin on the release of ACTH from the pituitary gland." *Endocrinology* **62**: 605-613 (1958).

C52,310/58

In rats, various lipid extracts of bovine hypothalamus as well as Pitressin (vasopressin) stimulated ACTH secretion. Morphine or cortisol inhibited the effect of the lipid extracts, but only morphine prevented ACTH discharge by Pitressin, which was obtained even after destruction of the ME. "It is concluded that the lipide extract requires the intactness of hypothalamic structures for its action, and that Pitressin contains the specific neurotransmitter."

Royce, P. C., Sayers, G.: "Extrahypothalamic interaction between Pitressin and ACTH." *Proc. Soc. Exp. Biol. Med.* **98**: 70-74 (1958). C54,346/58

Natural vasopressin depletes adrenal ascorbic acid in hypophysectomized rats and potentiates the corresponding action of ACTH, even after destruction of the ME. "Only part of this effect can be explained by release of ACTH from the pituitary since Pitressin will also deplete adrenal ascorbic acid in a lesioned rat which has been decapitated."

Schapiro, S., Marmorston, J., Sobel, H.: "Mobilization of the antidiuretic hormone and the secretion of ACTH following cold stress." *Endocrinology* **62**: 278-282 (1958).

C48,916/58

In both hydrated and dehydrated guinea

pigs, exposure to cold produced a "normal stress response," as determined by the rise in urinary corticoid excretion. The vasopressor activity of the hypothalamus and posterior pituitary was markedly diminished by dehydration. "Apparently, conditions which induce alterations in mobilization of the antidiuretic hormone do not necessarily induce parallel alterations in the secretion of ACTH in response to stress."

Koibuchi, E.: "The effects of hypothalamic lesions of the pituitary-adrenocortical system." *Endocrinol. Jap.* **5**: 89-98 (1958).

C57,340/58

In rats, lesions in the anterior hypothalamus and the anterior part of the medial hypothalamus caused atrophy of the hypophysis and adrenals. These changes were suppressed by vasopressin. "It seemed likely that the control center of ACTH release is found in the anterior hypothalamus or the anterior part of the medial hypothalamus, and that vasopressin accelerates the release of ACTH."

Kwaan, H. C., Bartelstone, H. J.: "Corticotropin release following injections of minute doses of arginine vasopressin into the third ventricle of the dog." *Endocrinology* **65**: 982-985 (1959).

C78,367/59

In dogs, injection of minute doses of vasopressin into the third ventricle produced marked rises in the 17-OHCS level of adrenal venous blood, whereas the same amounts administered intravenously were inactive. Oxytocin had no such effect by either route, even at dose levels twenty times larger.

Chauvet, J., Acher, R.: "Influence de la vasopressine sur la sécrétion de la corticotropine (ACTH)" (The effect of vasopressin on corticotropin [ACTH] secretion). *Ann. Endocrinol. (Paris)* **20**: 111-115 (1959).

C71,285/59

In rats, arginine-vasopressin stimulates ACTH secretion even after administration of large doses of cortisol which prevent the typical response to stressors.

Nichols, B. L. Jr., Guillemin, R.: "Endogenous and exogenous vasopressin on ACTH release." *Endocrinology* **64**: 914-920 (1959).

C69,487/59

Hilton, J. G., Scian, L. F., Westermann, C. D., Kruesi, O. R.: "Effect of synthetic lysine vasopressin on adrenocortical secretion." *Science* **129**: 971 (1959).

C66,821/59

In dogs, direct arterial perfusion of the adrenal with a fluid containing synthetic lysine-vasopressin stimulates cortisol secretion. This effect is local and is not mediated through the adenohypophysis.

Hilton, J. G.: "Adrenocorticotrophic action of antidiuretic hormone." *Circulation* **21**: 1038-1046 (1960).

C90,262/60

In hypophysectomized dogs, direct perfusion of the adrenals with synthetic lysine, arginine or acetyl arginine-vasopressin stimulated the cortex to secrete cortisol. Pressor activity and adrenotropic effects were independent of each other. Similar polypeptides, such as oxytocin, insulin, glucagon and pressor amines (EP, NEP) did not cause cortisol secretion under identical conditions. However, ACTH was active, and it also increased the rate of aldosterone production. "The probable role of arginine vasopressin as an important factor in the stress reaction is considered along with its postulated ability to activate adrenal phosphorylase."

Hilton, J. G., Scian, L. F., Westermann, C. D., Nakano, J., Kruesi, O. R.: "Vasopressin stimulation of the isolated adrenal glands: nature and mechanism of hydrocortisone secretion." *Endocrinology* **67**: 298-310 (1960).

C90,686/60

In hypophysectomized dogs, direct arterial perfusion of the adrenals with synthetic lysine, arginine or acetyl arginine-vasopressin stimulates cortisol secretion. Similar polypeptides, such as oxytocin, insulin and glucagon, as well as EP and NEP, fail to share this effect. ACTH consistently increases aldosterone secretion under identical conditions after hypophysectomy.

Nichols, B. L. Jr.: "The role of antidiuretic hormone in corticotrophin release." *Yale J. Biol. Med.* **33**: 415-434 (1961).

E94,376/61

Review summarizing numerous data which suggest that vasopressin may either stimulate or suppress ACTH secretion depending upon circumstances; in any event, "it seems justified to relegate the ADH theory of ACTH release to the emeritus role" (93 refs.).

Guillemin, R.: "Diabète insipide par lésion stéréotaxique de l'hypothalamus et fonction adrénocorticotrope. Rôle de la vasopressine dans la décharge de l'ACTH" (Diabetes insipidus following stereotaxic lesion of the hypothalamus and adrenocorticotrophic function. Role of vasopressin in the release of

ACTH). In: Courrier, R. and Guillemin, R., *Etudes d'Endocrinologie. 2. Rapports entre le Complexe Hypothalamo-Hypophysaire et la Fonction Adrénocorticotrope*, pp. 285-297. Paris: Hermann, 1961 (27 refs.).

J12,261/61

Hearn, W. R., Weber, E. J., Randolph, P. W., Barks, N. E.: "Corticotropin releasing activity of synthetic lysine vasopressin." *Proc. Soc. Exp. Biol. Med.* **107**: 515-517 (1961).

E99,221/61

In rats, even synthetic lysine-vasopressin has a "CRF-like" effect.

Martini, L., Pecile, A., Giuliani, G., Fraschini, F., Carraro, A.: "Neurohumoral control of the anterior pituitary gland." In: Nowakowski, O., *Gewebs- und Neurohormone Physiologie des Melanophorenhormons*, pp. 117-129. Berlin, Gottingen and Heidelberg: Springer-Verlag, 1962.

D47,375/62

In rats pretreated with large doses of dexamethasone to eliminate pituitary stress reactions, vasopressin, lysine-vasopressin and phenylalanyl-lysine-vasopressin considerably raise blood corticosterone titers, whereas pitocin, synthetic oxytocin, valyl-oxytocin and isoleucyl-oxytocin are poor ACTH releasers in this test.

Grindeland, R. E., Wherry, F. E., Anderson, E.: "Vasopressin and ACTH release." *Proc. Soc. Exp. Biol. Med.* **110**: 377-380 (1962).

D29,083/62

In rats, injection of vasopressin in minute amounts into the artery supplying an ACTH-secreting pituitary graft in the hind leg releases measurable quantities of ACTH, whereas it has no such effect if given intravenously, even at fifteen hundred times higher dose levels. "These findings suggest that vasopressin may be the ACTH-releasing neurohumor."

Rumsfeld, H. W. Jr., Porter, J. C.: "ACTH-releasing activity of bovine posterior pituitaries." *Endocrinology* **70**: 62-67 (1962).

D16,643/62

The ratios of vasopressor- and ACTH-releasing activity in bovine posterior pituitary extracts and arginine-vasopressin were not interdependent.

Goldman, H., Lindner, L.: "Antidiuretic hormone concentration in blood perfusing the adenohypophysis." *Experientia* **18**: 279-280 (1962).

D26,033/62

Contrary to earlier statements, the vasopressin content of blood perfusing the rat

pituitary is sufficient to account for ACTH secretion.

Arimura, A., Long, C. N. H.: "Influence of a small dose of vasopressin upon the pituitary-adrenal activation in the rat." *Jap. J. Physiol.* **12**: 411-422 (1962).

D41,881/62

Grindeland, R. E., Anderson, E.: "Synthetic vasopressin and ACTH release." *Fed. Proc.* **22**: 386 (1963).

G4,454/63

In rats with an ACTH-producing pituitary tumor, vasopressin, synthetic arginine-vasopressin and lysine-vasopressin were all active in causing ACTH release in proportion to their pressor activity. "It is postulated that vasopressin is the ACTH-releasing hormone."

Doepfner, W., Stürmer, E., Berde, B.: "On the corticotrophin-releasing activity of synthetic neurohypophysial hormones and some related peptides." *Endocrinology* **72**: 897-902 (1963).

D67,095/63

In rats, the ACTH-releasing activity of antidiuretic vasopressin and oxytocic posterior pituitary preparations was tested after blockade of ACTH discharge by morphine. "The pressor and the CRF activities of peptides related to the neurohypophysial hormones need not be strictly correlated."

Wied, D. de: "The site of the blocking action of dexamethasone on stress-induced pituitary ACTH release." *J. Endocrinol.* **29**: 29-37 (1964).

F10,254/64

In rats the corticotrophic effect of stressors and lysine-vasopressin was inhibited by subcutaneous dexamethasone, while that of ACTH was not affected. After extensive lesions were produced in the ME, dexamethasone suppressed the corticotrophic action of lysine-vasopressin and of hypothalamic extract. Dexamethasone did not significantly change the ACTH content of the pituitary in either intact or lesioned rats. "It is concluded that the blocking action of dexamethasone is located in the anterior pituitary."

Hearn, W. R., Lazzari, E. P., Weber, E. J.: "Studies on the corticotropin releasing factor (CRF)." *Tex. Rep. Biol. Med.* **22**: 208 (1964).

J12,071/64

Vasopressin could not be separated from CRF activity, and since even synthetic arginine- and lysine-vasopressin release ACTH, "it is concluded that vasopressin itself is most probably the 'physiological corticotropin-releasing factor.'"

Goldman, H.: "Vasopressin modulation of the distribution of blood flow in the unanesthetized rat." *Neuroendocrinology* 1: 23-30 (1966). F52,660/66

Experiments with infusion of vasopressin—mimicking its blood concentration during stress (hemorrhage)—suggest that at least in the rat ACTH secretion may be modulated by the effects of the posterior pituitary hormone upon blood flow in the anterior lobe.

Meyer, V., Knobil, E.: "Stimulation of growth hormone secretion by vasopressin in the rhesus monkey." *Endocrinology* 79: 1016-1018 (1966). F73,022/66

In unanesthetized rhesus monkeys restrained in primate chairs, vasopressin and lysine-vasopressin administered intravenously increase plasma STH levels, but "this action may not be a specific one."

Hedge, G. A., Yates, M. B., Marcus, R., Yates, F. E.: "Site of action of vasopressin in causing corticotropin release." *Endocrinology* 79: 328-340 (1966). F69,345/66

In rats, vasopressin produced a pronounced ACTH release when it was placed directly upon the ME after dexamethasone pretreatment. It was less active when injected into the anterior pituitary. From these and other observations, it was concluded that "vasopressin apparently acted directly on the hypothalamus to cause release of endogenous corticotropin-releasing factor."

McCann, S. M., Antunes-Rodrigues, J., Nallar, R., Valtin, H.: "Pituitary-adrenal function in the absence of vasopressin." *Endocrinology* 79: 1058-1064 (1966).

F74,055/66

In rats that had hereditary hypothalamic diabetes insipidus and which lacked vasopressin, stressors (ether, bleeding) raised plasma corticosterone, but to a significantly lesser extent than in normal controls of the same strain. The CRF activity in the stalk-ME and the pituitary ACTH concentration were essentially the same in the two groups. Presumably, "although vasopressin is not the corticotrophin-releasing factor, it may play a small role in adrenal cortical response to stress."

Anderson, E.: "Adrenocorticotrophin-releasing hormone in peripheral blood: increase during stress." *Science* 152: 379-380 (1966).

F65,555/66

In rats, various stressors, especially laparotomy under ether anesthesia, cause the discharge of CRF and vasopressin (ADH) into

the circulating blood, presumably from the portal circulation of the pituitary. In a footnote the author mentions that subsequent experiments showed that "the ACTH-releasing and antidiuretic activities involve separate hormones. In rats with the posterior pituitary lobe removed, the anterior pituitary and the hypophyseal portal circulation being left intact, there is no detectable ADH in the plasma after stress, but there is a high concentration of ACTH-RH. With the anterior pituitary removed and the entire neurohypophysis being left intact, there is an elevated concentration of ADH in the plasma after stress but no detectable ACTH-RH." [ACTH-RH = CRF (H.S.).]

Gwinup, G., Steinberg, T., King, C. G., Vernikos-Danellis, J.: "Vasopressin-induced ACTH secretion in man." *J. Clin. Endocrinol. Metab.* 27: 927-930 (1967). F85,329/67

In patients given lysine-8-vasopressin, the plasma ACTH concentration was raised, as determined by assays on hypophysectomized rats. Normal plasma to which comparable amounts of vasopressin were added, did not share this effect. Presumably, "vasopressin-induced steroidogenesis in man is principally due to ACTH secretion."

Arimura, A., Saito, T., Bowers, C. Y., Schally, A. V.: "Pituitary-adrenal activation in rats with hereditary hypothalamic diabetes insipidus." *Acta Endocrinol. (Kbh.)* 54: 155-165 (1967). F76,127/67

In rats with hereditary hypothalamic diabetes insipidus, plasma corticosterone concentrations are essentially normal, and they react to stress (ether, histamine, vasopressin, acetylcholine) as do controls. Since these polyuric rats lack vasopressin, the latter is unlikely to be the physiologic CRF. On the other hand, the CRF level in the hypothalamus of these hereditarily stigmatized rats is normal, although their posterior lobe contains no CRF but a normal amount of ACTH.

Czarny, D., James, V. H. T., Landon, J., Greenwood, F. C.: "Corticosteroid and growth-hormone response to synthetic lysine-vasopressin, natural vasopressin, saline solution, and venepuncture." *Lancet* August 20, 1968, pp. 126-129. H1,264/68

In man, both synthetic lysine-vasopressin and natural vasopressin given intramuscularly increased plasma corticoids regularly, but plasma STH rose only in some volunteers. Plasma corticoids and STH also rose in

several patients following intramuscular injection of saline when blood samples were obtained by intermittent venipuncture.

Ukai, M., Moran, W. H. Jr., Zimmermann, B.: "The role of visceral afferent pathways on vasopressin secretion and urinary excretory patterns during surgical stress." *Ann. Surg.* **168**: 16-28 (1968).

G60,105/68

In dogs, partial gastrectomy increases vasopressin secretion about thirtyfold. This response is not modified by transection of the vagal pathways, but it can be eliminated by cervical cordotomy or dorsal rhizotomy, "indicating that the ascending spinal pain pathways were serving as the predominant afferent pathway." The surgical trauma also decreases endogenous creatinine and osmolal clearance, urinary flow and sodium secretion. The vasopressin discharge is ascribed to stress.

Wied, D. de: "Influence of vasopressin and of a crude CRF preparation on pituitary ACTH-release in posterior-lobectomized rats." *Neuroendocrinology* **3**: 129-135 (1968).

H1,565/68

In posterior-lobectomized rats, arginine-vasopressin (unlike carbachol, angiotensin II or crude CRF) failed to elicit the pituitary-adrenal response, but chronic administration of Pitressin almost completely restored the pituitary-adrenal reaction to arginine-vasopressin. Since the corticotropin effect of neurogenic stressors is also reduced by posterior lobectomy, the results support the hypothesis that arginine-vasopressin is involved in the mechanism of ACTH release in response to neurogenic stressors.

Czakó, L., László, F. A., Kovács, K., Faredin, I., Tóth, I.: "Diurnal variations of the plasma cortisol level in diabetes insipidus." *Acta Med. Acad. Sci. Hung.* **26**: 197-201 (1969).

G67,342/69

In patients with diabetes insipidus, the circadian variations in plasma cortisol are normal. Thus, "the results obtained do not support the view that under physiological conditions vasopressin would be the neurohumoral regulator of ACTH secretion."

Wied, D. de: "Effects of peptide hormones on behavior." In: Ganong, W. F. and Martin, L., *Frontiers in Neuroendocrinology*, pp. 97-140. New York, London and Toronto: Oxford University Press, 1969.

E10,614/69

Review on the effects exerted by ACTH, vasopressin and MTH upon behavior.

Arimura, A., Schally, A. V., Bowers, C. Y.: "Corticotropin releasing activity of lysine vasopressin analogues." *Endocrinology* **84**: 579-583 (1969) (22 refs.). H10,015/69

Yates, F. E., Russell, S. M., Dallman, M. F., Hedge, G. A., McCann, S. M., Dhariwal, A. P. S.: "Potentiation by vasopressin of corticotropin release induced by corticotropin-releasing factor." *Endocrinology* **88**: 3-15 (1971) (36 refs.). H34,903/71

Valtin, H., Stewart, J., Sokol, H. W.: "Genetic control of the production of posterior pituitary principles." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. 4, Part 1, pp. 131-171. Washington, D.C.: American Physiological Society, 1974.

E10,727/74

Review on vasopressin and oxytocin secretion during stress in various species (215 refs.).

Robinson, A. G.: "Independent physiologic control of secretion of two neuropeptides in humans." *Clin. Res.* **22**: 348A (1974).

H90,222/74

Wiley, M. K., Pearlmuter, A. F., Miller, R. E.: "Decreased adrenal sensitivity to ACTH in the vasopressin-deficient (Brattleboro) rat." *Neuroendocrinology* **14**: 257-270 (1974).

H88,352/74

In vasopressin-deficient Brattleboro rats homozygous for diabetes insipidus, plasma corticosterone concentrations during stress (ether, laparotomy) rose much less than in genetically normal controls. That they did respond to some extent confirms that vasopressin is not identical with CRF. In vitro observations suggest that in the vasopressin-deficient strain the adrenal glands themselves are relatively insensitive to ACTH. The presence of vasopressin in the internal milieu during early life may permanently influence adrenal sensitivity (18 refs.).

Barnett, J. L., Cheeseman, P., Cheeseman, J., Douglas, J. M., Phillips, J. G.: "Adrenal responsiveness in ageing Brattleboro rats with hereditary diabetes insipidus." *Age and Aging* **3**: 189-195 (1974).

J17,972/74

"Although the resting plasma corticosterone levels were drastically depressed in homozygous DI [diabetes insipidus] rats, there was no impairment of the response to stress; the adrenal glands of homozygous rats were significantly more responsive to stress than the corresponding heterozygous rats."

ADRENALS

Changes in adrenal structure, as well as in catecholamine and corticoid secretion during stress have been discussed at length in the sections on the morphologic and chemical characteristics of the G.A.S. Cannon's classic work on the emergency reaction, with the acute discharge of catecholamines from the adrenal medulla and the sympathetic nervous system, upon exposure to fear, rage and hunger, was extensively discussed in our earlier monographs on stress (p. xiii). Here, we give special attention to subsequent investigations in this field, as well as to studies on corticoid production, and to the participation of the adrenal as a whole during the various phases of the G.A.S.

The most prominent adrenal changes during the alarm reaction are a discharge of chromaffin material, mainly EP, from the adrenal medulla, and of corticoids, lipid granules, cholesterol, and ascorbic acid, from the adrenal cortex. At the same time, there is pronounced hyperemia, with an increase in the blood supply of the gland. Soon afterwards, mitotic proliferation begins, especially in the fasciculata, with some functional hypertrophy of virtually all adrenal cells. As the stage of resistance develops, secretory granules accumulate again, both in the medulla and cortex, conjointly with cholesterol and ascorbic acid. Finally, in the stage of exhaustion, the manifestations of the alarm reaction tend to return, but this time often accompanied by necroses or hemorrhages.

These adrenal changes are undoubtedly of a defensive nature. They are useful especially for the acquisition of resistance to stressors that are quantitatively or qualitatively different from those to which the organism was previously exposed. Therefore, adrenalectomy is particularly detrimental during the initial stage of the G.A.S., whereas later it can be relatively well tolerated, despite continued exposure to the evocative stressor. Adrenal atrophy produced by various means, and especially by hypophysectomy, diminishes resistance almost as much as does complete adrenalectomy.

The thymicolymphatic involution characteristic of the G.A.S. is abolished by adrenalectomy following exposure to most stressors, including traumatic injuries, toxic doses of drugs, catecholamines, hemorrhage. The very few agents, such as x-rays and sex hormones, that continue to exert their lympholytic action in the absence of corticoids, do so presumably as the result of a direct effect upon the thymus, lymph nodes, spleen and other lymphatic organs. On the other hand, thyroidectomy, gonadectomy and a great variety of other surgical interventions do not considerably interfere with the thymicolymphatic involution produced by the G.A.S. It has been concluded, therefore, that the latter is the result of increased glucocorticoid secretion. However, after adrenalectomy in rats, maintenance on threshold doses of glucocorticoids (which do not cause considerable thymus involution by themselves) sensitizes them to the development of thymicolymphatic involution under the influence of stressors. This is due to a nonadrenal-mediated conditioning effect of stress that was mentioned previously; its mechanism is still not fully clarified.

The number of circulating lymphocytes and eosinophils roughly parallels the degree of thymicolymphatic involution during stress. This eosinopenia is likewise attributable to increased ACTH and glucocorticoid secretion and can be reproduced by exogenous ACTH and glucocorticoids.

Adrenalectomy increases the ACTH secretion of the pituitary owing to interruption of the corticoid feedback mechanism; this may or may not be associated with a drop

in the ACTH content of the adenohypophysis, depending upon the time elapsed after removal of the adrenals.

In adrenalectomized rats, the blood vessels of the mesoappendix become insensitive to topical application of NEP. This refractoriness is greatly enhanced by stressors but is counteracted by topical or systemic treatment with corticoids. Apparently, conditioning by the latter is necessary to permit the vessels to respond normally to NEP, and at the same time, to protect against toxic amounts of this catecholamine.

In mice, stress two hours after adrenalectomy causes a significant lymphocytosis lasting several hours. This "stress lymphocytosis" is not prevented by splenectomy; hence it cannot be attributed to evacuation of the splenic reservoir.

The effect of partial and complete adrenalectomy, at rest and upon exposure to stressors, will be discussed in the section on the corticoid feedback mechanism.

The hypothalamic CRF rhythm is not significantly affected by adrenalectomy in the rat; presumably it is of neural origin and independent of the corticoid feedback mechanism.

Adrenals

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* **17**: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction," characterized by adrenocortical enlargement with acute loss of lipids, thymicolympathic atrophy and loss of body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde or EP). Adrenalectomy and, to a lesser extent, hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug" but greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and the other manifestations of the alarm reaction "enable the organism to meet critical situations more efficiently."

Selye, H.: "The significance of the adrenals for adaptation." *Science* **85**: 247-248 (1937). 67,153/37

Rats "previously adapted to such stimuli as muscular exercise, cold or toxic doses of drugs will tolerate exposure to these same stimuli very well, even after the adrenals have been removed, while exposure to the same stimuli invariably kills not-adapted, adrenalectomized controls, with symptoms

characteristic of adrenal insufficiency and of the alarm reaction." Apparently, the adrenals are necessary for the acquisition of adaptation but are not necessary (or much less so) for its maintenance despite continued exposure.

Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937). 38,798/37

Hypophysectomy lessens the accidental involution of the thymus and adrenalectomy inhibits it completely, but both these operations greatly diminish resistance to all stressors examined. Thyroidectomy and ovariectomy do not considerably interfere with the thymicolympathic involution and splenic atrophy characteristic of the formalin-induced alarm reaction, nor do they significantly increase mortality.

Ingle, D. J.: "The time for the occurrence of cortico-adrenal hypertrophy in rats during continued work." *Am. J. Physiol.* **124**: 627-630 (1938). 75,145/38

In rats, muscular work elicited by faradic stimulation of the gastrocnemius causes adrenal hypertrophy which is prevented by hypophysectomy and hence is ascribed to stress-induced ACTH secretion.

Leblond, C. P., Segal, G.: "Action de la colchicine sur la surrénale et les organes lymphatiques" (Effect of colchicine on the adrenals and the lymphatic organs). *C.R. Soc. Biol. (Paris)* **128**: 995-996 (1938).

A50,424/38

In rats, colchicine produces extremely severe manifestations of the alarm reaction,

including adrenal enlargement and thymic-lymphatic atrophy. Adrenalectomy suppresses these actions of colchicine.

Hungerford, G. F.: "Effect of epinephrine in decreasing number of circulating mononuclear leucocytes in the rat." *Proc. Soc. Exp. Biol. Med.* **70**: 356-358 (1949).

B31,654/49

EP decreases the number of circulating mononuclear leukocytes in intact or adreno-demedullated rats, but does not do so after complete adrenalectomy and only slightly after hypophysectomy.

Sayers, G., Cheng, C. P.: "Adrenalectomy and pituitary adrenocorticotropic hormone content." *Proc. Soc. Exp. Biol. Med.* **70**: 61-64 (1949). B31,736/49

In rats the ACTH content of the pituitary is reduced by 80 percent twenty-four hours after adrenalectomy. Sham adrenalectomy and scalding cause lesser reductions of pituitary ACTH.

Fritz, I., Levine, R.: "Action of adrenal cortical steroids and nor-epinephrine on vascular responses of adrenalectomized rats" (abstracted). *Am. J. Physiol.* **163**: 713 (1950). B54,186/50

By use of the mesoappendix preparation of the rat, it is shown that vasoconstriction following topical application of NEP is impaired by formaldehyde-induced stress, especially after adrenalectomy, but can be restored by topical application of adrenocortical extract. These and other experiments support the concept that corticoids are necessary for the normal response of small vessels to vasoconstrictors.

Fritz, I., Levine, R.: "Action of adrenal cortical steroids and nor-epinephrine on vascular responses of stress in adrenalectomized rats." *Am. J. Physiol.* **165**: 456-465 (1951). B58,944/51

In adrenalectomized rats the blood vessels of the mesoappendix become refractory to topical application of NEP. Stress induced by formaldehyde given subcutaneously does not impair circulation in the mesoappendix of the normal rat but causes sluggishness of flow, and eventually stasis, prior to death after adrenalectomy. These changes can be prevented by Dibenamine, which also prolongs the survival time after formaldehyde treatment of adrenalectomized rats. Apparently, corticoids are necessary to permit the blood vessels to respond normally to NEP

and, at the same time, protect against toxic amounts of NEP.

Ramey, E. R., Goldstein, M. S., Fritz, I., Levine, R.: "Relation of nor-epinephrine and other autonomic agents to vascular collapse of stressed adrenalectomized animal." *Fed. Proc.* **10**: 108 (1951). B57,125/51

In dogs, adrenalectomy decreases the pressor response to NEP. This cannot be corrected by DOC, but adrenocortical extract largely restores normal responsiveness. Glucocorticoids even act topically in sensitizing small splanchnic vessels to NEP.

Dougherty, T. F., Kumagai, L. F.: "Influence of stress stimuli on lymphatic tissue of adrenalectomized mice." *Endocrinology* **48**: 691-699 (1951). B60,246/51

Mice stressed two hours after adrenalectomy developed a significant lymphocytosis lasting several hours; this was the reverse of the response seen in intact animals. After adrenalectomy the lymphatic organs of mice in sublethal anaphylaxis were actually enlarged. The stress lymphocytosis was not prevented by splenectomy, and hence it could not be ascribed to an evacuation of the splenic reservoir. The findings "are compatible with the concept that the stimulus of stress not only augments pituitary adrenocortical secretion which inhibits lymphatic tissue growth, but also augments directly or indirectly, lymphatic tissue growth promoting influences unrelated to adrenocortical secretion."

Goldstein, M. S., Ramey, E. R., Fritz, I., Levine, R.: "Reversal of effects of stress in adrenalectomized animals by autonomic blocking agents. Use of atropine, Banthine and Dibenamine." *Am. J. Physiol.* **171**: 92-99 (1952). B75,440/52

In adrenalectomized rats, resistance to formalin, hemorrhage, forced muscular exercise and cold was increased by autonomic blocking agents, such as atropine, Banthine, Dibenamine and Thephorin. Apparently, in the absence of corticoids, blockade of autonomic stimuli is beneficial.

Flückiger, E., Verzár, F.: "Überdauern der Adaptation an niedrigen atmosphärischen Druck, nachgewiesen an der Wärmeregulation" (Body temperature regulation indicating retained adaptation under reduced oxygen tension). *Helv. Physiol. Pharmacol. Acta* **11**: 67-72 (1953). B92,392/53

In rats exposed to reduced oxygen tension, the body temperature drops but returns to

normal after three to four days. "This 'retained adaptation' is not dependent on the presence of the adrenals. The phenomenon can also be seen in adrenalectomized rats kept alive with corticoids."

Gerschman, R., Gilbert, D. L., Nye, S. W., Nadig, P. W., Fenn, W. O.: "Role of adrenalectomy and adrenal-cortical hormones in oxygen poisoning." *Am. J. Physiol.* **178**: 346-350 (1954). B97,929/54

In rats, adrenalectomy increases survival after exposure to high oxygen pressure. This increase is counteracted by both adrenocortical extract and EP. Evidently, not all stressors are efficiently combatted by adrenal hormones.

Halász, B.: "Der zeitliche Ablauf von Veränderungen des Kernvolumens in der Nebennierenrinde" (The chronologic development of changes in cell nuclear volume in the adrenal cortex). *Acta Morphol. Acad. Sci. Hung.* **8**: 193-198 (1958).

J13,017/58

In the glomerulosa of the rat adrenal cortex, DOC induces a shrinkage of the nuclei during the first three days, which is followed by a swelling; only after the first week does the characteristic diminution in nuclear size become fully evident and persistent. The fasciculata shows no typical variations. ACTH acts mainly on the fasciculata by causing an initial swelling followed by a shrinkage in nuclear size which after three to five days leads to a persistent and considerable enlargement. Earlier data on the histologic actions induced by DOC and ACTH in the adrenal cortex are reviewed (7 refs.).

Hodges, J. R., Vernikos, J.: "Circulating corticotrophin in normal and adrenalectomized rats after stress." *Acta Endocrinol.* **30**: 188-196 (1959). C63,264/59

In adrenalectomized rats the stress of ether anesthesia caused a rapid rise and fall in the blood level of ACTH, as it did in intact controls. ACTH again became detectable in the blood ten days after adrenalectomy, and then it reached a high that persisted for weeks. The increase in the blood level of ACTH caused by anesthesia in adrenalectomized rats depended upon the resting level of the hormone. "The results support the existence of a dual mechanism regulating the secretion of adrenocorticotropic hormone and also provide evidence that its release can be modified by its resting level in the blood." The initial rapid rise in the secretion of

ACTH in response to stress is presumed to be under neural control, whereas the second, more prolonged phase depends predominantly upon the level of corticoids.

Bonfils, S., Rossi, G., Liefooghe, G., Lambing, A.: "'Ulcère' expérimental de contrainte du rat blanc. I. Méthodes. Fréquence des lésions. Modifications par certains procédés techniques et pharmacodynamiques" (Experimental restraint "ulcer" in the white rat. I. Methods. Frequency of lesions. Modifications by some technical and pharmacodynamic procedures). *Rev. Fr. Etudes Clin. Biol.* **4**: 146-150 (1959). J22,385/59

Description of a modification of Selye's restraint technique for the production of stress ulcers in the rat. Adrenalectomy did not influence, whereas cortisone and vagotomy diminished, the incidence of gastroduodenal ulcers.

Koch, B., Mialhe, C., Stutinsky, F.: "Action de diverses agressions (nervieuses ou humorales) sur l'acide ascorbique d'une autogreffe surrénalienne chez le Rat" (The action of various stressors [nervous or humoral] on the ascorbic acid of an adrenal autograft in the rat). *J. Physiol. (Paris)* **53**: 386-388 (1961). J23,527/61

Schapiro, S.: "Pituitary ACTH and compensatory adrenal hypertrophy in stress non-responsive infant rats." *Endocrinology* **71**: 986-989 (1962). D45,372/62

In newborn rats, adrenal ascorbic acid depletion and corticosterone synthesis fail to occur under the influence of stressors, but unilateral adrenalectomy causes pronounced compensatory hypertrophy of the contralateral gland.

Cope, C. L.: *Adrenal Steroids and Disease*, p. 827. Montreal: J B Lippincott, 1964. E4,976/64

Monograph on the role of corticoids in adaptation and disease, with a special section on the diseases of adaptation.

Hodges, J. R., Jones, M. T.: "Changes in pituitary corticotrophic function in the adrenalectomized rat." *J. Physiol. (Lond.)* **173**: 190-200 (1964). D18,782/64

In rats, adrenalectomy caused a rapid fall followed by a slower rise in pituitary ACTH concentration. The ACTH depletion, but not its subsequent repletion, was prevented by corticosterone. Mild stressors that did not significantly affect plasma ACTH in intact rats considerably raised it after adrenalect-

tomy. The stress-induced ACTH discharge was suppressed by small doses of corticosterone in the adrenalectomized rat, but there was no correlation between plasma corticosterone concentration and the degree of ACTH inhibition.

Porter, J. C., Klaiber, M. S.: "Relationship of input of ACTH to secretion of corticosterone in rats." *Am. J. Physiol.* **207**: 789-792 (1964). F22,653/64

Urquhart, J., Li, C. C.: "The dynamics of adrenocortical secretion." *Am. J. Physiol.* **214**: 73-75 (1968). F92,958/68

In hypophysectomized dogs, cortisol secretion was measured by adding ACTH at different rates to the perfused fluid through their adrenals. "The results with sinusoidal variations in ACTH concentration suggested that an apparent 3-min time constant is dominant in the adrenal response to ACTH. Two dynamic models for the adrenocortical response to ACTH are offered. Both models simulate the experimental results and are systems of conservation equations for known and postulated biochemical intermediates in the coupling between ACTH and cortisol biosynthesis."

Urquhart, J., Li, C. C.: "Dynamic testing and modeling of adrenocortical secretory function." *Ann. N.Y. Acad. Sci.* **156**: 756-778 (1969). H10,877/69

A review of the available literature that lends itself to the construction of models representing the various factors that regulate ACTH secretion and actions. Most of the work was performed on perfused canine adrenal glands subjected to several temporal patterns of stimulation by ACTH. [Such models can incorporate all known factors that influence adrenocortical secretion (chemical composition of the blood, blood flow, nervous stimuli, genetic elements, chronologic sequence of all stimulants, and so on), but of course, *in vivo* the number of modifying circumstances is virtually infinite. Hence, these models must necessarily be restricted to a description of known stimuli and modifying circumstances, the sequence of intermediates in biosynthesis and biodegradation of hormones, and the limited number of other variables which can be established only under highly specific conditions; thus they have little predictive value when compared to data amenable to programming in a computer (H.S.).]

Stear, E. B., Kadish, A. H. (eds.): *Hormonal Control Systems*, p. 304. New York: American Elsevier, 1969. E10,611/69

Proceedings of a symposium on biologic control systems, with contributions by various experts on the regulation of corticoid secretion. Special attempts have been made to develop mathematical models that lend themselves to computer simulation. The principal advantage of such systems is expressed as follows: "Computer simulations (models) of biological systems require that the static and dynamic characteristics of all the pertinent components and processes of the systems be identified and quantitatively specified; computer models are truly functional—they can change state with the flow of time, and therefore they expose the incompleteness of knowledge."

Hiroshige, T., Sakakura, M.: "Circadian rhythm of corticotropin-releasing activity in the hypothalamus of normal and adrenalectomized rats." *Neuroendocrinology* **7**: 25-36 (1971). H36,764/71

In the rat the CRF activity of the hypothalamus shows a definite circadian rhythm, with a peak at 18:00 and a minimum at 08:00, which closely parallels plasma corticosterone levels. The CRF rhythm is not significantly affected by adrenalectomy, and hence it is presumably of neural origin, being independent of the negative corticoid feedback mechanism.

Anitesco, C., Contulesco, A.: "Étude de l'influence du bruit et des vibrations sur le comportement des catécholamines dans l'agression sonore vibratoire industrielle" (Studies on the influence of noise and vibration on the behavior of catecholamines in industrial vibratory acoustic stress). *Arch. Mal. Prof.* **33**: 365-372 (1972). G95,398/72

The appearance of a significantly increased amount of VMA in the urine of a group of eighty subjects after four hours of exposure to noise and vibration in a bus construction factory "is interpreted as the expression of the impairment of the neuroendocrine-humoral ratio, by inciting the ascendant activating system." The depression by tranquilizers of the adrenal function by the diminution of VMA and the 17-KS values during night rest when compared to controls show an insufficiency of endocrine supply.

Guidotti, A., Costa, E.: "Association between increase in cyclic AMP and subsequent induction of tyrosine hydroxylase in

rat adrenal medulla. Experiments with swimming stress." *Nauyn Schmiedebergs Arch. Pharmacol.* **282**: 217-221 (1974).

J12,854/74

cAMP and cGMP (cyclic guanosine monophosphate) were separated from the medulla to determine the relationship between them, because from the literature cited it is clear that the induction of tyrosine hydroxylase activity in the chromaffin cells is preceded by changes in these compounds. When rats are placed in cold water "the swimming stress experiments are in agreement with the view that the enhancement of cAMP/cGMP concentration ratios may function as the second messengers for the induction of tyrosine hydroxylase in adrenal medulla" (12 refs.).

Jefcoate, C. R., Simpson, E. R., Boyd, G. S.: "Spectral properties of rat adrenal-mitochondrial cytochrome P-450." *Eur. J. Biochem.* **42**: 539-551 (1974).

J10,533/74

"A pH-sensitive cholesterol complex of cytochrome P-450_{sec} (side-chain cleavage) was quantitated by means of the pregnenolone difference spectrum. Adrenal mitochondria from 'stressed' rats had about twice as much of this cholesterol complex of cytochrome P-450_{sec} as adrenal mitochondria from rats

kept quiescent." The implication of this upon side-chain cleavage of cholesterol and formation of pregnenolone is discussed.

Ray, P. K., Choudhury, S. R.: "Response of solitary adrenal gland to surgical stress." *Histochem. J.* **7**: 127-137 (1975).

J24,030/75

Histochemical observations of various enzymes showed that trauma produces essentially the same response in intact and unilaterally adrenalectomized rats. However, after this operation the enzymatic responses in the remaining gland are significantly delayed by removal of the contralateral gland. "In experiments using ACTH, the overall pattern of esterase activity shows little deviation from that observed in untreated cases in both groups of animals. The findings indicate that in unilaterally adrenalectomized animals, superadded operative stimuli fail to evoke the early response characteristic of the normal adrenal glands. Such latency points to the vulnerability of their existing defense mechanisms. The remarkable similarity of adrenal response with or without exogenous ACTH in these animals suggests that the reason for a delayed response is rooted in the target organ itself, and is not due to an altered plasma ACTH level."

Epinephrine, Norepinephrine (EP, NEP)

Some of the earliest observations on the role of catecholamines in stress were concerned with their effect upon the nervous system.

In man, EP is not only discharged during stress but causes definite neuropsychologic changes when administered to normal individuals. Among these effects are trembling, crying, salivation, sweating, blushing, pallor, palpitations, moaning, shivering, gastrointestinal spasms and different forms of emotional arousal. The predominance of one or more of these symptoms appears to depend upon individual conditioning factors. Nervous mediation may also play a part in such EP-elicited somatic manifestations as polyuria, diarrhea, hypertension, tachycardia, hyperglycemia and glycosuria.

Recently, considerable work has been done on the effects of catecholamines when discharged from, or injected into, certain parts of the CNS. For details about these reactions, the reader should consult the abstract section.

In rats, swimming to exhaustion in cold water depleted brain NEP and 5-HT, but similar changes were also noted following exposure to a variety of other stressors. It was pointed out that this effect could not depend upon regulation by pituitary activity, since it occurred even after hypophysectomy and after treatment with LSD. However, other investigators reported a depletion of brain catecholamines after electroshock, with restoration within about four hours. In one study, electroshock increased NEP in rats' brains, whereas this was not the case after insulin shock.

In kittens, morphine diminished the NEP content of the brain stem concurrently with the EP store of the adrenals. Both these effects were inhibited by barbiturates. Cold and electroshock also decreased brain NEP in rats; this could be prevented by chlorpromazine, phenobarbital or MAO inhibitors. Differential gradient centrifugation of brain stem homogenates showed that NEP and 5-HT have approximately the same localization in the fraction composed almost entirely of nerve ending particles. Apparently, their release from here during stress is inhibited by MAO inhibitors and sedatives.

In seizure-susceptible mice, convulsive attacks produced by sound diminish the NEP content of the brain, especially in its subcortical layer. MAO inhibitors protect against the lethality of the seizures; these have therefore been ascribed to NEP depletion. However, following repeated exposure, the mice become resistant to the convulsive effect, yet even then their brain NEP drops. Perhaps here death depends upon a particularly rapid catecholamine loss.

In ground squirrels, the turnover of labeled NEP and EP was reduced during hibernation in most tissues, but particularly in the brain.

In guinea pigs, mice and rats, various stressors (fighting, electroshock, restraint, intracranial stimulation with implanted electrodes) decrease brain NEP in the cortex, subcortex, cerebellum, hypothalamus and brain stem to approximately the same degree, without significantly changing the brain 5-HT, GABA or dopamine concentration. Possibly, a decrease in brain NEP reflects intense emotional distress. In rats, hypothermia induced by swimming in cold water reduces brain NEP, but this can be prevented by rapid rewarming.

In rats submitted to the stressor effect of bone fractures, labeled EP localizes in particular cells of the hypothalamus (PVN), which may regulate the endocrine and metabolic changes during stress. However, radioactive EP granules could also be seen in other tissues at different times.

Various stressors enhanced the toxicity of D-amphetamine, perhaps through the release of NEP, but only some of those tested caused a significant increase in amphetamine toxicity and a decrease in brain NEP. Dopamine was not affected by these stimuli, possibly because it is distributed in a different way. NEP is located primarily in the hypothalamus and in other brain stem areas believed to represent central components of the sympathetic nervous system, while dopamine is predominantly situated in the basal ganglia associated with the extrapyramidal system.

During the early 1950s, it was thought that EP discharged from the adrenals was the primary factor in eliciting ACTH secretion during stress. Many of the numerous publications defending this view in spite of all the evidence against it will be found in the abstract section. Contrary to some earlier claims, it has been proven that stress does cause ACTH discharge, even in adrenal-demedullated or adrenalectomized rats, as well as after treatment with adrenergic blocking agents. It is undoubtedly true, however, that very large doses of EP, like any other stressor, can cause an ACTH discharge from the pituitary, and in many respects, corticoids and EP can potentiate each other's actions.

As previously stated, catecholamines may have an important part to play as neurohumoral mediators of the ACTH discharge mechanism in the CNS, but these effects do not depend upon the release of catecholamines by the adrenal medulla or by adrenergic nerve endings. The neurohumoral mediator of ACTH discharge is CRF.

In rats, fluorescence microscopy shows that catecholamines are plentiful in the zona palisadica of the ME. This storage is considerably increased after adrenalectomy and

is diminished by cortisol. Presumably, under conditions of increased CRF discharge, the dopamine and NEP content of the nerve terminals in this area rises, whereas blockade of CRF production is associated with an inverse catecholamine response. These and many other observations suggest that an adrenergic mechanism is involved in CRF release from the ME. However, even this often-confirmed conclusion has not remained uncontradicted. Certain investigators have claimed that reserpine (which depletes catecholamine stores) and α -MT (which blocks catecholamine synthesis) markedly reduce brain NEP and dopamine concentrations, but that plasma corticosterone levels remain unchanged in the rat, both at rest and after exposure to a variety of stressors. These findings allegedly suggest that "brain catecholamines do not play an essential role in stress-induced activation of the pituitary-adrenal system." In fact, some investigators are believed to have furnished evidence for a hypothalamic adrenergic system that inhibits ACTH secretion in the dog.

Microelectrophoresis allows deposition of minute amounts of soluble compounds in the immediate extracellular environment of single cells in the CNS, followed by direct monitoring of local single unit action potentials. This technique made it possible to identify dexamethasone-sensitive cells in the hypothalamus and midbrain, scattered over wide areas. Most of these cells are inhibited but some are activated by the steroid. They are also sensitive to electrophoretically-applied NEP and acetylcholine. The predominant action of the former was inhibition, that of the latter, stimulation.

Forced exercise enhances 5-HT and NEP metabolism in the forebrain and brain stem (especially the mesencephalon and pons-medulla regions) of the rat.

An extensive review of the literature led to the conclusion that there exists an adrenergic system in the brain that inhibits ACTH secretion. NEP, rather than dopamine, is generally considered to be responsible for this "tonic inhibition." Drugs that release active catecholamines from nerve endings inhibit ACTH discharge if they can pass the blood-brain barrier or are injected directly into the third ventricle or ME. Stressors deplete brain NEP and increase ACTH secretion. There is NEP and dopamine in the ME of the dog and rat. The NEP-containing neurons probably originate outside the ventral hypothalamus, since deafferentation of the latter causes virtual disappearance of NEP from the island. Dopamine- and NEP-containing neurons end near or on the portal vessels and hence could enter the portal blood flow and act directly on the pituitary, affecting ACTH secretion.

(The cells in the ME which convert neuronal input to humoral output are considered to be "neuroendocrine transducer cells," since they are neither neurons nor endocrine cells, but convert the nervous message into a hormonal one.)

Contrary to much of the previously mentioned literature, a recent publication states that in rats depletion of brain catecholamines by reserpine or 6-hydroxydopamine did not significantly alter the basal circadian rhythm or the stress-induced rise in plasma corticosterone, and the hypothalamic CRF levels remained virtually unchanged. In addition, more than doubling of brain amine concentrations by a MAO inhibitor also failed to alter these parameters. Hence it was concluded that "brain amines are of relatively little importance in the central regulation of ACTH secretion in the rat."

In rats, hypoxia decreased the NEP but not the 5-HT concentration of the forebrain. After implantation of electrodes into the lateral hypothalamus, self-stimulation rates increased while food and water ingestion decreased during the first twelve hours and subsequently returned to normal. "The results suggest a time-related activation of central adrenergic neuronal systems during exposure to hypoxia."

In rats, intraventricular injections of 6-hydroxydopamine (which does not cross the

blood-brain barrier) caused a lasting depletion of brain catecholamines, without affecting 5-HT or peripheral NEP. This was again unaccompanied by any noteworthy change in plasma or adrenal corticosterone, under ordinary conditions or after exposure to stressors. The suppression of corticoid production by dexamethasone likewise remained unaffected. Hence, it was again concluded that NEP is not involved in regulating pituitary-adrenocortical activity at rest or during stress and feedback inhibition.

The many contradictions in the literature on the effect of stressors upon the catecholamine content of nerve centers are probably due to the use of different experimental animals [species, age, sex] and techniques, and variable time intervals after stimulation when determinations are made.

Epinephrine, Norepinephrine (EP, NEP)

(See also our earlier stress monographs, p. xiii)

Marañon, G.: "Contribution à l'étude de l'action émotive de l'adrénaline" (Contribution to the study of emotive actions of adrenaline). *Rev. Fr. Endocrinol.* **2**: 301-325 (1924). 87,752/24

Description of various emotional responses to EP in man. Depending upon individual variations, these may be characterized predominantly by trembling, crying, salivation, sweating, blushing, pallor, palpitations, moaning, shivering, polyuria, diarrhea, gastrointestinal spasms, hypertension, hyperglycemia, glycosuria and other somatic manifestations.

Landis, C., Hunt, W. A.: "Adrenalin and emotion." *Psychol. Rev.* **39**: 467-485 (1932). 8,333/32

Early observations on the emotional changes produced by EP in some but not in other individuals, depending upon their predisposition.

Cantril, H.: "The roles of the situation and adrenalin in the induction of emotion." *Am. J. Psychol.* **46**: 568-579 (1934). 30,396/34

Review on the psychic and particularly the emotional effects of EP injections in man.

Vogt, M.: "Observations on some conditions affecting the rate of hormone output by the suprarenal cortex." *J. Physiol. (Lond.)* **103**: 317-332 (1944). B897/44

In eviscerated dogs and cats, intravenous infusion of EP causes intense stimulation of corticoid secretion which is allegedly direct and not mediated through the pituitary. [The latter statement is based on observations on a single decapitated dog.] This effect is ob-

tained with physiologic doses of EP and is of the order of several times the normal corticoid output. The action is independent of blood pressure and blood flow.

Long, C. N. H.: "The conditions associated with the secretion of the adrenal cortex." *Fed. Proc.* **6**: 461-471 (1947).

40,532/47

A review of the literature and personal observations on guinea pigs and rats suggest that "the stimulation of the elements of the autonomic nervous system with a concomitant release of epinephrine that occurs under a variety of conditions appears to be a major factor in the activation of the adrenotropic secretion from the anterior lobe" (24 refs.).

Gershberg, H., Fry, E. G., Brobeck, J. R., Long, C. N. H.: "The role of epinephrine in the secretion of the adrenal cortex." *Yale J. Biol. Med.* **23**: 32-51 (1950).

B51,987/50

Experiments on intact, hypophysectomized, and adrenal demedullated rats "seem to show without exception that ACTH is the intermediary of the epinephrine activity, and that the site of action of the epinephrine is the anterior lobe."

McDermott, W. V., Fry, E. G., Brobeck, J. R., Long, C. N. H.: "Mechanism of control of adrenocorticotropic hormone." *Yale J. Biol. Med.* **23**: 52-66 (1950).

B51,980/50

Experiments on rats led to the concept that ACTH discharge during stress occurs in two relatively independent and sequential phases. "The first or autonomic phase depends on the reflex secretion of epinephrine which directly activates the anterior pituitary, while the second or metabolic phase is

based upon the rate of utilization of adrenal cortical hormones within the organism." This once-popular concept (many aspects of which are now outdated) is illustrated in Figure 15.

Hume, D. M., Wittenstein, G. J.: "The relationship of the hypothalamus to pituitary-adrenocortical function." In: Mote, J. R., *Proceedings of the First Clinical ACTH Conference*, pp. 134-147. Philadelphia and Toronto: Blakiston, 1950. B46,961/50

A review of the literature and personal observations on dogs lead the authors to conclude that for ACTH release during stress, an intact hypothalamus is necessary to produce some hormonal material that stimulates the anterior lobe. Following operative trauma, intact nervous connections between

the injured area and the brain are indispensable for an ACTH discharge, although EP released by the splanchnics has a direct effect on the hypothalamic center.

Farrell, G. L., McCann, S. M.: "Detectable amounts of adrenocorticotropic hormone in blood following epinephrine." *Endocrinology* 50: 274-276 (1952).

B69,080/52

In rats, EP causes a particularly rapid and pronounced increase in blood ACTH.

Long, C. N. H.: "The role of epinephrine in the secretion of the adrenal cortex." In: Wolstenholme, G. E. W., *Ciba Foundation Colloquia on Endocrinology*, Vol. 4, pp. 139-147. London: J & A Churchill, 1952.

B76,073/52

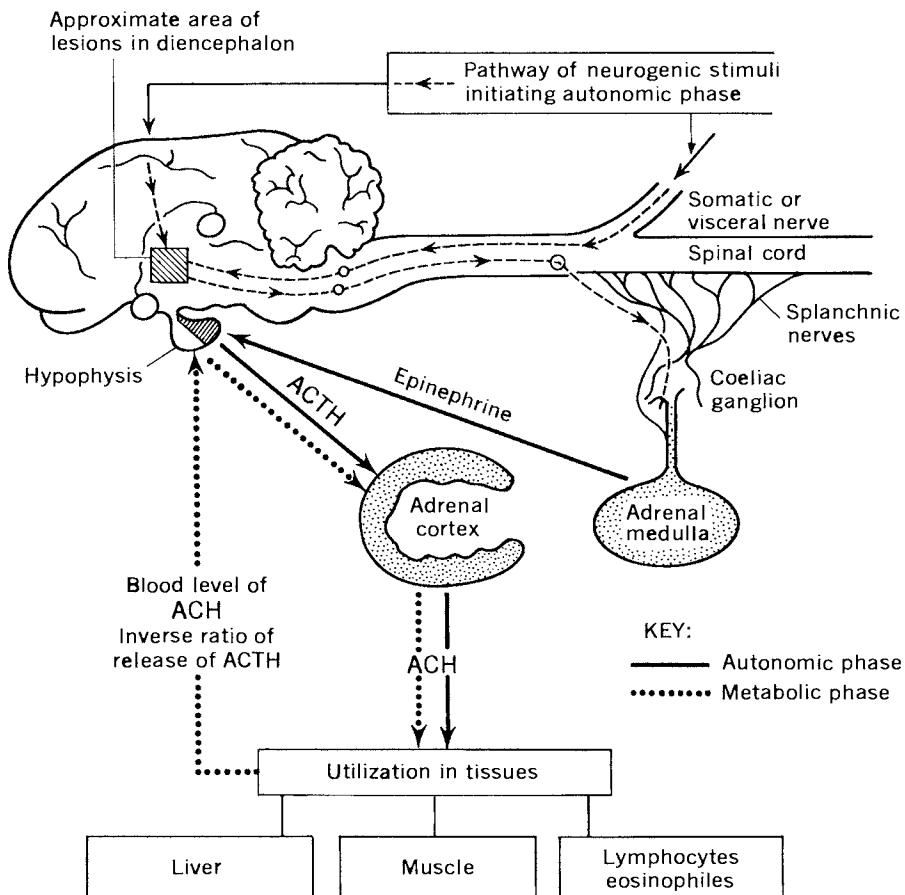


Figure 15. Diagrammatic representation of the proposed mechanism of control of the secretion of adrenal cortical hormones. (Reproduced from *Yale J. Biol. Med.* 23 (1950) by permission of W. V. McDermott *et al.* and Academic Press.)

Vogt, M.: "Plasma adrenaline and release of ACTH in normal and demedullated rats." *J. Physiol. (Lond.)* **118**: 588-594 (1952).
B77,512/52

Long, C. N. H.: "Regulation of ACTH secretion." *Rec. Prog. Horm. Res.* **7**: 75-97 (1952).
B68,650/52

Review of the mechanism of ACTH secretion, which is thought to be regulated partly by the ACTH and corticoid concentration of the blood (feedback) and partly through direct stimulation by EP and sympathetic nervous stimuli (49 refs.).

Gordon, M. L.: "An immediate response of the demedullated adrenal gland to stress." *Endocrinology* **7**: 13-18 (1952).

B48,952/52

The ascorbic acid concentration of the rat adrenal is constant following enucleation, and the gland exhibits normal ascorbic acid depletion after exposure to stress (insulin, histamine, cold). "It is therefore concluded that the adrenal medulla is not essential for the activation of the pituitary gland by stressing agents."

Vogt, M.: "The role of adrenaline in the response of the adrenal cortex to stress of various kinds, including emotional stress." In: Wolstenholme, G. E. W., *Ciba Foundation Colloquia on Endocrinology*, Vol. 4, pp. 154-166. London: J & A Churchill, 1952.

B76,075/52

Demedullation of the adrenals can still produce adrenal ascorbic acid depletion in rats exposed to various stressors.

Wolfson, W. Q.: "Inadequacy of epinephrine as an activator of the pituitary-adrenal system." *J. Clin. Endocrinol. Metab.* **13**: 125-128 (1953).
B77,156/53

Sandberg, A. A., Nelson, D. H., Palmer, J. G., Samuels, L. T., Tyler, F. H.: "The effects of epinephrine on the metabolism of 17-hydroxycorticosteroids in the human." *J. Clin. Endocrinol. Metab.* **13**: 629-647 (1953).
B82,624/53

In hormone metabolic studies on man, "no evidence was obtained that epinephrine stimulates steroid secretion by the adrenal cortex or modifies peripheral utilization of steroids." It is more probable "that epinephrine produces its adrenocortical-like cellular effects through a potentiation of the action of 17-hydroxycorticosteroids rather than through an effect on their secretion by the adrenal gland."

Hodges, J. R.: "The function of adrenaline in the production of pituitary adrenocorticotrophic activity." *J. Endocrinol.* **9**: 342-350 (1953).
B84,713/53

The adrenal ascorbic acid depletion produced by subcutaneous EP in rats was prevented by DOC but only at certain relative dose levels. Surgical trauma caused adrenal ascorbic acid depletion, even in rats with demedullated suprarenals. Here again, DOC inhibited cortical stimulation. Apparently, EP liberation is not an indispensable prerequisite for stress-induced ACTH production.

Swingle, W. W., Maxwell, R., Ben, M., Fedor, E. J., Baker, C., Eisler, M., Barlow, G.: "Epinephrine and resistance of hypophysectomized and adrenalectomized rats to stressor agents." *Am. J. Physiol.* **177**: 1-6 (1954).
B93,484/54

"The 24-hour adrenalectomized rat is extremely sensitive to intravenous infusions of globin and dextran, and reacts to both by an anaphylactoid syndrome terminating fatally in 87-93% of the animals. Prophylactic fore-treatment with cortisone confers adequate protection. The hypophysectomized rat, despite severe atrophy of the cortex, does not exhibit symptoms when similarly infused. However, when the adrenals are removed from such animals they become sensitized and die within a few minutes after infusion. Medullectomized rats lacking adrenal medullae, but with well regenerated cortices are also quite sensitive and most of them succumb when infused. The data indicate that epinephrine, released from the intact medulla by the stress of infusion, is the agent responsible for the surprising resistance shown by these hypophysectomized rats. Confirmation was obtained by markedly increasing resistance of adrenalectomized as well as adrenalectomized-hypophysectomized rats to globin by repeated pre- and postinfusion injections of epinephrine. Apparently the amine antagonizes the toxic action upon the peripheral circulation of some agent (possibly histamine) released from tissue cells by globin and dextran infusion, and thus prevents the anaphylactoid response to these two stressor agents."

Funkenstein, D. H., Meade, L. W.: "Nor-epinephrine-like and epinephrine-like substances and the elevation of blood pressure during acute stress." *J. Nerv. Ment. Dis.* **119**: 380-397 (1954).
C3,733/54

Saffran, M., Schally, A. V.: "The release

of corticotrophin by anterior pituitary tissue in vitro." *Can. J. Biochem.* **33**: 408-415 (1955).

C4,945/55

The release of ACTH by rat adenohypophyseal tissue in vitro was most intensely stimulated by combined application of posterior pituitary tissue and NEP. Either of these agents alone had little or no effect. "The posterior pituitary is probably involved in the response of the anterior pituitary-adrenocortical system to stress."

Roberts, S., Keller, M. R.: "Influence of epinephrine and cortisone on the metabolism of the hypophysis and hypothalamus of the rat." *Endocrinology* **57**: 64-69 (1955).

C6,336/55

Kosman, M. E., Gerard, R. W.: "The effect of adrenaline on a conditioned avoidance response." *J. Comp. Physiol. Psychol.* **48**: 506-508 (1955).

J13,312/55

In rats, EP caused a sharp decrease in the frequency of conditioned avoidance responses and a slight diminution of escape responses. These effects were prevented by phenoxybenzamine.

Euler, U. S. von: *Noradrenaline. Chemistry, Physiology, Pharmacology and Clinical Aspects*, p. 382. Springfield, Ill.: Charles C Thomas, 1956.

C17,899/56

Excellent and extensive monograph on NEP, including discussions of its chemistry, metabolism and release during rest and stress (about 750 refs.).

Kitay, J. I., Holub, D. A., Jailer, J. W.: "Hormonal regulation of pituitary adrenocorticotrophin." *Proc. Soc. Exp. Biol. Med.* **97**: 165-169 (1958).

C47,220/58

As determined by in vitro bioassays, "ACTH administration and adrenalectomy both resulted in a striking increase in pituitary ACTH content. Epinephrine and cortisone administration were both followed by significant depletion of pituitary ACTH."

Egdahl, R. H.: "The differential response of the adrenal cortex and medulla to bacterial endotoxin." *J. Clin. Invest.* **38**: 1120-1125 (1959).

G33,275/59

In dogs, spinal cord transection at C7 abolishes the adrenal medullary discharge by large doses of bacterial endotoxin but leaves febrile, hypotensive and adrenal cortical responses intact. "Epinephrine release is not necessary for the febrile and adrenocortical stimulating effects of endotoxin."

Endrőczi, E., Schreiber, G., Lissák, K.:

"The role of central nervous activating and inhibitory structures in the control of pituitary-adrenocortical function. Effects of intracerebral cholinergic and adrenergic stimulation." *Acta Physiol. Acad. Sci. Hung.* **24**: 211-221 (1963).

G12,029/63

In the cat, pituitary-adrenocortical activation evoked by cholinergic and adrenergic drugs (injected into various areas of the CNS) has been examined. "Carbaminoylcholine and eserine injected into the septum, preoptic region, anterolateral hypothalamus or into the dorsal tegmental area, were found to inhibit pituitary-adrenal activity. Cholinergic chemical stimulation of the medial and caudal hypothalamus, as well as of the posterior hypothalamus and ventral tegmentum resulted in an increase of ACTH secretion. Adrenaline, nor-adrenaline and ephedrine increased ACTH secretion only when injected into the area of the posterior hypothalamus and ventral tegmentum. The suppression of adrenocortical activity in response to the cholinergic stimulation of the inhibitory structures of the forebrain could be blocked by the adrenergic stimulation of the posterior hypothalamus." Apparently, chemical stimulation of the diencephalon and brain stem makes it possible to separate endocrine regulatory activities from complex behavioral reactions.

Paulsen, E. C., Hess, S. M.: "The rate of synthesis of catecholamines following depletion in guinea pig brain and heart." *J. Neuropath. Expt. Neurol.* **10**: 453-459 (1963).

D69,702/63

In guinea pigs, brain catecholamines were restored about four hours after "electroshock stress." This relatively slow rate suggests that the animals sustained an after-effect from the treatment. Data in the literature also indicate that electroshock decreases NEP in the rat brain, as does prolonged swimming in cold water, whereas "insulin stress" allegedly causes no change in the catecholamine content of the brain.

Barchas, J. D., Freedman, D. X.: "Brain amines: response to physiological stress." *Biochem. Pharmacol.* **12**: 1232-1238 (1963).

E29,915/63

In rats, swimming to exhaustion, especially in cold water, caused depletion of brain 5-HT and NEP. Similar changes could not be obtained by having them run in a revolving cage because under the conditions of the experiment the rats soon gave up and just allowed themselves to be dragged. Immersion

of the rats in cold water did reproduce the catecholamine depletion, whereas several other stressors (electroshock, starvation, hypoxia, surgery, adrenalectomy) were inactive in this respect. The effect is not dependent upon the pituitary-adrenocortical system, since active stressors deplete brain catecholamines even after hypophysectomy, as does LSD. It is noteworthy that drugs which induce a similar change in brain amines produce a unique pattern of central excitation, acting on brain mechanisms concerned with metabolic and physiologic temperature regulation. "If the stressors have such a central action, a role for the biogenic amines in central as well as in peripheral aspects of temperature regulation should be sought."

Moore, K. E., Lariviere, E. W.: "Effects of stress and D-amphetamine on rat brain catecholamines." *Biochem. Pharmacol.* **13**: 1098-1100 (1964). G17,075/64

Various stressors increased the toxicity of D-amphetamine, perhaps through the release of NEP. Among the stressors examined (restraint, swimming, electroshock, sound), only some caused a significant increase in amphetamine toxicity and a decrease in brain NEP. In the latter respect, grid-shocked rats were particularly responsive. The depletion of brain NEP by stressors and D-amphetamine might be due to release through excessive stimulation and subsequent destruction at a rate faster than its synthesis. "Dopamine, on the other hand, is not affected by these particular stimuli. This differential depletion of catecholamines in response to various stimuli can perhaps be explained by the fact that they are distributed differently within the brain. Norepinephrine is primarily located in the hypothalamus and other brain stem areas that are believed to represent the central component of the sympathetic nervous system; dopamine is primarily located in the basal ganglia-areas associated with the extrapyramidal system."

Maynert, E. W., Levi, R.: "Stress-induced release of brain norepinephrine and its inhibition by drugs." *J. Pharmacol. Exp. Ther.* **143**: 90-95 (1964). F193/64

In kittens, morphine diminishes the NEP content of the brain stem and the EP store of the adrenal. Both these effects are inhibited by barbiturate anesthesia. Certain stressors (cold, electric shock) likewise decrease brain NEP in rats. Neither brain stem 5-HT nor whole brain acetylcholine is

changed under conditions causing a 40 percent reduction in NEP. After one hour of rest, the NEP is replenished. Sedative doses of chlorpromazine or phenobarbital, unlike strongly depressant amounts of morphine, suppress the release of brain stem NEP in shocked rats. The shock-induced decrease in NEP is also blocked by an MAO inhibitor (Catron).

Levi, R., Maynert, E. W.: "The subcellular localization of brain-stem norepinephrine and 5-hydroxytryptamine in stressed rats." *Biochem. Pharmacol.* **13**: 615-621 (1964).

G11,756/64

Electroshock decreased the total amount of brain stem NEP in unpretreated, but not in phenobarbital-sedated rats; it rose above normal in both shocked and unshocked rats treated with 1-phenyl-2-hydrazinopropane (Catron). The 5-HT concentration was altered only after treatment with Catron. Differential, gradient-density centrifugation of brain stem homogenates showed that NEP and 5-HT have approximately the same localization, about 25 percent being found in the fraction composed almost entirely of nerve ending particles. "It is suggested that in animals treated with sedatives or monoamine oxidase inhibitors the brain-stem NEP, ordinarily released by stress, fails to leave the nerve endings."

Rosecrans, J. A., Feo, J. J. de: "The interrelationships between chronic restraint stress and reserpine sedation." *Arch. Int. Pharmacodyn. Ther.* **157**: 487-497 (1965).

F54,866/65

In rats, stress by restraint initially increased the 5-HT and decreased the NEP content of the brain. "Reserpinized stress animals were more easily handled at first, but became more excitable and difficult to handle as the experiment progressed." This change appeared to correlate with the continued depletion of brain NEP because the brain 5-HT remained approximately constant. The possible protective effect of reserpine is considered in connection with the G.A.S.

Lehmann, A.: "Action de crises répétées d'épilepsie acoustique sur le taux de noradrénaline des zones corticales et sous-corticales du cerveau de souris" (Effects of repeated acoustic epileptic seizures on noradrenaline levels of the cortical and subcortical zones of the brain in mice.) *C.R. Soc. Biol. (Paris)* **159**: 62-64 (1965). F44,990/65

In seizure-susceptible mice, repeated expo-

sure to sound produces eventually fatal convulsive attacks. Mortality is increased by reserpine but is decreased by MAO inhibitors. Audiogenic seizures, especially if they are lethal, greatly diminish the NEP content of the brain, particularly in its subcortical layer. In conjunction with the observation that MAO inhibitors protect, it may be assumed that NEP depletion is the cause of lethality in audiogenic seizures. However, oft-repeated exposure to sound elicits convulsions of diminishing intensity and eventually complete insensitivity ensues. Yet even in these resistant animals, the brain NEP concentration is low. Perhaps lethality depends upon a particularly rapid catecholamine loss.

Akmayev, I. G., Donáth, T.: "Die Katecholamine der Zona palisadica der Eminentia mediana des Hypothalamus bei Adrenalektomie, Hydrocortisonverabreichung und Stress" (Catecholamines in the zona palisadica of the hypothalamic median eminence after adrenalectomy, hydrocortisone administration, and stress). *Z. Mikrosk. Anat. Forsch.* **74**: 83-91 (1965). G37,707/65

In rats, fluorescence microscopy indicates that catecholamines are plentiful in the zona palisadica of the ME. This storage is considerably increased after adrenalectomy and is diminished by cortisol. Presumably, under conditions of enhanced CRF production, the dopamine and NEP content of the nerve terminals rises in this region, whereas blockade of CRF production is associated with an inverse catecholamine response.

Draskoczy, P. R., Lyman, C. P.: "Turnover of catecholamines (CA) during hibernation." *Pharmacologist* **7**: 167 (1965).

J8,151/65

In ground squirrels the turnover rate of labeled NEP and EP during hibernation was greatly reduced in most tissues, particularly in the brain.

Matsui, T., Kobayashi, H.: "Histochemical demonstration of monoamine oxidase in the hypothalamo-hypophysial system of the tree sparrow and the rat." *Z. Zellforsch.* **68**: 172-182 (1965). G35,199/65

In the rat and sparrow the distribution of MAO activity in the ME was essentially similar: "(1) slight or no MAO activity was observed in the ependymal layer, (2) relatively strong activity was revealed in the tissue just beneath the ependymal layer, (3) strong activity was revealed in the outer layer, particularly in the tissues surrounding capillary

loops of the primary plexus. It is suggested that an adrenergic mechanism functions in the median eminence."

Cantril, H., Hunt, W. A.: "Emotional effects produced by the injection of adrenalin." *Am. J. Psychol.* **44**: 300-307 (1966). J13,317/66

Summary of clinical data concerning the various pleasant or unpleasant emotional responses to EP injections in different people.

Bliss, E. L., Zwanziger, J.: "Brain amines and emotional stress." *J. Psychiatr. Res.* **4**: 189-198 (1966). G43,710/66

In guinea pigs, mice and rats in which emotional stress was produced by combat, electric shocks, immobilization, or intracranial stimulation via implanted electrodes, brain NEP decreased in the cortex, subcortex, cerebellum, hypothalamus and brain stem to approximately the same degree. Under these circumstances, the brain concentration of 5-HT, GABA and dopamine remained stable. It appears that decreases of brain NEP may reflect intense emotional distress (22 refs.).

Gordon, R., Spector, S., Sjoerdsma, A., Udenfriend, S.: "Increased synthesis of norepinephrine and epinephrine in the intact rat during exercise and exposure to cold." *J. Pharmacol. Exp. Ther.* **153**: 440-447 (1966).

F70,167/66

In rats, exercise or cold caused little if any change in the NEP content of the brain, heart and spleen. Appreciable decreases were noted only in adrenal EP following severe exercise. However, after treatment with the tyrosine hydroxylase inhibitor α -MT prior to exercise or exposure to cold, NEP and EP levels fell markedly in most tissues, and incorporation of radiotyrosine into the catecholamines was enhanced after exercise. "These findings indicate that the increased sympathetic stimulation, presumably associated with such stressful conditions, induces increased synthesis of norepinephrine levels and epinephrine. The regulatory mechanism most likely operates at the tyrosine hydroxylase step, which is rate-limiting."

Ordy, J. M., Samorajski, T., Schroeder, D.: "Concurrent changes in hypothalamic and cardiac catecholamine levels after anesthetics, tranquilizers and stress in a subhuman primate." *J. Pharmacol. Exp. Ther.* **152**: 445-457 (1966). F67,727/66

In squirrel monkeys, various stressors cause a concurrent depletion of hypothalamic

and cardiac NEP. Pretreatment with chlorpromazine or haloperidol inhibits both these effects.

Ruther, E., Ackenheil, M., Matussek, N.: "Beitrag zum Noradrenalin- und Serotonin-Stoffwechsel im Rattenhirn nach Stress-Zuständen" (Contribution to norepinephrine and serotonin metabolism in the rat brain following stress conditions). *Arzneim. Forsch.* **16**: 261-263 (1966). F63,682/66

Euler, U. S. von: "Adrenal medullary secretion and its neural control." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 283-333. New York and London: Academic Press, 1967. E6,914/67

Monograph on the physiology of catecholamines, with special reference to the control of their release by the nervous system, beginning with the "*piqûre diabétique*" of Claude Bernard (nineteenth century) and the work of Karplus and Kreidl (1909). The

importance of the hypothalamus as a center for EP secretion has been the subject of innumerable investigations, especially after accurate quantitative techniques were developed for the measurement of EP and NEP in blood, urine and tissues. The exact determination of the pathways that terminate in the splanchnic nerves that stimulate the secretory activity of the adrenal medulla is complex, because stimulation of widely different parts of the CNS, including the cerebral cortex, hypothalamus and midbrain, can produce catecholamine discharges. Furthermore, stimulation of some regions enhances, while that of others inhibits, catecholamine release, and the central regulation of EP and NEP is selectively influenced by distinct regions, as summarized in Figure 16. Special sections are devoted to the morphology of the adrenal medulla in various species, including subcellular storage particles, chemistry and biosynthesis, and to the principal peripheral

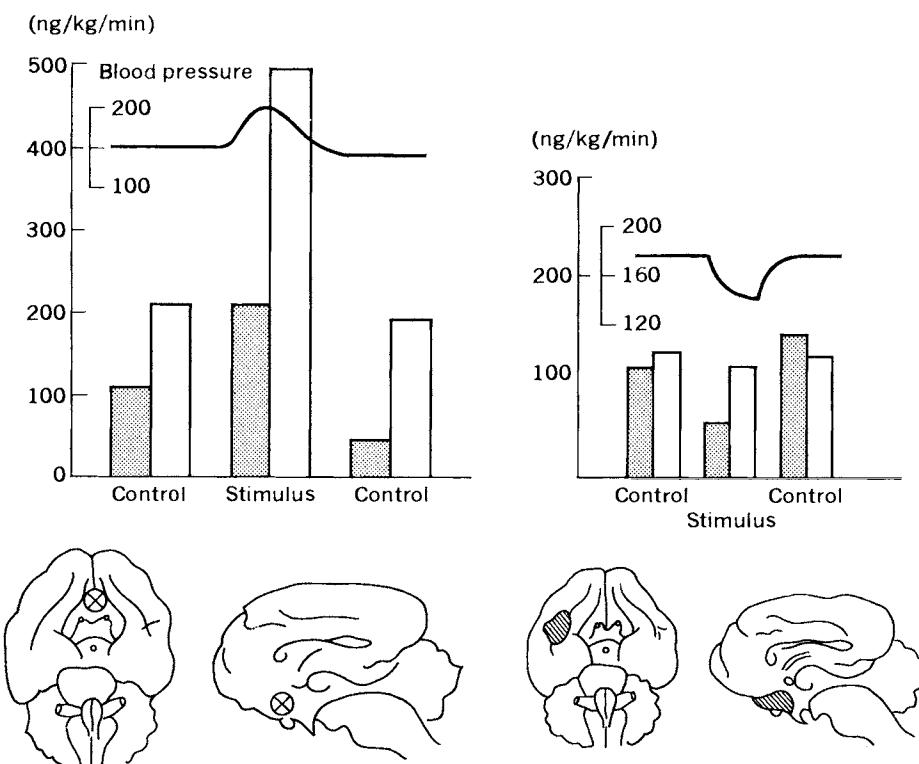


Figure 16. Secretion from left suprarenal gland in the cat before, during and after stimulation of the medial orbital cortex (left) and lateral orbital cortex (right) as indicated on the figure. Darkened columns, epinephrine; plain columns, norepinephrine. (Reproduced from *Neuroendocrinology* 2 (1967) by permission of U. S. von Euler and Academic Press.)

actions of catecholamines when the subject is at rest and during stress (several hundred refs.).

Smelik, P. G.: "ACTH secretion after depletion of hypothalamic monoamines by reserpine implants." *Neuroendocrinology* **2**: 247-254 (1967). F90,175/67

In rats, implantation of reserpine into the hypothalamus reduced the regional 5-HT and catecholamine content. Despite the depletion of hypothalamic monoamines, subsequent systemic treatment with reserpine, chlorpromazine, vasopressin, and emotional or traumatic stress caused the usual hypersecretion of ACTH. Presumably, "under these experimental conditions, there is no indication that monoamines present in the hypothalamus are involved in the control of pituitary ACTH secretion."

Ganong, W. F., Lorenzen, L.: "Brain neurohumors and endocrine function." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 583-640. New York and London: Academic Press, 1967. E6,920/67

Extensive review on neurohormones, particularly catecholamines, 5-HT, acetylcholine, histamine, substance P, γ -aminobutyric acid, and dopamine (about 250 refs.).

Carr, L. A., Moore, K. E.: "Effects of reserpine and α -methyltyrosine on brain catecholamines and the pituitary-adrenal response to stress." *Neuroendocrinology* **3**: 285-302 (1968). H3,332/68

In rats given reserpine (which depletes catecholamine stores) or α -MT (which blocks catecholamine synthesis), the brain content of NEP and dopamine was markedly reduced, but plasma corticosterone levels were essentially unchanged at rest as well as after treatment with stressors (ether, histamine, formalin, restraint, changes in environment). "The results suggest that brain catecholamines do not play an essential role in stress-induced activation of the pituitary-adrenal system."

Welch, B. L., Welch, A. S.: "Differential activation by restraint stress of a mechanism to conserve brain catecholamines and serotonin in mice differing in excitability." *Nature* **218**: 575-577 (1968). F98,490/68

Bliss, E. L., Ailion, J., Zwanziger, J.: "Metabolism of norepinephrine, serotonin and dopamine in rat brain with stress." *J. Pharmacol. Exp. Ther.* **164**: 122-134 (1968). H4,230/68

"The stress of foot shock in rats induces large decreases in the level of brain norepinephrine but does not greatly alter the concentration of serotonin or dopamine in brain."

Euler, U. S. von: "Some aspects of the mechanisms involved in adrenergic neurotransmission." *Perspect. Biol. Med.* **12**: 79-94 (1968) (68 refs.). H5,081/68

Nielson, H. C., Fleming, R. M.: "Effects of electroconvulsive shock and prior stress on brain amine levels." *Exp. Neurol.* **20**: 21-30 (1968). G54,821/68

Thierry, A.-M., Javoy, F., Glowinski, J., Kety, S. S.: "Effects of stress on the metabolism of norepinephrine, dopamine and serotonin in the central nervous system of the rat. I. Modifications of norepinephrine turnover." *J. Pharmacol. Exp. Ther.* **163**: 163-171 (1968). H2,261/68

By use of radioactive NEP, 5-HT and dopamine, it was found that stress (electroshock) did not significantly influence the endogenous level of NEP but markedly raised its turnover in NEP-containing neurons of the brain stem-mesencephalon and spinal cord. "This stress increased the synthesis of 5HT in the brainstem-mesencephalon as seen by the greater increase of endogenous 5HT after monoamine oxidase inhibition but did not affect the disappearance of intracisternally administered H³-5HT. Changes in NE turnover regulation induced by electric foot shocks were studied in various conditions. There was an enhanced turnover of NE in the brainstem-mesencephalon when higher intensities of stimulation were used; this was associated with an increased accumulation of H³-normetanephrine; no modification was seen when the frequency of stimulation was increased. NE turnover during an acute stress session was enhanced to a greater degree when rats were previously subjected to many stress sessions. The initial accumulation of H³-NE in the brainstem-mesencephalon was decreased just after an acute stress and increased 24 hr after the last electric shock stress session of a chronic stress treatment."

Scapagnini, U., Preziosi, P., Schaefferdryver, A. de: "Influence of restraint stress, corticosterone and betamethasone on brain amine levels." *Pharmacol. Res. Commun.* **1**: 63-69 (1969). G80,096/69

In rats, the changes in brain 5-HT, dopamine and NEP provoked by restraint do not

seem to result from the negative feedback effect of endogenous corticosterone.

Bliss, E. L., Ailion, J.: "Response of neurogenic amines to aggregation and strangers." *J. Pharmacol. Exp. Ther.* **168**: 258-263 (1969).

H15,845/69

Aggregation of mice unaccustomed to each other caused a decrease in brain NEP and an acceleration of its catabolism. 5-HT levels remained unchanged, although 5-HIAA concentrations in the brain rose, indicating an increased catabolism of 5-HT. "Dopamine levels in brain and its catabolism were unaffected. At the same time no changes in norepinephrine metabolism could be detected in the adrenal, heart or spleen. The intermingling of strangers without aggregation also decreased brain norepinephrine. A more severe stress of footshock to rats not only diminished brain norepinephrine but also radically reduced catecholamine levels in the adrenal and spleen. These observations suggest that emotional disturbances activate the norepinephrine and serotonin systems in brain."

Rosecrans, J. A.: "Brain amine changes in stressed and normal rats pretreated with various drugs." *Arch. Int. Pharmacodyn. Ther.* **180**: 460-470 (1969).

H18,475/69

In rats exposed to the stressor effect of vibration, 5-HT and NEP concentrations were determined in various areas of the brain. Apparently, NEP neurons were stimulated while the 5-HT systems were depressed. The latter, however, "were activated if this amine was depleted prior to stress, indicating the presence of a 5-HT negative feedback system. Lastly, there were differences observed in brain area responsiveness to stress, indicating the existence of different neuronal populations in the areas studied."

Fuxe, K., Hökfelt, T.: "Catecholamines in the hypothalamus and the pituitary gland." In: Ganong, W. F. and Martini, L., *Frontiers in Neuroendocrinology*, pp. 47-96. New York, London and Toronto: Oxford University Press, 1969.

E10,613/69

Fluorescence microscopy studies of noradrenergic and dopaminergic afferents in the ME as influenced by stress.

Loon, G. R. van, Hilger, L., Cohen, R., Ganong, W. F.: "Evidence for a hypothalamic adrenergic system that inhibits ACTH secretion in the dog." *Fed. Proc.* **28**: 438 (1969).

H9,633/69

Steiner, F. A., Ruf, K., Akert, K.: "Steroid-sensitive neurones in rat brain: anatomical localization and responses to neurohumours and ACTH." *Brain Res.* **12**: 74-85 (1969).

H28,002/69

Microelectrophoresis allows deposition of minute amounts of soluble compounds in the immediate extracellular environment of single cells in the CNS and permits direct monitoring of the local response by recording single unit action potentials. In rats, it has been shown with this technique that dexamethasone-sensitive cells can be identified accurately and localized in the hypothalamus and midbrain, scattered over wide areas. The large majority of these cells are clearly inhibited, but some are activated. No steroid-sensitive neurons were found in the cortex, dorsal hypothalamus or thalamus. The steroid-sensitive neurons were responsive to microelectrophoretically applied NEP and acetylcholine. The predominant action of the former was inhibition, that of the latter was stimulation. ACTH activated the steroid-sensitive neurons. Presumably, "specific nerve cells in the hypothalamus and midbrain are sensitive to both hormonal and humoral factors and involved in negative and positive feedback actions of the hormones."

Schaepdryver, A. de, Preziosi, P., Scapagnini, U.: "Brain monoamines and adrenocortical activation." *Br. J. Pharmacol.* **35**: 460-467 (1969).

G65,782/69

No strict correlation was found between depletion of brain monoamine stores by various drugs and corticoid secretion in rats. Restraint increased brain 5-HT and greatly stimulated corticosterone discharge. "Brain amine content does not seem to play an important part in the control of corticotrophin releasing factor in corticotrophin secretion by the pituitary gland. The relationship between hypothalamic monamines and other neurohumours is discussed."

Glowinski, J.: "Metabolism of catecholamines in the central nervous system and correlation with hypothalamic functions." In: Martini, L., Motta, M. et al., *The Hypothalamus*, pp. 139-152. New York and London: Academic Press, 1970.

J12,266/70

Within a review on catecholamine metabolism in the CNS, a small section is devoted to the literature, which suggests that noradrenergic and serotonergic neurons may

play a role in stress, especially in connection with the release of ACTH.

Stone, E. A.: "Behavioral and neurochemical effects of acute swim stress are due to hypothermia." *Life Sci. [I]* **9**: 877-888 (1970). G77,276/70

In rats, forced swimming at 15°C causes hypothermia, inactivity and reduction of brain NEP. These changes can be prevented by rapid rewarming or by swimming in 37°C water.

Sparber, S. B.: "Stress-induced increases in catecholamines in the brain of the young chick." *J. Pharm. Pharmacol.* **22**: 880 (1970). H32,080/70

Blaszkowski, T. P., Feo, J. J. de, Guarino, A. M.: "Central vs. peripheral catecholamines in rats during adaptation to chronic restraint stress." *Pharmacology* **4**: 321-333 (1970). H36,516/70

Reserpine pretreatment increases the mortality of rats exposed to the stress of restraint, presumably because of its central rather than peripheral NEP-depleting action.

Thierry, A.-M., Blanc, G., Glowinski, J.: "Preferential utilization of newly synthesized norepinephrine in the brain stem of stressed rats." *Eur. J. Pharmacol.* **10**: 139-142 (1970). H24,015/70

Thierry, A.-M., Blanc, G., Glowinski, J.: "Effect of stress on the disposition of catecholamines localized in various intraneuronal storage forms in the brain stem of the rat." *J. Neurochem.* **18**: 449-461 (1971). G82,745/71

Corrodi, H., Fuxe, K., Lidbrink, P., Olson, L.: "Minor tranquilizers, stress and central catecholamine neurons." *Brain Res.* **29**: 1-16 (1971). G85,849/71

Chlordiazepoxide, diazepam and nitrazepam blocked the stress-induced stimulation of NEP neurons by decreasing their nervous activity. Chlordiazepoxide and diazepam potentiated the stress (restraint)-induced fall in nervous activity in ascending dopaminergic neurons. Stress combined with these drugs therefore decreased dopamine turnover in the telencephalon in comparison with normal rats (67 refs.).

Huttunen, M. O.: "Persistent alteration of turnover of brain noradrenaline in the offspring of rats subjected to stress during pregnancy." *Nature* **230**: 53-55 (1971). H36,187/71

Shaliapina, V. G., Rakitskaia, V. V.: "Central monoaminergic structures and their role in regulation of stress reactions." *Probl. Endokrinol. (Mosk.)* **17** No. 2: 107-114 (1971) (Russian). H39,411/71

Review on monoaminergic structures in the CNS and their role in the regulation of stress reactions.

Scapagnini, U., Loon, G. R. van, Moberg, G. P., Preziosi, P., Ganong, W. F.: "Evidence for a central adrenergic inhibition of ACTH secretion in rat." *Naunyn Schmiedebergs Arch. Pharmacol.* **269**: 408-409 (1971). G83,796/71

Brief abstract of experiments with dopa, α -MT, guanethidine and FLA-63 that induced alterations in hypothalamic NEP, supporting the idea of a central adrenergic mechanism inhibiting ACTH secretion, and suggesting that NEP rather than dopamine is responsible for such "tonic inhibition."

Loon, G. R. van, Scapagnini, U., Moberg, G. P., Ganong, W. F.: "Evidence for central adrenergic neural inhibition of ACTH secretion in the rat." *Endocrinology* **89**: 1464-1469 (1971). H49,479/71

"A significant negative correlation was found between plasma corticosterone and hypothalamic contents of norepinephrine and dopamine after administration of α -MT and L-dopa. The administration into the third ventricle of the brain of a systemically ineffective dose of α -MT increased plasma corticosterone 9 hr. later. These data support our hypothesis of central adrenergic neural inhibition of ACTH secretion in rats."

Loon, G. R. van, Hilger, L., King, A. B., Boryczka, A. T., Ganong, W. F.: "Inhibitory effect of L-dihydroxyphenylalanine on the adrenal venous 17-hydroxycorticosteroid response to surgical stress in dogs." *Endocrinology* **88**: 1404-1414 (1971). H39,650/71

In dogs the adrenal venous 17-OHCS elevation after surgical stress was suppressed by L-dopa but not by NEP or intravenous dopamine. "The minimum effective dose of L-dopa that inhibited the 17-OHCS response to stress was decreased by the monoamine oxidase inhibitor, pargyline, and increased by the catecholamine synthesis inhibitor, α -methyl-p-tyrosine. These data support the hypothesis of a central adrenergic neural system which inhibits ACTH secretion in dogs" (42 refs.).

Stone, E. A.: "Hypothalamic norepineph-

rine after acute stress." *Brain. Res.* **35**: 260-263 (1971). H65,343/71

Loon, G. R. van, Scapagnini, U., Cohen, R., Ganong, W. F.: "Effect of intraventricular administration of adrenergic drugs on the adrenal venous 17-hydroxycorticosteroid response to surgical stress in the dog." *Neuroendocrinology* **8**: 257-272 (1971).

H48,631/71

In dogs, intraventricular administration of several adrenergic drugs suppresses 17-OHCS secretion in response to laparotomy. The same is true of the catecholamine precursor L-dopa and the MAO inhibitor α -ethyltryptamine. On the other hand, tyramine (which releases catecholamines from nerve endings) blocks the 17-OHCS response when given intraventricularly, but not when given systemically. "These data support our previously presented hypothesis that a central adrenergic neural system inhibits ACTH secretion in dogs."

Kirshner, N., Viveros, O. H.: "The secretory cycle in the adrenal medulla." *Pharmacol. Rev.* **24**: 385-398 (1972).

G92,827/72

Review on the synthesis, storage, release and recovery of catecholamines, initiated by acetylcholine at the splanchnic-adrenal-medullary synapses (73 refs.).

Elo, H., Tirri, R.: "Effect of forced motility on the noradrenaline and 5-hydroxytryptamine metabolism in different parts of the rat brain." *Psychopharmacologia* **26**: 195-200 (1972). G93,807/72

Forced motility in a treadmill enhances 5-HT metabolism in the rat forebrain within one hour; this is followed by an increase in the brain stem, especially the mesencephalon-pons-medulla regions. The changes almost disappear after fifty minutes of rest. NEP metabolism is also increased under similar conditions in the rat brain stem.

Ohara, K., Isobe, Y., Sato, H.: "Heat tolerance and catecholamine content in the hypothalamus of the rat." *J. Physiol. Soc. Jap.* **34**: 549-550 (1972). H79,325/72

In rats, exposure to heat caused an initial elevation of NEP with a decrease in dopamine in the hypothalamus, interpreted as "an alarm reaction against heat stress," presumably necessary for adaptation to high ambient temperatures.

Scapagnini, U., Preziosi, P.: "Role of brain norepinephrine and serotonin in the

tonic and phasic regulation of hypothalamic hypophyseal adrenal axis." *Arch. Int. Pharmacodyn. Ther.* **196** Supp: 205-220 (1972). H56,654/72

Résumé of the literature and the extensive experiments of the authors and their co-workers led to the following main conclusions: (1) there is an adrenergic system in the brain that inhibits ACTH secretion. Drugs that release active catecholamines from nerve endings block ACTH discharge if they can pass the blood-brain barrier or are injected directly into the third ventricle or ME. Stressors deplete brain NEP and increase ACTH secretion. Admittedly, the amount of drugs necessary for inhibition is large compared to the normal catecholamine levels present in the brain, and hence their action is of doubtful physiologic significance. They may act merely by constricting the portal vessels so that CRF cannot reach an adequate concentration in the adenohypophysis. Among the drugs used to explore the ACTH inhibitory adrenergic mechanism were: amphetamine, α -ethyltryptamine, L-dopa, tyramine, α -MT, guanethidine, FLA-63 (an inhibitor of dopamine- β -oxidase), L-threo-dihydroxy-phenyl-serine (DOPS), which selectively repletes NEP after depletion of NEP and dopamine by α -MT, phentolamine (an α -blocking agent) and so on. (2) 5-HT appears to regulate the circadian variations of ACTH secretion by the limbic system. Its concentration is especially large in the raphé nuclei (containing the highest level of serotonergic cell bodies), particularly the amygdala and hippocampus, in which it shows circadian variations. Destruction of these nuclei abolishes the circadian plasma corticosterone rhythm.

Ganong, W. F.: "Evidence for a central noradrenergic system that inhibits ACTH secretion." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 254-266. Basel and New York: S Karger, 1972.

E10,568/72

Observations in the dog and rat suggest the existence of a central noradrenergic system that inhibits ACTH secretion. There is NEP, as well as dopamine, in the ME. The NEP-containing neurons probably originate outside the ventral hypothalamus, since deafferentation of the latter causes virtual disappearance of NEP from the island. Dopamine- and NEP-containing neurons end near or on the portal vessels, and hence they could

enter the portal blood and act directly on the pituitary affecting ACTH secretion.

Thierry, A.-M.: "Effect of stress on various characteristics of norepinephrine metabolism in central noradrenergic neurons." *Adv. Exp. Med. Biol.* **33**: 501-508 (1972).

J23,806/72

Lidbrink, P., Corrodi, H., Fuxé, K., Olson, L.: "Barbiturates and meprobamate: decreases in catecholamine turnover of central dopamine and noradrenaline neuronal systems and the influence of immobilization stress." *Brain Res.* **45**: 507-524 (1972).

G95,413/72

Bendikov, É. A., Basaeva, A. I.: "The use of DOPA in replacement therapy in disturbances of circulatory regulation during stress." *Biull. Éksp. Biol. Med.* **76** No. 12: 36-39 (1973). Engl. trans.: *Bull. Exp. Biol. Med.* **76**: 1414-1416 (1973). J20,146/73

In cats, stress produced by injection of potassium chloride into the lateral ventricles caused depletion of NEP in the hypothalamus, with inhibition of sympathetic vaso-motor tone. These changes could be corrected by injection of DOPA.

Lee, C.-H., Morita, A., Saito, H., Takagi, K.: "Changes in catecholamine levels of mouse brain during oscillation-stress." *Chem. Pharm. Bull. (Tokyo)* **21**: 2768-2770 (1973). J24,138/73

In mice subjected to vibration for two hours, the NEP levels of the brain decreased considerably. These observations are in disagreement with earlier findings, according to which stress decreases the level of brain NEP unless resynthesis is simultaneously blocked.

Korf, J., Aghajanian, G. K., Roth, R. H.: "Increased turnover of norepinephrine in the rat cerebral cortex during stress: role of the locus coeruleus." *Neuropharmacology* **12**: 933-938 (1973). J21,582/73

"The noradrenergic nerve terminals in the rat cerebral cortex are mainly supplied by norepinephrine-containing neurones originating in the locus coeruleus." Stress increases the turnover of NEP in this location. Apparently, "the locus coeruleus plays an important role in mediating the effect of stress on the metabolism of norepinephrine in the cerebral cortex."

Smith, A. D.: "Mechanisms involved in the release of noradrenaline from sympathetic nerves." *Br. Med. Bull.* **29**: 123-129 (1973). J2,975/73

Review of the mechanisms responsible for

NEP release from sympathetic nerve endings in vivo and in vitro, with special reference to the underlying biochemical and ultrastructural phenomena. The possible events during stimulus-secretion coupling are summarized in Figure 17 (p. 1072), a diagram of the life history of noradrenergic vesicles (based on Figure 15 of Smith & Winkler, 1972).

Pletscher, A., Prada, M. da, Steffen, H., Berneis, K. H., Lütold, B.: "Evidence of two mechanisms for the storage of catecholamines in adrenal chromaffin granules." *Life Sci.* **13**: cxxix-cxxx (1973). J6,310/73

Observations on isolated membranes of bovine chromaffin granules revealed two mechanisms of catecholamine storage. "At the level of the granular membrane the amines are pumped into the organelles by an ATP/Mg⁺⁺-dependent process. Within the organelles, the amines interact with ATP and possibly chromogranins, whereby the diffusion of the amines out of the granules is reduced. This enables the amine pump to maintain the very high concentration gradient found in vivo. On the other hand, the loose bonding of the intragranular amines warrants the reversibility of the storage process enabling the amines to be rapidly liberated, e.g. during the release process."

Kvetnansky, R.: "Neural and endocrine regulation of adrenal catecholamine biosynthesis in stress." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 55-66. Bratislava: Slovak Academy of Sciences, 1973. E10,457/73

In rats adapted to the stress of restraint, adrenal medullary enzymatic biosynthesis of catecholamines was increased under the influence both of corticoids and nervous stimulation (12 refs.).

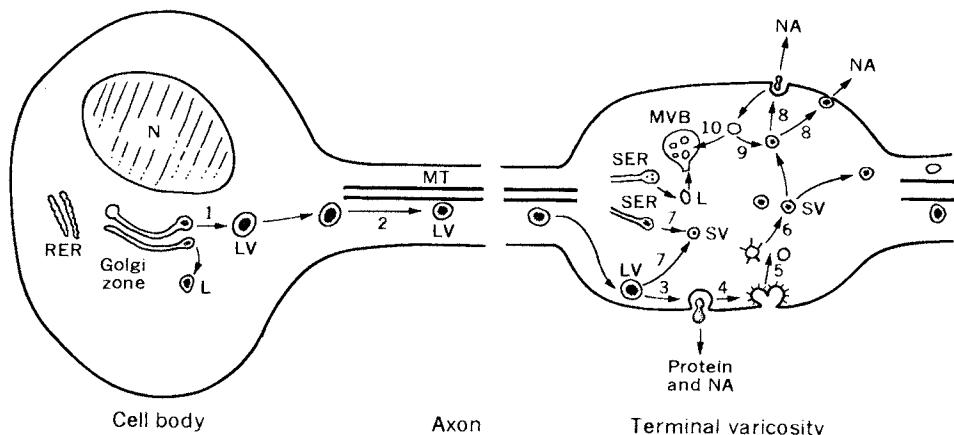
Terry, E. N., Clauss, R. H., Rouen, L. R., Redisch, W.: "Catecholamines and vasomotion." *Cor Vasa* **15**: 222-234 (1973). J9,746/73

Extensive review on the role of catecholamines in stress reactions (50 refs.).

Iversen, L. L.: "Catecholamine uptake processes." *Br. Med. Bull.* **29**: 130-135 (1973). J2,976/73

Detailed description of four mechanisms of neuronal and extraneuronal catecholamine uptake which affect the metabolism, inactivation and pharmacologic actions of these substances.

Anokhina, I. P., Zabrodin, G. D., Svirino-

**KEY:**

L: primary lysosome; LV: large noradrenergic vesicle; MT: microtubule; MVB: multivesicular body; N: nucleus; RER: rough endoplasmic reticulum; SER: smooth endoplasmic reticulum; SV: small noradrenergic vesicle

- 1: large noradrenergic vesicles originate from the Golgi apparatus
- 2: large vesicles are transported along the axon by a process involving microtubules
- 3: large vesicles secrete proteins and NA by exocytosis
- 4: membrane of large vesicle is converted into small coated pits
- 5: coated pits bud from plasma membrane to give coated vesicles which become electron-lucent small vesicles
- 6: electron-lucent small vesicles take up or synthesize NA and become small noradrenergic vesicles
- 7: alternative possible modes of formation of small vesicles—either by budding from SER or by fission of intact large vesicle
- 8: small vesicles release their content either by exocytosis or by forming a tight junction with plasma membrane
- 9: empty small vesicles are re-charged with NA
- 10: empty small vesicles are ultimately digested in multivesicular bodies

Figure 17. Possible events in the life-history of noradrenergic vesicles (based on Fig. 15 of Smith and Winkler, 1972). (Reproduced from *Brit. Med. Bull.* 29 (1973) by permission.)

vskii, I. E.: "Neurochemical mechanisms of formation of psychopathologic conditions due to emotional stress." *Zh. Nevropatol. Psichiatr.* 73 No. 12: 1825-1833 (1973) (Russian). J16,960/73

Studies on changes in catecholamine and 5-HT metabolism in various brain areas of rats exposed to different stressors.

Johansson, G., Frankenhaeuser, M.: "Temporal factors in sympato-adrenomedullary activity following acute behavioral activation." *Biol. Psychol.* 1: 63-73 (1973). J11,366/73

In healthy young males subjected to complex choice-reaction tasks, the mean EP output during arousal increased but showed considerable individual variations in intensity and duration. "When subjects whose adrenaline output decreased rapidly were com-

pared with those whose adrenaline output decreased slowly, it was found that 'rapid decreasers' had higher baseline levels of adrenaline, performed better on the choice-reaction task, and had lower scores in neuroticism. The significance of temporal factors in adrenaline-mediated adjustment to environmental stressors is discussed."

Prasad, G. C., Siddiqui, M. Z., Udupa, K. N.: "Autoradiographic studies on the role of adrenaline in stress by using H³ adrenaline." *Am. J. Roentgenol.* 118: 852-860 (1973). J5,383/73

By use of labeled EP in rats submitted to the stress of bone fractures, it was possible to "localize the particular cells in the hypothalamus (PVN) which could be responsible for the endocrine and metabolic changes in the body after stress. The radioactive adrenaline

granules could be seen in the various tissues at different intervals, including the thyroid gland, adrenal gland, heart muscle, liver, kidney, etc., suggesting the site of action of adrenaline on these tissues at different periods."

Endrőczi, E., Tallian, F.: "Catecholaminergic control of pituitary function." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 15-24. Bratislava: Slovak Academy of Sciences, 1973. E10,454/73

In rats, ovariectomy decreases hypothalamic catecholamines, and these can be restored by intrahypothalamic injections of estradiol. Bilateral preoptic lesions also decrease hypothalamic catecholamine concentrations, but this effect cannot be counteracted by estradiol. Hypothalamic catecholamines are raised in lactating rats and by implantation of LTH into the ME.

Scapagnini, U., Annunziato, L., Preziosi, P.: "Role of brain norepinephrine in stress regulation." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 25-36. Bratislava: Slovak Academy of Sciences, 1973. E10,455/73

Review of the literature and personal observations in dogs which partly clarified but did not resolve the problem of whether cerebral NEP as a "transmitter is just a tonic inhibitor that has to be removed in order to activate the system, or is additionally involved in the feedback regulation that follows plasmatic corticosteroid increase" (25 refs.).

Glowinski, J.: "Some characteristics of the 'functional' and 'main storage' compartments in central catecholaminergic neurons." *Brain Res.* **62**: 489-493 (1973). J8,854/73

The author postulates a two-compartment model of catecholamine storage in central nerve endings: one a "functional," the other a "main storage" pool. Isotope studies on rat brains indicate enhanced utilization of NEP in the "main storage" compartment "in a variety of circumstances such as intense stress, repeated electroshock sessions, deprivation of paradoxical sleep, adrenalectomy" (21 refs.).

Fahringer, E. E., Foley, E. L., Redgate, E. S.: "Pituitary adrenal response to ketamine and the inhibition of the response by catecholaminergic blockade." *Neuroendocrinology* **14**: 151-164 (1974). H86,423/74

When given intraperitoneally, ketamine, a

centrally acting nonbarbiturate anesthetic, caused a rise in the corticosterone content of rat plasma which was abolished by hypophysectomy or dexamethasone. This response was not much altered by pretreatment with atropine or phentolamine but was significantly diminished by propranolol or haloperidol. The authors assume that the "response to ketamine is mediated through a facilitatory α -adrenergic and/or dopaminergic pathway or some hybrid thereof, and that ketamine is a convenient and useful agent for testing pituitary adrenal responsiveness in the rat."

Wied, D. de, Jong, W. de: "Drug effects and hypothalamic-anterior pituitary function." *Annu. Rev. Pharmacol.* **14**: 389-412 (1974). J12,125/74

Review of the literature on the effect of various drugs upon the secretion of adenohypophyseal hormones suggests that monoamines control the discharge of many releasing factors from the ME. The neuroendocrine transducer cells differ from neurons as well as from endocrine cells in that they convert neuronal input to humoral output (206 refs.).

Ellison, G. D., Bresler, D. E.: "Tests of emotional behavior in rats following depletion of norepinephrine, of serotonin, or of both." *Psychopharmacologia* **34**: 275-288 (1974). J9,987/74

Schildkraut, J. J.: "Biogenic amines and affective disorders." *Annu. Rev. Med.* **25**: 333-348 (1974). J12,641/74

Review of the literature and personal observations indicate that "different subgroups of patients with depressive disorders may exhibit different specific abnormalities in the metabolism of norepinephrine or other biogenic amines," particularly dopamine and 5-HT. The relationship between stress and metabolic changes in these substances is considered, but not regarded as proven (119 refs.).

Abe, K., Hiroshige, T.: "Changes in plasma corticosterone and hypothalamic CRF levels following intraventricular injection or drug-induced changes of brain biogenic amines in the rat." *Neuroendocrinology* **14**: 195-211 (1974). H86,427/74

In rats, "brain amines were depleted by pretreatment with either reserpine or 6-hydroxydopamine. In spite of the persistence of marked depletion of hypothalamic NEP content, the basal circadian rhythm as well as stress-induced changes in both plasma corticosterone and hypothalamic CRF levels

were preserved in almost the normal fashion. In addition, more than two-fold increases of brain amine concentration by pretreatment with a MAO inhibitor affected neither basal circadian rhythm nor a stress-induced increase in the plasma corticosterone. These observations suggest strongly that brain amines are of relatively little importance in the central regulation of ACTH secretion in the rat." NEP, dopamine, carbachol and GABA were injected into the lateral ventricles, and in large doses all of them except GABA elicited a significant increase in ACTH release.

Costa, E., Meek, J. L.: "Regulation of biosynthesis of catecholamines and serotonin in the CNS." *Annu. Rev. Pharmacol.* **14**: 491-511 (1974). J12,127/74

Review of catecholamine and 5-HT synthesis in the nervous system under various conditions including stress. Benzodiazepines (minor tranquilizers) block the increase in NEP turnover produced by stress, in doses devoid of any such effect at rest. They might directly affect a system of neurons that, in stress, influence noradrenergic neurons (161 refs.).

Hoeldtke, R.: "Catecholamine metabolism in health and disease." *Metabolism* **23**: 663-686 (1974). H87,374/74

Review of catecholamine metabolism in health, during stress and under the influence of various diseases which specifically alter it (216 refs.).

Koob, G. F., Annau, Z.: "Behavioral and neurochemical alterations induced by hypoxia in rats." *Am. J. Physiol.* **227**: 73-78 (1974). H89,535/74

In rats, hypoxia caused a decrease in the NEP content, but no change in the 5-HT concentration, of the forebrain. In rats with electrodes implanted into the lateral hypothalamus, "self-stimulation rates increased while food and water intake decreased during the first 12 h and subsequently returned toward control levels.... The results suggest a time-related activation of central adrenergic neuronal systems during exposure to hypoxia." The observation of a differential effect of hypoxia on NEP and 5-HT agrees with several earlier studies using other stressors (36 refs.).

Kumeda, H., Uchimura, H., Kawabata, T., Maeda, Y., Okamoto, O., Kawa, A., Kane-

his, T.: "Role of brain noradrenaline in the regulation of pituitary-adrenocortical functions." *J. Endocrinol.* **62**: 161-162 (1974). H90,058/74

In rats, intraventricular injections of 6-hydroxydopamine (which does not cross the blood-brain barrier) caused lasting depletion of brain catecholamines without affecting 5-HT or peripheral NEP. Fourteen days later the NEP content of the hypothalamus and brain stem decreased by about 30 percent, and no appreciable amount of NEP was detectable in the cortex or midbrain. This depletion did not influence plasma or adrenal corticosterone, nor did it prevent increased corticosterone secretion after exposure to stressors (sound, restraint, ether, vasopressin) or suppression of corticoid production by dexamethasone. It is concluded that NEP is not involved in regulating pituitary-adrenocortical activity at rest, during stress or during feedback inhibition.

Modigh, K.: "Effects of social stress on the turnover of brain catecholamines and 5-hydroxytryptamine in mice." *Acta Pharmacol. Toxicol. (Kbh.)* **34**: 97-105 (1974). J16,345/74

Male mice, at first isolated, then brought together, immediately start to fight, and exhibit characteristic changes in the turnover of brain catecholamines and 5-HT.

Cuello, A. C., Shoemaker, W. J., Ganong, W. F.: "Effect of 6-hydroxydopamine on hypothalamic norepinephrine and dopamine content, ultrastructure of the median eminence, and plasma corticosterone." *Brain Res.* **78**: 57-69 (1974). J15,544/74

In rats, injection of 6-hydroxydopamine intraperitoneally or into the third ventricle reduced hypothalamic NEP and elevated plasma corticosterone, suggesting increased ACTH secretion. There were degenerative changes in a few neurons ending in the external layer of the ME, while other neurons in the same region remained unaffected. Hypothalamic NEP and plasma corticosterone returned to normal fifteen days after the intraperitoneal injection, whereas this was not yet the case after intraventricular administration of the drug. In both groups, neuronal debris accumulated in the phagocytes, but most neurons remained normal. Presumably, NEP-containing neurons end in the external layer of the ME, and the central adrenergic system inhibits ACTH secretion. After fifteen days, a yet unknown mechanism compensates

for the decrease in NEP, and ACTH release returns to normal.

Palkovits, M., Brownstein, M., Saavedra, J. M., Axelrod, J.: "Norepinephrine and dopamine content of hypothalamic nuclei of the rat." *Brain Res.* **77**: 137-149 (1974).

J15,433/74

In rats, various hypothalamic nuclei contain three to twenty times more NEP and dopamine than does the cerebral cortex. The nuclei are very uneven as regards their amine content, but the ME is among the regions richest in dopamine and has only about half as much NEP. "All of the hypothalamic nuclei contain dopamine. It is highly concentrated in the rostral subdivisions of the arcuate nucleus, the paraventricular and dorsomedial nuclei, the retrochiasmatic area, the medial posterior subdivision of the ventromedial nucleus and in the medial forebrain bundle at the posterior hypothalamic level. The highest concentrations of norepinephrine were found in the paraventricular and dorsomedial nuclei and in the retrochiasmatic area. The rostral subdivisions of the arcuate nucleus and the periventricular and preoptic suprachiasmatic nuclei are also rich in norepinephrine" (29 refs.).

Brown, R. M., Snider, S. R., Carlsson, A.: Changes in biogenic amine synthesis and turnover induced by hypoxia and/or foot shock stress. II. The central nervous system." *J. Neural Transm.* **35**: 293-305 (1974).

J25,021/74

Ögren, S. O., Fuxe, K.: "Learning, brain noradrenaline and the pituitary-adrenal axis." *Med. Biol.* **52**: 399-405 (1974).

J24,846/74

In rats, the NEP pathways to the forebrain were destroyed by the injection of 6-hydroxydopamine (6-OH-DA) into the coeruleo-cortico (dorsal) bundle without significantly impairing retention of the conditioned avoidance response (CAR). However, when 6-OH-DA lesions were combined with adrenalectomy, "there was a marked reduction of the retention of CAR and a complete failure to relearn the CAR."

Johansson, G.: "Relation of biogenic

amines to aggressive behaviour." *Med. Biol.* **52**: 189-192 (1974) (33 refs.).

J17,685/74

Annunziato, L., Renzo, G. F. di, Lombardi, G., Preziosi, P., Scapagnini, U.: "Catecholaminergic control of thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) secretion." *Br. J. Pharmacol.* **52**: 442P-443P (1974). H97,357/74

Pretreatment of rats with α -MT significantly enhanced ACTH secretion, both under normal conditions and upon exposure to cold. Concurrent administration of DOPA reduced this effect in normal animals. TTH release was diminished by α -MT only in cold-stressed rats. The results are considered as being compatible with the concept that catecholamines influence ACTH and TTH secretion in opposite ways.

Stern, W. C., Morgane, P. J., Miller, M., Resnick, O.: "Protein malnutrition in rats: response of brain amines and behavior to foot shock stress." *Exp. Neurol.* **47**: 56-67 (1975).

J23,635/75

"Regional brain levels of the amines and 5-hydroxyindoleacetic acid showed little change in normal rats following up to 90 min. of shock, whereas depletions of up to 50% occurred in chronically protein malnourished rats. These neurochemical changes in the chronically malnourished rats were pronounced in the diencephalon and in the mid-brain-pons-medulla brain regions. Normal rats which were switched in adulthood to the low protein diet showed minimal decreases in brain amine and 5-hydroxyindoleacetic acid levels following foot shock. This suggests that the effects observed in the chronically malnourished rats reflect a developmental interaction and were not due to the diet being administered at the time of testing" (25 refs.).

Frohman, L. A., Stachura, M. E.: "Neuropharmacologic control of neuroendocrine function in man." *Metabolism* **24**: 211-234 (1975) (160 refs.).

H98,919/75

A review of the literature on neuroendocrine function in general leads to the suggestion that hypophyseal function may be regulated by the hypothalamus as summarized in Figure 18 (p. 1076).

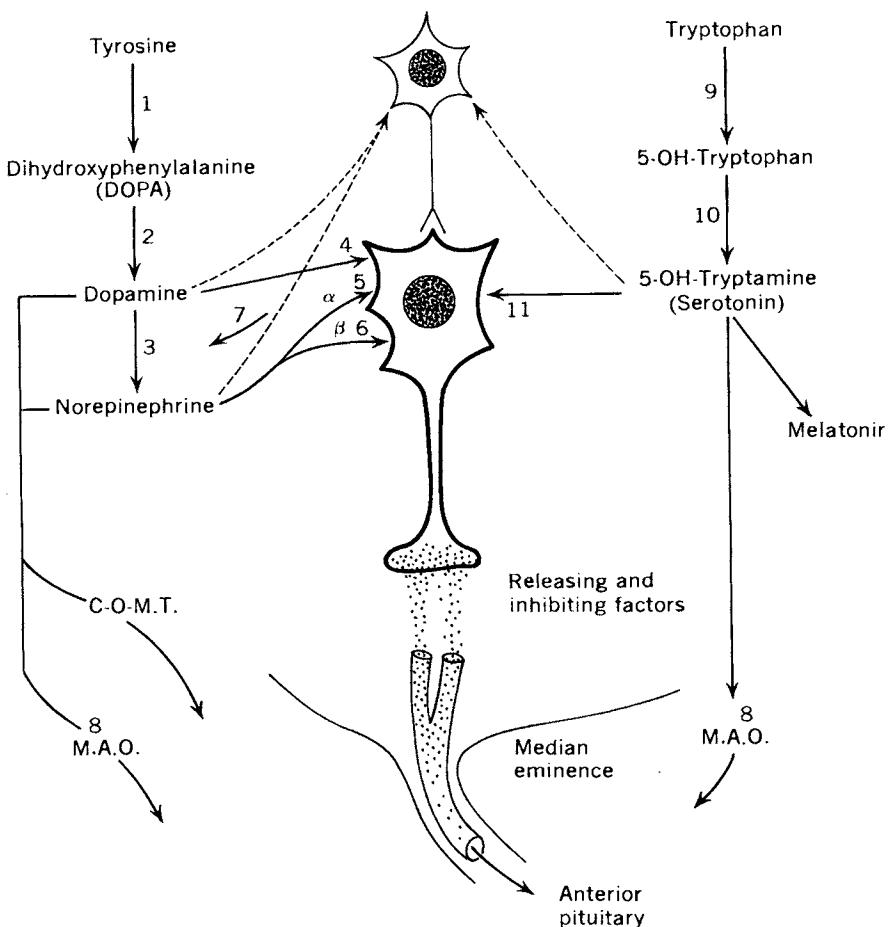


Figure 18. Schematic representation of potential monoamine relationships to the hormone-secreting neurons of the hypothalamus. The numbers refer to enzymatic steps or to sites of possible neuropharmacologic effect. (Reproduced from *Metabolism* 24 (1975) by permission of L. A. Frohman and M. E. Stachura, and Grune & Stratton.)

Dopamine

Many of the data concerning the possible role of dopamine in the regulation of stress reactions have been discussed in the sections on EP, NEP and 5-HT, since changes in these compounds were often studied comparatively, and it would be unnecessarily repetitious to describe them separately under each of these headings.

It should be pointed out here, however, that according to most investigators, NEP rather than dopamine is the principal tonic inhibitor of corticosterone secretion, although—as we will see—5-HT also may play a role in the neural control of the pituitary-adrenal axis.

Fluorescent microscopic studies showed noradrenergic but not dopaminergic fibers in the subependymal layer of the ME in the dog.

In man, dopa has been said to increase STH secretion by stimulating the discharge

of STH-RF (STH-releasing factor), but acromegalics may exhibit an inverse response. The dopaminergic control of STH secretion is allegedly under the influence of the diencephalon in man.

Dopamine

(See also our earlier stress monographs, p. xiii)

Holling, H. E.: "Effect of embarrassment on blood flow to skeletal muscle." *Trans. Am. Clin. Climat. Assoc.* **76**: 49-59 (1965).

J23,409/65

"Embarrassment provoked by heckling during the performance of mental arithmetic is associated with an increase in the blood flow to skeletal muscle of the limbs.... Dopamine is more likely to be the agent concerned than epinephrine, norepinephrine, or isoprorenaline. The hypothesis is suggested that dopamine enters the bloodstream from stores in the lungs."

Akmayev, I. G., Donath, T.: "The role of sympathetic innervation of the hypophysis in the transport of neurosecretory substances into the blood circulation." *Probl. Endokrinol. Gormonoter.* **12** No. 6: 90-94 (1966) (Russian). F74,162/66

Fluorescence studies on the neurohypophysis of the rat to determine NEP and dopamine levels within terminal sympathetic nerve fibers. "In acute stress the noradrenalin and the dopamine content seems to be increased in the terminal sympathetic nerve fibers. Catecholamine content in the sympathetic nerve fiber terminals of the pars posterior of the neurohypophysis and its increase in acute stress are discussed in connection with the transport of the neurosecretion hormonally-active substances into the blood circulation."

Goldberg, M. E., Salama, A. I.: "Relationship of brain dopamine to stress-induced changes in seizure susceptibility." *Eur. J. Pharmacol.* **10**: 333-338 (1970).

H26,394/70

"Mice stressed in a revolving drum exhibited a biphasic increase in the latency to tonic extension following maximal electroshock. The prolonged increase in seizure latency was paralleled by an increase in brain dopamine levels." These changes were prevented by α -MT, given before the stressor. No alterations in brain NEP or 5-HT were noted. These and other observations suggest

that "stress may possibly result in decreased utilization of dopamine in the brain."

Bliss, E. L., Ailion, J.: "Relationship of stress and activity to brain dopamine and homovanillic acid." *Life Sci. [I]* **10**: 1161-1169 (1971). G87,998/71

Scapagnini, U., Loon, G. R. van, Moberg, G. P., Preziosi, P., Ganong, W. F.: "Evidence for central norepinephrine-mediated inhibition of ACTH secretion in the rat." *Neuroendocrinology* **10**: 155-160 (1972).

H58,393/72

Experiments with guanethidine injected into the third ventricle to deplete the hypothalamus of catecholamines, and with FLA-63, an inhibitor of dopamine- β -oxidase, suggest that the adrenergic blockade of corticosterone secretion is mediated by NEP rather than by dopamine.

Lidbrink, P., Corrodi, H., Fuxe, K., Olson, L.: "Barbiturates and meprobamate: decreases in catecholamine turnover of central dopamine and noradrenaline neuronal systems and the influence of immobilization stress." *Brain Res.* **45**: 507-524 (1972).

G95,413/72

Bendikov, É. A., Basaeva, A. I.: "The use of DOPA in replacement therapy in disturbances of circulatory regulation during stress." *Biull. Éksp. Biol. Med.* **76** No. 12: 36-39 (1973) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **76**: 1414-1416 (1973). J20,146/73

In cats, stress produced by injection of potassium chloride into the lateral ventricles caused depletion of NEP in the hypothalamus, with inhibition of sympathetic vaso-motor tone. These changes could be corrected by injection of DOPA.

Collu, R., Jéquier, J. C., Letarte, J., Leboeuf, F., Ducharme, J. R.: "Effect of stress and hypothalamic deafferentation on the secretion of growth hormone in the rat." *Neuroendocrinology* **11**: 183-190 (1973).

H68,127/73

Ether and auditory stressors were equally effective in diminishing plasma STH (radioimmunoassay) in controls and frontally deafferented rats. Ether also inhibited STH secretion in completely deafferented animals,

whereas auditory stress was ineffective. α -MT pretreatment blocked the effect of ether after complete deafferentation. These and other data "seem to indicate that ether stress is transmitted through a humoral, dopaminergic pathway, while auditory stress follows a nervous pathway." [The many observations suggesting increased STH secretion during stress are not discussed (H.S.).]

Giordano, G., Marugo, M., Minuto, F., Barreca, T., Foppiani, E.: "L-dopa e secrezione dell'ormone somatotropo nell'uomo" (L-dopa and somatotropic hormone secretion in man). *Folia Endocrinol.* (Roma) **26**: 523-537 (1973). H83,472/73

In man, L-dopa causes increased secretion of STH by stimulating the discharge of STH-RF.

Chiodini, P. G., Liuzzi, A., Cremascoli, G., Botalla, L.: "Modificazioni della somatotropinemia in acromegalicci a seguito di somministrazione di L. dopa" (Modification of somatotropinemia in acromegalics following administration of L-dopa). *Folia Endocrinol.* (Roma) **26**: 497-502 (1973). H83,469/73

Unlike normal individuals, acromegalics respond to L-dopa by inhibition of STH secretion.

Cavagnini, F., Pontiroli, A. E., Raggi, U., Peracchi, M., Malinvern, A.: "Controllo dopaminergico dell'asse diencefalo-ipofisario per la secrezione di ormone somatotropo" (Dopaminergic control of the diencephalo-hypophyseal axis for the secretion of somatotropic hormone). *Folia Endocrinol.* (Roma) **26**: 483-489 (1973). H83,467/73

Literature and personal observations suggesting dopaminergic control of STH secretion under the influence of the diencephalon in man.

Fahringer, E. E., Foley, E. L., Redgate, E. S.: "Pituitary adrenal response to ketamine and the inhibition of the response by catecholaminergic blockade." *Neuroendocrinology* **14**: 151-164 (1974). H86,423/74

When given intraperitoneally, ketamine, a centrally-acting nonbarbiturate anesthetic, caused a rise in the corticosterone content of rat plasma which was abolished by hypophysectomy or dexamethasone. This response was not much altered by pretreatment with atropine or phentolamine but was significantly diminished by propranolol or haloperidol. The authors assume that the "response to ketamine is mediated through a facilitatory α -

adrenergic and/or dopaminergic pathway or some hybrid thereof, and that ketamine is a convenient and useful agent for testing pituitary adrenal responsiveness in the rat."

Balestreri, R., Bertolini, S., Elicio, N.: "Osservazioni sull'influenza della L-dopa sull'asse ipotalamo-ipofisi-corticosurrene nell'uomo" (Observations on the influence of L-dopa on the hypophyseal-adrenocortical axis in man). *Boll. Soc. Ital. Biol. Sper.* **50**: 397-403 (1974). J24,409/74

Johansson, G.: "Relation of biogenic amines to aggressive behaviour." *Med. Biol.* **52**: 189-192 (1974) (33 refs.). J17,685/74

Calas, A., Hartwig, H. G., Collin, J. P.: "Noradrenergic innervation of the median eminence. Microspectrofluorimetric and pharmacological study in the duck, *Anas platyrhynchos*." *Z. Zellforsch. Mikrosk. Anat.* **147**: 491-504 (1974). J13,342/74

Fluorescence microscopy demonstration of noradrenergic, but not dopaminergic fibers, in the subependymal layer of the ME in the duck.

Iversen, S. D.: "6-Hydroxydopamine: a chemical lesion technique for studying the role of amine neurotransmitters in behavior." In: Schmitt, F. O. and Worden, F. G., *The Neurosciences. Third Study Program*, pp. 705-711. Cambridge, Mass. and London: MIT Press, 1974. J17,225/74

Ungerstedt, U.: "Brain dopamine neurons and behavior." In: Schmitt, F. O. and Worden, F. G., *The Neurosciences. Third Study Program*, pp. 695-703. Cambridge, Mass. and London: MIT Press, 1974. J17,224/74

Stricker, E. M., Zigmond, M. J.: "Effects on homeostasis of intraventricular injections of 6-hydroxydopamine in rats." *J. Comp. Physiol. Psychol.* **86**: 973-994 (1974). J13,658/74

Comparison of 6-hydroxydopamine-induced cerebral dopamine depletion and lateral hypothalamic damage, with regard to their effects upon various adaptive functions, especially during heat stress in the rat.

Gouget, A., Duvernoy, J., Bugnon, C.: "Recherches sur la participation du tractus infundibulaire dopaminergique dans le fonctionnement de l'axe corticotrope" (Investigation on the participation of the dopaminergic infundibular tract in the activity of the cor-

ticotropic axis). *Bull. Assoc. Anat. (Nancy)* **58**: 315-322 (1974). J17,278/74

By use of the Falck-Hillarp histochemical fluorescence method, an important decrease in monoamines was demonstrated fifteen days after adrenalectomy in the rat ME. This decrease indicates a diminution of dopamine in the terminals of the infundibular tract. "A kinetic study of the rate of MA depletion in control and adrenalectomized rats, treated by

α -MT, confirms an accelerated turnover and an important discharge of DA with CRF release in the portal vessels."

Hutchins, D. A., Pearson, J. D. M., Sharman, D. F.: "An altered metabolism of dopamine in the striatal tissue of mice made aggressive by isolation." *Br. J. Pharmacol.* **51**: 115-116 (1974). H89,221/74

Corticoids

The crucial part played by glucocorticoids in stress reactions has been discussed in so many connections throughout this volume, as well as in our earlier stress monographs, that we need not recapitulate all the pertinent data here.

Briefly, glucocorticoid secretion depends entirely, or almost entirely, upon the direct effect of ACTH on the cortical cells; it can be demonstrated even by adding ACTH to adrenocortical slices in tissue culture. It may be mentioned that, although negligible in practice, some residual glucocorticoid secretion apparently does occur even in the absence of the pituitary, perhaps owing to stimulation by some extrahypophyseal ACTH-like principle and/or adenohypophyseal cells in the pars tuberalis. In many species such as the rat, this body remains attached to the ME after hypophysectomy performed by a conventional technique.

The principal role of the glucocorticoids is to increase stress resistance in general, to inhibit inflammation and various types of immune reactions, and to cause thymic-lymphatic atrophy, lymphopenia, eosinopenia and gluconeogenesis.

The active fraction of the excess corticoids circulates in the blood in free form, but it can be inactivated by chemical degradation or by binding to transcortin and certain other plasma proteins, as well as by excretion in urine and sweat. Sweat contains a significant fraction of the total amount of excreted corticoids, but because of technical difficulties it has not been subjected to as careful an analysis as the blood and urinary elimination products.

Much less is known about the mechanism regulating mineralocorticoid secretion. In hypophysectomized dogs, ACTH increased not only cortisol but also aldosterone production. Complete midbrain transection does not prevent the high rate of aldosterone secretion caused by hemorrhage or caval constriction in the dog. Renin and potassium are other powerful stimulators of aldosterone production, and it is becoming increasingly evident that mineralocorticoids also play an important role in the G.A.S. However, according to recent observations, ACTH stimulates mostly the production of nonaldosterone mineralocorticoids.

Corticoids

(See also our earlier stress monographs, p. xiii)

Nichols, J., Miller, A. T. Jr.: "Excretion of adrenal corticoids in the sweat." *Proc. Soc. Exp. Biol. Med.* **69**: 448-449 (1948).

B28,608/48

In man, exposure to heat and intense muscular exercise increase the rate of corticoid excretion in sweat more than in urine. Hence, "it is a reasonable assumption that it indicates an activation of the adrenal cortex in response to the stresses of heat and strenuous exertion. Our results also emphasize the

fact that in stresses associated with sweating, a significant fraction of the total corticoid excretion is accounted for in the sweat."

Swingle, W. W., Eisler, M., Ben, M., Maxwell, R., Baker, C., Le Brie, S. J.: "Eosinopenia induced by stress in adrenalectomized dogs." *Am. J. Physiol.* **178**: 341-345 (1954). B97,928/54

In adrenalectomized dogs maintained on DOC, stress still elicits eosinopenia. It is assumed that glucocorticoids are not totally indispensable for this reaction and that under certain circumstances, eosinopenia may also be produced through the discharge of catecholamines or other adrenal mechanisms.

Perrini, M., Bonomo, L., Ferrara, R., Leonardi, M.: "Degradazione del cortisone da parte del fegato di ratti normali e sottoposti a stress" (Degradation of cortisone [adrenocortical preparation] by the liver of normal rats and of rats under stress). *Folia Endocrinol. (Roma)* **7**: 641-650 (1954). C1,348/54

Saunders, F. J.: "Survival of adrenalectomized mice after several types of stress and the effects of various steroids." *Endocrinology* **58**: 412-419 (1956). D90,569/56

Jasmin, G., Bois, P.: "Anti-inflammatory corticosteroids: their pharmacological evaluation." *Int. Rec. Med.* **172**: 731-736 (1959). C77,973/59

In rats, the anti-inflammatory effect (granuloma pouch technique) of restraint during starvation can, whereas that of cortisol cannot, be largely inhibited by food administration. Several other glucocorticoid effects dissimilar to those elicited by stress are discussed (30 refs.).

Hilton, J. G.: "Adrenocorticotrophic action of antidiuretic hormone." *Circulation* **21**: 1038-1046 (1960). C90,262/60

In hypophysectomized dogs, direct perfusion of the adrenals with synthetic lysine, arginine or acetyl arginine-vasopressin stimulated the cortex to secrete cortisol. Pressor activity and adrenotropic effects were independent of each other. Similar polypeptides such as oxytocin, insulin, glucagon and pressor amines (EP, NEP), did not cause cortisol secretion under identical conditions. However, ACTH was active and increased the rate of aldosterone production. "The probable role of arginine vasopressin as an important factor in the stress reaction is considered along with its postulated ability to activate adrenal phosphorylase."

Hilton, J. G., Scian, L. F., Westermann, C. D., Nakano, J., Kruesi, O. R.: "Vasopressin stimulation of the isolated adrenal glands: nature and mechanism of hydrocortisone secretion." *Endocrinology* **67**: 298-310 (1960). C90,686/60

In hypophysectomized dogs, direct arterial perfusion of the adrenals with synthetic lysine, arginine or acetyl arginine-vasopressin stimulates cortisol secretion. Similar polypeptides, such as oxytocin, insulin and glucagon, as well as EP and NEP, do not produce this effect. ACTH consistently increases aldosterone secretion under identical conditions after hypophysectomy.

Sayers, G., Royce, P. C.: "Regulation of the secretory activity of the adrenal cortex." In: Astwood, E. B., *Clinical Endocrinology*, Vol. 1, pp. 323-334. New York and London: Grune & Stratton, 1960. D143/60

Review of the authors' earlier work which confirms that ACTH is the stimulant for glucocorticoid secretion but has only a minor role in the discharge of aldosterone. "A center in the brain, in or near the pineal complex, elaborates a hormone which acts directly on the glomerulosa of the adrenal to exert the major regulatory influence on the rate of secretion of aldosterone. The hormone has been appropriately named adrenoglomerulotropin (or glomerulotropin)." The stimulatory mechanisms of these two hormones are summarized in Figure 19 (p. 1081).

Davis, J. O., Anderson, E., Carpenter, C. C. J., Ayers, C. R., Haymaker, W., Spence, W. T.: "Aldosterone and corticosterone secretion following midbrain transection." *Am. J. Physiol.* **200**: 437-443 (1961). D2,868/61

In dogs, "complete midbrain transection does not interfere with the high rate of aldosterone secretion which occurs in response to acute blood loss or following caval constriction if venous pressure is maintained at the high control level."

Holzbauer, M.: "The part played by ACTH in determining the rate of aldosterone secretion during operative stress." *J. Physiol. (Lond.)* **172**: 138-149 (1964). D17,639/64

In dogs, ACTH increases not only glucocorticoid but to some extent also aldosterone secretion. Both these corticoids are produced at a subnormal level after hypophysectomy.

Paré, W. P., McCarthy, T. E.: "Urinary sodium and potassium and prolonged en-

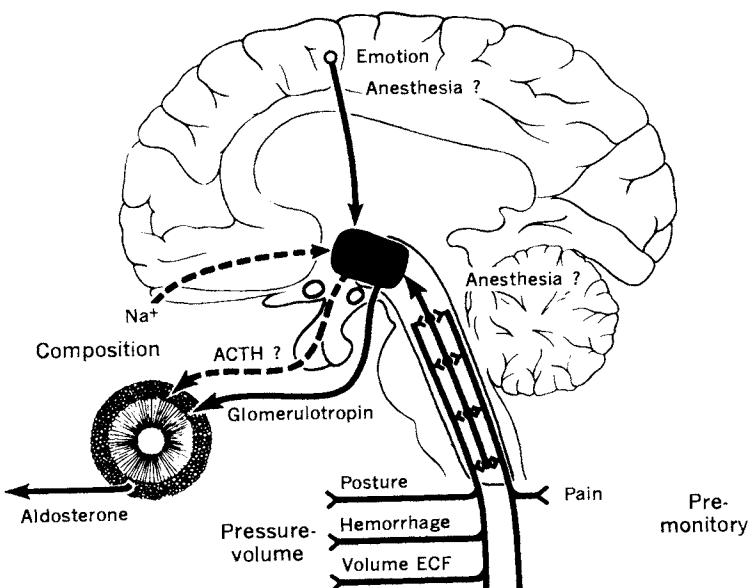
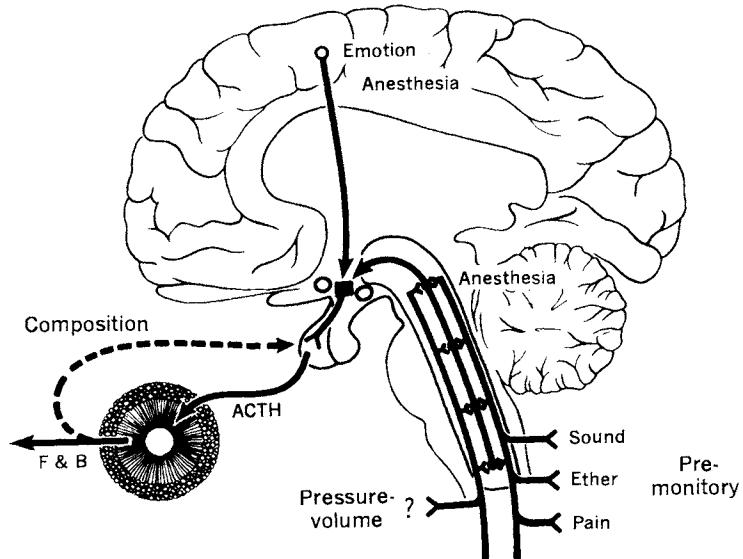


Figure 19. Top. Regulation of ACTH output. Bottom. Regulation of adrenoglomerulotropin (glomerulotropin) output. (Reproduced from *Clinical Endocrinology*, Vol. 1, Figs. 6 and 7, p. 333 (1960) by permission of G. Sayers and P. C. Royce and Grune & Stratton.) [The existence of a "glomerulotropin" is still in doubt (H.S.).]

vironmental stress." *J. Genet. Psychol.* **108**: 135-142 (1966). J21,567/66

Rats exposed to stressors (sound, electroshock) "manifest a significant eosinopenia and adrenal hypertrophy. Estimates of Na and K during the stress period do not manifest a shift in electrolyte balance for stress animals. The authors conclude that the adrenal mineralocorticoids do not participate in the physiological response to chronic environmental stress."

Vecsei, P., Kessler, H.: "In vivo conversion of corticosterone into aldosterone in rats treated with ACTH or submitted to stress." *Experientia* **26**: 1015-1016 (1970).

H31,555/70

Studies on the in vivo conversion of corticosterone to aldosterone in rat adrenals revealed a diminution after ACTH pretreatment, but not upon chronic exposure to other stressors. It is concluded that the adrenocortical effect of stress is not mediated exclusively through ACTH secretion.

Warburton, D. M.: "Modern biochemical concepts of anxiety. Implications for psychopharmacological treatment." *Int. Pharmacopsychiatry* **9**: 189-205 (1974).

J21,388/74

In man, "corticosteroids produce agitation and enhance anxiety. It is proposed that anxiety results from the neurochemical changes induced by corticosteroids. Evidence was presented to show that the critical changes for anxiety are due to modifications in serotonin pathways in the tegmental region of the midbrain."

Pratt, J. H., Melby, J. C.: "Alterations in aldosterone metabolism induced by adrenocorticotropin (ACTH)" (abstracted). *Program Am. Soc. Clin. Invest.*, 66th Ann. Meeting, p. 62a. Atlantic City, N.J., 1974.

H88,771/74

In man, "repository ACTH injected every 12 h for 6 days induced a five-fold increment in the aldosterone secretion rate and a four-fold increment in urinary tetrahydroaldosterone excretion by day 6, whereas plasma concentrations of aldosterone did not change significantly." It appears that increased mineralocorticoid activity after ACTH is due almost exclusively to the enhanced production of nonaldosterone mineralocorticoids. Probably, "the augmented metabolic clearance rate for aldosterone after ACTH stimulation can to an extent regulate aldosterone activity and may be a mechanism for escape from aldosterone effect."

Corticoid Feedback

The idea that an excess of blood corticoids can depress further production of the same hormones and thereby help maintain homeostasis is very old. It has been known since the nineteenth century that, following removal of one adrenal gland, the other undergoes "compensatory hypertrophy," presumably as a result of some self-regulating mechanism that helps repair the loss. This idea was formulated at a time when it was difficult to accept, since the adrenals were not yet known to have any physiologic function. However, it was subsequently observed that transplants of adrenals do not grow well in the presence of an intact gland, and that regeneration after partial adrenalectomy can be blocked by adrenocortical extract.

An extraordinarily large number of publications dealt and continue to deal with this "corticoid feedback mechanism," since it plays an extremely important role in governing the functional efficacy of the hypothalamo-pituitary-adrenocortical axis during stress. Additional relevant data will be found in the next section on Corticoid "Utilization."

It has been learned that purified corticoids are much more effective than cortical extracts in suppressing ACTH secretion and that this inhibitory effect generally parallels glucocorticoid activity. Hence, some of the highly potent synthetic glucocorticoids are even more efficacious in this respect than cortisol, cortisone or corticosterone. Now, in both experimental and clinical medicine, dexamethasone (a powerful synthetic glucocorticoid) is most frequently employed for the suppression of adrenocortical

growth and secretion. After such a blockade, ACTH release can be readily obtained by CRF but not by ordinarily effective doses of vasopressin or other releasing agents. In fact, stimulation of the dexamethasone-suppressed rat adrenal is a standard technique for the assay of CRF, which is otherwise possible only after surgical destruction of the ME.

In patients, dexamethasone almost completely suppresses ACTH and cortisol secretion, but this inhibition can be overcome by stress even when the blood steroid levels are very high. Patients with Cushing's syndrome are comparatively refractory to dexamethasone inhibition.

Following interruption of corticoid treatment at dose levels sufficient to inhibit the secretory activity of the cortex, stress resistance is diminished; presumably, the atrophic cortical cells require some time to recover their normal structure and functional efficiency. In the event of compensatory atrophy produced by DOC, a decrease in stress resistance is manifest even during hormone treatment, because this virtually pure mineralocorticoid inhibits the hyperglycemia of the alarm reaction (presumably useful as a source of energy during stress) by diminishing glucocorticoid production. These observations, made in 1942, first showed that "overdosage with one of the compounds produced by an endocrine cell can interfere with the production by the same cell of other hormonal compounds." Hence, "symptoms of overdosage with hormones produced by a certain endocrine cell type may coexist with signs of deficiency in the hormone production of the same cell." Since even after maximal suppression of adrenocortical secretion by corticoids, ACTH retains its activity, the blockade cannot be at the adrenal level.

Of course, the fact that prolonged treatment with glucocorticoids makes animals and man comparatively insensitive to ACTH most probably depends merely upon the atrophy of the cortical cells, which prevents them from responding optimally and rapidly to stimulation. It is important to remember, however, that in both mice and rats, an essentially pure mineralocorticoid such as DOC can also cause marked involution of the adrenal cortex. We have designated this negative feedback by corticoids as "compensatory atrophy." In rats exposed to cold, aldosterone suppressed the release of ACTH about one-third as actively as did cortisone, but eight times more than DOC.

Many investigators attempted to analyze the possible role of this mechanism in regulating adrenocortical function during stress. Although it was demonstrated as early as 1940 that not only glucocorticoids, but even DOC can considerably diminish adrenocortical stimulation by various stressors, a few investigators persisted in disregarding these facts. They postulated that during stress corticoid homeostasis can be maintained only because an enhanced corticoid production automatically diminishes ACTH secretion and thus maintains a normal blood ACTH level. This antiquated theory does not require detailed consideration today as it is incompatible with the most generally-accepted characteristic of the stress response: the rise in blood ACTH and corticoids during the alarm reaction. Still, because of the numerous and vehement discussions about this subject in the past, we will return to it again in the next section, Corticoid "Utilization," which lists publications maintaining that stress induces an increased consumption of corticoids and that the resulting drop of these hormones below normal would be the decisive stimulus for the rise in ACTH secretion.

It is noteworthy, however, that the histologic structure of the adrenal cortex after overdosage with gluco- or mineralocorticoids differs somewhat from that of hypophysectomized animals; hence we must conclude that either some pituitary influences can

escape feedback inhibition or that corticoids also have some direct effects upon the adrenal cortex.

Raising the blood glucocorticoid level (by exogenous steroids) several times above that reached during stress still fails to inhibit further ACTH secretion upon exposure to a stressor. These findings, and many of our earliest experiments as well as the observations of other investigators to be discussed again in the section on Corticoid "Utilization," clearly show that it is precisely during stress that ACTH secretion becomes largely independent of blood corticoid levels.

In rats, adrenalectomy causes an immediate increase in plasma corticotropin and a drop in hypophyseal ACTH content. About three weeks are necessary for both these levels to return toward normal.

Adrenalectomy causes a rapid fall followed by a slower elevation of the pituitary ACTH concentration in the rat. The ACTH depletion, but not its subsequent repletion, is prevented by corticosterone.

According to early investigators, the rat plasma ACTH level rises significantly only about ten days after complete adrenalectomy, but as previously mentioned, these claims have not been confirmed. In stressed adrenalectomized rats, intravenous cortisol blocks ACTH release within one or two minutes. This observation illustrates the extraordinary rapidity of the corticoid feedback action. (Yet perhaps adjustment to stress is much more rapid than to adrenal insufficiency.) It must be emphasized that not only the discharge but also the adenohypophyseal storage of ACTH (and presumably its synthesis) are blocked by corticoids. It would appear that CRF is not only an ACTH-releasing factor but also one that promotes its manufacture in the adenohypophysis.

In midbrain-sectioned rats, the corticoid feedback mechanisms are slow both after a drop (uniadrenalectomy) or a rise (dexamethasone) of blood corticoids. The mid-brain may act as a modulator of ACTH control without being indispensable for it.

Dexamethasone-induced inhibition of ACTH secretion is more pronounced in intact than in hypothalamically deafferented rats. Presumably, the negative feedback occurs in the hypothalamus but is modified by extrahypothalamic structures.

Implantation of glucocorticoids into the ME region is particularly effective in blocking ACTH secretion.

In rats with diabetes insipidus produced by hypothalamic lesions, compensatory atrophy of the adrenals can still be elicited by cortisol. Large doses of cortisol diminish the antidiuretic response to electric shocks and decrease the plasma vasopressin titer in stressed rats. It was concluded that corticoids block the release of ACTH both by a direct effect upon the pituitary and by diminishing the secretion of vasopressin that can stimulate ACTH release, although it is much less active than CRF in this respect.

Contrary to the most generally-accepted views, certain observations suggest that dexamethasone acts mainly on the adenohypophysis to inhibit ACTH secretion, because its blocking effect is not prevented by extensive lesions in the ME of the rat. Furthermore, it has been claimed that dexamethasone can suppress the corticotrophic action of vasopressin and hypothalamic extract. As previously mentioned, several investigators agree that some of the corticoid feedback may occur at the adenohypophyseal level, but according to the majority opinion, blockade at the ME level is much more important.

Dexamethasone inhibits the release of ACTH in adenohypophyseal monolayer tissue cultures. This is further proof that some direct corticoid feedback in the anterior lobe is possible, even if quantitatively not very important.

There is also some evidence that basal and stress-induced ACTH discharges are subject to corticoid feedback in different areas and that the mechanisms underlying the two phenomena may be dissociated.

The fact that some feedback inhibition has been obtained by glucocorticoid pellets placed in the forebrain of the rat might depend upon hormone transport through the ventricular system to a single feedback site in the basal hypothalamus or adenohypophysis.

In cats, intracerebral microinjections of cortisol considerably altered the unit activity of neurons, as indicated by their firing rate. The results suggest reciprocation between the midbrain and the contralateral posterior diencephalon. Neurons in the posterior diencephalon appear to be more sensitive to local application of cortisol than those in the midbrain.

In conscious, chair-confined monkeys, the rise in plasma 17-OHCS following intravenous cortisol is modified by electric stimulation of certain brain regions. A negative feedback effect of injected cortisol is demonstrable after stimulation of the amygdaloid but not of the hypothalamic nuclei. The results suggested that the neural mechanism for negative feedback is located between the amygdala and the hypothalamus.

In hypophysectomized rats with ten heterotopic pituitary transplants, neither cortisol implants in the ME nor even destruction of the latter depresses adrenocortical function, whereas systemic administration of larger doses of dexamethasone blocks corticoid secretion, even under these conditions. Cortisol implants in the ME caused adrenal atrophy only in intact rats, not in those with heterotopic pituitaries. Hence, it was concluded that the ME may be of importance in feedback regulation of ACTH only by virtue of its location at the source of the portal blood supply. Larger quantities of pituitary tissue can secrete an adequate amount of ACTH even without stimulation by CRF from the ME. In other words, ACTH secretion would not be necessarily dependent upon, but only quantitatively enhanced by, CRF.

Inhibition of CRF and hence of ACTH secretion by glucocorticoids results in manifest EM changes in the ME of the rat. This confirms the current view that corticoid feedback occurs mainly, if not exclusively, at the ME level. However, some inhibitory feedback action upon the adenohypophyseal cells themselves has not been completely excluded, mainly because heavy chronic overdosage with dexamethasone does appear to diminish the sensitivity of the anterior lobe even to CRF, though only to a very mild degree.

In rats, the spontaneous firing of hypothalamic single cell units was increased by hypothalamic deafferentation, and could not be diminished by cortisol. However, time studies revealed an initial reduction in the rate of discharge related to decreased ACTH secretion during corticoid feedback. Dexamethasone-sensitive neurons are situated over wide areas of the hypothalamus and midbrain; in most of these, firing is stimulated, but in some it is inhibited, by the corticoid. NEP and dopamine suppressed, whereas acetylcholine activated, the dexamethasone-sensitive neurons. Hence, the latter are apparently responsive both to corticoids and to other humoral mediators.

In rats, ACTH concentration in the intermediate lobe is considerably higher than in the adenohypophysis. However, one month after adrenalectomy, the ACTH content of the anterior lobe increased threefold, whereas that of the intermediate lobe remained unchanged. After treatment with cortisol the ACTH concentration in the adenohypophysis diminished markedly; in the intermediate lobe, no significant change occurred.

There is much evidence that protein-bound corticosterone has little, if any, inhibitory effect upon ACTH discharge.

In rats, thyroxine increases transcortin binding sites, thereby inhibiting corticoid feedback, since only the unbound and not the total corticosterone concentration is effective in this respect. On the other hand, in man, cortisol cancels the enhancing effect of thyroxine on transcortin binding.

Implantation of corticosterone pellets in neonatal rats may exert a permanent suppressive effect upon corticoid production, detectable even during adult life.

A distinction has also been made between "fast feedback," which occurs within minutes following treatment with small doses of corticosterone in rats under surgical stress, and "delayed feedback," which commences only after one hour and requires larger doses of corticosterone but is of longer duration. Some corticoids are synergists, others antagonists, in these feedbacks which are said to have different mechanisms and separate receptors. According to recent investigations, delayed corticoid feedback exists at both the hypothalamic and the pituitary levels, whereas fast feedbacks are mediated only through the hypothalamus.

Several investigators have attempted to design schematized models indicating the various sites at which stimulators and inhibitors of ACTH release take effect. These are undoubtedly useful in clarifying our views about the underlying mechanisms, but because of the innumerable conditioning factors that modify such responses *in vivo*, we are still very far from being able to use such models as a basis for prediction of the reactions that will occur under given circumstances.

There is some evidence that cortisol suppresses not only ACTH but also STH secretion.

Corticoid Feedback

(See also our earlier stress monographs, p. xiii, and Mathematical Models under Various Other Theories)

Stilling, H.: "Note sur l'hypertrophie compensatrice des capsules surrenales" (Notes on compensatory hypertrophy of the adrenal glands). *Rev. Méd. (Paris)* 8: 459-461 (1888). 35,886/1888

In young unlike in old rabbits, the removal of one adrenal causes an immediate lipid discharge followed by mitoses in the cortical cells, eventually resulting in "compensatory hypertrophy." This contradicts the view still held by many (in 1888!) that the adrenals have no physiologic function.

Ingle, D. J., Kendall, E. C.: "Atrophy of the adrenal cortex of the rat produced by the administration of large amounts of cortin." *Science* 86: 245 (1937). 68,992/37

It has been shown that transplants of adrenals in the rat do not regenerate in the presence of one intact gland. Furthermore, the regeneration of enucleated adrenals is

blocked by adrenocortical extract, and intravenous injection of the latter causes adrenal atrophy unless ACTH is simultaneously administered. It is concluded that "when the physiologic requirements for cortin are increased there is an increase in the output of the adrenotropic principle, and when cortin is present in the body fluids in excess of physiologic requirements the output of adrenotropic secretions from the pituitary is suppressed."

Ingle, D. J.: "The effects of administering large amounts of cortin on the adrenal cortices of normal and hypophysectomized rats." *Am. J. Physiol.* 124: 369-371 (1938).

90,976/38

Normal rats treated with "cortin" (adrenocortical extract) exhibit cortical atrophy.

Ingle, D. J., Higgins, G. M., Kendall, E. C.: "Atrophy of the adrenal cortex in the rat produced by administration of large amounts of cortin." *Anat. Rec.* 71: 363-372 (1938).

72,172/38

In rats, adrenocortical atrophy can be produced by injections of "cortin," which blocks

the action of adrenotropic anterior pituitary preparations. [This seemingly induced insensitivity to ACTH was probably due to inappropriate proportions of the latter and the injected corticoids. Actually, this observation might have served as the first proof of a corticoid feedback upon ACTH production but, as published, the phenomenon appeared to result from insensitivity of the cortical cells (H.S.).]

Selye, H.: "Compensatory atrophy of the adrenals." *J.A.M.A.* **115**: 2246-2252 (1940).

A32,884/40

In both mice and rats, DOC causes marked involution of the adrenal cortex, presumably through inhibition of ACTH production; yet the histologic structure of these adrenal cortices differs somewhat from that in hypophysectomized rodents. The phenomenon is designated as "compensatory atrophy."

Selye, H., Dosne, C., Bassett, L., Whitaker, J.: "On the therapeutic value of adrenal cortical hormones in traumatic shock and allied conditions." *Can. Med. Assoc. J.* **43**: 1-8 (1940). A32,768/40

In rats, prolonged treatment with DOC causes adrenocortical atrophy, and to some extent even prevents the adrenal enlargement normally produced by stressors (for example, surgical trauma).

Selye, H., Dosne, C.: "Physiological significance of compensatory adrenal atrophy." *Endocrinology* **30**: 581-584 (1942).

A37,249/42

In rats, large doses of DOC inhibit but do not prevent the adrenal enlargement characteristic of the alarm reaction following treatment with such stressors as cold, formaldehyde, atropine, trauma or forced muscular exercise. As a result of this inhibition, the resistance of the DOC-treated animals to stressors is subnormal, since they are unable to produce optimal amounts of glucocorticoids. The hyperglycemia of the alarm reaction (presumably useful in providing energy during stress) is likewise diminished by DOC pretreatment. It is apparent that "overdosage with one of the compounds produced by an endocrine cell can interfere with the production by the same cell of other hormonal compounds (in this case corticoids, such as corticosterone, active in carbohydrate metabolism). As a result of this interference, symptoms of overdosage with hormones produced by a certain endocrine cell type may

coexist with signs of deficiency in the hormone production of that same cell."

Tepperman, J., Engel, F. L., Long, C. N. H.: "A review of adrenal cortical hypertrophy." *Endocrinology* **32**: 373-402 (1943). A58,184/43

Houssay, B. A., Pinto, R. M.: "Interrelación hipófiso-suprarrenal demostrada por parabiosis" (Hypophyse-adrenal interrelation, as demonstrated by parabiosis). *Rev. Soc. Argent. Biol.* **20**: 39-48 (1944).

A94,483/44

In a pair of parabiotically united rats, adrenalectomy of one twin causes adrenal hypertrophy and thymus atrophy in its partner. This response is diminished by DOC administration.

Sayers, G., Sayers, M. A.: "Regulatory effect of adrenal cortical extract on elaboration of pituitary adrenotropic hormone." *Proc. Soc. Exp. Biol. Med.* **60**: 162-163 (1945).

B1,108/45

In rats, adrenocortical extract prevents the loss of adrenal ascorbic acid following exposure to cold, but it does not interfere with the effect of exogenous ACTH. Presumably, the "rate of release of adrenotropic hormone from the pituitary is regulated by the concentration of adrenal cortical hormones in the blood and tissues."

Moya, F., Selye, H.: "Effect of desoxycorticosterone upon hypophyseal corticotrophin production." *Proc. Soc. Exp. Biol. Med.* **68**: 529-531 (1948). B19,381/48

Even enormous anesthetic doses of DOC cannot prevent the decrease in adrenal ascorbic acid content following exposure to cold. Hence, mere lack of corticoids cannot be the decisive cause of ACTH discharge during stress.

Taylor, A. B., Albert, A., Sprague, R. G.: "Adrenotropic activity of human blood." *Endocrinology* **45**: 335-343 (1949).

B39,400/49

In patients with adrenal cortical insufficiency, ACTH could be demonstrated in the blood via a method that failed to show its presence in normal controls.

Gemzell, C. A., Dyke, D. C., Van, Tobias, C. A., Evans, H. M.: "Increase in the formation and secretion of ACTH following adrenalectomy." *Endocrinology* **49**: 325-336 (1951). B62,285/51

In rats, adrenalectomy causes an immediate increase in plasma ACTH with a corre-

sponding drop in the ACTH content of the adenohypophysis. The steady state is reached after approximately three weeks, at which time the ACTH levels in both plasma and pituitary are about normal.

Long, C. N. H.: "Regulation of ACTH secretion." *Rec. Prog. Horm. Res.* **7**: 75-97 (1952). B68,650/52

Review of the mechanism of ACTH secretion, which is thought to be regulated partly by the ACTH and corticoid concentration of the blood (feedback) and partly through direct stimulation by EP and sympathetic nervous stimuli (49 refs.).

Abelson, D., Baron, D. N.: "The effect of cortisone acetate on adrenal ascorbic acid depletion following stress." *Lancet* October 4, 1952, pp. 663-664. B74,513/52

Forgács, P., Hajdu, L.: "Adrenocorticotrop hormon (ACTH) elválasztás gátlása cortisonnal" (Inhibition of adrenocorticotrophic hormone [ACTH] secretion by cortisone). *Kisér. Orvostud.* **5**: 444-448 (1953) (Hungarian). B95,464/53

In unilaterally adrenalectomized rats, cortisone prevents ACTH discharge, whereas ascorbic acid does not. Exogenous ACTH retains its corticoid-mobilizing effect despite excess exogenous cortisone, which indicates that the block is not at the adrenal level.

Hodges, J. R.: "Review article. The pituitary-adrenal relationship." *J. Pharm. Pharmacol.* **8**: 481-496 (1953).

J7,386/53

Review of the early literature on corticoids inhibiting ACTH secretion during stress (98 refs.).

Hodges, J. R.: "The effect of desoxycorticosterone acetate on the release of adrenocorticotrophin by the pituitary gland." *Br. J. Pharmacol.* **8**: 242-247 (1953).

B86,006/53

In rats, adrenal ascorbic acid depletion after unilateral adrenalectomy was only partially inhibited by DOC, and "since ACTH was still effective in producing adrenal ascorbic acid depletion, it was considered that DOCA had not prevented the stress-induced fall in adrenal ascorbic acid concentration by a direct action on the adrenal cortex." In fact, very large doses of intraperitoneal DOC caused adrenal ascorbic acid depletion by themselves.

Renzi, A. A., Gilman, M., Gaunt, R.: "ACTH-suppressing action of aldosterone."

Proc. Soc. Exp. Biol. Med. **87**: 144-145 (1954). B99,669/54

In rats exposed to cold, aldosterone suppressed the release of ACTH about one-third as actively as cortisone, but eight times more than DOC.

Hodges, J. R.: "The effect of cortisone acetate on the secretion of adrenocorticotrophic hormone by the adenohypophysis." *J. Endocrinol.* **10**: 173-178 (1954).

B90,265/54

In rats, cortisone given subcutaneously or orally elicited no change in adrenal ascorbic acid content but it reduced the latter considerably upon intraperitoneal administration. This "was apparently due to a nonspecific effect caused by the intraperitoneal administration of suspended matter." Pretreatment of rats with large doses of cortisone diminished, but did not abolish, the ascorbic acid depletion normally produced by unilaterally adrenalectomy.

Sydnor, K. L.: "Blood ACTH in the stressed adrenalectomized rat after intravenous injection of hydrocortisone." *Endocrinology* **56**: 204-208 (1955). C1,808/55

In stressed adrenalectomized rats, intravenous cortisol blocks ACTH release within one or two minutes.

Farrell, G. L., Laqueur, G.: "Reduction of pituitary content of ACTH by cortisone." *Endocrinology* **56**: 471-473 (1955).

J12,872/55

In dogs, cortisone decreases the ACTH content of the pituitary.

Roberts, S., Keller, M. R.: "Influence of epinephrine and cortisone on the metabolism of the hypophysis and hypothalamus of the rat." *Endocrinology* **57**: 64-69 (1955).

C6,336/55

Barrett, A. M., Hodges, J. R.: "The effect of stress on the level of adrenocorticotrophin in the plasma of normal and adrenalectomized rats." *J. Endocrinol.* **14**: 292-296 (1956). C25,992/56

The literature on Sayers' feedback theory of corticoid secretion during stress is reviewed, and the concept is rejected because adrenalectomized animals, which have a high ACTH level, show a further increase in response to stress. Furthermore, sham and true adrenalectomies produce almost identical elevations of blood ACTH.

Rose, S., Nelson, J.: "Hydrocortisone and

A.C.T.H. release." *Aust. J. Exp. Biol. Med. Sci.* **34**: 77-80 (1956). C23,003/56

In rats with a micro-injector permanently implanted in the hypophyseal fossa or next to it, cortisol is much more effective in preventing compensatory hypertrophy of the contralateral gland following unilateralec-tomy when applied directly to the hypophysis than when injected elsewhere. "These experiments support the view that adrenal steroids act directly at the level of the pars distalis to inhibit ACTH release." [It would be difficult to exclude the possibility that the corticoids injected into the hypophyseal fossa did not also reach the ME in a higher concentration than when administered at a distance from the hypophysis (H.S.).]

Ohler, E. A., Sevy, R. W.: "Inhibition of stress induced adrenal ascorbic acid depletion by morphine, dibenzylidine, and adrenal cortex extract." *Endocrinology* **59**: 347-355 (1956). C23,020/56

In rats the adrenal ascorbic acid depletion produced by sham adrenalectomy, unilateralec-tomy, EP, hydroxyamphetamine or vasopressin could be inhibited by morphine. Adrenocortical extract blocked the response to operative stress and to catecholamines but not to vasopressin. Dibenzylidine suppressed only the reaction to catecholamines.

Collins, E. J.: "Steroid-induced adrenal-pituitary hypofunction." *Endocrinology* **58**: 777-780 (1956). C17,662/56

In rats, cortisol-induced adrenocortical atrophy depends on an effect upon the pituitary, not the adrenal. The latter, although rendered atrophic by the glucocorticoid, responds normally to ACTH.

Brodish, A., Long, C. N. H.: "Changes in the blood ACTH under various experimental conditions studied by means of a cross-circulation technique." *Endocrinology* **59**: 666-676 (1956). C26,209/56

A unilaterally or bilaterally adrenalectomized rat was united by crosscirculation with a hypophysectomized partner at various times after application of a stimulus to ACTH release, which could be measured by the changes in adrenal ascorbic acid in the hypophysectomized animal. "The high rate of ACTH secretion, following the application of a severe stress such as unilateral or bilateral adrenalectomy, can be maintained for approximately two hours, after which time the blood ACTH level gradually diminishes and is not detectable in 6 hours. However,

after a milder stress, such as that associated with the cannulation of the femoral blood vessels prior to cross-circulation, a steady moderate rate of ACTH secretion can be maintained throughout a 12-hour period studied. The disappearance of ACTH from the blood 6 hours after a severe stress is not due to increased blood level of adrenal cortical hormones, since it also occurs after bilateral adrenalectomy. Neither is this phenomenon due to exhaustion of pituitary ACTH, for if a second stress is applied at this time, marked elevation of blood ACTH occurs." Following application of a severe stress, the ACTH secretion curve is biphasic, suggesting a dual mechanism of its regulation.

Langecker, H., Lurie, R.: "Die Hemmung der Corticotropin-Sekretion durch Steroide" (The suppression of corticotropin secretion by steroids). *Acta Endocrinol.* **25**: 54-58 (1957). C43,951/57

In unilateralec-tomized rats, compensatory hypertrophy of the contralateral gland can be suppressed by cortisone, cortisol or DOC, but not by 17 α -hydroxyprogesterone, pregnan-21-ol-3,20-dione, or dehydroepiandrosterone. "Animals, which have received cortisone, are insensitive to corticotrophin. Because this effect is also found in hypophysecomized animals, an adrenal mechanism is discussed."

Richards, J. B., Pruitt, R. L.: "Hydrocortisone suppression of stress-induced adrenal 17-hydroxycorticosteroid secretion in dogs." *Endocrinology* **60**: 99-104 (1957).

C27,393/57

In pentobarbital-anesthetized dogs, maximal adrenal 17-OHCS secretion occurred when the dogs were subjected to the stressor effect of exposure to 20 percent carbon dioxide or the surgical trauma of adrenal vein cannulation. In either case, the adrenocortical stimulation was depressed by constant intravenous infusion of cortisol for one hour prior to and during stress.

Wexler, B. C., Dolgin, A. E., Zaroslinski, J. F., Tryczynski, E. W.: "Effects of a bacterial polysaccharide (Piromen) on the pituitary-adrenal axis: cortisone blockade of Piromen-induced release of ACTH." *Endocrinology* **63**: 201-204 (1958).

C56,640/58

In rats, ACTH release by bacterial polysaccharide (Piromen) is blocked by cortisone but not by DOC.

Birmingham, M. K., Kurlents, E.: "Inactivation of ACTH by isolated rat adrenals and inhibition of corticoid formation by adrenocortical hormones." *Endocrinology* **62**: 47-60 (1958). D78,083/58

Schapiro, S., Marmorston, J., Sobel, H.: "The steroid feedback mechanism." *Am. J. Physiol.* **192**: 58-62 (1958).

C47,514/58

The four-hour eosinopenia was used as a criterion for ACTH secretion in rats. DOC inhibited endogenous ACTH mobilization following stress in intact rats, probably "by blocking the secretion from a cerebral structure, presumably the hypothalamus, of a pituitary stimulating substance."

McCann, S. M., Fruit, A., Fulford, B. D.: "Studies on the loci of action of cortical hormones in inhibiting the release of adrenocorticotropic hormone." *Endocrinology* **63**: 29-42 (1958). J12,362/58

In rats with diabetes insipidus produced by hypothalamic lesions, compensatory adrenal atrophy can still be elicited by cortisol. Large doses of cortisol diminish the antidiuretic response to a mild electric shock and decrease the vasopressor titer in the peripheral blood of stressed rats. "It was concluded that adrenal steroids block the release of ACTH from the pituitary by 1) a direct action on the pituitary gland, and 2) by decreasing the release of antidiuretic hormone, the presumed neuro-humor stimulating ACTH release" (24 refs.).

Halász, B.: "Der zeitliche Ablauf von Veränderungen des Kernvolumens in der Nebennierenrinde" (The chronologic development of changes in cell nuclear volume in the adrenal cortex). *Acta Morphol. Acad. Sci. Hung.* **8**: 193-198 (1958).

J13,017/58

In the glomerulosa of the rat adrenal cortex, DOC induces a shrinkage of the nuclei during the first three days, followed by a swelling; only after the first week does the characteristic diminution in nuclear size become fully evident and persistent. The fasciculata shows no typical variations. ACTH acts mainly on the fasciculata, causing an initial swelling followed by a shrinkage in nuclear size which after three to five days leads to a persistent and considerable enlargement. Earlier data on the histologic actions induced by DOC and ACTH in the adrenal cortex are reviewed (7 refs.).

Hodges, J. R., Vernikos, J.: "Influence of

circulating adrenocorticotrophin on the pituitary adrenocorticotropic response to stress in the adrenalectomized rat." *Nature* **182**: 725 (1958). C61,601/58

In rats, adrenalectomy first increases the ACTH content of the pituitary, but at least two weeks are required before it adapts itself also to secrete and maintain a great excess of this hormone. Tests performed at various intervals during this time showed that the largest increase in circulating ACTH occurred in rats with the lowest initial blood values, and apparently the high serum level of ACTH inhibits its own secretion through an "auto feedback" mechanism.

Kitay, J. I., Holub, D. A., Jailer, J. W.: "Hormonal regulation of pituitary adrenocorticotrophin." *Proc. Soc. Exp. Biol. Med.* **97**: 165-169 (1958). C47,220/58

As determined by in vitro bioassays, "ACTH administration and adrenalectomy both resulted in a striking increase in pituitary ACTH content. Epinephrine and cortisone administration were both followed by significant depletion of pituitary ACTH."

Cox, G. S., Hodges, J. R., Vernikos, J.: "The effect of adrenalectomy on the circulating level of adrenocorticotropic hormone in the rat." *J. Endocrinol.* **17**: 177-181 (1958). C55,901/58

In rats, blood ACTH levels rose significantly only about ten days after complete adrenalectomy. Apparently, the pituitary requires a long time to adapt itself by increasing ACTH output after total deprivation of corticoids.

Kitay, J. I., Holub, D. A., Jailer, J. W.: "Extra-adrenal action of exogenous ACTH; inhibition of pituitary ACTH secretion." *Fed. Proc.* **17**: 87 (1958). C51,673/58

In adrenalectomized rats, ACTH increases, whereas cortisone decreases, the ACTH content of the pituitary. During exposure to a standard stressor, exogenous ACTH inhibits the usual release from the adenohypophysis. Presumably, that is why the hormone accumulates in the gland when exogenously administered.

Fortier, C., Groot, J. de: "Adenohypophyseal corticotrophin and plasma free corticosteroids during regeneration of the enucleated rat adrenal gland." *Am. J. Physiol.* **196**: 589-592 (1959). C65,671/59

Observations on partially adrenalectomized rats suggest that "both release and synthesis of ACTH are accelerated by hypo-

and depressed by hypercorticoidism." Yet the effect is predominantly exerted on synthesis.

Wied, D. de, Mirsky, I. A.: "The action of Δ^1 -hydrocortisone on the antidiuretic and adrenocorticotropic responses to noxious stimuli," *Endocrinology* **64**: 955-966 (1959).

C69,492/59

Rats given large doses of prednisolone do not exhibit a decrease in adrenal ascorbic acid concentration after exposure to painful stimuli or injection with histamine or nicotine, and they respond normally to ACTH. The dose of intraperitoneal vasopressin needed to produce a significant decrease in adrenal ascorbic acid is about ten times above normal. The antidiuretic response to stress is likewise suppressed by large doses of prednisolone. Presumably, this glucocorticoid "does not affect the responsiveness of the hypothalamus, it decreases markedly the responsiveness of the adenohypophysis and neurohypophysis of animals exposed to noxious stimuli."

Fortier, C.: "Effect of hydrocortisone on pituitary ACTH and adrenal weight in the rat," *Proc. Soc. Exp. Biol. Med.* **100**: 16-19 (1959).

C63,512/59

Fortier, C.: "Pituitary ACTH and plasma free corticosteroids following bilateral adrenalectomy in the rat," *Proc. Soc. Exp. Biol. Med.* **100**: 13-16 (1959).

C63,511/59

Péron, F. G., Dorfman, R. I.: "A method for the evaluation of adrenocorticotropic hormone suppressing action of corticoids," *Endocrinology* **64**: 431-436 (1959).

C64,745/59

Reck, D. C., Fortier, C.: "Adrenal ascorbic acid and corticosteroidogenesis following unilateral adrenalectomy in the rat," *Proc. Soc. Exp. Biol. Med.* **104**: 610-613 (1960).

C92,939/60

Following unilateral adrenalectomy in rats, adrenal ascorbic acid depletion is more closely related in time to release than to synthesis of corticosterone.

Péron, F. G., Moncloa, F., Dorfman, R. I.: "Studies on the possible inhibitory effect of corticosterone on corticosteroidogenesis at the adrenal level in the rat," *Endocrinology* **67**: 379-388 (1960).

C90,696/60

Hypophsectomized rats and the adrenals of intact rats maintained *in vitro* showed diminished corticoid production following the administration of ACTH in the presence of excess corticosterone. Presumably, "the circulating levels of blood corticosterone in the

rat may control its production by acting directly on the adrenal gland by inhibiting the action of ACTH." [In an addendum, the authors state that the *in vitro* experiments could not be confirmed subsequently; however, ACTH stimulation of the adrenals of hypophsectomized rats *in vivo* was inhibited by both cortisol and cortisone (H.S.).]

Hodges, J. R., Vernikos, J.: "The effects of hydrocortisone on the level of corticotrophin in the blood and pituitary glands of adrenalectomized and of stressed-adrenalectomized rats," *J. Physiol. (Lond.)* **150**: 683-693 (1960).

C84,916/60

In adrenalectomized rats, the blood ACTH level was high but rose even further under stress (ether anesthesia). Large doses of cortisol, given intravenously 180 seconds after stress, rapidly reduced the high blood concentration of ACTH, but only to the pre-existing level. Adrenalectomy resulted in a slight fall followed by a marked rise in pituitary ACTH. This elevation was also prevented by cortisol. The latter almost completely inhibited the rise in blood ACTH after adrenalectomy, but it did not block the marked elevation of the blood levels caused by stress. "The results add further support to the hypothesis that the action of corticoids in controlling pituitary adrenocorticotropic activity is mainly on corticotrophin synthesis."

Endrőczi, E., Lissák, K., Tekeres, M.: "Hormonal 'feed-back' regulation of pituitary-adrenocortical activity," *Acta Physiol. Acad. Sci. Hung.* **18**: 301-307 (1961) (13 refs.).

E57,283/61

Barrett, A. M.: "The effect of cortisone and hydrocortisone on the plasma levels of corticotrophin in the rat, after an acute stress," *J. Pharm. Pharmacol.* **13**: 20-25 (1961).

D13,892/61

Yates, F. E., Leeman, S. E., Glenister, D. W., Dallman, M. F.: "Interaction between plasma corticosterone concentration and adrenocorticotropin-releasing stimuli in the rat: evidence for the reset of an endocrine feedback control," *Endocrinology* **69**: 67-80 (1961).

D7,734/61

Experiments on rats given varying doses of histamine (which increases corticosterone production) in combination with corticosterone support "the hypothesis that the rapid rises in plasma corticosteroid concentration which follow many varied stimuli are caused by a reset of the negative feedback con-

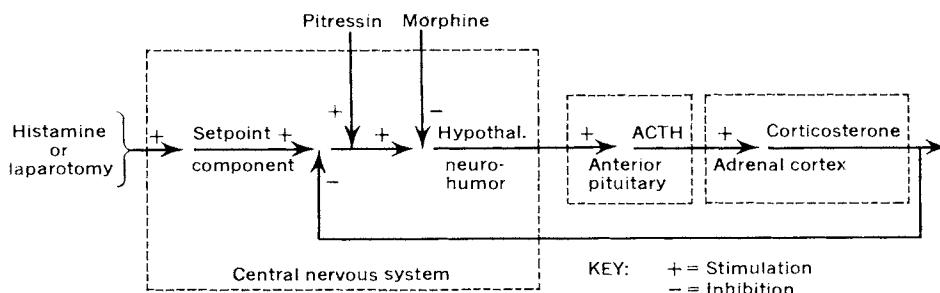


Figure 20. Relative localization of ACTH-releasing actions of nonspecific stimuli (histamine, laparotomy), pitressin and hypothalamic neurohumor. The relative localization of sites of inhibition of ACTH release by corticosterone and morphine are also indicated. (Reproduced from *Endocrinology* 70 (1962) by permission of S. E. Leeman *et al.* and Charles C Thomas, Publisher, Springfield, Ill.)

trol of plasma corticosteroid concentration to regulate at higher levels."

Smelik, P. G., Sawyer, C. H.: "Effects of implantation of cortisol into the brain stem or pituitary gland on the adrenal response to stress in the rabbit." *Acta Endocrinol.* (Kh.) 41: 561-570 (1962) D43,088/62

In rabbits, the increase in plasma corticoids induced by restraint was inhibited by implanting cortisol in the anterior ME and in the postoptic region. It was inhibited to a lesser extent by implants in the anteromedial hypothalamus between the supraoptic and paraventricular nuclei and the ME. Similar implants in the posterior hypothalamus, mesencephalon or adenohypophysis were ineffective.

Yates, F. E., Urquhart, J.: "Control of plasma concentrations of adrenocortical hormones." *Physiol. Rev.* 42: 359-443 (1962). D30,548/62

Very meticulous and detailed review of the literature on the stressors and feedback systems responsible for corticoid concentrations in the plasma and tissues (727 refs.).

Leeman, S. E., Glenister, D. W., Yates, F. E.: "Characterization of a calf hypothalamic extract with adrenocorticotropic-releasing properties: evidence for a central nervous system site for corticosteroid inhibition of adrenocorticotropic release." *Endocrinology* 70: 249-262 (1962). D36,341/62

On the basis of observations in rats, a schematic drawing (Figure 20) was constructed that indicates sites at which stimula-

tors and inhibitors of ACTH-release exert their actions.

Kendall, J. W. Jr.: "Studies on inhibition of corticotropin and thyrotropin release utilizing microinjections into the pituitary." *Endocrinology* 71: 452-455 (1962). D31,357/62

In rats, injection of dexamethasone directly into the pituitary "was no more effective in suppressing adrenal venous corticosterone secretion than an equal amount administered subcutaneously."

Hedner, P., Rerup, C.: "Plasma corticosteroid levels and adrenal ascorbic acid after intravenous corticotrophin injections and 'stressful' stimuli in the rat." *Acta Endocrinol.* 39: 527-538 (1962). D21,246/62

In rats the increase in plasma corticoid levels unlike the depletion of adrenal ascorbic acid produced by ether anesthesia is blocked by dexamethasone. The corresponding effects of unilateral adrenalectomy are less readily influenced. Apparently, corticoids can only partially inhibit stress-induced endogenous corticoid discharge. [Of course, if these feedback mechanisms were perfect during stress, the latter could never significantly increase corticoid production (H.S.).]

Hodges, J. R., Vernikos-Danellis, J.: "Pituitary and blood corticotrophin changes in adrenalectomized rats maintained on physiological doses of corticosteroids." *Acta Endocrinol.* 39: 79-86 (1962). D16,314/62

In adrenalectomized rats, the rise in plasma ACTH after mild stress (ether) was greater

than in controls. This hyperexcitability of the pituitary was not diminished by corticoids alone, but was considerably reduced by adrenocortical extracts plus ascorbic acid. Perhaps corticoids control the rate of ACTH synthesis, but other factors, including ascorbic acid, regulate pituitary responsiveness to stress-induced ACTH secretion.

Hodges, J. R., Jones, M. T.: "Corticotrophin release in the cortisol-treated rat." *J. Physiol. (Lond.)* **163**: 391-398 (1962).

D36,943/62

Observations in rats "support the hypothesis that ACTH release is controlled by a dual mechanism. The initial phase of ACTH secretion in response to acute stress is blocked by corticosteroids, but the second prolonged phase in response to chronic stress is not."

McCarty, D. J. Jr.: "The patient on long term adrenocortical steroid therapy." *Am. J. Cardiol.* **12**: 342-345 (1963). E25,875/63

Arnoldsson, H., Helander, E.: "The reaction of the pituitary-adrenocortical system to stress after prolonged corticosteroid therapy." *Acta Med. Scand.* **173**: 769-774 (1963).

E21,191/63

James, V. H. T., Landon, J.: "The response of the pituitary-adrenal axis to the infusion of dexamethasone." *J. Endocrinol.* **26**: xxxi-xxxii (1963). E30,543/63

Observations on normal patients suggest that dexamethasone causes virtually complete suppression of ACTH and cortisol secretion, but this inhibition can be overcome by stress, even though the blood steroid levels are extremely high. Patients with Cushing's syndrome are comparatively refractory to dexamethasone inhibition.

Chowers, I., Feldman, S., Davidson, J. M.: "Effects of intrahypothalamic crystalline steroids on acute ACTH secretion." *Am. J. Physiol.* **205**: 671-673 (1963).

E28,859/63

In rats, implantation of crystalline cortisol in the ME region caused adrenal atrophy and inhibition of ACTH secretion after unilateradrenalectomy (adrenal ascorbic acid test). Similar testosterone implants elicited an essentially inverse response. The rats with cortisol implants in the pituitary had normal adrenal weights and ACTH reactions.

Smelik, P. G.: "Relation between blood level of corticoids and their inhibiting effect on the hypophyseal stress response." *Proc.*

Soc. Exp. Biol. Med. **113**: 616-619 (1963).

E21,483/63

In rats, large doses of subcutaneous corticosterone suppressed adrenal corticoid production in vitro following exposure to stress in vivo, but there was no parallelism between this inhibition and the plasma corticosterone levels. "It is concluded that pituitary impairment by corticoid administration is not correlated with the existing blood level of corticoids."

Stark, E., Fachet, J.: "The effect of blood corticoid levels on ACTH-release caused by stress." *Acta Med. Acad. Sci. Hung.* **19**: 367-370 (1963).

G17,876/63

In rats, "pharmacological doses of corticoids suppressed the release of ACTH in the non-stressed animals, they did not inhibit ACTH-release due to formalin: this in spite of the fact that the exogenous hormone levels considerably exceeded the corticosterone concentration following stress. It would appear that the mechanism of the negative feed-back cannot be invoked as the sole explanation for the ACTH-release due to stress."

Smelik, P. G.: "Failure to inhibit corticotrophin secretion by experimentally induced increases in corticoid levels." *Acta Endocrinol. (Kh.)* **44**: 36-46 (1963).

E25,508/63

In rats, corticosterone infusions greatly raising the blood corticosterone levels failed to inhibit adrenocortical activation by histamine or ACTH. "These data are not in agreement with the 'variable set point control theory,' and demonstrate that physiological variations in plasma corticoid concentration do not affect the acute stress-induced corticotrophin release."

Estep, H. L., Island, D. P., Ney, R. L., Liddle, G. W.: "Pituitary-adrenal dynamics during surgical stress." *J. Clin. Endocrinol. Metab.* **23**: 419-425 (1963). D66,683/63

Pelvic laparotomy caused an increase in plasma 17-OHCS, even in patients treated with large doses of dexamethasone before and/or during the operation. Furthermore, secretion of substance S indicated that ACTH continued to stimulate the adrenals; infusions of cortisol, which maintained high blood levels of this natural glucocorticoid, failed to prevent the stress-induced ACTH increase in the plasma. "It is concluded that during the stress of laparotomy the behavior of the human pituitary-adrenal system does

not conform to the specifications of a negative feedback mechanism."

Hodges, J. R., Jones, M. T.: "The effect of injected corticosterone on the release of adrenocorticotrophic hormone in rats exposed to acute stress." *J. Physiol.* (Lond.) **167**: 30-37 (1963). D68,641/63

In rats, "corticosterone in doses sufficient to raise the blood concentration of the steroid to up to four times the maximal level induced by stress did not diminish the further rise in corticosterone or the elevation in blood ACTH and only slightly reduced the adrenal ascorbic-acid depletion normally caused by sham-adrenalectomy." It is concluded that during stress the secretion of ACTH is independent of the blood corticosterone level.

Bohus, B., Endrőczi, E.: "The effect of endogenous diminution of corticosteroid level on pituitary-adrenocortical function." *Acta Physiol. Acad. Sci. Hung.* **25**: 351-358 (1964). G33,534/64

In anesthetized dogs the adrenal vein was directly connected with the hepatic portal circulation; this led to a rapid increase in the corticoid concentration of the adrenal vein blood, which was prevented by morphine. Presumably, "the plasma corticosteroid level increases the pituitary-adrenocortical activity through a hormonal feedback mechanism."

Wied, D. de: "The site of the blocking action of dexamethasone on stress-induced pituitary ACTH release." *J. Endocrinol.* **29**: 29-37 (1964). F10,254/64

In rats, the corticotropic effect of stressors and of lysine-vasopressin was inhibited by dexamethasone given subcutaneously, while that of ACTH was not affected. After extensive lesions in the ME, dexamethasone also suppressed the corticotrophic action of lysine-vasopressin and of hypothalamic extract. Dexamethasone did not significantly change the ACTH content of the pituitary in either intact or lesioned rats. "It is concluded that the blocking action of dexamethasone is located in the anterior pituitary."

Fraschini, F., Mangili, G., Motta, M., Martini, L.: "Midbrain and feedback control of adrenocorticotrophic secretion." *Endocrinology* **75**: 765-769 (1964). F23,994/64

In midbrain-sectioned rats with decreased (unilateral adrenalectomy) or increased (dexamethasone) blood corticoids, the feedback mechanisms are slow. Apparently, "the mid-

brain-sectioned animal does not realize then that its blood levels of corticoids are changed until extremely high or extremely low levels of blood corticoids are reached; only when such values are attained can the servomechanisms responding to these fluctuations thus be brought into play in the midbrain-sectioned animals. The hypothesis is put forward that, in addition to an ACTH-activating, an ACTH-inhibiting and a stress-facilitating system, the midbrain might participate in ACTH control by acting as a sort of modulator."

Hodges, J. R., Jones, M. T.: "Changes in pituitary corticotrophic function in the adrenalectomized rat." *J. Physiol.* (Lond.) **173**: 190-200 (1954). D18,782/64

In rats, adrenalectomy caused a rapid fall, followed by a slower rise, in pituitary ACTH. The ACTH depletion, but not its subsequent repletion, was prevented by corticosterone after adrenalectomy. Mild stressors, which did not significantly affect plasma ACTH in intact rats, considerably raised it after adrenalectomy. The stress-induced ACTH discharge was suppressed by small doses of corticosterone in the adrenalectomized rat, but there was no correlation between the plasma corticosterone concentration and the degree of ACTH inhibition.

Smelik, P. G., Sawyer, C. H.: "Hypothalamic structures involved in the adrenocortical feedback action on pituitary corticotrophin secretion." *Prog. Brain Res.* **5**: 132-134 (1964). J13,013/64

Detailed study on the effect of cortisol implants in various parts of the hypothalamus upon plasma cortisol rises elicited in rabbits by restraint.

Vernikos-Danellis, J., Anderson, E., Trigg, L., Dickinson, J.: "Feedback mechanisms regulating ACTH secretion." *Program 47th Meeting Endocrinol. Soc.*, p. 27. New York, 1965. F39,944/65

In rats bearing ACTH-producing tumors, "inhibition of ACTH secretion by maximal endogenous levels of corticoids is slow to develop and even under conditions when such high levels persist for a considerable length of time the response to stress is not completely prevented. Furthermore, in the absence of corticoids an extra-pituitary source of ACTH may inhibit adenohypophyseal ACTH synthesis and secretion."

Hodges, J. R., Jones, M. T.: "Some observations on the role of corticosteroids in controlling the adrenocorticotrophic activity

of the pituitary gland." *J. Endocrinol.* **31**: 20-21 (1965). F31,585/65

In rats whose blood corticoid levels were maintained within the physiologic range, stress (sham adrenalectomy) did not diminish the rise in plasma corticosterone or blood ACTH. "Thus it appears that the release of adrenocorticotropic hormone is independent of changes in blood corticoid concentration within the physiological range and that the 'reset' hypothesis is untenable." On the other hand, in adrenalectomized rats, the already high levels of blood ACTH are further increased by a mild stress (ether) that is insufficient to produce a detectable discharge of this hormone in intact animals. The fall in pituitary ACTH caused by adrenalectomy is prevented by replacement therapy with corticoids. Presumably, "a negative feedback mechanism is not of prime importance in regulating pituitary adrenocorticotropic activity. However, corticoids appear to have some function in controlling ACTH secretion."

Corbin, A., Mangili, G., Motta, M., Martini, L.: "Effect of hypothalamic steroid implantations on ACTH feedback mechanisms." *Endocrinology* **76**: 811-818 (1965).

F39,146/65

In rats, dexamethasone and, to a lesser extent, cortisol implants into the ME reduced plasma and adrenal corticosterone levels as well as adrenal weight. Dexamethasone implants into the pituitary cerebral cortex or midbrain periventricular gray proved to be ineffective, but when placed into the midbrain lateral reticular formation they lowered plasma and adrenal corticosterone levels.

Hodges, J. R.: "The control of pituitary corticotrophic function." *J. Psychosom. Res.* **9**: 63-66 (1965). G34,469/65

Bohus, B., Endrőczi, E., Lissák, K.: "Studies on the control of the pituitary-adrenal system: stress and humoral feedback control." *Acta Physiol. Acad. Sci. Hung.* **27**: 279-284 (1965). G34,304/65

Donald, R. A.: "Dexamethasone suppression of the plasma corticosterone response to stress in the rat." *J. Physiol. (Lond.)* **182**: 603-611 (1966).

G37,597/66

Fortier, C.: "Nervous control of ACTH secretion." In: Harris, G. W. and Donovan,

B. T., *The Pituitary Gland*, Vol. 2, pp. 195-234, London: Butterworths, 1966.

J11,292/66

Excellent review on the hypothalamic and limbic control of ACTH secretion, with particular reference to the corticoid feedback mechanisms during stress (more than 300 refs.).

Kawai, A., Yates, R. E.: "Interference with feedback inhibition of adrenocorticotropin release by protein binding of corticosterone." *Endocrinology* **79**: 1040-1046 (1966).

F74,052/66

In rats, intravenous histamine causes nearly maximal ACTH release, as indicated by plasma and adrenal corticosterone content. Unbound corticosterone, given intravenously before histamine, impairs ACTH release, but not if injected in the presence of corticosterone-binding plasma proteins. It is not certain, however, that impairment of the negative feedback action of corticosterone by its binding proteins occurs at low corticosterone concentrations.

Pecile, A., Müller, E.: "Suppressive action of corticosteroids on the secretion of growth hormone." *J. Endocrinol.* **36**: 401-408 (1966).

F74,460/66

In rats, cortisol suppresses not only ACTH but also STH secretion. The latter effect is apparently due to impairment of the release mechanism, as shown by the lack of an STH-releasing response to insulin hypoglycemia.

Feldman, S., Conforti, N., Davidson, J. M.: "Adrenocortical responses in rats with corticosteroid and reserpine implants." *Neuroendocrinology* **1**: 228-239 (1966).

F68,591/66

In rats, dexamethasone or cortisol pellets implanted into the ME inhibited compensatory hypertrophy of the remaining adrenal following unilateral suprarenalectomy. Dexamethasone implants into the pituitary itself caused only slight inhibition. Similar implants of reserpine or subcutaneous injections of the substance could not be shown "to be involved in the negative feedback regulation of ACTH secretion by corticosteroids."

Slusher, M. A., Hyde, J. E., Laufer, M.: "Effect of intracerebral hydrocortisone on unit activity of diencephalon and midbrain in cats." *J. Neurophysiol.* **29**: 157-169 (1966).

G39,577/66

In cats, within ten minutes of intravenous injection of 25 mg. cortisol, "a significant al-

teration in firing rate was seen for the majority of recorded units in hypothalamus and zona incerta. Following intracerebral microinjection of 250 µg. of hydrocortisone into the midbrain, alterations in spontaneous activity of diencephalic units tended to be more delayed than after intravenous injection. Intra-hypothalamic injection was followed by alteration of half of all studied midbrain units within 10 min. The results suggest a reciprocal functional link between the midbrain and the contralateral posterior diencephalon. In addition, neurons in the posterior diencephalon would appear to be more sensitive to local application of hydrocortisone than neurons in the midbrain."

McHugh, P. R., Smith, G. P.: "Negative feedback in adrenocortical response to limbic stimulation in Macaca mulatta." *Am. J. Physiol.* **213**: 1445-1450 (1967).

F92,213/67

In conscious, chair-confined Macaca mulatta, the rise in plasma 17-OHCS following intravenous administration of cortisol was modified by stimulation of certain brain regions with bipolar electrodes. The results furnished "evidence for a negative feedback effect of injected hydrocortisone on the 17-OHCS response to amygdaloid stimulation but not to hypothalamic stimulation and suggest the presence of a neural mechanism for negative feedback located functionally between amygdala and hypothalamus."

Arimura, A., Saito, T., Schally, A. V.: "Assays for corticotropin-releasing factor (CRF) using rats treated with morphine, chlorpromazine, dexamethasone and Nembutal." *Endocrinology* **81**: 235-245 (1967).

F87,059/67

Rats pretreated with chlorpromazine, morphine and Nembutal showed consistently greater rises in plasma corticosterone than those given dexamethasone, morphine and Nembutal upon administration of CRF preparations from rat stalk ME, β -CRF, α -CRF or hypothalamic CRF. "This suggests a direct suppression of the CRF activity by dexamethasone." These and other observations also indicate that chlorpromazine + morphine + Nembutal-treated rats "have many advantages as a new assay preparation for CRF and can be used with greater ease and reliability."

Furukawa, T., Isobe, S., Yano, I.: "The counteraction against the dexamethasone-induced adrenal inhibition by cold stress."

Jap. J. Pharmacol. **17**: 519-524 (1967).
F96,231/67

EM studies on rats show that cold stress can only partially overcome dexamethasone-induced adrenocortical inhibition.

Asfeldt, V. H., Elb, S.: "Hypothalamo-pituitary-adrenal response during major surgical stress." *Acta Endocrinol. (Kh.)* **59**: 67-75 (1968).
H2,076/68

As indicated by the fall in plasma corticosteroids during surgical interventions in man, "suppression by dexamethasone has no influence on the hypothalamic pituitary adrenal response to major acute stress."

Takebe, K., Kunita, H., Sakakura, M., Horiuchi, Y.: "Effect of dexamethasone on ACTH release induced by lysine vasopressin in man; time interval between dexamethasone and vasopressin injection." *J. Clin. Endocrinol. Metab.* **28**: 644-650 (1968).

F98,960/68

Hill, C. D., Singer, B.: "Inhibition of the response to pituitary adrenocorticotropic hormone in the hypophysectomized rat by circulatory corticosterone." *J. Endocrinol.* **42**: 301-309 (1968).
H3,713/68

Experiments on hypophysectomized rats receiving constant infusions of ACTH and corticosterone revealed that the inhibitory effect of the latter on the adrenal response to ACTH can be demonstrated within the gland at plasma corticosterone levels comparable to those found during surgical stress. The earlier literature is cited from which the authors conclude that "the results obtained are compatible with the hypothesis that a feedback mechanism exists at the adrenal level in which corticosterone regulates its own rate of biosynthesis by a primary effect on the rate of synthesis of a regulator protein or some cofactor."

Davidson, J. M., Jones, L. E., Levine, S.: "Feedback regulation of adrenocorticotropin secretion in 'basal' and 'stress' conditions: acute and chronic effects of intrahypothalamic corticoid implantation." *Endocrinology* **82**: 655-663 (1968) (29 refs.).
F97,901/68

Stark, E., Gyévai, A., Ács, Z., Szalay, K. S., Varga, B.: "The site of the blocking action of dexamethasone on ACTH secretion: in vivo and in vitro studies." *Neuroendocrinology* **3**: 275-284 (1968).
H3,331/68

In anesthetized dogs, dexamethasone (200

$\mu\text{g}.$) infused into the hypophysis failed to affect ACTH secretion during the first three hours. Added to a medium of pituitary cells in vitro, dexamethasone was likewise ineffective in altering ACTH secretion. Presumably, "when in contact with hypophyseal cells, dexamethasone has no inhibitory effect on ACTH release in the stressed animal or on the basic ACTH secretion in vitro."

Grimm, Y., Kendall, J. W.: "A study of feedback suppression of ACTH secretion utilizing glucocorticoid implants in the hypothalamus: the comparative effects of cortisol, corticosterone, and their 21-acetates." *Neuroendocrinology* 3: 55-63 (1968).

F97,897/68

In rats, implants of cholesterol into the ME caused no change in the rise of plasma corticosterone following "standard ether stress." Cortisol, corticosterone and their 21-acetates were effective, but the duration of the feedback depended upon their solubility and absorption.

Kendall, J. W., Allen, C.: "Studies on the glucocorticoid feedback control of ACTH secretion." *Endocrinology* 82: 397-405 (1968).

F94,626/68

In intact rats, implants of cortisol in the ME inhibited corticosterone secretion, whereas similar implants in the cerebral cortex were inactive. In contrast, neither implants of cortisol nor even lesions in the ME depressed adrenocortical function in hypophysectomized rats with ten heterotopic pituitaries. Systemically administered dexamethasone suppressed corticoid secretion, even in the latter group. Cortisol implants in the ME caused adrenal atrophy in intact rats, but not in those with heterotopic pituitaries. Hence, "the median eminence may be of importance in feedback regulation of ACTH in intact rats only by virtue of its location at the origin of the pituitary stalk where the hypophyseal blood supply begins." At least the principal site of corticoid feedback appears to be in the pituitary itself.

Bohus, B., Nyakas, C., Lissák, K.: "Involvement of suprahypothalamic structures in the hormonal feedback action of corticosteroids." *Acta Physiol. Acad. Sci. Hung.* 34: 1-8 (1968).

G64,428/68

From observations on rats with cortisol implants in several suprahypothalamic regions, it was "concluded that the hormonal feedback effect of corticosteroids involves various fore- and midbrain areas. It is sug-

gested that the suprahypothalamic corticosteroid-sensitive structures are playing a role in the feedback control of the stress-induced but not of the basal ACTH secretion."

Zimmermann, E., Critchlow, V.: "Negative feedback and pituitary-adrenal function in female rats." *Am. J. Physiol.* 216: 148-155 (1969). H6,475/69

In female rats, 100 $\mu\text{g}/\text{kg}$. of dexamethasone injected subcutaneously at noon suppressed the diurnal variations in plasma corticosterone but not its rise during stress (ether, restraint, handling). Apparently, "it is possible, on the basis of sensitivity to negative feedback, to dissociate mechanisms underlying nonstress pituitary-adrenal function from those which support acute responses to the stresses used in these studies."

Sirett, N. E., Gibbs, F. P.: "Dexamethasone suppression of ACTH release: effect of the interval between steroid administration and the application of stimuli known to release ACTH." *Endocrinology* 85: 355-359 (1969). H15,825/69

Hodges, J. R., Sadow, J.: "Hypothalamo-pituitary-adrenal function in the rat after prolonged treatment with cortisol." *Br. J. Pharmacol.* 36: 489-495 (1969).

G68,229/69

In rats chronically treated with cortisol, the functional activity of the hypothalamo-pituitary-adrenal system gradually recovers after steroid withdrawal, and sensitivity to ACTH returns more rapidly than normal ACTH secretion. Presumably, the transitory impairment of function is due both to reduced responsiveness of the adrenal to ACTH and to failure of the pituitary to discharge this hormone.

Russell, S. M., Dhariwal, A. P. S., McCann, S. M., Yates, F. E.: "Inhibition by dexamethasone of the in vivo pituitary response to corticotrophin-releasing factor (CRF)." *Endocrinology* 85: 512-521 (1969) (41 refs.). H16,365/69

Smelik, P. G.: "The effect of a CRF preparation on ACTH release in rats bearing hypothalamic dexamethasone implants: a study on the 'implantation paradox.'" *Neuroendocrinology* 5: 193-204 (1969). H20,907/69

Ten and eighteen hours after implantation of dexamethasone in the hypothalamus of rats, ACTH secretion could be obtained by CRF but not by vasopressin or other known

releasing stimuli. However, a gradual decrease in pituitary-adrenal responsiveness to CRF was also noted. "It is concluded that the dexamethasone blockade is exerted primarily on the hypothalamic level, but that an eventual transport of the implanted substance to the anterior pituitary may account for the decrease in pituitary sensitivity. However, this could also be due to the absence of endogenous CRF. The sensitivity and specificity of the 10-h dexamethasone-implanted rat would provide a suitable assay preparation for CRF."

Yates, F. E., Brennan, R. D., Urquhart, J.: "Adrenal glucocorticoid control system." *Fed. Proc.* **28**: 71-83 (1969). H7,417/69

Review of contemporary knowledge on the feedback systems regulating inhibition of ACTH, with special reference to computer simulation. It appears that corticoids block adrenal activation by stressors up to a maximum, after which increased severity of the stressor will be effective even in the presence of excess glucocorticoids. "When double dose-response maps of adrenocortical function are made by plotting the response of the adrenocortical system against the strength of the stressful stimulus and obtaining a curve for each condition of corticosteroid pretreatment ranging from none to the maximally effective dose, and beyond, it can be seen that the feedback inhibition property of the adrenocortical system has noncompetitive saturation characteristics. This saturation characteristic explains why many investigators fail to be impressed with the capacity of corticosteroids to inhibit stress response. In those cases in which the failure of inhibition is observed, the strength of the stimulus is very high, and beyond the saturation level for the feedback system. When stimulus strength is lower, however, the feedback inhibition is apparent" (48 refs.).

Dunn, J., Critchlow, V.: "Feedback suppression of 'non-stress' pituitary-adrenal function in rats with forebrain removed." *Neuroendocrinology* **4**: 296-308 (1969).

H14,759/69

In rats, forebrain removal or brain stem transection did not interfere with the suppression of corticoid secretion by dexamethasone, "suggesting that negative feedback acts in part directly on the anterior pituitary." Rats with large hypothalamic islands had unusually high plasma corticosterone levels, whereas those with basal hypothalamic islands, pituitary islands or brain stem transec-

tions maintained their blood corticoids essentially within normal limits.

Dallman, M. F., Yates, F. E.: "Dynamic asymmetries in the corticosteroid feedback path and distribution-metabolism-binding elements of the adrenocortical system." *Ann. N.Y. Acad. Sci.* **156**: 696-721 (1969).

H10,875/69

In rats, "the adrenocortical system appears to have asymmetrical dynamic properties that could qualify it to serve as one channel, or rein, in multiple-channel chemical control arrangements."

Smelik, P. G.: "The regulation of ACTH secretion." *Acta Physiol. Pharmacol. Neerl.* **15**: 123-135 (1969).

G67,350/69

Bohus, B.: "Evaluation of the role of the feedback effect of corticosteroids in the control of pituitary ACTH release." *Acta Physiol. Acad. Sci. Hung.* **35**: 141-148 (1969).

G68,251/69

In rats pretreated with corticosterone, the acute ACTH release caused by restraint or hemidiadrenalectomy remains unaffected, but the action of chronic stressors is suppressed. Sensitivity to exogenous ACTH is unchanged.

Arimura, A., Bowers, C. Y., Schally, A. V., Saito, M., Miller, M. C.: "Effect of corticotropin-releasing factor, dexamethasone and actinomycin D on the release of ACTH from rat pituitaries in vivo and in vitro." *Endocrinology* **85**: 300-311 (1969).

H15,815/69

Comparative in vivo and in vitro studies in rats, using actinomycin D to block DNA-dependent RNA synthesis led the authors to conclude that: "1) Dexamethasone suppresses the action of CRF at the pituitary level, 2) this dexamethasone blockade does not develop immediately, 3) dexamethasone-blockade of CRF requires a process which involves DNA-dependent RNA synthesis, and 4) the process of ACTH release by CRF does not require RNA synthesis" (34 refs.).

Zimmermann, E., Critchlow, V.: "Suppression of pituitary-adrenal function with physiological plasma levels of corticosterone." *Neuroendocrinology* **5**: 183-192 (1969).

H20,906/69

Steiner, F. A., Ruf, K., Akert, K.: "Steroid-sensitive neurones in rat brain: anatomical localization and responses to neurohumours and ACTH." *Brain Res.* **12**: 74-85 (1969).

H28,002/69

Microelectrophoresis allows deposition of minute amounts of soluble compounds in the immediate extracellular environment of single cells in the CNS, and permits direct monitoring of the local response by recording single unit action potentials. In rats, it has been shown with this technique that dexamethasone-sensitive cells can be accurately identified and localized in the hypothalamus and midbrain, scattered over wide areas. The large majority of these cells are clearly inhibited, but some are activated. No steroid-sensitive neurons were found in the cortex, dorsal hypothalamus or thalamus. The steroid-sensitive neurons were responsive to microelectrophoretically applied NEP and acetylcholine. The predominant action of the former was inhibition, while that of the latter was stimulation. ACTH activated the steroid-sensitive neurons. Presumably, "specific nerve cells in the hypothalamus and midbrain are sensitive to both hormonal and humoral factors and involved in negative and positive feedback actions of the hormones."

French, F. S., Macfie, J. A., Williams, T. F., Wyk, J. J. van: "Cushing's syndrome with a paradoxical response to dexamethasone." *Am. J. Med.* **47**: 619-624 (1969).

G70,061/69

In a patient with Cushing's syndrome due to a basophil hypophyseal adenoma, dexamethasone enhanced urinary 17-OHCS and 17-KS excretion as well as plasma ACTH activity. Metyrapone caused an initial rise in urinary 17-KS due to an augmentation of tetrahydro-11-deoxycortisol, as expected, but a much larger increase in adrenal corticoid release occurred on the second and third days and was associated with the reappearance of urinary cortisol metabolites.

Ceresa, F., Angeli, A., Bocuzzi, G., Molino, G.: "Once-a-day neurally stimulated and basal ACTH secretion phases in man and their response to corticoid inhibition." *J. Clin. Endocrinol. Metab.* **29**: 1074-1082 (1969). H15,880/69

In man, submaximal infusion doses of 6-methylprednisolone or dexamethasone led to partial blockade of the nocturnal and early morning urinary 17-OHCS excretion, but no inhibition occurred from 22:00 to midnight unless very massive doses of dexamethasone were administered. It is concluded that "the ACTH-secreting system has 2 daily activity phases with different control mechanisms. One in the nocturnal early morning hours is

the result of neural activity directed to the hypothalamus, superimposed on the basal activity and responsible for the circadian rhythm. This once-a-day impulse would appear to be linked to the rapid eye movement sleep stages. Corticoid-induced inhibition in submaximal doses is possible only during this phase. The second phase is characterized by a steady basal activity lasting 24 hr. It is independent of the early morning hour impulse and is resistant to all but massive doses of corticoids."

Hedge, G. A., Smelik, P. G.: "The action of dexamethasone and vasopressin on hypothalamic CRF production and release." *Neuroendocrinology* **4**: 242-253 (1969).

H14,752/69

In rats, pretreatment with dexamethasone abolished the pituitary-adrenal response to ether or surgical trauma. However, insertion of a cannula into the anterior hypothalamus or injection of vasopressin still elicited transient adrenocortical secretion. Following repeated hypothalamic stimulation or adaptation to handling, subsequent dexamethasone injections had a reduced effect, but the response to CRF preparations remained unchanged. "The data were interpreted to indicate that dexamethasone blocks the production rather than the release of CRF, and that mechanical stimulation of the hypothalamus and vasopressin are able to deplete the CRF stored in the CRF-producing neurons."

Kendall, J. W., Grimm, Y., Shimshak, G.: "Relation of cerebrospinal fluid circulation to the ACTH-suppressing effects of corticosteroid implants in the rat brain." *Endocrinology* **85**: 200-208 (1969). H15,802/69

In rats, pellets of corticosterone or dexamethasone were placed in various regions of the ventricular system, and their effect upon ether-induced ACTH secretion was determined. "It is suggested that reported extra-hypothalamic feedback receptor sites in the rat forebrain can be explained on the basis of transport of corticosteroid from the sites of placement through the ventricular system to a single feedback site located in the basal hypothalamus or anterior pituitary."

Fortier, C., Labrie, F., Pelletier, G., Raynaud, J. P., Ducommun, P., Delgado, A., Labrie, R., Ho-Kim, M.-A.: "Recent studies on the feedback control of ACTH secretion, with particular reference to the role of transcortin in pituitary thyroid-adrenocorti-

cal interactions." In: Wolstenholme, G. E. W. and Knight, J., *Ciba Foundation Symposium on Control Processes in Multicellular Organisms*, pp. 178-209. London: J & A Churchill, 1970. G74,630/70

In rats, thyroxine increases transcartin binding sites and thereby influences the feedback control of ACTH secretion, since the unbound, not the total, corticosterone concentration is the variable factor during this homeostatic reaction. On the other hand, in man, cortisol enhances the effect of thyroxine on transcartin binding, and this multiplies the action of the thyroid hormone upon the corticoid feedback.

Gonzalez-Luque, A., L'age, M., Dhariwal, A. P. S., Yates, F. E. "Stimulation of corticotropin release by corticotropin-releasing factor (CRF) or by vasopressin following intrapituitary infusions in unanesthetized dogs: inhibition of the responses by dexamethasone." *Endocrinology* 86: 1134-1142 (1970) (28 refs.). H25,228/70

Fleischer, N., Rawls, W.: "Adrenocorticotropin (ACTH) synthesis and release in rat pituitary monolayer culture: the effect of dexamethasone." *Clin. Res.* 18: 30 (1970).

H33,211/70

Dexamethasone inhibits the release of ACTH in pituitary monolayers without affecting its synthesis.

Smelik, P. G.: "Adrenocortical feedback control of pituitary adrenal activity." *Prog. Brain Res.* 32: 21-24 (1970).

H45,305/70

Personal observations and review of the literature show that the feedback action of corticoids upon ACTH secretion is primarily on the hypothalamus and to some extent on the pituitary, depending upon dosage, timing and so on. "Such findings may cause some confusion in the literature, because they can be, and have been used, as evidence for or against either a hypothalamic or a pituitary site of action. Only if careful dose and time relationships are established experimentally, it will become clear that the conclusions are dependent on the experimental parameters; and that both structures can be affected, the hypothalamus being the most sensitive one."

Feldman, S., Sarne, Y.: "Effect of cortisol on single cell activity in hypothalamic islands." *Brain Res.* 23: 67-75 (1970).

H45,936/70

In rats with hypothalamic deafferentation (Halász knife), the spontaneous firing of hy-

pothalamic single cell units was increased and could not be diminished by cortisol. "However, when the firing was analysed in individual neurones for longer periods, both before and following cortisol administration, significant changes in the rate and pattern of discharge were found, indicating that the hormone has a direct effect on hypothalamic neurones. The most prominent effect was an initial reduction in the rate of discharge and this may possibly be related to a decrease in corticotropin releasing factor activity produced by corticosteroids at hypothalamic levels."

Feldman, S., Dafny, N.: "Effects of cortisol on unit activity in the hypothalamus of the rat." *Exp. Neurol.* 27: 375-387 (1970).

G76,224/70

In rats, cortisol increased the rate of spontaneous firing in both the anterior-tuberal and posterior hypothalamus. Sciatic stimulation enhanced cell firing in the anterior-tuberal hypothalamus of nontreated rats, while in the cortisol-treated animals, the unit discharge rate was decreased in the anterior-tuberal hypothalamus and increased in the posterior hypothalamus.

Steiner, F. A.: "Effects of ACTH and corticosteroids on single neurons in the hypothalamus." *Prog. Brain Res.* 32: 102-107 (1970).

H45,491/70

By use of a microelectrophoretic application in anesthetized rats, it was found that "dexamethasone phosphate-sensitive neurons were localized in the hypothalamus, and in the midbrain scattered over wide areas. Of these neurons, the large majority was clearly inhibited and a small number activated. No steroid-sensitive neurons were found in the cortex, the dorsal hippocampus, or in the thalamus. Locally delivered synthetic ACTH activated the steroid-sensitive neurons. Noradrenaline and dopamine inhibited, and acetylcholine activated dexamethasone-sensitive neurons. These results could indicate that specific nerve cells in the hypothalamus and midbrain are sensitive to both hormonal and neurohumoural factors."

Bohus, B., Strashimirov, D.: "Localization and specificity of corticosteroid 'feedback receptors' at the hypothalamo-hypophyseal level; comparative effects of various steroids implanted in the median eminence or the anterior pituitary of the rat." *Neuroendocrinology* 6: 197-209 (1970).

H28,814/70

In rats, "suppression of ACTH release was

observed after the implantation of dexamethasone, cortisol, corticosterone, 11-dehydrocorticosterone and 11-deoxycorticosterone (DOC) in the anterior median eminence. 11-Deoxycortisol (Reichstein's substance S), tetrahydrocortisol, pregnenolone, progesterone, and testosterone were ineffective when implanted in this region. Infundibular dexamethasone, cortisol and 11-deoxycorticosterone implants suppressed ACTH release, while other steroids were not effective. Dexamethasone and 11-deoxycorticosterone also suppressed ACTH release when implanted bilaterally in the anterior pituitary." Presumably, corticoid feedback receptors exist in both the hypothalamus and the anterior pituitary.

Fortier, C., Delgado, A., Ducommun, P., Ducommun, S., Dupont, A., Jobin, M., Kraicer, J., MacIntosh-Hardt, B., Marceau, H., Mialhe, P., Mialhe-Voloss, C., Rerup, C., Rees, G. P. van: "Functional interrelationships between the adenohypophysis, thyroid, adrenal cortex and gonads." *Can. Med. Assoc. J.* **103**: 864-874 (1970).

H30,500/70

In the intact rat, thyroxine increases transcartin binding sites. "The unbound, as opposed to total, corticosterone concentration is the variable under feedback control and, in view of the unaltered metabolic clearance rate of corticosterone in the rat, the binding capacity of transcartin is entirely responsible, in this species, for the adjustment of ACTH and corticosterone secretion to altered thyroid activity." The metabolic clearance rate of corticosterone is independent of thyroid activity, because access of the corticoid to inactivation sites in the liver nullifies the enhancement by thyroxine of hepatic-reducing capacity. In man the binding capacity of transcartin is independent of thyroid activity, because cortisol enhances the effect of thyroxine on transcartin binding in proportion to the enhancement by the thyroid hormone of corticoid inactivation.

Bhattacharyya, T. K., Ghosh, A.: "Influence of surgical and steroidical bursectomy on the behavior of adrenal ascorbic acid during stress in juvenile pigeons." *Gen. Comp. Endocrinol.* **15**: 420-424 (1970).

H35,126/70

In juvenile pigeons, bursectomy facilitated the depletion of adrenal ascorbic acid during stress (formalin). Cortisol caused involution of the bursa but left adrenal ascorbic acid levels unaltered after exposure to stress.

Blumenfield, M., Rose, L. I., Richmond, L. H., Beiring, S. C.: "Dexamethasone suppression in basic trainees under stress." *Arch. Gen. Psychiatry* **23**: 299-304 (1970).

G78,353/70

In man, "emotional stress can be a cause for the failure of dexamethasone suppression."

Szot, R. J., Murphy, S. D.: "Phenobarbital and dexamethasone inhibition of the adrenocortical response of rats to toxic chemicals and other stresses." *Toxicol. Appl. Pharmacol.* **17**: 761-773 (1970).

G80,047/70

Hodges, J. R., Mitchley, S.: "Circadian rhythm in plasma corticosterone concentration and pituitary adrenocorticotrophic response to stress in the betamethasone treated rat." *Br. J. Pharmacol.* **39**: 192P-193P (1970).

J21,250/70

Hodges, J. R., Mitchley, S.: "The effect of betamethasone on circadian and stress-induced pituitary-adrenocortical function in the rat." *Br. J. Pharmacol.* **38**: 719-724 (1970).

G74,439/70

"Both the circadian and stress-induced changes in plasma corticosterone concentration were abolished by the inclusion of betamethasone in the drinking water of rats." Adrenal sensitivity to ACTH remained unimpaired by betamethasone.

Urquhart, J., Krall, R. L., Li, C. C.: "Adrenocortical secretory function—communications and control aspects." *Automatica* **6**: 193-205 (1970).

J11,823/70

After reviewing their observations on the stimulation of corticoid secretion by ACTH in the canine adrenal, the authors "have developed a seventh order state variable model of this process in terms of current knowledge about the mechanisms of cortisol biosynthesis. The modeling plays a dual heuristic role: (1) at the very least, it provides a phenomenological description of adrenocortical secretory function for use in larger models of pituitary-adrenal control mechanisms, and (2) it is an aid in evaluating postulated mechanisms by which ACTH acts on the kinetic parameters of cortisol biosynthesis."

Takebe, K., Kunita, H., Sakakura, M., Horiuchi, Y., Mashimo, K.: "Suppressive effect of dexamethasone on the rise of CRF activity in the median eminence induced by stress." *Endocrinology* **89**: 1014-1019 (1971).

H47,039/71

In rats, dexamethasone blocked the stress-

induced (surgery) rise in the CRF level of the ME and in the plasma corticosterone concentration. The pituitaries of dexamethasone-treated rats responded to ME extract in a normal manner. It is concluded that the dexamethasone-induced inhibition acts mainly at or above the hypothalamic level.

Hodges, J. R., Mitchley, S.: "Effects of stress and betamethasone on the production of corticosterone by the rat adrenal gland in vitro." *Br. J. Pharmacol.* **41**: 640-647 (1971). G84,324/71

Betamethasone had no effect on glucocorticoid production in vitro when added directly to the incubation medium of previously stressed rats. Presumably, feedback control does not occur at the adrenal level.

Zimmermann, E., Smyrl, R., Critchlow, V.: "Suppression of pituitary-adrenal response to stress with physiological plasma levels of corticosterone in the female rat." *Neuroendocrinology* **10**: 246-256 (1972).

H61,506/72

Small doses of dexamethasone "abolished non-stress pituitary-adrenal function and blocked acute (15 min) corticosterone responses to 1 min ether, 3 min heat, and 1 or 3 min supination, but not those to 3 min ether, immobilization, or cold."

Riegler, G. D., Hess, G. D.: "Chronic and acute dexamethasone suppression of stress activation of the adrenal cortex in young and aged rats." *Neuroendocrinology* **9**: 175-187 (1972). H54,322/72

The corticoid feedback mechanism is much less effective in old than in young rats exposed to ether vapor.

Smellik, P. G.: "Feedback actions of adrenocortical hormones." *Acta Med. Acad. Sci. Hung.* **29**: 89-96 (1972). J10,356/72

Review of the literature and personal observations suggest that hypothalamic centers exert a tonic influence on ACTH secretion and also regulate its rhythmic circadian variations and increased release during stress. Activation of the system can be suppressed by corticoids through a feedback in the hypothalamus, "presumably located in the cell bodies of the CRF neurons. These neurons are capable of summing excitatory and inhibitory stimuli, which can be either neural or humoral and after summation they will send a releasing signal of an exactly determined intensity to the anterior pituitary." Sayers' theory that increased utilization of corticoids during stress is re-

sponsible for an effective feedback to inhibit further ACTH secretions is rejected, since it was based on an "incorrect assumption, i.e., that stress would cause an initial fall in corticoid levels. As soon as direct measurement of corticoid titers could be performed, it appeared that such an initial fall does not take place."

Ondo, J. G., Kitay, J. I.: "Effects of dexamethasone and stressful stimuli on hypothalamic electrical activity in rats with diencephalic islands." *Neuroendocrinology* **9**: 215-227 (1972). H56,043/72

In rats with diencephalic islands (Cross and Kitay technique), dexamethasone was shown to have a direct effect on the neurons of the isolated basal hypothalamus. However, vasopressin and histamine, which have an inverse effect on ACTH discharge, similarly inhibited the firing of hypothalamic neurons. Thus, "a simple explanation relating neuronal firing rate and the mechanisms involved in the control of ACTH secretion is obviously not possible." The literature on the effects of various hormones on hypothalamic neurons is reviewed.

Papaikonomou, E.: "A cybernetic approach to the hypothalamo-pituitary/adrenal system." *Prog. Brain Res.* **38**: 293-302 (1972).

J11,299/72

Brief summary of the author's mathematical approach to the cybernetic regulation of the hypothalamus-pituitary-adrenal feedback system.

Endrőczi, E.: "Role of glucocorticoids in controlling pituitary-adrenal function." *Acta Med. Acad. Sci. Hung.* **29**: 49-59 (1972) (23 refs.).

J10,352/72

Espinier, E. A., Hart, D. S., Beaven, D. W.: "Cortisol secretion during acute stress and response to dexamethasone in sheep with adrenal transplants." *Endocrinology* **90**: 1510-1514 (1972). H55,924/72

In sheep with adrenal autotransplants, intermittent peaks in cortisol release and a biphasic response to stress were observed. It was also noted that a "rapid rise and fall in adrenal cortisol secretion occurs in sheep and that, despite a maximal adrenal response to stress, dexamethasone (70-115 µg/kg) can completely inhibit this response for 6-7 hr."

Jones, M. T., Brush, F. R., Neame, R. L. B.: "Characteristics of fast feedback control

of corticotrophin release by corticosteroids." *J. Endocrinol.* **55**: 489-497 (1972).

H64,133/72

Wittkowski, W., Bock, R.: "Electron microscopical studies of the median eminence following interference with the feedback system anterior pituitary-adrenal cortex." In: Knigge, K. M., Scott, D. E. et al., *Brain-Endocrine Interaction. Median Eminence: Structure and Function*, pp. 171-180. Basel and New York: S Karger, 1972.

E10,567/72

EM studies on the ME in adrenalectomized or cortisol-treated rats illustrate the structural basis of the feedback mechanism. The diameter of "Gomori-positive" elementary granules in the zona externa is variable but never attains that of the granules in the zona interna. The "findings support the assumption that different hormones and their carrier substances are concerned—oxytocin and vasopressin in the zona interna and the CRF in the zona externa."

Kraicer, J., Gosbee, J. L., Bencosme, S. A.: "Pars intermedia and pars distalis: two sites of ACTH production in the rat hypophysis." *Neuroendocrinology* **11**: 156-176 (1973). H68,125/73

In rats "the concentration of ACTH in the pars intermedia is considerably greater than that in the pars distalis. At 1 month after adrenalectomy, the ACTH concentration in the pars distalis increased 3-fold, while that in the pars intermedia remained unchanged. Following chronic administration of cortisol, the ACTH concentration in the pars distalis fell to 27% of the control, while the fall in ACTH concentration in the pars intermedia was not significant.... Although a relation between the pars intermedia and ACTH is established, this relation is different from that between the pars distalis and ACTH."

Dallman, M. F., Jones, M. T.: "Corticosteroid feedback control of stress-induced ACTH secretion." In: Brodish, A. and Redgate, E. S., *Brain-Pituitary-Adrenal Interrelationships*, pp. 176-196. Basel, München and Paris: S Karger, 1973. J11,222/73

In rats "the net result of both stress and corticosterone feedback signals is a continually responsive system that does not secrete too much ACTH but always secretes enough. Acutely, the rise of corticosterone stimulated by increased ACTH levels acts through a rate-sensitive or fast-feedback path to rapidly limit the duration of ACTH

secretion; and chronically, two or more hours after corticosterone levels have been elevated there is a decrease in the amount of ACTH secreted in response to stress. Stress itself, however, appears to facilitate the response of some element of the adrenocortical system above the adrenal to subsequent stress."

Smelik, P. G., Papaikonomou, E.: "Steroid feedback mechanisms in pituitary-adrenal function." *Prog. Brain Res.* **39**: 99-109 (1973). J11,300/73

Analysis of the pituitary-hypothalamus system in terms of a feedback loop. "The system does not operate with a fixed or variable set-point, but should be considered as a servomechanism, which follows the variable needs for glucocorticoids. The amount of CRF released depends on a summation by a hypothalamic comparator of neural and humoral stimuli, which can be positive or negative." The capacity of the feedback signal is limited and has only a stabilizing function. There is no qualitative difference between the basal state of the system and its response to stress. [In the discussion Hodges states, "in spite of the work which Dr. Smelik has presented, I still believe that while corticosteroids may control the basal level of ACTH secretion and corticotrophin synthesis, a feedback mechanism controlling stress-induced ACTH secretion is of little physiological significance" (H.S.).]

Goldman, L., Winget, C., Hollingshead, G. W., Levine, S.: "Postweaning development of negative feedback in the pituitary-adrenal system of the rat." *Neuroendocrinology* **12**: 199-211 (1973). H74,726/73

Given before ether or electroshock, "pretreatment with peripherally injected dexamethasone completely blocked a plasma corticosterone increase, in response to an ether and blood sampling stress in adults, but only partially reduced this response in weanlings. The failure of basal hypothalamic implants of corticoids to differentiate between ages in their ability to inhibit this stress response supported the suggestion of extra-hypothalamic inhibitory systems as the loci of the deficit in weanlings."

Kraulis, I., Traikov, H., Li, M. P., Birmingham, M. K.: "The effects of corticosterone, 18-OH-DOC, DOC and 11 β -hydroxyprogesterone on the adrenal pituitary axis of the stressed rat." *J. Steroid Biochem.* **4**: 129-137 (1973). J2,229/73

Progesterone and 18-OH-DOC, unlike corticosterone, 11 β -hydroxyprogesterone, and DOC, failed to inhibit the ACTH discharge in rats stressed either with ether or by a change of environment.

Langholz, J., L'age, M.: "Disturbance of the feedback mechanism of the adrenocortical system in the alloxan diabetic rat." *Acta Endocrinol.* (Kbh.) **72** Supp. 171: 31 (1973). H68,831/73

Dallman, M. F., Jones, M. T.: "Corticosteroid feedback control of ACTH secretion: effect of stress-induced corticosterone secretion on subsequent stress responses in the rat." *Endocrinology* **92**: 1367-1375 (1973). H70,213/73

The authors conclude from their experiments and a survey of the literature that in adrenalectomized rats "corticosterone does act to inhibit ACTH secretion, but that stress causes a prolonged period of hyper-responsiveness in either CNS or anterior pituitary components of the adrenocortical system."

Briaud, B.: "Réponse corticosurrénalienne aux agressions neurotropes et systémiques après injection de corticostéroïdes" (Adrenocortical response to neurotropic and systemic stress after corticosteroid injection). *J. Physiol.* (Paris) **66**: 259-270 (1973). J7,439/73

In rats, about twice as much corticosterone or dexamethasone is needed to inhibit the adrenal response to systemic (ether) than to neurogenic (sound) stress of equal intensity.

Melby, J. C.: "Systemic corticosteroid therapy: pharmacology and endocrinologic considerations." *Ann. Intern. Med.* **81**: 505-512 (1974). J16,876/74

In patients with rheumatoid arthritis, pyrogen therapy was often superior to treatment with glucocorticoids. "High-dose corticosteroid therapy abolished the hypothalamic-pituitary-adrenal response to pyrogen stress, whereas low doses of steroids produced only insignificant alterations to the response to pyrogen stress. Other studies involving testing of the negative feedback response (metyrapone test) may be abnormal even at rather modest doses of corticosteroids."

Buckingham, J. C., Hodges, J. R.: "Interrelationships of pituitary and plasma corticotrophin and plasma corticosterone in adrenalectomized and stressed, adrenalectomized rats." *J. Endocrinol.* **63**: 213-222 (1974). H95,881/74

Experiments on rats exposed to ether vapor "suggest that the synthesis and the basal release of ACTH are directly controlled by the concentration of corticosteroid in the blood, but the corticosteroids exert only a delayed effect in modulating the stress-induced release of the hormone."

Zurbrügg, R. P., Zimmermann, E., Oetliker, O. H.: "Adrenocortical function following long-term corticosteroid treatment." *Helv. Paediatr. Acta* **29**: 221-235 (1974).

J16,948/74

In patients on chronic prednisone therapy, ACTH discharge during stress or injection of ACTH causes subnormal glucocorticoid secretion, even several weeks after discontinuation of treatment (82 refs.).

Turner, B. B., Taylor, A. N.: "Neonatal corticosterone treatment: persistence of reduced corticosteroid levels in adult rats." *Fed. Proc.* **33**: 206 (1974). H83,817/74

In rats, implantation of corticosterone pellets during the first three weeks of life may exert a permanent suppressive effect upon adrenal corticoid production, detectable after they become adults.

Mitro, A., Németh, S., Mikulaj, L.: "Inhibition of the adrenal response to various stressors by hydrocortisone administration into the brain ventricles." *Gen. Comp. Endocrinol.* **22**: 361 (1974). H83,191/74

Buckingham, J., Hodges, J. R.: "Corticosterone in the control of corticotrophin secretion in the rat." *J. Endocrinol.* **61**: xxvi-xxvii (1974). H87,553/74

Experiments on intact and adrenalectomized rats treated with corticosterone and exposed to the stressor effect of mild ether anesthesia "suggest that, under 'normal' physiological conditions, blood corticosteroids are involved in the control of the basal secretion of ACTH but that they do not affect the stress-induced release of the hormone."

Jones, M. T., Tiptaft, E. M., Brush, F. R., Fergusson, D. A. N., Neame, R. L. B.: "Evidence for dual corticosteroid-receptor mechanisms in the feedback control of adrenocorticotrophin secretion." *J. Endocrinol.* **60**: 223-233 (1974). H83,403/74

In rats, fast feedback of ACTH secretion during surgically induced stress occurs within minutes of treatment with small doses of corticosterone but is of short duration. Delayed feedback occurs after 1 hour or more,

and requires larger doses of corticosterone. The latter and cortisol are synergists in both these feedbacks, whereas DOC and 11-desoxycortisol are antagonists of fast and agonists of delayed feedback. "It is concluded that the two feedback mechanisms have different dynamics and separate receptors."

Brush, F. R., Dallman, M., Jones, M. T., Tiptaft, E.: "Corticosteroid feedback at the pituitary level." *J. Endocrinol.* 61: lxiv-lxv (1974). H87,801/74

ACTH secretion is regulated by both a fast and a delayed corticoid feedback. From corticosterone production in the adrenals of ME-lesioned rats, it is concluded that "delayed corticosteroid feedback exists at both the hypothalamic and pituitary levels, but that some corticosteroids feedback exclusively at the hypothalamus."

Chattopadhyay, S., Uniyal, M.: "The interaction of stress and corticosteroid on the hypothalamus as reflected by GABA content." *5th Asia & Oceania Congr. Endocr.*, p. 48. Chandigarh, India, 1974. H82,064/74

In rats the negative feedback influence of circulating corticosteroids and the administration of triamcinolone induced a low GABA concentration in the hypothalamus, whereas exposure to stress led to a higher GABA level than in the controls. "The interaction of stress-induced excitation and negative feedback inhibition owing to increased concentration of corticosteroid may involve GABA in the integrative processes of the hypothalamus."

Daly, J. R., Fleisher, M. R., Chambers, D. J., Bitensky, L., Chayen, J.: "Application of the cytochemical bioassay for corticotrophin to clinical and physiological studies in man." *Clin. Endocrinol. (Oxf.)* 3: 335-345 (1974).

H88,166/74

In rheumatoid arthritics chronically treated with ACTH, insulin hypoglycemia causes a subnormal rise in plasma ACTH, yet the plasma cortisol level is identical to that in the controls. Presumably, the adrenal in ACTH-treated patients is hypersensitive and responds to subnormal amounts of ACTH with an enhanced cortisol secretion. However, the difference is very slight, and only the rate of response, measured by the slope of the steepest part of the curve, differs significantly. Hence, strong ACTH treatment alters only the rate of ACTH release in response to hypoglycemia, not the total amount

secreted. In contrast, prolonged corticoid treatment greatly reduces the ACTH discharge following insulin hypoglycemia.

Buckingham, J. C., Hodges, J. R.: "The redox bioassay technique for the direct assessment of pituitary adrenocorticotrophic activity in the rat." *Clin. Endocrinol. (Oxf.)* 3: 347-348 (1974). H88,167/74

The rise in plasma and pituitary ACTH that occurs after adrenalectomy or adrenalenucleation in rats is inversely correlated with plasma corticosterone levels, but the elevation after mild stress (ether anesthesia) is not. "It appears that under 'normal' physiological conditions the blood corticosteroids are involved in the control of both the synthesis and the basal secretion of ACTH but that they do not affect the stress induced release of the hormone."

Papaikonomou, E.: *Biocybernetics, Bio-systems Analysis and the Pituitary Adrenal System*, p. 334. Purmerend, Netherlands: Nooy's Drukkerij, 1974. E10,437/74

A monograph that combines insight and wit in applying the principles of systems analysis strategy and biocybernetics to the study of the pituitary-adrenocortical apparatus in relation to the G. A. S. Sayers' hypothesis about the activation of ACTH secretion by a negative feedback due to increased utilization of glucocorticoids during stress was not supported by subsequent experiments. It was replaced by Yates' theory that stress activates a controller of the system in the hypothalamus. Then Smelik provided evidence of an integral controller of the system with a derivative controller sensitive to negative rates of change of blood glucocorticoids. In studies concerning the regulation of corticoid secretion, it is essential to consider the ACTH concentration of the blood, and the flow, as separate input variables, and to distinguish between the effect of free and protein-bound corticoids. The author summarizes his concept as follows: "At the lowest level we put the anterior pituitary (adenohypophysis) [and the adrenal cortex], along with local metabolic regulators in peripheral tissues and organs, which are under the control of glucocorticoids. Under normal (non-stress) conditions there will be an optimal activity pattern for this level with a corresponding optimal set of characteristics and parameters of its elements; these are established during postnatal development."

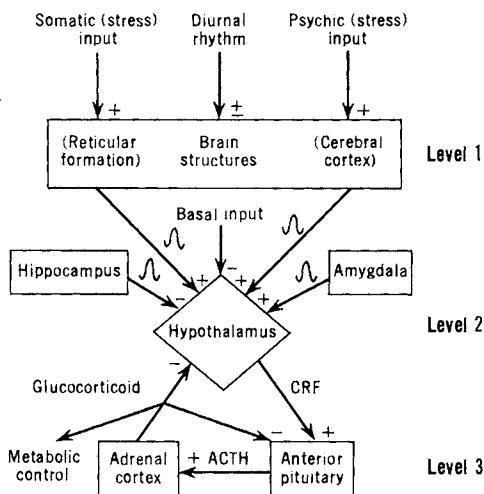


Figure 21. A three-level model of communication and control hierarchy in the pituitary adrenal system. (Reproduced from *Biocybernetics, Biosystems Analysis, and the Pituitary Adrenal System* (1974), Fig. 6-8, p. 170, by permission of E. Papaikonomou and Nooy's Drukkerij.)

"A feature of autoregulation is exhibited here by means of the DBM elements (distribution, binding, and metabolism, not shown in the scheme), and by the mildly modulating (inhibitory) effect of glucocorticoids on the pituitary response to CRF. Since this activity will have to be constant as long as nothing changes at the lowest level, (this is a corollary of the hypothesis of homeostasis of Claude Bernard), the only thing needed for the resting function of this level is a constant stimulus from a higher level; apart from this constant stimulus, the lowest level is virtually autonomously functioning.

"At the second level there is the hypothalamus from which the command signal to the lowest level originates, along with two other brain structures, the amygdala and the hippocampus (the first with an excitatory and the second with an inhibitory action on the hypothalamus; it should be noted that this may be an oversimplification: Some other brain structures like the midbrain and the thalamus may also be involved). We actually distinguish two sublevels in this second level of control: the hypothalamus lower, the amygdala and the hippocampus higher. When something happens in the lowest level, (e.g., some metabolic change, external disturbance of ACTH or glucocorticoid levels by injection, etc.), then the CRF command signal

(output of the hypothalamus) changes accordingly to counteract the deviations; these deviations are, of course, monitored at the second level ("feedback" of glucocorticoids); if they are not too big by the hypothalamus, but if they are extreme also by the amygdala and the hippocampus. Here information about the deviations is integrated with information from other parts of the organism (tissues or other homeostatic mechanisms), and the resulting control signal is sent forward to the lowest level.

"Finally, when an external stimulus such as *psychic stress* (e.g., anxiety, fear, a new environment, etc.), or *somatic stress* (e.g., trauma, surgery, noxious substances, etc.), appears, which brings the whole organism in danger, then the highest control level comes into action. We think that at this level are the cerebral cortex (monitoring psychic stress) and the brain stress reticular formation (where somatic stress is monitored); some other structures intervening between the above ones and the second level structures may also be actively involved. Information about the stimulus is here correlated and integrated with stored information about the consequences of similar stimuli in the past and a control action is taken to increase (never decrease) the activity of the lowest level; this will take place by first changing

the activity of the second level, which will then result in an amplification of the output of this level, the CRF signal. This signal shows under resting conditions a diurnal oscillation (correlated with the sleep-and-wake schedule) that probably is generated at the highest control level" (about 450 refs.).

Feldman, S., Conforti, N., Chowers, I.: "Effect of dexamethasone on adrenocortical responses in intact and hypothalamically deafferented rats." *Isr. J. Med. Sci.* **10**: 572 (1974). H89,689/74

Inhibition of ACTH secretion by dexamethasone is more pronounced in intact than in hypothalamically deafferented rats. Apparently, the negative feedback of corticoids is exerted at the hypothalamic level, but

extrahypothalamic structures also participate in it.

Vermesh, I., Ryzhenkov, V. E.: "Functional condition of the hypophysis-adrenal system in rats with deafferented hypothalamus; the action of dexamethasone and nialamide." *Probl. Endokrinol.* **20** No. 3: 67-70 (1974) (Russian). H92,315/74

In rats with a completely deafferented MBH, the basal plasma corticosterone level rose; this elevation could be inhibited by dexamethasone or nialamide. "At the same time suppression of corticosterone secretion in stress [restraint] by nialamide was stronger in comparison with dexamethasone. Nialamide potentiated the depressive action of dexamethasone on the basal corticosterone secretion, but not under stress."

Corticoid "Utilization"

Some data concerning the "utilization" theory of corticoids as a means of regulating their production during stress have been discussed in the previous section, Corticoid Feedback; for the sake of completeness, these should also be consulted.

The question whether hormones are actually consumed by their receptors during the performance of their roles or act merely by their presence (as catalysts do) remains unsettled. However, beginning some twenty-five years ago, Sayers and his co-workers published a large number of papers in support of the concept that corticoid production increases during stress as a consequence of diminished feedback-inhibition of ACTH secretion, because the tissue utilization of corticoids rises. Yet as early as 1948 we showed that even enormous anesthetic doses of DOC failed to prevent the decrease in adrenal ascorbic acid content following exposure to cold. Hence we concluded that mere lack of corticoids could not be the decisive factor eliciting an ACTH discharge during stress.

It is hardly necessary today to reexamine all the arguments mustered in favor of the corticoid "utilization" theory, which held that "the tissues of the organism with a normal pituitary-adrenal system are never subjected to a plethora of cortical hormones as implied in the 'diseases of adaptation' thesis of Selye." If it were true that the feedback mechanism works perfectly during stress, the latter could never induce an increase in corticoid production, which it undoubtedly does. The complex theories and schematic drawings that attempted to coordinate increased corticoid utilization with nervous and catecholamine-regulated stimulation of ACTH secretion are listed in the abstract section merely for historical reasons, because they gave rise to a very large number of publications that the uninitiated worker in this field might otherwise be unable to evaluate.

The most significant fact to remember is that the corticoid feedback mechanism, though extremely important for homeostasis during near-physiologic conditions, becomes ineffective precisely during stress. This failure is of the greatest importance for the maintenance of homeostasis, since an adaptive increase in corticoid production would be impossible if the feedback mechanism continued to function perfectly, thus

interfering with the provision of an excess of corticoids at times of stress, when normal amounts are clearly insufficient.

It might have been argued that DOC, even in doses high enough to produce anesthesia, is not as potent as glucocorticoids in inhibiting ACTH secretion during stress. However, we found that even toxic doses of exogenous glucocorticoids (for example, cortisone) or endogenous steroids of this type (cortisol, corticosterone), secreted during stress, fail to prevent the ACTH discharge characteristic of the alarm reaction. Hence, the theory that a depletion of corticoids, owing to increased utilization, could explain the stress-induced ACTH discharge has by now been generally rejected.

If further arguments were needed, it might be mentioned that intravenous cortisol is less rapidly cleared from the blood in man during surgical stress than otherwise. Presumably, blood clearance of the hormone not only fails to be enhanced because of increased utilization but is actually delayed. Furthermore, in adrenalectomized dogs, the eosinopenic effect of cortisol is augmented by surgical interventions. "These and other data throw doubt on the hypothesis that increased corticoid utilization is responsible for the pituitary release of ACTH in the response to operative trauma." Finally, adrenalectomized animals are particularly sensitive to the ACTH-discharging effect of stressors, although they have no corticoids to start with and hence could not consume them during stress.

Corticoid "Utilization"

(See also our earlier stress monographs, p. xiii)

Tepperman, J., Engel, F. L., Long, C. N. H.: "A review of adrenal cortical hypertrophy." *Endocrinology* 32: 373-402 (1943). A58,184/43

Sayers, G., Sayers, M. A.: "Regulation of pituitary adrenocorticotrophic activity during the response of the rat to acute stress." *Endocrinology* 40: 265-273 (1947).

98,805/47

In rats, various stressors (heat, cold, histamine, EP, bacterial toxins and so on) fail to stimulate the adrenal cortex if sufficient amounts of glucocorticoids are supplied (as indicated by adrenal ascorbic acid content). "It would appear reasonable to suppose that the great variety of non-specific stresses increases pituitary adrenocorticotrophic activity by a common mechanism, namely, by increasing the requirement of the peripheral tissue cells for cortical hormone(s)."

Moya, F., Selye, H.: "Effect of desoxycorticosterone upon hypophyseal corticotrophin production." *Proc. Soc. Exp. Biol. Med.* 68: 529-531 (1948). B19,381/48

Even enormous anesthetic doses of DOC cannot prevent the decrease in adrenal ascorbic acid content following exposure to

cold. Hence, mere lack of corticoids cannot be the decisive cause of ACTH discharge during stress.

Sayers, G.: "Pituitary regulation of adrenal cortical activity." In: Soskin, S., *Progress in Clinical Endocrinology*, pp. 122-130. New York: Grune & Stratton, 1950.

B47,555/50

The author recapitulates his arguments in favor of enhanced "utilization" of corticoids during stress that would prevent the development of diseases of adaptation, owing to conditioning that increases sensitivity to pathogens. "It appears that the tissues of the organism with a normal pituitary-adrenal system are never subjected to a plethora of cortical hormones as is implied in the 'diseases of adaptation' thesis of Selye" (26 refs.).

Sayers, G.: "The adrenal cortex and homeostasis." *Physiol. Rev.* 30: 241-320 (1950).

B49,880/50

Extensive review of the literature on factors regulating corticoid production during stress. It is stated that stressors can increase the "utilization" of corticoids and might act as a feedback system, in that the resulting state of hypocorticism would stimulate ACTH secretion. Special sections are devoted to indices of the rate of corticoid discharge, the different types of corti-

coids, the G. A. S., the diseases of adaptation and so on (519 refs.).

McDermott, W. V., Fry, E. G., Brobeck, J. R., Long, C. N. H.: "Mechanism of control of adrenocorticotropic hormone." *Yale J. Biol. Med.* **23**: 52-66 (1950).

B51,980/50

Experiments on rats led to the concept that ACTH discharge during stress proceeds in two relatively independent and sequential phases. "The first or autonomic phase depends on the reflex secretion of epinephrine which directly activates the anterior pituitary, while the second or metabolic phase is based upon the rate of utilization of adrenal cortical hormones within the organism."

Hall, C. E., Finerty, J. C., Hall, O., Hess, M.: "The effect of acute and chronic desoxycorticosterone acetate pretreatment on the pituitary-adrenal response to stress." *Endocrinology* **48**: 591-595 (1951).

B59,640/51

Neither acute treatment with anesthetic doses of DOC nor chronic administration of smaller doses of the steroid affects adrenal ascorbic acid concentration. Such dosages also fail to prevent the characteristic stress response to burns. These findings are incompatible with the "corticoid utilization" theory of ACTH stimulation during stress.

Sayers, G.: "Regulation of the secretory activity of the adrenal cortex." *Am. J. Med.* **10**: 539-548 (1951).

B58,574/51

Review of the author's interpretation of corticoid secretion during stress. "In severe stress, anoxia or toxins may act directly on the adenohypophysis to induce discharge of ACTH. The fact that adenohypophyseal transplants discharge ACTH in response to stress indicates that direct neural or neurovascular connections are not essential elements in the regulatory scheme." It is primarily the increased "utilization" of corticoids during stress that causes a state of relative hypocorticism, stimulating ACTH secretion. "The concept emphasizes the determining role which the peripheral tissues, by their rate of 'utilization' of cortical hormone, exert in regulating pituitary adrenocorticotropic activity." The distinction between glucocorticoids and mineralocorticoids is rejected because it "implies that the secretion of the adrenal cortex may vary in composition according to the requirements of the organism." The findings reported by other laboratories that corticoids cannot

produce stress-induced adrenal ascorbic acid depletion may be explained by assuming that the "rate of 'utilization' of cortical hormone appears to be exceedingly fast during severe stress." Even "epinephrine may act like other non-specific agents and stresses to increase tissue 'utilization' of cortical hormone with a consequent lowering of venous blood titer of the hormone." Since transplants of adenohypophysis into the anterior chamber of the eye discharge ACTH during stress, "it appears that neither direct neural nor neurovascular connections with the hypothalamus are essential for the discharge of ACTH from the adenohypophysis" (86 refs.). [See later abstracts; virtually every one of these conclusions has since been contradicted (H.S.).]

Sayers, G.: "Regulation of pituitary corticotropin activity." In: Ralli, E. P., *Adrenal Cortex*, pp. 48-87. New York: Josiah Macy Jr. Foundation, 1951.

B60,495/51

In rats, manipulation of the intestines causes increased corticoid secretion (blood eosinophil test) in one hour, with it reaching a maximum in four hours. Following adrenal demedullation, suitable placement of lesions in the diencephalon, or transection of the spinal cord at the level of the third dorsal vertebra, this reaction still occurs but is greatly delayed. "We interpret this to mean that the reflex pathway for the secretion of epinephrine has been interrupted either by demedullation of the adrenals or by destruction of the ganglia in the brain stem that are concerned with this reflex." Presumably, the discharge of EP merely reinforces the ACTH-releasing mechanism. The most important regulator of ACTH is the blood level of corticoids, which drops during stress because of increased "utilization" by the tissues. Transection of the infundibulum does not interfere with the response of the pituitary to acute stress, as shown by many previous investigators; therefore, direct neural connections between the gland and the hypothalamus are not necessary, but this does not rule out messages transmitted through the hypophyseal portal system. The author believes that the work of several among his predecessors has shown conclusively that the fact "that adenohypophyseal transplants discharge ACTH in response to stress indicates that direct neural or neurovascular connections are not essential elements in the regulatory scheme. However, the experiments do not rule out the possibility that the hypothalamus has a modifying influence upon

pituitary adrenocorticotrophic activity." The literature on the inhibition of stress-induced ACTH discharge by DOC and cortisone is reviewed and confirmed, although the blockade is not complete and can be broken through by very severe stress. In the discussion of this paper, Selye confirms that such experiments have been performed at his institute, but still emphasizes that "the important point, however, is that there must be a mechanism, other than the level of circulating corticoids, which regulates ACTH discharge during stress. Otherwise, it would be impossible to understand how such an ACTH discharge could be effected in the presence of overwhelmingly large amounts of exogenous corticoids" (68 refs.).

Fortier, C., Yrarrazaval, S., Selye, H.: "Limitations of the ACTH regulating effect of corticoids." *Am. J. Physiol.* **165**: 466-468 (1951). B53,351/51

Even very large doses of cortisone given subcutaneously or intraperitoneally "failed to prevent or even to significantly decrease the adrenal ascorbic acid depletion resulting from various types of severe stress. These results show that ACTH release in response to stress is compatible with a high level of circulating corticoids and that hypocorticoidism is not the sole responsible agent of the activation of the adrenocorticotrophic function."

Sandberg, A. A., Eik-Nes, K., Samuels, L. T., Tyler, F. H.: "The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man." *J. Clin. Invest.* **33**: 1509-1516 (1954). B99,413/54

In man, surgery causes a rapid increase in plasma 17-OHCS within the first hour. Intravenous cortisol is not cleared from the blood as rapidly during surgical stress as otherwise. Presumably, not only increased corticoid secretion but also decreased clearance contribute to the raised blood corticoid levels.

Cowie, A. T., Ganong, W. F., Hume, D. M.: "The eosinopenic response to graded doses of hydrocortisone in the adrenalectomized dog with and without surgical trauma." *Endocrinology* **55**: 745-750 (1954). C264/54

The eosinopenic effect of low doses of cortisol is enhanced by surgical trauma, even in adrenalectomized dogs. "These and other data throw doubt on the hypothesis that increased corticoid utilization is responsible for

the pituitary release of ACTH in response to operative trauma."

Ulrich, F., Long, C. N. H.: "Effects of stress on serum C¹⁴ levels in rats following administration of hydrocortisone-4-C¹⁴ and corticosterone-4-C^{14".} *Endocrinology* **59**: 170-180 (1956). C22,143/56

"Although little, if any, positive evidence was found to substantiate the concept of increased peripheral utilization of adrenocortical hormones during stress, the evidence obtained from these experiments would seem to warrant a conclusion of 'not proven' as regards this theory."

Eik-Nes, K. B., Samuels, L. T.: "Metabolism of cortisol in normal and 'stressed' dogs." *Endocrinology* **63**: 82-88 (1958).

C55,691/58

In dogs exposed to various stressors, the blood clearance of intravenous injections of cortisol is normal or even delayed. "Mechanisms other than increased 'utilization' of adrenal steroids might therefore be responsible for augmented ACTH secretion in conditions of 'stress'."

Ingle, D. J., Ingle, D. J.: "The relationship of the adrenal glands to diseases of adaptation." *Acta Endocrinol. (Kh.)* **50** Supp.: 89-92 (1960). C92,395/60

Recapitulation of the authors' experiments on the permissive (conditioning) action of glucocorticoids. The production of diseases of adaptation by excess corticoid secretion during stress is questioned on the basis of the assumption that, under stress, more corticoids are utilized for resistance, which is also why Cushingoid symptoms do not occur. Still, the authors admit that some symptoms of corticoid excess are evident during stress. They conclude that "suppression of some but not all symptoms of hypercorticalism by stressors may be related to the well known fact that the need of the organism for cortical hormones is greatly increased by severe stress." [It is difficult to see how removal of excess corticoids by enhanced utilization could selectively annul only some of their effects (H.S.).]

Ingle, D. J., Young, S.: "Effect of cortisone acetate and of certain stressors on blood pressure and on the pathology of heart and kidney in uninephrectomized male rats." *Endocrinology* **70**: 806-814 (1962).

D25,297/62

Stressors (formaldehyde, bone fractures)

"did not block the loss of weight or the regression of thymus and spleen in rats overdosed with cortisone."

Smelik, P. G.: "Relation between blood level of corticoids and their inhibiting effect on the hypophyseal stress response." *Proc. Soc. Exp. Biol. Med.* **113**: 616-619 (1963).

E21,483/63

In rats, large subcutaneous doses of corticosterone suppressed adrenal corticoid production in vitro following exposure to stress in vivo, but there was no parallelism between this inhibition and the plasma corticosterone levels. "It is concluded that pituitary impairment by corticoid administration is not correlated with the existing blood level of corticoids."

Deckx, R., Moor, P. de, Denef, C., Raus, J.: "Effect of adrenalectomy, sham operation or ACTH on the cortisol metabolizing enzymes of rat liver homogenate." *Metabolism* **14**: 264-270 (1965). F32,028/65

In female rats, the direct effect of ACTH on the metabolism of cortisol by liver homogenate differs from that of stress. These circumstances may explain the many apparent contradictions concerning the effect of stress upon the overall rate of corticoid metabolism (21 refs.).

Estep, H. L., Litchfield, D. L., Taylor, J. P., Tucker, H. S. G. Jr.: "Acute effect of traumatic stress on cortisol metabolism in man." *J. Clin. Endocrinol. Metab.* **26**: 513-517 (1966). F66,349/66

"Plasma disappearance rates of 4-¹⁴C-cor-

tisol or unlabeled cortisol, or both, were measured in relatively healthy patients before and again during laparotomy. The biologic half-time of labeled cortisol during surgery was unchanged or decreased slightly from the control value." A slight delay in the removal of exogenous cortisol during stress may be partly explained as the consequence of increased adrenal secretion and elevated plasma levels of endogenous cortisol.

Panaretto, B. A., Vickery, M. R.: "The rates of plasma cortisol entry and clearance in sheep before and during their exposure to a cold, wet environment." *J. Endocrinol.* **47**: 273-285 (1970). H28,932/70

In sheep exposed to cold, "decreased cortisol clearance rates did not appear to contribute to the great increases in plasma concentration until rectal temperature was about 34°." Curiously, the adrenal cortex and liver of the sheep were heavily infiltrated with fat after severe hypothermia.

Courtney, G. A., Marotta, S. F.: "Adrenocortical steroids during acute exposure to environmental stresses: I. Disappearance of infused cortisol." *Aerosp. Med.* **43**: 46-51 (1972). J20,019/72

Courtney, G. A., Marotta, F.: "II. Uptake and release of infused cortisol by the hind limb of dogs." *Aerosp. Med.* **43**: 52-55 (1972). J20,018/72

In dogs, the disappearance rate of infused cortisol was not very consistently affected by a variety of stressors.

Transcortin

Most of the actions of corticoids are masked when the steroids are bound to carriers. This phenomenon has been touched upon briefly in the section on the Corticoid Feedback mechanism, since ability to inhibit ACTH secretion is also limited to free corticoids.

It is important, therefore, that corticoids, as many other steroid hormones, are primarily carried in the blood as conjugates bound to plasma proteins (especially globulin). One of these proteins, which has a particularly high affinity for cortisol, has been named transcortin. It is thought to bind cortisol and corticosterone at different sites on its molecule. Other hormonal steroids are bound to transcortin only weakly or not at all. It is only when the blood cortisol concentration exceeds transcortin capacity that marked physiologic effects appear (for example, during stress or after ACTH administration).

Comparatively little is known about the effect of stress upon the transcortin con-

centration of the blood, except that in the presence of greatly raised corticoid levels, a large portion of the protein is bound to the steroids.

One of the most important roles of thyroxine during stress is its ability to stimulate transcortin binding in the rat, whereas corticosterone and to a lesser extent other steroid hormones exert an inhibitory effect on transcortin-binding in the regulation of pituitary-adrenocortical interactions.

Transcortin

(See also our earlier stress monographs, p. xiii)

Sandberg, A. A., Slaunwhite, W. R. Jr., Antoniades, H. N.: "The binding of steroids and steroid conjugates to human plasma proteins." *Rec. Prog. Horm. Res.* **13**: 209-260 (1957). C38,184/57

One of the first detailed reviews of data showing that corticoids and other steroid hormones are carried mainly in the blood as conjugates bound to plasma proteins (54 refs.).

Daughaday, W. H.: "Steroid protein interactions." *Physiol. Rev.* **39**: 885-902 (1959). C77,548/59

Review on the binding of various steroids by plasma and tissue proteins, with a special section on the corticoid-binding globulin of the serum (69 refs.).

Slaunwhite, W. R. Jr., Sandberg, A. A.: "Transcortin: a corticosteroid-binding protein of plasma." *J. Clin. Invest.* **38**: 384-391 (1959). C64,399/59

Characterization of protein in human plasma having a high affinity for cortisol. The authors "propose to call this protein transcortin." Competition experiments indicate that cortisol and corticosterone are bound at different sites. Estrogens, androgens and progesterone are only weakly, or not at all, bound to transcortin. Probably, corticoids bound to transcortin are biologically inactive. Only when the cortisol concentration of the blood exceeds transcortin capacity do marked physiologic effects appear (for example, during stress or after ACTH administration). The chemical characteristics of this hormone are briefly described.

Daughaday, W. H., Mariz, I. K.: "The binding of steroid hormones by plasma proteins." In: Pincus, G. and Vollmer, E. P., *Biological Activities of Steroids in Relation*

to Cancer, pp. 61-73. New York and London: Academic Press, 1960. J12,259/60

Various proteins in human plasma bind estrogens, progesterone, testosterone and corticoids. An α -globulin is particularly effective in binding cortisol, but its concentration is so small that it can bind only 20 μ g. per 100 ml. of plasma. "The binding site(s) of the corticosteroid-binding globulin seem to be relatively specific for the corticosteroid hormones." In pregnancy and after administration of estrogens, there appears an additional protein that resembles the corticoid-binding globulin in its electrophoretic behavior, but its binding properties are less influenced by temperature.

Steenburg, R. W., Smith, L. L., Moore, F. D.: "Conjugated 17 hydroxycorticosteroids in plasma: measurement and significance in relation to surgical trauma." *J. Clin. Endocrinol. Metab.* **21**: 39-52 (1961).

C98,414/61

In man, gastrectomy caused a rapid rise in the level of serum free 17-OHCS and a slower elevation of conjugated 17-OHCS, but these differences were not statistically significant. In adrenalectomized dogs receiving constant intravenous infusions of cortisol, laparotomy elicited a rise in plasma free 17-OHCS, but this manifestation of a delay in steroid metabolism was not correlated with a fall in the plasma level of conjugated 17-OHCS, which remained the same or actually increased." It is concluded that the serum concentration of glucuronide conjugates is determined by multiple factors, only one of which is the rate of their production. As such, their concentration in serum does not reflect the changes in the rate of steroid metabolism that often occur following surgical operations."

Slaunwhite, W. R. Jr., Lockie, G. N., Back, N., Sandberg, A. A.: "Inactivity in vivo of transcortin-bound cortisol." *Science* **135**: 1062-1063 (1962). D20,991/62

As indicated by liver glycogen maintenance in adrenalectomized mice, transcortin-bound cortisol is biologically inactive.

Sandberg, A. A., Slaunwhite, W. R. Jr.: "Transcortin: a corticosteroid-binding protein of plasma. V. In vitro inhibition of cortisol metabolism." *J. Clin. Invest.* **42**: 51-54 (1963). E44,895/63

"In an in vitro system, employing either human or rat liver microsomes, transcortin competes efficiently for hydrocortisone with the enzyme systems responsible for the reduction of the steroid, resulting in lesser metabolism of hydrocortisone in the presence of transcortin" (10 refs.).

Murray, D.: "Cortisol binding to plasma proteins in man in health, stress and at death." *J. Endocrinol.* **39**: 571-591 (1967).

J22,565/67

Labrie, F., Raynaud, J. P., Pelletier, G., Ducommun, P., Fortier, C.: "Corticosterone-binding by transcortin and pituitary-thyroid-adrenocortical interactions in the rat." In: Jasmin, G., *Endocrine Aspects of Disease Processes*, pp. 20-26. St. Louis: Warren H Green, 1968. E7,614/68

In rats, graded doses of thyroxine cause progressive increases in adrenal weight, presumably as a consequence of enhanced ACTH secretion. At the same time, there is a step-wise elevation of total plasma corticosterone without significant alteration in the absolute level of the unbound fraction. Presumably, only free corticosterone is responsible for the feedback mechanism, while the binding capacity of transcortin is responsible for adjustments in the rate of corticosterone secretion to changes in thyroid activity. Furthermore, "thyroxine alone has a direct enhancing effect on the binding capacity of transcortin" and "the stimulating effect of estrogen and progesterone is exerted through the pituitary-thyroid axis."

Stark, E., Acs, Z., Szalay, K. S.: "Further studies on the hypophyseal-adrenocortical response to various stressing procedures in ACTH-treated rats." *Acta Physiol. Acad. Sci. Hung.* **36**: 55-61 (1969). G74,546/69

Following five consecutive daily injections of ACTH, the plasma transcortin level decreases significantly in the rat.

Fortier, C., Labrie, F., Pelletier, G., Raynaud, J. P., Ducommun, P., Delgado, A.,

Labrie, R., Ho-Kim, M.-A.: "Recent studies on the feedback control of ACTH secretion, with particular reference to the role of transcortin in pituitary thyroid-adrenocortical interactions." In: Wolstenholme, G. E. W. and Knight, J., *Ciba Foundation Symposium on Control Processes in Multicellular Organisms*, pp. 178-209. London: J & A Churchill, 1970. G74,630/70

In rats, thyroxine increases transcortin binding sites and thereby influences the feedback control of ACTH secretion, since the unbound, not the total, corticosterone concentration is the variable factor during this homeostatic reaction. On the other hand, in man, cortisol enhances the effect of thyroxine on transcortin binding, and this multiplies the action of the thyroid hormone upon the corticoid feedback.

Fortier, C., Delgado, A., Ducommun, P., Ducommun, S., Dupont, A., Jobin, M., Kraicer, J., MacIntosh-Hardt, B., Marceau, H., Mialhe, P., Mialhe-Voloss, C., Rerup, C., Rees, G. P. van: "Functional interrelationships between the adenohypophysis, thyroid, adrenal cortex and gonads." *Can. Med. Assoc. J.* **103**: 864-874 (1970). H30,500/70

Excellent review, based mostly on the authors' investigations. They reached the following conclusions: "Thyroxine alone having a direct stimulating effect on transcortin binding, appears as the final common pathway in the mediation of the stimulating effects induced by estradiol and progesterone in the intact animal. Corticosterone and, to a lesser extent, estradiol, progesterone and testosterone exert inhibitory effects on transcortin binding in the hypophysectomized animal. Transcortin binding thus seems to play a key role, in the rat, as target and agent of hormonal interactions." These complex interrelations are summarized in Figure 22 (p. 1114).

Marple, D. N., Cassens, R. G., Topel, D. G., Christian, L. L.: "Porcine corticosteroid-binding globulin: binding properties and levels in stress-susceptible swine." *J. Anim. Sci.* **38**: 1224-1228 (1974).

J21,599/74

"Swine from a herd bred to be stress-susceptible had significantly higher mean plasma cortisol and corticosteroid-binding globulin (CBG) levels with a significantly lower mean cortisol-CBG association constant than normal swine."

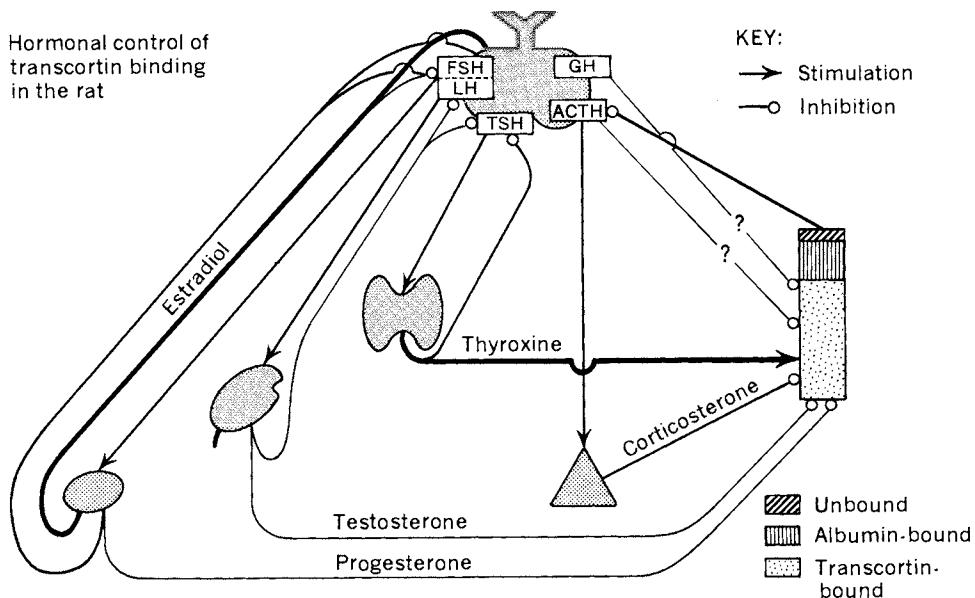


Figure 22. Interactions between the adenohypophysis, thyroid, adrenal cortex and gonads, showing the role of the thyroid and of corticosteroid-binding by transcortin in the adjustment of pituitary-adrenocortical activity in the rat. (Reproduced from *Can. Med. Assoc. J.* 103 (1970) by permission.)

THE SHIFT IN ADENOHYPOPHYSAL ACTIVITY

Even the earliest experiments on the G.A.S. showed clearly that during stress, when stimulation of adrenocortical development and function is of vital importance, other functions including somatic growth, sexual development, lactation and thyroid activity, are almost invariably diminished. From this it was concluded that during emergencies the increased production of life-maintaining ACTH is accomplished at the expense of other less urgently needed hypophyseal principles. It seemed reasonable to assume that, when the anterior pituitary is maximally engaged in the production of one type of hormone (ACTH), its ability to produce other principles (STH, LTH, LH, FSH, TTH) must be diminished. However, this interpretation was based exclusively on structural and functional changes during stress. Subsequent hormone determinations showed that in many instances a stress-induced rise in ACTH production is in fact associated with a diminution in the elaboration of other adenohypophyseal principles. Yet this is not always the case; sometimes it is not the production, but only the effect of other pituitary hormones that is reduced, presumably as a result of inhibitory conditioning factors.

Soon after the formulation of the hypophyseal shift theory, it was shown that, in rats exposed to various stressors, there is a reduction in the uptake of ^{131}I by the thyroid, evidenced by radioautographic observations. It was concluded that stress decreases TTH production. On the other hand, as we have mentioned elsewhere, certain strains of wild rabbits develop acute hyperthyroidism under the influence of stress produced by fear. In rats, exposure to cold increases not only ACTH but also gonado-

tropic hormone production, as indicated by precocious puberty, and it is well known that exposure to low temperatures augments thyroid activity to maintain homeostasis through an increase in the BMR.

Extensive subsequent investigations showed that the most diverse stressors decrease radioiodine uptake by the rat thyroid simultaneously with an increase in ACTH secretion; but this is not an infallible sign of thyroid activity, since stress and cortisone increase the renal clearance of iodine. On the other hand, in adrenalectomized animals, this response remained demonstrable and hence it was assumed that "inhibition of thyroid activity seen after exposure to stress is due to a decreased secretion of pituitary thyrotrophic hormone."

Hormone determination in the adenohypophysis of the rat revealed that after certain interventions the storage of ACTH may be diminished concurrently with an increased gonadotropin concentration, but that the two phenomena are not strictly interdependent. Hence, the "shift in pituitary hormone formation" can be modified by numerous circumstances, and is not an unavoidable consequence of increased secretion of one pituitary hormone.

During acute stress, the rat may show a sudden simultaneous release of both ACTH and gonadotropins, which appears to be incompatible with the theory of a "shift in anterior pituitary hormone secretion."

Other experiments suggest that the stress-induced "pituitary shift . . . might be a hypothalamic rather than a pituitary phenomenon." Thus animals given an intracarotid injection of hypothalamic extract—containing ACTH-, FSH-, LH- and TTH-releasing factors—can secrete all these hormones simultaneously. Other data also support the view that the shift takes place in the hypothalamus and results from the inability of the latter to produce all the releasing factors at the same time.

The situation is further complicated by the fact that thyroxine raises the corticoid-binding capacity of transcortin.

In rats, acute stress increases the ACTH and decreases the TTH content of the plasma, which would support the "hypophyseal shift" theory, but when ACTH secretion is blocked by dexamethasone or other agents, the decrease in TTH secretion persists. These observations have been considered to be incompatible with the shift theory but this is not necessarily so. The metabolic processes preparing an adenohypophyseal cell for ACTH production may interfere with the secretion of TTH, even if an actual discharge of ACTH is blocked by the feedback mechanism. Furthermore, the concurrent rise in TTH and ACTH secretion during cold is a poor example; exposure to low temperatures makes a very strong specific demand upon homeostatic mechanisms that maintain the body temperature, and under these conditions, the inhibitory effect of the shift phenomenon may be overcome. During continuous nervous stimulation, there may be a concurrent increase in the functional activity of the thyroid and the pituitary in the rat, but the investigators were careful to point out that occasional exceptions of this kind do not necessarily indicate that the shift does not occur under the influence of other stressors.

In rats, a variety of stressors caused a rise in plasma corticosterone with a corresponding fall in STH. These findings were considered to be consonant with the pituitary shift theory.

In summary, it may be said that the original observations made in the 1930s—that, during chronic exposure to stress, increased adrenal activity is associated with a diminution of most if not all other phenomena governed by the anterior pituitary—have received ample confirmation. A shift in adenohypophyseal activity is undoubtedly

characteristic of severe chronic stress. On the other hand, it is equally clear that the difficulty of producing several hormones simultaneously can be overcome if the stimulus is sufficiently severe. For example, during exposure to cold or at normal temperatures in certain species of wild rabbits, the specific impulse to produce excess TTH is so strong that it occurs despite a simultaneous rise in ACTH secretion. Furthermore, there is some doubt whether the shift really occurs at the adenohypophyseal level or in the hypothalamic centers regulating the production of the various releasing factors. Finally, we now have more evidence than we had forty years ago, when the shift theory was first formulated, that manifestations of adenohypophyseal activity do not depend merely upon the amount of anterior pituitary hormone secreted but, to an equal and often greater degree, upon conditioning factors modifying the receptivity of target organs to anterior pituitary hormones.

Much further work will be necessary to elucidate all the implications of the shift theory, but from a practical point of view the original concept is as valid today as it was when first enunciated; during stress, the safeguarding of an increased adrenocortical activity, indispensable for maintenance of life, must take preference over many other phenomena controlled by the adenohypophysis, such as the sexual cycle, fertility, lactation, somatic growth and thyroid activity. Whatever the underlying mechanism—and it is not necessarily always the same—examination of patients or experimental animals under chronic stress shows that the high degree of adrenocortical activity is maintained during severe and chronic emergencies, often at the expense of other less urgently required manifestations of life.

The Shift in Adenohypophyseal Activity

(See also our earlier stress monographs, p. xiii)

Dohan, F. C.: "Effect of low atmospheric pressure on the adrenals, thymus and testes of rats." *Proc. Soc. Exp. Biol. Med.* **49**: 404-408 (1942). A37,744/42

"Rats exposed to low atmospheric pressure for more than 2 days exhibited a significant increase in adrenal weight and a significant decrease in the weight of the thymus and testes. This pattern is similar to that found following other forms of stress." These observations are in consonance with the "pituitary shift" theory.

Selye, H.: *Textbook of Endocrinology*, p. 914. Montreal: Acta, 1947. 94,572/47

Experiments on rats exposed to various stressors indicate that growth, sexual development, lactation and thyroid activity are almost invariably diminished, whereas adrenal cortical stimulation is uniformly augmented. It is concluded that "in emergencies, an increased production of the life-maintaining corticotrophic hormone is accomplished at the expense of other, less urgently needed, hypophysial principles."

Bogoroch, R., Timiras, P.: "The response of the thyroid gland of the rat to severe stress." *Endocrinology* **49**: 548-556 (1951).

B59,195/51

In rats, various stressors (formalin, spinal cord transection, muscular exercise) depressed the uptake of ^{131}I in the thyroid, as indicated by radioautographic studies. "It was suggested that stress caused a decrease or suppression of thyrotrophic stimulation."

Mandl, A. M., Zuckerman, S.: "Factors influencing the onset of puberty in albino rats." *J. Endocrinol.* **8**: 357-364 (1952).

B75,210/52

In rats, exposure to cold accelerates the vaginal opening (a sign of puberty), whereas rough handling and a high-protein diet have no such effect. Possibly, certain types of "nonspecific 'stress'" may bring about a raised output of gonadotrophin as well as of ACTH, and thus secondarily stimulate ovarian activity."

Conner, M. H., Shaffner, C. S.: "Effect of altered thyroidal and gonadal activity on size of endocrine glands and resistance to stress in the chick." *Endocrinology* **55**: 45-53 (1954).

B95,026/54

Trolle, D.: "Experimental and clinical investigations on the pregnanediol excretion in human urine. IV. Depression of the corpus luteum function following hormone administration and under stress." *Acta Endocrinol.* (Kh.) **20**: 57-62 (1955). C9,372/55

Jänkälä, E. O., Näätänen, E. K.: "Effect of intense mental strain on the morphological picture of the testes." *Ann. Med. Exp. Fenn.* **33**: 231-238 (1955). C9,646/55

Harris, G. W.: "The reciprocal relationship between the thyroid and adrenocortical responses to stress." In: Wolstenholme, G. E. W. and Cameron, M. P., *Ciba Foundation Colloquia on Endocrinology*, Vol. 8, pp. 531-550. London: J & A Churchill, 1955. C3,662/55

Review of the literature indicating that a variety of stressors (typhoid vaccine, trauma, fasting, cold, heat, formalin, spinal cord transection, anoxia, starvation, tourniquet shock) decrease the uptake of radioiodine by the thyroid of the rat although they simultaneously increase ACTH secretion. However, radioiodine uptake by the thyroid during stress does not give a specific indication of thyroid activity, since stress and cortisone enhance the renal clearance of iodine and may thus lead to an apparent decrease in thyroid uptake, because less radioiodine is available. Animals with their adrenals denervated or removed (while maintained on a constant cortisone regime) show a similar response, and hence it is assumed that "the inhibition of thyroid activity seen after exposure to stress is due to a decreased secretion of pituitary thyrotrophic hormone."

Nowell, N. W., Jones, I. C.: "Some aspects of the storage and secretion of corticotrophin and gonadotrophins." *Acta Endocrinol.* **26**: 273-285 (1957). C43,163/57

Comparative estimates of the ACTH and gonadotropin content of the adenohypophysis in male and female intact, castrated and adrenal-enucleated rats and those exposed to "cold stress" led the authors to the conclusion that, "under certain conditions, firstly, the storage of corticotrophin may be diminished when that of gonadotrophins is increased but this is not necessarily associated with a diminution of corticotrophin secretion; secondly, when the production of corticotrophin is increased, the storage of gonadotrophins may be lessened in some cases and there may be some diminution in gonadotro-

phin secretion; thirdly, the rate of secretion of corticotrophin is not primarily related to the rate of secretion of gonadotrophins but may be secondarily so, through the influence of other factors, including the sex steroids; fourthly, cold stress is accompanied by the liberation of stored corticotrophin which may be associated with some gonadotrophin release in females but not in males." Hence the "shift in pituitary hormone formation" can be modified by numerous circumstances and is not an unavoidable consequence of increased secretion of one adenohypophyseal hormone.

Arvay, A., Balázsy, L.: "Changes in the gonadotropic function of the adenohypophysis in response to nervous stress." *Acta Physiol. Acad. Sci. Hung.* **14**: 317-325 (1958). C69,256/58

On the basis of cytochemical changes in the rat pituitary, it is assumed that stressors increase gonadotropin production with simultaneous enhancement of ACTH release. This would be incompatible with the theory of a "shift in anterior pituitary hormone secretion" during stress.

Igarashi, M., Tohma, K., Ozawa, M., Hosaka, H., Matsumoto, S.: "Pathogenesis of psychogenic amenorrhea and anovulation." *Int. J. Fertil.* **10**: 311-319 (1965).

F54,882/65

In women with amenorrhea or anovulation following psychogenic stress, hypersecretion of ACTH coincided with low elimination of FSH, 17-KS and 17-OHCS. "Selye proposed a hypothesis called the 'shift theory' that stress increases ACTH secretion from the pituitary at the sacrifice of gonadotropin secretion. His hypothesis was not based on assay of gonadotropin, but only on finding of ovarian atrophy in rats under stress. Therefore our results seem to give the first actual supportive evidence to Selye's hypothesis."

Ramirez, V. D., Moore, D., McCann, S. M.: "Independence of luteinizing hormone and adrenocorticotrophin secretion in the rat." *Proc. Soc. Exp. Biol. Med.* **118**: 169-173 (1965). F30,129/65

In spayed rats, adrenalectomy causes only a "borderline rise" in plasma LH, whereas large doses of cortisol fail to affect it, although they suppress the ACTH concentration in the pituitary and elevate the LH level. Apparently, "alteration in target gland steroids produces specific effects on LH in

the case of ovarian steroids, and ACTH in the case of cortical steroids."

Martini, L., Fraschini, F., Motta, M.: "New data on the nervous control of the pituitary gland." 2nd Int. Congr. on Hormonal Steroids, Milan, 1966. *Int. Congr. Ser. No. 111*, p. 94. Amsterdam and New York: Excerpta Medica, 1966. J13,139/66

Brief abstract describing animal experiments which suggest that the stress-induced "pituitary shift . . . might be a hypothalamic rather than a pituitary phenomenon." Thus, animals [species not stated] given an intracarotid injection of a hypothalamic extract containing the releasing factors for ACTH, FSH, LH, STH and TTH, can secrete all these hormones simultaneously. "Additional support for the hypothesis that the 'shift' takes place in the hypothalamus comes from the data indicating that in situations in which the pituitary shifts from one hormone to another an analogous 'shift' occurs in the synthesis and/or release of the corresponding hypothalamic releasing factors."

Labrie, F., Raynaud, J. P., Pelletier, G., Ducommun, P., Fortier, C.: "Corticosterone-binding by transcartin and pituitary-thyroid-adrenocortical interactions in the rat." In: Jasmin, G., *Endocrine Aspects of Disease Processes*, pp. 20-23, St. Louis: Warren H Green, 1968. E7,614/68

In rats, graded doses of thyroxine cause progressive increases in adrenal weight, presumably as a consequence of enhanced ACTH secretion. At the same time, there is a step-wise elevation of total plasma corticosterone without significant alteration in the absolute level of the unbound fraction. Presumably, only free corticosterone is responsible for the feedback mechanism, while the binding capacity of transcartin is responsible for adjustments in the rate of corticosterone secretion to changes in thyroid activity. Furthermore, "thyroxine alone has a direct enhancing effect on the binding capacity of transcartin" and "the stimulating effect of estrogen and progesterone is exerted through the pituitary-thyroid axis."

Ducommun, P.: "Corticosterone-binding by transcartin and pituitary-thyroid-adrenocortical interactions in the rat: discussion." In: Jasmin, G., *Endocrine Aspects of Disease Processes*, pp. 23-26. St. Louis: Warren H Green, 1968. E10,627/68

In rats, acute stress [kind not stated] suddenly increases the ACTH and diminishes the TTH content of the plasma, a finding

that would agree with the "hypophyseal shift" theory. However, when ACTH release is blocked by dexamethasone-Nembutal, TTH secretion continues to fall. Conversely, exposure to cold elicits a simultaneous increase in plasma ACTH and TTH.

Arvay, Á., Balogh, A., Ladányi, P., Takács, I., Benkő, K.: "Effect of intensive nervous stimulation on the fine structure of the adenohypophysis and its target organs." *Acta Endocrinol. (Kbh.)* 68: 749-758 (1971).

H50,211/71

In rats subjected to prolonged nervous stimulation, EM studies of the pituitary-adrenal cortex, thyroid and ovaries suggested increased functional activity. This finding appears to be in contradiction to the "pituitary shift" theory, but such multiple pituitary hormone stimulation may not occur under the influence of other stressors.

Ajika, K., Kalra, S. P., Fawcett, C. P., Krulich, L., McCann, S. M.: "The effect of stress and Nembutal on plasma levels of gonadotropins and prolactin in ovariectomized rats." *Endocrinology* 90: 707-715 (1972).

H52,545/72

"The stress of etherization and bleeding produced an elevation within 2 min in the plasma levels of prolactin, LH, and FSH in ovariectomized rats. . . . Nembutal blocked the stress-induced elevations of plasma prolactin and LH but did not affect the levels of FSH. The effect of Nembutal is thought to be on the CNS since the Nembutalized rats responded to hypothalamic extract or ovine LRF with dramatic elevations in plasma LH." [Evidently, under these acute stress conditions, a shift in adenohypophyseal hormone production does not interfere with a simultaneous secretion of several anterior pituitary hormones (H.S.).]

Kokka, N., Garcia, J. F., George, R., Elliott, H. W.: "Growth hormone and ACTH secretion: evidence for an inverse relationship in rats." *Endocrinology* 90: 735-743 (1972).

H52,549/72

In rats, noise, vibration, ether, cold, insulin, pentylenetetrazol, amphetamine and 2-D-deoxyglucose caused a rise in plasma corticosterone with a corresponding fall in STH. Gentling or administration of pentobarbital lowered corticosterone and increased STH in plasma. The results are interpreted as indicating an inverse relationship between ACTH and STH secretion; this finding agrees with the "pituitary shift" theory.

Leppäläluoto, J., Ranta, T., Lybeck, H., Varis, R.: "Effect of TRH, and short-term exposure to experimental stress or cold on the serum immunoassayable TSH concentration in the rat." *Acta Physiol. Scand.* **90**: 640-644 (1974). J13,381/74

Various acute stressors temporarily raise plasma TTH levels, but this is followed by a lasting and pronounced decrease. Only cold causes a specific increase in plasma TTH activity. "The inhibition of TSH [TTH] secretion in response to stress refutes the hypothesis that stressful stimuli activate the thyroid gland."

Rosen, E. F., Petty, L. C.: "Food deprivation effects on some estrogen-sensitive responses in female rats." *Physiol. Behav.* **12**: 767-770 (1974). J12,899/74

Observations in man during famines, as well as experiments on the folliculoid sensitivity of rats and other animals during stress, suggest that "food deprivation may interfere with sexual activity by altering the female's behavior more than the male's. Thus, any control over reproduction which may occur in a famine area may be due to changes in the female's behavior, which provide fewer or lower intensity stimuli to the male....

This is part of the response to stress discussed by Selye."

Inoue, S., Nagasaki, H., Iriki, M.: "Total sleep deprivation and weight increases of the reproductive organs in male rats." *Endocrinol. Jap.* **21**: 283-286 (1974). H92,991/74

In rats, long-term sleep deprivation in a cage, where they were continuously forced to move in order to avoid electric shocks, caused hypertrophy of the adrenals, testes, ventral prostates and seminal vesicles. "It is supposed that either the sleep deprivation *per se* or stressful conditions accompanied with the treatment caused a hypersecretion of hypophyseal and testicular hormones." [It is unusual for chronic stress to produce hypertrophy of the sex organs, and these observations appear to be incompatible with the pituitary-shift theory (H.S.).]

Euker, J. S., Meites, J., Riegler, G. D.: "Effects of acute stress on serum LH and prolactin in intact, castrate and dexamethasone-treated male rats." *Endocrinology* **96**: 85-92 (1975). H98,033/75

In rats, ACTH, LTH and LH concentrations in the blood may be increased by some stressors. Hence, a shift in anterior pituitary production is by no means the rule.

SYNTOXIC AND CATATOXIC HORMONES

The participation of syntoxic and catatotoxic hormones in stress reactions was the topic of one of my earlier monographs on the mechanism of the G.A.S. (*Hormones and Resistance*, 1971). There I tried to distinguish between two types of adaptive steroids that control essentially different processes:

1. The syntoxic steroids (e.g., cortisol, triamcinolone, aldosterone, desoxycorticosterone) permit adjustment to topical or systemic injury without directly attacking the aggressor. They create conditions for coexistence with toxic agents, either through passive indulgence to them (e.g., antiphlogistics), or by actively stimulating the formation of a granulomatous barricade, which tends to isolate the irritant from the surrounding tissue (e.g., prophlogistics). Through similar mechanisms, the syntoxic steroids also promote repair (e.g., cicatrization).

The systemic action of the syntoxic steroids is mainly of the "life-maintaining corticoid" type; it is highly efficient in restoring the nonspecific resistance of adrenal-deficient organisms to normal, but then, it reaches a plateau above which tolerance is not easily raised. Only in a few instances (e.g., damage due to endotoxins, inflammatory irritants, immune reactions, lathyrogenic compounds) can syntoxic steroids increase tolerance far above normal because here, the "disease" is primarily due to active morbid reactions of the tissues, not to passive, direct

tissue damage by the exogenous aggressor. Thus, endotoxin shock is thought to be caused mainly by the liberation of enzymes normally sequestered in lysosomes, whereas inflammation, various pathogenic immune reactions (allergies, anaphylaxis, homograft rejection) and osteolathyrysm represent excessive responses of the body to different types of irritation. In all these cases, homeostasis is achieved by adjusting the body's reaction to the damaging agent, not by destroying the latter.

2. **The catatoxic steroids** (e.g., ethylestrenol, spironolactone, certain cyano-steroids) act primarily by stimulating aggressive reactions which destroy toxic substances (e.g., by accelerating their metabolic degradation). They do not merely restore a deficient resistance to normal (as do the glucocorticoids after adrenalectomy), but they are capable of raising it far above the norm. Sometimes this reaction defeats its purpose, because the products of metabolic degradation are more toxic than the original drug which was to be inactivated. Yet, the response is still catatoxic since it attacks the aggressor. For similar reasons, we speak of allergy and anaphylaxis as "immune reactions," although they actually produce damage.

There are many overlaps between syntoxic and catatoxic steroid actions, for example, the stimulation of inflammation may lead to topical degradation of the irritant by enzyme activation in the inflammatory focus; furthermore, certain primarily syntoxic glucocorticoids (e.g., dexamethasone) may also enhance the hepatic detoxication of barbiturates. Yet, the distinction between the two categories is justified because, usually, individual hormones act predominantly by eliciting one or the other reaction form. Furthermore, available evidence suggests that the two types of defense are mediated through essentially distinct mechanisms.

There can be no doubt that during stress an increased amount of syntoxic steroids (for example, cortisol, corticosterone) is produced in response to the need to maintain homeostasis. The same is true of catecholamines, since more than the resting level of these hormones is required to maintain health when unusual demands for adaptation are made. However, this has never been proven for catatoxic steroids. The latter are undoubtedly manufactured by the body since natural testoids, corticoids and luteoids have been proven to exert definite catatoxic effects. Thus, for example, even at a normal blood level, testosterone participates in the detoxication of barbiturates through its catatoxic activity, since resistance to these drugs decreases below normal after castration and can be restored by exogenous testoids. Yet the fundamental question whether increased amounts of these or other catatoxic steroids are actually produced for the maintenance of homeostasis in reply to needs created by stress has not yet been definitively answered.

Syntoxic and Catatoxic Hormones

(See also our earlier stress monographs, p. xiii)

Selye, H.: *Hormones and Resistance*, 2 vols., p. 1140. New York, Heidelberg and Berlin: Springer-Verlag, 1971. G79,100/71

Encyclopedic treatise on the role of various hormones in resistance to specific and stres-

sor agents. First detailed description of the difference between syntoxic and catatoxic hormones and the results of extensive screenings of steroids for these actions. Among all compounds tested, pregnenolone- 16α -carbonitrile (PCN) proved to be the most active catatoxic substance.

Wassermann, D., Wassermann, M., Cucos,

S., Djavaherian, M.: "Function of adrenal gland-zona fasciculata in rats receiving polychlorinated biphenyls." *Environ. Res.* **6**: 334-338 (1973). J6,552/73

In rats given toxic polychlorinated biphenyls, the plasma corticosterone levels rose sharply, and characteristic structural changes developed in the fasciculata of the adrenals. "The results are interpreted as evidence of the need for a higher level of glucosteroids in defense against the stressor character of PCBs-1221 and perhaps also of the need for cataotoxic activity of glucosteroids."

Kourounakis, P., Szabo, S., Selye, H.: "Effect of fluorosteroids upon drug response and metabolism." *Biochem. Pharmacol.* In press. J4,268/75

In rats, in vivo observations on the paralysis produced by zoxazolamine and parallel studies on the blood clearance of this toxicant showed that "PCN and spironolactone protect via increased drug metabolism, triamcinolone and ACTH via decreased organ sensitivity, and the remaining fluorosteroids via both prophylactic mechanisms."

OTHER HORMONES AND HORMONE-LIKE SUBSTANCES

The participation of other hormones in stress reactions has already been discussed in connection with the chemical characteristics of the G.A.S., where data on changes in the blood and tissue concentrations of various hormones and related substances have been listed. The observations on the stressor effect of various hormones and hormone-like substances other than those mentioned in the preceding pages, as well as changes in their metabolism during stress, have shown that insulin, glucagon, thyroid hormones, and possibly even pineal and thymus hormones, participate in the mechanism of stress reactions. The same is true of such hormone-like substances as 5-HT, histamine, acetylcholine, prostaglandins and GABA, which appear to fulfill very important roles, not only as systemic mediators, but also as local transmitters of impulses, especially in the CNS. 5-HT deserves special attention.

5-HT. Studies with radioactive NEP and 5-HT in rats reveal that various stressors deplete brain NEP, but at least initially, increase the 5-HT content, especially of the brain stem-mesencephalon and spinal cord. It has also been demonstrated that a variety of stressors increase the concentration of 5-HIAA and tryptophan in the rat brain and that the rise in 5-HT is most persistent and pronounced if 5-HT degradation is blocked by MAO inhibitors. Cortisol increases hepatic tryptophan pyrolase activity, 5-HT and 5-HIAA, at least in rats of certain age groups.

Presumably, the rise in brain 5-HT that is characteristic of stress is largely dependent upon enzymatic processes affecting its degradation and resynthesis. However, in all these respects, the literature is far from unanimous, perhaps largely because certain authors have neglected to consider the time curve of 5-HT during stress, which by some is attributed to the existence of a 5-HT negative feedback system. Furthermore, there are obvious differences between the responses of various brain areas in this respect. In any event, it appears to be well established that brain NEP and 5-HT concentrations do not always vary in a parallel fashion during stress, because when NEP is depleted, 5-HT is either raised or at least unchanged. Several investigators have come to the conclusion that serotonergic neurons may play an important part in ACTH release.

5-HT concentration is highest in the raphé nuclei (containing the highest level of serotonergic cell bodies), particularly the amygdala and hippocampus, in which it

shows definite circadian variations. Destruction of these nuclei abolishes the circadian plasma corticosterone rhythm in the rat.

According to some investigators, acute stress induces a biphasic response in the hypothalamic 5-HT content. It consists of an initial decrease (which precedes the increase in plasma corticosterone and is independent of the pituitary-adrenal system), followed by a second phase, which is characterized by a rise in hypothalamic 5-HT with a subsequent return to normal. It is noteworthy that, despite the enormous literature dealing with 5-HT metabolism during stress and its relation to ACTH discharge, almost every statement made by one author has been contradicted by another. Hence, despite the large number of data on record, a critical reexamination of this entire field, both with regard to the existing literature and by well-planned additional experiments, appears to be of the utmost importance. It is for efforts of this kind that we hope that the present encyclopedic survey of the field may have the greatest heuristic value.

Other Hormones and Hormone-like Substances

(See also our earlier stress monographs, p. xiii, and cf. Hormones and Hormone-like Substances under Characteristic Manifestations of Stress, and Various Mechanisms)

Thyroid. Selye, H.: "Studies on adaptation." *Endocrinology* **21**: 169-188 (1937).

B95,026/37

Hypophysectomy lessens the accidental involution of the thymus, and adrenalectomy inhibits it completely, but both these operations greatly diminish resistance to all stressors examined. Thyroidectomy and ovariectomy do not considerably interfere with the thymicolympathic involution and splenic atrophy characteristic of the formalin-induced alarm reaction, nor do they significantly increase mortality.

Conner, M. H., Shaffner, C. S.: "Effect of altered thyroidal and gonadal activity on size of endocrine glands and resistance to stress in the chick." *Endocrinology* **55**: 45-53 (1954).

B95,026/54

Skebelskaia, I. B.: "Thyroid gland reaction to 'stress' after the exclusion of the adrenocorticotrophic function of the hypophysis." *Probl. Endokrinol. Gormonoter.* **5** No. 6: 3-6 (1959) (Russian). D98,428/59

Notti, P., Santoro, G.: "Tiroide e 'stress'" (The thyroid and stress). *Riv. Patol. Clin.* **14**: 755-762 (1959). C90,723/59

Brown-Grant, K., Pethes, G.: "The response of the thyroid gland of the guinea-pig

to stress." *J. Physiol. (Lond.)* **151**: 40-50 (1960).

C85,485/60

Guinea pigs respond to diverse stressors (noise, cold, tissue damage, EP, vasopressin, typhoid vaccine, diphtheria toxin, electroshock) with a reduction in the rate of ^{131}I release from the thyroid, and a similar reaction is obtained with ACTH and cortisol. "It is concluded that the guinea-pig responds to acute stress with a prompt but reversible decrease in thyroid activity, as has been observed in other species."

Skebelskaia, I. B.: "The effect of caffeine on the reaction of the thyroid gland to 'stress.'" *Probl. Endokrinol. Gormonoter.* **6** No. 2: 7-10 (1960) (Russian). D51,474/60

Studies on the effect of increased "excitation" in the CNS induced by caffeine on the reaction of the thyroid gland to the ACTH injection (1 Unit and 5 Units) and to 'stress' (tail amputation). As established, the reduction of the ability of the gland to accumulate ^{131}I , usually appearing after the ACTH injection or under 'stress,' is much weaker in rats receiving a preliminary administration of caffeine (50 mg); this may evidently be explained by the intensified excretion of the thyrotropic hormone from the hypophysis of experimental animals."

Asch, L., Weryha, A., Aron, C.: "Données nouvelles sur le fonctionnement thyroïdien au cours du stress chez le rat" (New data on thyroid function during stress in the rat). *C.R. Soc. Biol. (Paris)* **155**: 646-649 (1961). D14,512/61

In rats, during stress, the decrease in the fixation of radioiodine by the thyroid is not due to diminished TTH production, since it

persists even after administration of massive doses of TTH.

Skebelskaia, I. B., Bagramian, E. R.: "Reaction of the thyroid gland of hypophysectomized rats to stress." *Probl. Endokrinol. Gormonoter.* 8 No. 6: 27-30 (1962) (Russian). D47,086/62

Kawai, A.: "Pituitary adrenocorticotrophic activity in altered thyroid function." *Endocrinol. Jap.* 9: 113-120 (1962).

D35,705/62

Observations on rats suggest that "the thyroid hormone is an important factor which controls the capacity of the pituitary gland to release ACTH in response to stress."

Skebelskaia, I. B.: "On the mechanism of the thyroid gland functional changes in stress." *Probl. Endokrinol. Gormonoter.* 9 Nos. 1-2: 111-118 (1963) (Russian).

D53,208/63

Review of data on the role of the thyroid in the G.A.S.

Dörr, D.: "Der Einfluss der Schilddrüsenfunktion auf die Stressreaktion beim Hund" (Influence of thyroid function on the stress reaction in the dog). *Langenbecks Arch. Klin. Chir.* 319: 988-991 (1967). J23,968/67

Steigrad, A.: "Kleine Blutdruckamplitude bei Hypercholesterinämie. Beobachtungen über den Einfluss von Stress und Schilddrüsenfunktion" (Small blood pressure amplitude in hypercholesterolemia. Studies on the influence of stress and thyroid function). *Praxis* 57: 1225-1228 (1968).

H14,750/68

In man, psychogenic stress increases the blood cholesterol level. At the same time, thyroid activity (blood PBI) is usually, but not always, diminished (26 refs.).

Dewhurst, K. E., Kabir, D. J. el, Harris, G. W., Mandelbrote, B. M.: "A review of the effect of stress on the activity of the central nervous-pituitary-thyroid axis in animals and man." *Confin. Neurol.* 30: 161-196 (1968) (about 160 refs.). G62,591/68

Balze, F. A. de la, Socolsky, R. C., Janches, M., Paoli, J. C. de, Cordero Funes, J., Goldberg, V.: "Effect of bacterial pyrogen on the thyroid uptake of ^{131}I and urinary excretion of 17-hydroxycorticosteroid in normal subjects." *Folia Endocrinol. (Roma)* 21: 611-620 (1968). H13,317/68

Langer, P., Lichardus, B.: "Thyroid function and its fluctuations during and after

short-term stress and dexamethasone administration in rats." *Neuroendocrinology* 4: 112-121 (1969). H10,095/69

Sugiyama, T.: "Effect of parotin on stress response inhibition due to thyroidectomy." *Shikwa Gaku* 69: 1221-1231 (1969) (Japanese). J23,109/69

Melander, A.: "Studies on the thyroid activity in the mouse. 2. The effects of stress and other changes in corticotrophin secretion." *Acta Endocrinol. (Kh.)* 64: 569-576 (1970). H27,389/70

In mice, acute stress decreased TTH and thyroid hormone release, whereas chronic stress prevented this fall in TTH.

Reklewska, B., Tomaszewska, L., Kaciuba-Uscilko, H., Kożłowski, S.: "Changes in the thyroid and adrenal glands during prolonged immobilization of rats." *Bull. Acad. Pol. Sci. [Biol.]* 20: 685-689 (1972). H80,415/72

Leppäläluoto, J., Ranta, T., Lybeck, H., Varis, R.: "Effect of TRH, and short-term exposure to experimental stress or cold on the serum immunoassayable TSH concentration in the rat." *Acta Physiol. Scand.* 90: 640-644 (1974). J13,381/74

Various acute stressors temporarily raise plasma TTH levels, but this is followed by a lasting and pronounced decrease. Only cold causes a specific increase in plasma TTH activity. "The inhibition of TSH [TTH] secretion in response to stress refutes the hypothesis that stressful stimuli activate the thyroid gland."

Meserve, L. A., Leathem, J. H.: "Neonatal hyperthyroidism and maturation of the rat hypothalamo-hypophyseal-adrenal axis." *Proc. Soc. Exp. Biol. Med.* 147: 510-512 (1974). H97,672/74

In rats, thyroid feeding during pregnancy does not change the basal level of corticosterone in their pups but accelerates the maturation of the hypothalamo-hypophyseal-adrenal axis, as indicated by the response to ether stress or ACTH (30 refs.).

Gonads. Selye, H.: "Studies on adaptation." *Endocrinology* 21: 169-188 (1937). 38,798/37

Hypophysectomy lessens the accidental involution of the thymus, and adrenalectomy inhibits it completely, but both these operations greatly diminish resistance to all stressors examined. Thyroidectomy and ovariectomy do not considerably interfere with the

thymicolumphatic involution and splenic atrophy characteristic of the formalin-induced alarm reaction, nor do they significantly increase mortality.

Conner, M. H., Shaffner, C. S.: "Effect of altered thyroidal and gonadal activity on size of endocrine glands and resistance to stress in the chick." *Endocrinology* **55**: 45-53 (1954).
B95,026/54

Pineal. Holban, R., Sahlešanu, V.: "Modification de la réaction éosinopénique lors d'un stress, chez les animaux éiphysectomisés" (Alteration of the eosinopenic reaction under stress in epiphysectomized animals). *Rev. Sci. Méd. (Bucur.)* **5**: 49-51 (1960).

J24,542/60

"In epiphysectomized rats (unlike in those which have been subjected to a sham operation only), the formol stress is not followed by eosinopenia." It is suggested that the pineal is indispensable for the normal development of the alarm reaction.

Miline, R., Devecerski, V., Krstic, R.: "Les modifications épiphysaires dans le stress et en particulier dans les névroses expérimentales d'effroi" (Epiphyseal changes in stress and especially in experimental neuroses due to fright). *Probl. Actuels Endocrinol. Nutr. Ser. No. 10*: 229-256 (1967). F81,524/67

Kinson, G., Wahid, A. K., Singer, B.: "Effect of chronic pinealectomy on adrenocortical hormone secretion rates in normal and hypertensive rats." *Gen. Comp. Endocrinol.* **8**: 445-454 (1967). F80,842/67

Experiments on rats indicate that one month after pinealectomy, aldosterone and corticosterone secretion is significantly increased. "These chronic ablation studies suggest that the pineal gland normally exerts an inhibitory effect on the adrenal cortex which is not confined to aldosterone."

Miline, R., Krstić, R., Devečerski, V.: "Sur le comportement de la glande pinéale dans des conditions de stress" (On the behavior of the pineal gland under conditions of stress). *Acta Anat. (Basel)* **71**: 352-402 (1968). G68,038/68

Description of changes in the pineal gland of restrained rats. "The results obtained indicate the progressive nature of the reaction of the pineal gland and the stress of constraint. The authors believe that the pineal gland plays a sensoneuroendocrine role."

Miline, R.: "Role of the pineal in cold

adaptation: general discussion." In: Wolstenholme, G. E. W. and Knight, J., *The Pineal Gland*, pp. 372-373. Edinburgh and London: Churchill Livingstone, 1971.

J14,884/71

Dyer, R. S., Weldon, D. A., Mento, A. J.: "Pinealectomy and two-way avoidance in the guinea pig (*Cavia porcellus*)."*Physiol. Behav.* **12**: 671-673 (1974). J13,148/74

In guinea pigs, pinealectomy had no effect on two-way avoidance learning. "This suggests that blindness-induced facilitation of two-way avoidance in guinea pigs is not a result of the hormonal changes in the pineal known to accompany variations in visual input." These findings are considered interesting in connection with stress reactions because ACTH secretion is thought to be partly controlled by the pineal gland.

Reiter, R. J.: "Pineal regulation of hypothalamic-pituitary axis: gonadotrophins." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. IV, Part 2, pp. 519-550. Washington, D.C.: American Physiological Society, 1974.

E10,763/74

Chazov, E. I., Golikov, P. P., Bobkova, A. S., Fominikh, E. S.: "The effect of epiphysis on stress." *Patol. Fiziol. Éksp. Ter.* No. 5: 12-17 (1974) (Russian). J25,498/74

"The rate of corticosterone decreased in the epiphysectomized rats during the neuro-reflex phase of systemic stress; as to the metabolic phase, there occurred an increase in the rate of aldosterone, corticosterone, 18-OH-DOC secretion, and the adrenal glands gained weight. Consequently, epiphysis takes part in the development of the general adaptation syndrome."

Thymicolumphatic Apparatus and Bursa. Nigeon-Dureuil, M., Rabinowicz, M., Rahandraha, T., Ratsimamanga, A. R.: "Signification des variations pondérales et biochimiques transitoires de l'hypophyse, de la surrénaïale et du thymus, au cours d'un stimulus continu de moyenne intensité, le froid à 6°" (Significance of the transitory ponderal and biochemical variations of the hypophysis, adrenal, and thymus during exposure to a continuous stimulus of moderate intensity, cold at 6°). *C.R. Soc. Biol. (Paris)* **146**: 370-377 (1952). B75,131/52

In rats exposed to moderate cold, the various manifestations of the G.A.S. show periodic fluctuations, probably due to successive

discharges and storage of hormones. The thymus allegedly can store corticoids and thereby provide an additional reserve. [The authors promised subsequent papers in which these concepts would be elaborated (H.S.).]

Chisci, R.: "Importanza del timo nella sindrome di adattamento. Nota III—Gli effetti dello stress e della somministrazione di ACTH sull'apparato genitale femminile delle ratte normali e stimizzate" (Importance of the thymus in the adaptation syndrome. Note III—Effects of stress and of adrenocorticotrophic hormone on female genitalia of normal and stimulated rats). *Folia Endocrinol.* (Roma) **8**: 525-543 (1955). C8,681/55

In rats, "typical manifestations of the 'alarm reaction' by the cold stress (such as anestrus ovulations, corticoids-estrogens antagonism, fatty infiltration of the liver etc.) are clearly augmented and prolonged by thymectomy so that the adaptation process becomes delayed."

Perek, M., Eilat, A.: "The bursa of Fabricius and adrenal ascorbic acid depletion following ACTH injections in chicks." *J. Endocrinol.* **20**: 251-255 (1960). C86,536/60

Weltman, A. S., Sackler, A. M.: "Effects of thymectomy on the resistance of rats to drowning and histamine stress." *Nature* **192**: 460-461 (1961).

D14,302/61

Thymectomy increased the resistance of the rat to various stressors.

Sackler, A. M., Weltman, A. S., Jurtschuk, P. Jr.: "Effect of splenectomy on the resistance of rats to histamine stress." *Nature* **190**: 274 (1961). E79,123/61

In the rat, "splenectomy tends to increase tolerance to histamine stress."

Csaba, G., Törö, I., Horváth, C., Acs, T., Mold, K.: "Thymus and stress." *J. Endocrinol.* **23**: 423-431 (1962). D17,079/62

Thymectomy slightly exacerbated the course of formalin arthritis, and allegedly "cortisone, which prevented or arrested the arthritis in intact rats, produced serious aggravation of the condition in thymectomized animals. The action of the thymus is not apparently hormonal but depends on the presence of thymic tissue. It seems that this phenomenon is connected with the participation of the thymus in polysaccharide metabolism."

Miller, J. F. A. P., Dukor, P.: *Die Biologie des Thymus nach dem heutigen Stande der*

Forschung (The present status of thymus biology), p. 98. Basel and New York: S Karger, 1964. E4,014/64

Only cursory reference is made to the thymus involution induced by stress; its possible significance in immunologic responses of adults is difficult to appraise (several hundred refs.).

Huston, T. M., Subhas, T.: "The influence of environmental temperature upon adrenal activity of bursectomized chicks." *Poultry Sci.* **47**: 1760-1763 (1968). J23,073/68

Although earlier experiments showed that severe stress causes involution of the bursa in chicks, moderate cold has no such effect. In bursectomized chicks, adrenal ascorbic acid content diminishes, particularly after exposure to stress.

Freeman, B. M.: "The bursa of Fabricius and adrenal cortical activity in *Gallus domesticus*." *Comp. Biochem. Physiol.* **29**: 639-646 (1969). H12,554/69

The depletion of ascorbic acid from the adrenals of chickens is diminished and general resistance increased following bursectomy.

Malyzhev, V. A., Sutkovoi, D. A.: "The effect of thymectomy in guinea pigs on urinary excretion of 17-oxy corticosteroids under normal conditions and in stress." *Patol. Fiziol. Éksp. Ter.* **14** Nos. 5-6: 31-34 (1970) (Russian). J22,295/70

"As shown in guinea pigs thymectomized at immature age, urinary excretion of 17-oxy corticosteroids was almost halved four months after the operation in comparison with intact animals. A more prolonged than normal activation of adrenal cortex was seen both at the early and at the late periods after thymectomy, when these animals were subjected to the action of unfavourable factors, such as operation or inflammation."

Bhattacharyya, T. K., Ghosh, A.: "Influence of surgical and steroid-induced bursectomy on the behavior of adrenal ascorbic acid during stress in juvenile pigeons." *Gen. Comp. Endocrinol.* **15**: 420-424 (1970). H35,126/70

In juvenile pigeons, bursectomy facilitated the depletion of adrenal ascorbic acid during stress (formalin). Cortisol caused involution of the bursa but left adrenal ascorbic acid levels unaltered after exposure to stress.

Watanabe, I., Cabrera-Peralta, C., Pescinini, I. A., Mello, A.: "Efeito da ablação do timo no crescimento de segmentos encefálicos de

ratios" (Effects of thymus ablation on encephalic segment growth of rats). *Rev. Bras. Pesqui. Med. Biol.* **5**: 237-241 (1972) (Portuguese). H81,499/72

"Since the thymus is the organ in the body most responsive to 'stress' and since encephalic structures have a close relation to 'stress,'" the various brain regions were carefully examined in rats after thymectomy on the fourteenth day of life, and certain structural anomalies were observed. [On the basis of the description, the relationship of the latter to stress is not evident (H.S.).]

Pethes, G., Muray, T., Péczely, P.: "Effect of stress on corticosterone production of bursectomized chicken." *Gen. Comp. Endocrinol.* **22**: 400 (1974). H83,307/74

In bursectomized chickens, adrenal weight, adrenal corticosterone production, and pituitary ACTH content were not altered. The effect of stressors (cold, heat, ether) upon corticosterone production was not prevented by bursectomy.

Toma, V., Giurgea, R.: "Dynamics of nucleic acids and total proteins in the thymus and the bursa of Fabricius of chickens, under the action of cortisol." *Zentralbl. Veterinaermed. [A]* **21**: 506-513 (1974) (Roumanian).

J19,096/74

Trainin, N., Levo, Y., Rotter, V.: "Resistance to hydrocortisone conferred upon thymocytes by a thymic humoral factor." *Eur. J. Immunol.* **4**: 634-637 (1974).

J19,417/74

Treatment of murine thymus cells with a thymus humoral factor increased their capacity to elicit a graft-versus-host reaction in vitro and to resist cortisol.

Marx, J.: "Aging research (II): pacemakers for aging?" *Science* **186**: 1196-1197 (1974). H96,194/74

Review of the literature on aging. An informative discussion of the theory according to which involution of the thymus, and the consequent immunologic incompetence, may be at the basis of the genetically determined "biological clock" responsible for the rate of aging.

Toma, V., Giurgea, R.: "Lowering of the ^{32}P -uptake in the thymus, pancreas and adrenals after Bernardi-Comșa thymic extract administration." *Rev. Roum. Méd.* **12**: 109-112 (1974) (Roumanian). J19,093/74

Svendsen, U. G.: "Thymus dependency of periarteritis nodosa in DOCA and salt

treated mice." *Acta Pathol. Microbiol. Scand. [A]* **82**: 30-34 (1974). J16,185/74

Severe periarteritis nodosa develops in the kidneys, with fewer lesions in the heart and pancreas, in unilaterally nephrectomized, haired NMRI mice treated with DOC plus sodium chloride, but not in littermates with congenital thymus aplasia.

5-HT. (See also our earlier stress monographs, p. xiii, and cf. 5-HT under Hormones and Hormone-like Substances in the section on Characteristic Manifestations of Stress).

Liberson, W. T., Bernsohn, J., Wilson, A., Daly, V.: "Brain serotonin content and behavioral stress." *J. Neuropsychiatry* **5**: 363-365 (1964). D17,697/64

In guinea pigs, prolonged hypnosis training significantly decreased the 5-HT content of the cortex and hippocampus, and to a lesser degree, of the brain stem and cerebellum.

Rosecrans, J. A., Feo, J. J. de: "The interrelationships between chronic restraint stress and reserpine sedation." *Arch. Int. Pharmacodyn. Ther.* **157**: 487-497 (1965).

F54,866/65

In rats, stress by restraint initially increased the 5-HT and decreased the NEP content of the brain. "Reserpinized stress animals were more easily handled at first, but became more excitable and difficult to handle as the experiment progressed." This change appeared to correlate with the continued depletion of brain NEP because the brain 5-HT remained approximately constant. The possible protective effect of reserpine is considered in connection with the G.A.S.

Ruther, E., Ackenheil, M., Matussek, N.: "Beitrag zum Noradrenalin- und Serotonin-Stoffwechsel im Rattenhirn nach Stress-Zuständen" (Contribution to norepinephrine and serotonin metabolism in the rat brain following stress conditions). *Arzneim. Forsch.* **16**: 261-263 (1966). F63,682/66

Ganong, W. F., Lorenzen, L.: "Brain neuromodulators and endocrine function." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 583-640. New York and London: Academic Press, 1967. E6,920/67

Extensive review on neurohormones, particularly catecholamines, 5-HT, acetylcholine, histamine, substance P, γ -aminobutyric acid, and dopamine (about 250 refs.).

Coppen, A.: "The biochemistry of affective

disorders." *Br. J. Psychiatry* **113**: 1237-1264 (1967). G51,286/67

Review on changes in catecholamines, indole derivatives and electrolytes in various affective disorders which may be of pathogenic importance, and which also may be responsible for the effectiveness of psychotropic drugs (187 refs.).

Smelik, P. G.: "ACTH secretion after depletion of hypothalamic monoamines by reserpine implants." *Neuroendocrinology* **2**: 247-254 (1967). F90,175/67

In rats, implantation of reserpine into the hypothalamus depleted the regional 5-HT and catecholamine content. Nevertheless, subsequent systemic treatment with reserpine, chlorpromazine, vasopressin, and emotional and traumatic stress was not modified by the depletion of hypothalamic monoamines. Presumably, "under these experimental conditions there is no indication that monoamines present in the hypothalamus are involved in the control of pituitary ACTH secretion."

Dixit, B. N., Buckley, J. P.: "Circadian changes in brain 5-hydroxytryptamine and plasma corticosterone in the rat." *Life Sci.* **6**: 755-758 (1967). J12,743/67

Experiments on rats "do not indicate any specific time-relationship between changes in brain 5-HT and plasma corticosterone" although both show circadian rhythmicity.

Woolley, D. W.: "Involvement of the hormone serotonin in emotion and mind." In: Glass, D. C., *Biology and Behavior. Neurophysiology and Emotion*, pp. 108-116. New York: Rockefeller University Press, 1967.

J11,136/67

Welch, B. L., Welch, A. S.: "Differential activation by restraint stress of a mechanism to conserve brain catecholamines and serotonin in mice differing in excitability." *Nature* **218**: 575-577 (1968).

F98,490/68

Thierry, A.-M., Javoy, F., Glowinski, J., Kety, S. S.: "Effects of stress on the metabolism of norepinephrine, dopamine and serotonin in the central nervous system of the rat. I. Modifications of norepinephrine turnover." *J. Pharmacol. Exp. Ther.* **163**: 163-171 (1968). H2,261/68

By use of radioactive NEP, 5-HT and dopamine, it was found that stress (electroshock) did not significantly influence the endogenous level of NEP but markedly raised its turnover in NEP-containing neurons of

the brainstem-mesencephalon and spinal cord. "This stress increased the synthesis of 5HT in the brainstem-mesencephalon as seen by the greater increase of endogenous 5HT after monoamine oxidase inhibition but did not affect the disappearance of intracisternally administered H³-5HT. Changes in NE turnover regulation induced by electric foot shocks were studied in various conditions. There was an enhanced turnover of NE in the brainstem-mesencephalon when higher intensities of stimulation were used; this was associated with an increased accumulation of H³-nor-metanephrine; no modification was seen when the frequency of stimulation was increased. NE turnover during an acute stress session was enhanced to a greater degree when rats were previously subjected to many stress sessions. The initial accumulation of H³-NE in the brainstem-mesencephalon was decreased just after an acute stress and increased 24 hr after the last electric shock stress session of a chronic stress treatment."

Thierry, A.-M., Fekete, M., Glowinski, J.: "Effects of stress on the metabolism of noradrenaline, dopamine and serotonin (5-HT) in the central nervous system of the rat. II. Modifications of serotonin metabolism." *Eur. J. Pharmacol.* **4**: 384-389 (1968). H5,942/68

Stress induced by mild electric shock to the feet slightly increased the 5-HT content of the brain stem-mesencephalon. "The formation of ³H-5HT from ³H-tryptophan (TRY) was significantly increased in the brain of stressed animals and the utilization of this labelled amine synthesized endogenously was markedly accelerated during the stress situation."

Nielson, H. C., Fleming, R. M.: "Effects of electroconvulsive shock and prior stress on brain amine levels." *Exp. Neurol.* **20**: 21-30 (1968). G54,821/68

Welch, A. S., Welch, B. L.: "Effect of stress and para-chlorophenylalanine upon brain serotonin, 5-hydroxyindoleacetic acid and catecholamines in grouped and isolated mice." *Biochem. Pharmacol.* **17**: 699-708 (1968). G57,744/68

Bliss, E. L., Ailion, J., Zwanziger, J.: "Metabolism of norepinephrine, serotonin and dopamine in rat brain with stress." *J. Pharmacol. Exp. Ther.* **164**: 122-134 (1968).

H4,230/68

"The stress of foot shock in rats induces large decreases in the level of brain norepi-

nephrine but does not greatly alter the concentration of serotonin or dopamine in brain."

Goldberg, M. E., Salama, A. I.: "Amphetamine toxicity and brain monoamines in three models of stress." *Toxicol. Appl. Pharmacol.* **14**: 447-456 (1969). G66,997/69

In the mouse and rat, a significant rise in the level of brain stem 5-HT was caused by trauma or electroshock but not by cold. "This increase was obtained in animals subjected to stress alone, or those given the highest possible nonlethal dose of amphetamine. These same doses did not augment the catecholamine-releasing properties of amphetamine in drum- or electric shock-stressed animals. It does not appear that stress potentiates the effects of amphetamine, as no evidence of excitation was obtained in stressed animals given amphetamine. It is postulated that amphetamine enhances the effects of stress."

Nisticò, G., Preziosi, P.: "Brain and liver tryptophan pathways and adrenocortical activation during restraint stress." *Pharmacol. Res. Commun.* **1**: 363-368 (1969).

G80,145/69

In rats, the increase in plasma corticosterone produced by restraint is associated with a rise in tryptophan pyrolase and a fall in brain 5-HT which are not correlated with the duration of the stress. The decrease in 5-HIAA during the first hour is followed by a progressive increase. Apparently, during stress "the tryptophan shunt from the serotonin to the kynurene pathway is almost abolished."

Rosecrans, J. A.: "Brain amine changes in stressed and normal rats pretreated with various drugs." *Arch. Int. Pharmacodyn. Ther.* **180**: 460-470 (1969). H18,475/69

In rats exposed to the stressor effect of vibration, 5-HT and NEP concentrations were determined in various areas of the brain. Apparently, NEP neurons were stimulated while the 5-HT systems were depressed. The latter, however, "were activated if this amine was depleted prior to stress, indicating the presence of a 5-HT negative feedback system. Lastly, there were differences observed in brain area responsiveness to stress, indicating the existence of different neuronal populations in the areas studied."

Bliss, E. L., Ailion, J.: "Response of neuromodulatory amines to aggregation and strangers."

J. Pharmacol. Exp. Ther. **168**: 258-263 (1969). H15,845/69

Aggregation of mice unaccustomed to each other caused a decrease in brain NEP and an acceleration of its catabolism. 5-HT levels remained unchanged, although 5-HIAA concentrations in the brain rose, indicating an increased catabolism of 5-HT. "Dopamine levels in brain and its catabolism were unaffected. At the same time no changes in norepinephrine metabolism could be detected in the adrenal, heart or spleen. The intermingling of strangers without aggregation also decreased brain norepinephrine. A more severe stress of footshock to rats not only diminished brain norepinephrine but also radically reduced catecholamine levels in the adrenal and spleen. These observations suggest that emotional disturbances activate the norepinephrine and serotonin systems in brain."

Scapagnini, U., Preziosi, P., Schaepdryver, A. de: "Influence of restraint stress, corticosterone and betamethasone on brain amine levels." *Pharmacol. Res. Commun.* **1**: 63-69 (1969). G80,096/69

In rats, the changes in brain 5-HT, dopamine and NEP provoked by restraint do not seem to result from the negative feedback effect of endogenous corticosterone.

Dixit, B. N., Buckley, J. P.: "Brain 5-hydroxytryptamine and anterior pituitary activation by stress." *Neuroendocrinology* **4**: 32-41 (1969). H8,973/69

Rosecrans, J. A., Sheard, M. H.: "Effects of an acute stress on forebrain 5-hydroxytryptamine (5-HT) metabolism in C.N.S. lesioned and drug pretreated rats." *Eur. J. Pharmacol.* **6**: 197-199 (1969).

H14,042/69

In rats exposed to the stress of horizontal oscillation, PCPA pretreatment and medial forebrain bundle lesions facilitated 5-HT turnover in the response to stress. Raphé lesions, on the other hand, prevented this facilitation of indoleamine turnover. "The results obtained were explained on the basis of an operative negative feedback system in stressed rats. The lack of a change in raphé lesioned rats further reinforced the concept that most forebrain 5-HT containing neurons are the result of axons extending from this nucleus."

Rosecrans, J. A.: "Effects of acute stress on forebrain 5-hydroxytryptamine metabo-

lism and pituitary adrenal function." *Eur. J. Pharmacol.* **9**: 170-174 (1970).

H22,576/70

"Male rats were paired according to equivalent spontaneous activity (curiosity), and were subjected to a more subtle stress of passive avoidance (one trial learning). This procedure consisted of determining how much time a rat would spend in a cage in which it had been shocked 24 hr previously. Pituitary-adrenal function was stimulated in rats who had learned this response, while non-learners exhibited no such change. In contrast, forebrain 5-hydroxytryptamine metabolism was reduced in learners and stimulated in non-learners."

Glowinski, J.: "Metabolism of catecholamines in the central nervous system and correlation with hypothalamic functions." In: Martini, L., Motta, M. et al. *The Hypothalamus*, pp. 139-152. New York and London: Academic Press, 1970. J12,266/70

Within a review on catecholamine metabolism in the CNS, a small section is devoted to the literature suggesting that in stress, noradrenergic and serotonergic neurons may play a role, especially in connection with the release of ACTH.

Billinson, M. R.: "Prematurity and low birth weight litters: a mechanism elicited by thermal stress." *Am. J. Obstet. Gynecol.* **108**: 970-974 (1970). H45,391/70

In rats, "thermal stress" increases 5-HT excretion which may be accompanied by premature delivery or low birth weight of the litters.

Thierry, A. M., Blanc, G., Glowinski, J.: "Effect of stress on the disposition of catecholamines localized in various intraneuronal storage forms in the brain stem of the rat." *J. Neurochem.* **18**: 449-461 (1971).

G82,745/71

Scapagnini, U., Moberg, G. P., Loon, G. R. van, Groot, J. de, Ganong, W. F.: "Relation of brain 5-hydroxytryptamine content to the diurnal variation in plasma corticosterone in the rat." *Neuroendocrinology* **7**: 90-96 (1971). H36,747/71

In rats, the 5-HT content of the hippocampus and amygdala exhibits a circadian rhythm which roughly parallels that of plasma corticosterone. PCPA, which blocks 5-HT synthesis, increases the a.m. and decreases the p.m. plasma corticosterone levels, so that the circadian variations are largely

eliminated. "The results suggest that 'serotonergic' neurons play a role in the diurnal fluctuation in pituitary-adrenal function."

Curzon, G.: "Effects of adrenal hormones and stress on brain serotonin." *Am. J. Clin. Nutr.* **24**: 830-834 (1971) (20 refs.).

G85,082/71

Curzon, G.: "Relationships between stress and brain 5-hydroxytryptamine and their possible significance in affective disorders." *J. Psychiatr. Res.* **9**: 243-252 (1972).

G95,120/72

In rats, "immobilization stress caused a prolonged increase of pyrolase and a transient fall of brain 5-HT. These changes were largely prevented by previous adrenalectomy." Brain 5-HIAA increased, in both intact and adrenalectomized rats. These findings may have a bearing upon the pathogenesis of depression.

Elo, H., Tirri, R.: "Effect of forced motility on the noradrenaline and 5-hydroxytryptamine metabolism in different parts of the rat brain." *Psychopharmacologia* **26**: 195-200 (1972).

G93,807/72

Forced motility in a treadmill enhances 5-HT metabolism in the rat forebrain within one hour, and this is followed by an increase in the brain stem, especially the mesencephalon-pons medulla regions. The changes disappear almost completely after fifty minutes of rest. NEP metabolism is also increased under similar conditions in the rat brainstem.

McLeod, W. R., McLeod, M. F.: "Indoleamines and the cerebrospinal fluid." In: Davies, B., Carroll, B. J. et al., *Depressive Illness. Some Research Studies*, Sect. 3, pp. 209-225. Springfield, Ill.: Charles C Thomas, 1972. E10,507/72

Depressed patients, unlike those suffering from other psychiatric disorders, have subnormal 5-HIAA levels in the CSF. A positive correlation exists between the CSF 5-HIAA values and the plasma 11-OHCS in depressed patients, before and after the dexamethasone suppression test.

Vermes, I., Telegdy, G.: "Effect of intraventricular injection and intrahypothalamic implantation of serotonin on the hypothalamo-hypophyseal-adrenal system in the rat." *Acta Physiol. Acad. Sci. Hung.* **42**: 49-59 (1972).

J4,627/72

In rats, intraventricular injection of 5-HT did not change the basal corticosterone pro-

duction but inhibited the activation of the hypothalamo-pituitary-adrenocortical system by intraventricular volume increase and surgical stress. 5-HT implanted into the anterior or posterior hypothalamus had no effect on the activation induced by ether stress, but when placed into the medial hypothalamus, it abolished the increase in corticosterone secretion produced by ether, without altering the basal discharge. "Thus, serotonin may play a physiological role in the inhibition of the hypothalamo-hypophyseal-adrenal system and one of the sites of action is the medial hypothalamus." This view is supported by literature suggesting that the hypothalamic "serotonergic" system may inhibit the pituitary-adrenal axis, and that drugs blocking 5-HT synthesis or decreasing the brain 5-HT concentration facilitate the activation of the pituitary-adrenocortical system; MAO inhibitors, which increase brain 5-HT, decrease stress-induced adrenocortical activation.

Curzon, G., Joseph, M. H., Knott, P. J.: "Effects of immobilization and food deprivation on rat brain tryptophan metabolism." *J. Neurochem.* **19**: 1967-1979 (1972).

J19,890/72

"Withdrawal of food or immobilization both led to changes in rat brain tryptophan metabolism. Brain tryptophan and 5-hydroxyindolyacetic acid concentrations both increased while changes in 5-hydroxytryptamine were much smaller."

Scapagnini, U., Preziosi, P.: "Role of brain norepinephrine and serotonin in the tonic and phasic regulation of hypothalamic hypophyseal adrenal axis." *Arch. Int. Pharmacodyn. Ther.* **196** Suppl.: 205-220 (1972).

H56,654/72

Résumé of the literature and the extensive experiments of the authors and their co-workers led to the following main conclusions: (1) there is an adrenergic system in the brain that inhibits ACTH secretion. Drugs that release active catecholamines from nerve endings block ACTH discharge if they can pass the blood-brain barrier or are injected directly into the third ventricle or ME. Stressors deplete brain NEP and increase ACTH secretion. Admittedly, the amount of drugs necessary for inhibition is large, compared to the normal catecholamine levels present in the brain and hence their action is of doubtful physiologic significance. They may act merely by constricting the portal vessels so that CRF cannot reach an ade-

quate concentration in the adenohypophysis. Among the drugs used to explore the ACTH inhibitory adrenergic mechanism were: amphetamine, α -ethyltryptamine, L-dopa, tyramine, α -MT, guanethidine, FLA-63 (an inhibitor of dopamine- β -oxidase) and L-threo-dihydroxy-phenyl-serine or "DOPS," which selectively repletes NEP after depletion of NEP and dopamine by α -MT, phentolamine (an α -blocking agent), and so on. (2) 5-HT appears to regulate the circadian variations of ACTH secretion by the limbic system. Its concentration is particularly high in the raphé nuclei (containing the highest level of serotonergic cell bodies), particularly the amygdala and hippocampus, in which it shows circadian variations. Destruction of these nuclei abolishes the circadian plasma corticosterone rhythm.

Glowinski, J., Hamon, M., Héry, F.: "Regulation of 5-HT synthesis in central serotonergic neurons." *Symp. Drug Abuse and Metabolic Regulation of Neurotransmitter*, pp. 239-257. La Jolla, Calif., 1972.

J15,063/72

Review and personal observations on the role of 5-HT, especially in the central regulation of stress responses (about 50 refs.).

Bliss, E. L., Thatcher, W., Ailion, J.: "Relationship of stress to brain serotonin and 5-hydroxyindoleacetic acid." *J. Psychiatr. Res.* **9**: 71-80 (1972). G91,750/72

In mice and rats, a variety of stressors, "including foot shock, restraint, swimming, positioning on inverted pots, and residence in a noxious habitat, will increase the concentration of 5-HIAA in the brains," presumably as a result of an augmented metabolism of brain 5-HT.

Golda, V., Stránský, Z., Petr, R., Herink, J., Žáková, Z.: "Brain serotonin in stressed, adrenalectomized and septal rats." *Activ. Nerv. Sup.* (Praha) **14**: 215-217 (1972). J20,547/72

Vermes, I., Dull, G., Telegdy, G., Lissák, K.: "Possible role of serotonin in the monoamines-induced inhibition of the stress mechanism in the rat." *Acta Physiol. Acad. Sci. Hung.* **42**: 219-223 (1972). J6,598/72

Pharmacologic studies in rats suggest that "the inhibition of stress by monoamines is mediated via increased hypothalamic serotonin content."

Vermes, I., Telegdy, G., Lissák, K.: "Correlation between hypothalamic serotonin con-

tent and adrenal function during acute stress. Effect of adrenal corticosteroids on hypothalamic serotonin content." *Acta Physiol. Acad. Sci. Hung.* **43**: 33-42 (1973).

J9,322/73

Various stressors (surgical trauma, formalin, electroshock, histamine, cold, restraint, ether) decreased the 5-HT content of the hypothalamus in the rat, with a concurrent increase in plasma corticosterone, within thirty minutes of application. A single dose of corticosterone increased the plasma level of this hormone and the hypothalamic 5-HT content. It also restored the otherwise low 5-HT concentration in the hypothalamus of adrenalectomized rats. ACTH increased corticosterone secretion and hypothalamic 5-HT, but only in the presence of the adrenal. Apparently, "acute stress induces a biphasic change in the hypothalamic serotonin content. The first phase consists of a decrease of the hypothalamic serotonin content, which precedes the increase in plasma corticosterone level and seems to be independent of the pituitary-adrenal system, and a second phase characterized by an increase of the hypothalamic serotonin level and its return to normal."

Yuwiler, A., Geller, E., Schapiro, S.: "Effect of neonatal corticoids on tryptophan pyrolase and brain serotonin." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 215-228. Bratislava: Slovak Academy of Sciences, 1973.

E10,470/73

In newborn rats, a single injection of cortisol induces tryptophan pyrolase and diminishes both the 5-HT content of the brain and body growth. These results are discussed in relation to the function of tryptophan in stress.

Calogero, B.: "Variazioni del turnover delle amine biogene nel sistema nervoso centrale del ratto dopo stimolazione acustica" (Biogenic amine changes in the central nervous system following acoustic stimulation in the rat). *Minerva Otorinolaringol.* **23**: 55-60 (1973).

J4,054/73

Intense auditory stimulation causes significant changes in the catecholamine and 5-HT content of the temporal cortex, amygdala, and hypothalamus of the rat. "Serotonin may inhibit the transmission of impulses through the auditory pathway under protracted stimulation."

Yuwiler, A., Geller, E.: "Rat liver tryptophan oxygenase induced by neonatal corticoid

administration and its effect on brain serotonin." *Enzyme* **15**: 161-168 (1973).

J11,698/73

A single injection of cortisol into newborn rats prematurely induces tryptophan oxygenase in the liver, "with a concomitant reduction in serotonin concentration in the thalamic-hypothalamic and pontine areas of the brain. The ability of tryptophan to behave as a metabolic regulator may be important in the organism's response to stress."

Vermes, I., Telegdy, G.: "Effect of 5-hydroxytryptamine on stress-induced adrenal function in the guinea pig." *Acta Physiol. Acad. Sci. Hung.* **43**: 99-103 (1973).

J12,927/73

"The hypothalamic serotoninergic mechanism exerts an inhibitory action on the stress-induced increase of hypothalamo-pituitary-adrenal function in the guinea pig." 5-HT introduced into the lateral ventricle inhibited the adrenal corticoid secretion increased by surgical stress. After implantation of 5-HT crystals into the ME, basal secretion was unchanged, but the increase of adrenal corticoid secretion was prevented.

Vermes, I., Molnár, D., Telegdy, G.: "Hypothalamic serotonin content and pituitary-adrenal function following hypothalamic deafferentation." *Acta Physiol. Acad. Sci. Hung.* **43**: 239-245 (1973).

J12,931/73

In rats, partial or total deafferentation of the hypothalamus decreases the adrenal response to "ether stress" and concurrently diminishes hypothalamic 5-HT concentration. The findings support the concept that "serotonin plays an inhibitory role in the function of the hypothalamo-pituitary-adrenal axis, and indicate that serotoninergic fibres are reaching the hypothalamus from the anterior and antero-superior parts."

Vermes, I., Telegdy, G.: "Adrenal function following drug-induced alterations of the hypothalamic serotonin content." *Acta Physiol. Acad. Sci. Hung.* **43**: 105-114 (1973).

J12,928/73

In rats, PCPA lowers the hypothalamic 5-HT content and facilitates stimulation of corticosterone secretion by "ether stress." Nialamide increases hypothalamic 5-HT but blocks the adrenal response to stress. Reserpine lowers hypothalamic 5-HT and enhances the basal corticoid secretion. However, after "ether stress" there is no response either in hypothalamic 5-HT content or adrenal function. In any event, the results suggest

that "the changes induced in the stress mechanism by different drugs are related to their action on the hypothalamic serotonin level. Its increase inhibits, while its decrease facilitates, the stress-induced activation of pituitary-adrenal function."

Thierry, A. M.: "Effects of stress on the metabolism of serotonin and norepinephrine in the central nervous system of the rat." In: Németh, Š., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 37-53. Bratislava: Slovak Academy of Sciences, 1973. E10,456/73

In rats, stress induced by electroshock over a period of three hours activated both 5-HT and NEP neurons in various brain structures, increasing the turnover of these compounds. The same stress applied for only fifteen minutes activated central NEP neurons, apparently because 5-HT neurons are less sensitive to mild stress (31 refs.).

Radulovački, M.: "Comparison of effects of paradoxical sleep deprivation and immobilization stress on 5-hydroxyindoleacetic acid in cerebrospinal fluid." *Brain Res.* **60**: 255-258 (1973). J21,552/73

Anokhina, I. P., Zabrodin, G. D., Svirinovskii, I. E.: "Neurochemical mechanisms of formation of psychopathologic conditions due to emotional stress." *Zh. Nevropatol. Psichiatr.* **73** No. 12: 1825-1833 (1973) (Russian). J16,960/73

Studies on changes in catecholamine and 5-HT metabolism in various brain areas of rats exposed to different stressors.

Abe, K., Hiroshige, T.: "Changes in plasma corticosterone and hypothalamic CRF levels following intraventricular injection or drug-induced changes of brain biogenic amines in the rat." *Neuroendocrinology* **14**: 195-211 (1974). H86,427/74

In rats, "brain amines were depleted by pretreatment with either reserpine or 6-hydroxydopamine. In spite of the persistence of marked depletion of hypothalamic NE content, the basal circadian rhythm as well as stress-induced changes in both plasma corticosterone and hypothalamic CRF levels were preserved in almost the normal fashion. In addition, more than two-fold increases of brain amine concentration by pretreatment with a MAO inhibitor affected neither basal circadian rhythm nor a stress-induced increase in the plasma corticosterone. These observations suggest strongly that brain amines are of relatively little importance in

the central regulation of ACTH secretion in the rat." NEP, dopamine, carbachol and GABA were injected into the lateral ventricles in large doses, and all of them except GABA elicited a significant increase in ACTH discharge.

Koob, G. F., Annau, Z.: "Behavioral and neurochemical alterations induced by hypoxia in rats." *Am. J. Physiol.* **227**: 73-78 (1974). H89,535/74

In rats, hypoxia caused a decrease in the NEP content, but no change in the 5-HT concentration of the forebrain. In rats with electrodes implanted in the lateral hypothalamus, "self-stimulation rates increased while food and water intake decreased during the first 12 h and subsequently returned toward control levels... The results suggest a time-related activation of central adrenergic neuronal systems during exposure to hypoxia." The observation of a differential effect of hypoxia on NEP and 5-HT agrees with several earlier studies using other stressors (36 refs.).

Ellison, G. D., Bresler, D. E.: "Tests of emotional behavior in rats following depletion of norepinephrine, of serotonin, or of both." *Psychopharmacologia* **34**: 275-288 (1974). J9,987/74

Costa, E., Meek, J. L.: "Regulation of biosynthesis of catecholamines and serotonin in the CNS." *Annu. Rev. Pharmacol.* **14**: 491-511 (1974). J12,127/74

Review on catecholamine and 5-HT synthesis in the nervous system under various conditions, including stress. "Benzodiazepines (minor tranquilizers) block the increase in NE turnover produced by stress, in doses devoid of any effect on amine turnover in normal animals. One of the mechanisms discussed above might be directly affected by the benzodiazepines, but they might directly affect another system of neurons that in stress influence noradrenergic neurons" (161 refs.).

Modigh, K.: "Functional aspects of 5-hydroxytryptamine turnover in the central nervous system." *Acta Physiol. Scand. Supp.* **403**: 1-56 (1974). H88,890/74

Experiments in mice induced to fight after prolonged isolation showed that "the concentration of tryptophan and the accumulation of 5-HTP in brain were higher in the fighting animals than in control animals which remained isolated. The rate of depletion of 5-HT after inhibition of synthesis

was, however, almost identical in fighting and isolated animals. In conclusion, the increased synthesis of 5-HT occurring during fighting is probably secondary to the increase in concentration of tryptophan in brain, and occurs independently of the impulse activity in 5-HT neurons."

Ladisich, W.: "Stress und Serotoninstoffwechsel in verschiedenen Arealen des Zentralnervensystems der Ratte" (Stress affecting the serotonin metabolism in different regions of the central nervous system in the rat). *Arzneim. Forsch.* **24**: 1025-1027 (1974).

H88,829/74

In rats, electric footshock caused a pronounced increase in 5-HIAA in the raphe and septum, whereas 5-HT concentrations rose mainly in the septum, thalamus and hypothalamus. In general, "septum and raphe appeared to be the regions whose 5-HT metabolism was mostly changed by the stress of electric footshock."

Schildkraut, J. J.: "Biogenic amines and affective disorders." *Annu. Rev. Med.* **25**: 333-348 (1974).

J12,641/74

Review of the literature and personal observations indicate that "different subgroups of patients with depressive disorders may exhibit different specific abnormalities in the metabolism of norepinephrine or other biogenic amines," particularly dopamine and 5-HT. The relationship between stress and metabolic changes in these substances is considered, but not regarded as being of proven significance (119 refs.).

Hodge, G. K., Butcher, L. L.: "5-Hydroxytryptamine correlates of isolation-induced aggression in mice." *Eur. J. Pharmacol.* **28**: 326-337 (1974).

H93,909/74

Gromova, E. A., Sovetov, A. N., Semionova, T. P., Vekshina, N. L.: "Chemical nature of central mechanisms of emotional behavior during the conditioning." *Proc. Satellite Symp. Emotions and Visceral Functions*, pp. 15-16. Baku, USSR, 1974.

J17,524/74

Studies on changes in 5-HT and NEP content of various brain regions during psychogenic stress in the rat.

Modigh, K.: "Effects of social stress on the turnover of brain catecholamines and 5-hydroxytryptamine in mice." *Acta Pharmacol. (Kbh.)* **34**: 97-105 (1974).

J16,345/74

Male mice, at first isolated, then brought

together, immediately start to fight, and exhibit characteristic changes in the turnover of brain catecholamines and 5-HT.

Makarova, L. V., Bazarevich, G. I., Likhentshtein, A. O.: "Role played by the serotonin-monoaminoxidase system in the changes of functional condition of the adrenal cortex in traumatic shock." *Probl. Endokrinol.* **20** No. 5: 72-74 (1974) (Russian).

H95,572/74

In dogs, stress induced by traumatic shock produces characteristic changes in 5-HT-monoaminoxidase activity, which are related to the secretion of corticoids.

Johansson, G.: "Relation of biogenic amines to aggressive behaviour." *Med. Biol.* **52**: 189-192 (1974) (33 refs.).

J17,685/74

Green, A. R., Curzon, G.: "Effects of hydrocortisone and immobilization on tryptophan metabolism in brain and liver of rats of different ages." *Biochem. Pharmacol.* **24**: 713-716 (1975).

H99,235/75

In rats, restraint or cortisol increased hepatic tryptophan pyrolase activity and (in certain age groups) 5-HT and 5-HIAA concentrations in the brain.

Stern, W. C., Morgane, P. J., Miller, M., Resnick, O.: "Protein malnutrition in rats: response of brain amines and behavior to foot shock stress." *Exp. Neurol.* **47**: 56-67 (1975).

J23,635/75

"Regional brain levels of the amines and 5-hydroxyindoleacetic acid showed little change in normal rats following up to 90 min. of shock, whereas depletions of up to 50% occurred in chronically protein malnourished rats. These neurochemical changes in the chronically malnourished rats were pronounced in the diencephalon and in the midbrain-pons-medulla brain regions. Normal rats which were switched in adulthood to the low protein diet showed minimal decreases in brain amine and 5-hydroxyindoleacetic acid levels following foot shock. This suggests that the effects observed in the chronically malnourished rats reflect a developmental interaction and were not due to the diet being administered at the time of testing" (25 refs.).

Woolf, C. J., Laburn, H. P., Willies, G. H., Rosendorff, C.: "Hypothalamic heating and cooling in monoamine-depleted rabbits." *Am. J. Physiol.* **228**: 569-574 (1975).

H99,314/75

In rabbits, 5-HT inhibits the vasomotor response to "heat stress" and activates heat conservation during "cold stress." Presumably, "the integrity of the monoaminergic system is vital for the correct functioning of the hypothalamus in maintaining a constant body temperature."

Ladisch, W.: "Influence of stress on regional brain serotonin metabolism after progesterone treatment and upon plasma progesterone in the rat." *J. Neural Transm.* **36:** 33-42 (1975). J24,802/75

"When electric footshock was administered to ovariectomized rats pretreated with progesterone or its vehicle, there were generally higher 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) concentrations after progesterone. 5-HT levels were significantly higher in thalamus, hippocampus, raphé, and frontal cortex, 5-HIAA rose significantly in hippocampus, raphé, and frontal cortex. Whereas after electric footshock alone the septum showed highest increases of 5-HT and 5-HIAA and hippocampus ranged last, after pretreatment with progesterone increases of 5-HT and 5-HIAA were least pronounced in septum but rather high in hippocampus."

Histamine. (See also our earlier stress monographs, p. xiii, and cf. Histamine under Hormones and Hormone-like Substances in the section on Characteristic Manifestations of Stress)

Selye, H.: "Further evidence in support of the alarm reaction theory of adrenal insufficiency." *Am. J. Physiol.* **119:** 400-401 (1937). 68,414/37

Brief description of observations which "lead us to assume that the liberation from the tissues of certain toxic metabolites with histamine-like pharmacological effect is the primary cause both of the alarm reaction and of adrenal insufficiency."

Guillemin, R., Fortier, C.: "Role of histamine in the hypothalamo-hypophyseal response to stress." *Trans. N.Y. Acad. Sci.* **15:** 138-140 (1953). B80,534/53

In rats pretreated with Phenergan and exposed to various "neurotropic" (sound, restraint) or "systemic" (cold, histamine) stressors, only histamine became incapable of causing an adrenal ascorbic acid discharge. "These results do not support the view that histamine may be an important factor and, in no way, an indispensable link in hypothalamo-pituitary alteration due to neurotropic

stress." They also show that histamine cannot be the only humoral agent responsible for pituitary stimulation during stress.

Schnitzer, A.: "Histamin und Stress" (Histamine and stress). *Münch. Med. Wochenschr.* **97:** 446-469 (1955).

J25,677/55

Histamine liberation is considered to be a characteristic manifestation of the alarm reaction and may cause sudden death in corticoid-deficient patients receiving short-wave therapy.

Korovnikov, K. A.: "Significance of enzymes activity alterations in pathogenesis." *Vopr. Med. Khim.* **9:** 137-142 (1963) (Russian).

G14,879/63

In rats the histamine content of the muscles during intensive muscular work or cooling decreased significantly, whereas that of the blood remained unchanged. The histaminase activity of the blood increased slightly.

Ganong, W. F., Lorenzen, L.: "Brain neurohumors and endocrine function." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 583-640. New York and London: Academic Press, 1967.

E6,920/67

Extensive review on neurohormones, particularly catecholamines, 5-HT, acetylcholine, histamine, substance P, γ -aminobutyric acid and dopamine (about 250 refs.).

Makarov, I. A.: "Role of histaminemia in changes of the eosinophil count during stress." *Vrach. Delo No. 1:* 77-79 (1971) (Russian).

J19,053/71

Observations on the rat and man suggest that "histamin may be the cause of eosinopenia and eosinophilia. Local histaminemia is accompanied by eosinopenia, total by eosinophilia. It is concluded that poststress eosinopenia develops due to prevailing migration of eosinophils into tissues with an increased histamin content as compared with their mobilization from the bone marrow. Blocking of endogenous histamin leads only to mobilization of cells from the bone marrow causing [the] paradoxical character of the reaction."

Makarov, I. A.: "Role of the adrenals in the development of post-stress eosinopenia." *Ter. Arkh.* **44** No. 11: 53-58 (1972) (Russian).

H91,719/72

There is no evidence of a direct destruction of blood eosinophils by glucocorticoids. Ob-

servations in rats and patients suggest that stress eosinopenia is produced by "local freeing of endogenous histamin in a number of organs. Glucocorticoids play an auxiliary role of a creator of an appropriate gradient of histamin concentration in the blood and tissues causing migration of eosinophils in the tissue. This confirmed the fact of blocking eosinopenia by dimedrol premedication. A regular drop in the markedness of eosinopenia observed in stress in patients with considerable hypercorticism can be attributed to the increase of the level of natural antagonist of histamin—heparin in patients of such kind."

Acetylcholine. Mazzone, R., Sozio, N., Padoleccchia, N.: "Effetti della sensibilizzazione colinergica sulla sindrome reattiva allo 'stress'" (Effect of cholinergic sensitization on the syndrome reactive to stress). *Boll. Soc. Ital. Biol. Sper.* **36**: 157-159 (1960). J23,135/60

Cholinergic drugs increase reactivity to pain-induced stress in the rabbit. These and other experiments with eserine and atropine suggest that "the stress reaction develops in a zone sensitive to acetylcholine but not to atropine, and thus furnish indirect evidence of the role of this reticular formation in the organization of defense mechanisms."

Ganong, W. F., Lorenzen, L.: "Brain neurohumors and endocrine function." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 583-640. New York and London: Academic Press, 1967. E6,920/67

Extensive review on neurohormones particularly catecholamines, 5-HT, acetylcholine, histamine, substance P, γ -aminobutyric acid and dopamine (about 250 refs.).

Johansson, G.: "Relation of biogenic amines to aggressive behaviour." *Med. Biol.* **52**: 189-192 (1974) (33 refs.). J17,685/74

Prostaglandins. Flynn, J. T., Reed, E. A.: "Arterial prostaglandin levels following hemorrhagic shock in the dog." *Fed. Proc.* **33**: 317 (1974). H84,078/74

"During hemorrhagic stress, it appears that arterial pg levels are elevated, and that the E and F types may be of greatest physiological importance."

Usardi, M. M., Franceschini, J., Mandelli, V., Daturi, S., Mizzotti, R.: "Prostaglandins

VIII: a proposed role for PGE₂ in the genesis of stress-induced gastric ulcers." *Prostaglandins* **8**: 43-51 (1974). J18,077/74

"A protective effect on stress-induced gastric ulcers has been demonstrated for PGE₂ and PGF_{2 α} in rats."

GABA. Reynolds, R. W., Meeker, M. R.: "Thiosemicarbazide injection followed by electric shock increases resistance to stress in rats." *Science* **151**: 1101-1102 (1966). F62,497/66

In rats, pretreatment with thiosemicarbazide (which lowers GABA concentrations in the brain) offers considerable protection against gastric ulcers produced by electroshock or immobilization.

Moreva, E. V.: "Biochemical changes in the brain during reflexes causing degeneration of the gastric mucosa." *Biull. Èksp. Biol. Med.* **62** No. 7: 49-52 (1966) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **62**: 772-774 (1966). J24,289/66

In rats stressed by combined electroshock and restraint, the development of gastric lesions was accompanied by a "reduction in the level of bound acetylcholine mainly in the hypothalamic region and by a decrease in the amount of free acetylcholine mainly in the cerebral hemisphere." The GABA level of the brain was likewise diminished.

Ganong, W. F., Lorenzen, L.: "Brain neurohumors and endocrine function." In: Martini, L. and Ganong, W. F., *Neuroendocrinology*, Vol. 2, pp. 583-640. New York and London: Academic Press, 1967.

E6,920/67

Extensive review on neurohormones, particularly catecholamines, 5-HT, acetylcholine, histamine, substance P, γ -aminobutyric acid, and dopamine (about 250 refs.).

Chattopadhyay, S., Uniyal, M.: "The interaction of stress and corticosteroid on the hypothalamus as reflected by GABA content." *5th Asia & Oceania Congr. Endocr.*, p. 48. Chandigarh, India, 1974.

H82,064/74

In rats the negative feedback influence of circulating corticosteroids and the administration of triamcinolone induced a low GABA concentration in the hypothalamus, whereas exposure to stress led to a higher GABA level than in the controls. "The interaction of stress-induced excitation and negative feedback inhibition owing to increased concentration of corticosteroid may involve GABA in

the integrative processes of the hypothalamus."

Makara, G. B., Stark, E.: "Effect of gamma-aminobutyric acid (GABA) and GABA antagonist drugs on ACTH release." *Neuroendocrinology* **16**: 178-190 (1974).

H98,366/74

On the basis of pharmacologic evidence in the rat, the authors "suggest that GABA may be an inhibitory neurotransmitter of hypothalamic interneurons and/or afferent pathways involved in the regulation of ACTH release."

Varia. Skinner, W. A., Mathews, R. D., Parkhurst, R. M.: "Alarm reaction of the top smelt, *Atherinops affinis* (Ayres)." *Science* **138**: 681-682 (1962). D38,493/62

Induction of the alarm reaction (characterized by rapid swimming, jumping, severe seizures) with the isolated "alarm substance" of the top smelt. The authors claim the reaction to the *pheromone* is species specific.

Unoza, A.: "Fluctuation of adrenal cholesterol and corticosterone levels during stress induced by histamine." *Shikwa Gaku* **68**: 1650-1659 (1968) (Japanese).

J24,735/68

Discussion of *parotin* in relation to hormones produced during stress.

Sugiyama, T.: "Effect of *parotin* on stress response inhibition due to thyroidectomy." *Shikwa Gaku* **69**: 1221-1231 (1969) (Japanese). J23,109/69

Forsyth, R. P., Hoffbrand, B. I., Melmon, K. L.: "Hemodynamic effects of angiotensin in normal and environmentally stressed monkeys." *Circulation* **44**: 119-129 (1971). G84,832/71

Avoidance schedules and other environmental stressors greatly sensitized rhesus monkeys to the pressor effect of infused *angiotensin II*.

Igarashi, T.: "Influence of sialoadenectomy and cyanide [as well as *parotin*] on the stress loop." *Shikwa Gaku* **71**: 1356-1370 (1971) (Japanese). J24,561/71

Balestreri, R., Bertolini, S., Elicio, N., Costa, S.: "Glucagone e funzione del sistema ipotalamo-ipofisocorticosurrenalico nell'uomo" (Glucagon and function of the hypothalamic-hypophyseal-adrenocortical system in man). *Boll. Soc. Ital. Biol. Sper.* **50**: 417-423 (1974). J24,412/74

Experiments on man suggest the possibility that *glucagon* might act as a releasing factor of CRF. [The authors admit that the evidence in favor of this interpretation is still very problematic (H.S.).]

VARIOUS MECHANISMS THE FIRST MEDIATOR

Ever since the first description of the G.A.S., one of the most intriguing problems concerning its mediation was the identification of the stimulus responsible for alerting the organism to the existence of danger or increased demand. For example, in the case of a local burn to a leg, or of fear, or of hemorrhage, what could be the first mediator carrying the same message of stress from the first target of the eliciting agent (the leg, the CNS, or the cardiovascular system) to the centers initiating the stereotyped G.A.S. response? We have learned a good deal about the subsequent links in this biologic chain reaction that permit the relay of information (through the hypothalamus, pituitary, adrenal and so on), but little progress has been made in understanding how the most diverse stimuli, initiated in different parts of the body, can communicate the same message: that a state of stress exists.

The first working hypothesis postulated that any demand upon any tissue would liberate some ubiquitous toxic metabolite, that is, a by-product of increased tissue activity of any kind.

Histamine was initially suspected to play this role, since it can be liberated from many tissues under the influence of diverse stimuli, and it produces increased capillary

permeability and shock such as are seen in acute stress. Also, it causes a particularly pronounced corticoid discharge and is especially toxic to adrenalectomized animals. However, antihistaminics failed to protect rats against neurotropic (sound, restraint) or systemic (cold) stressors, counteracting only the effects of histamine itself. Hence, it was concluded that histamine could not be the only humoral agent responsible for pituitary stimulation during stress.

Of course, it is by no means proven that the nonspecificity of the stress reaction is due to its invariable initiation by the same substance; it might be that the receptors in the regulating centers (for example, the hypothalamus) react stereotypically to a great number of chemical messengers brought to them by the blood whenever there is any kind of increased demand anywhere in the body. Indeed, we have no proof that the first mediating agent is a substance (or group of substances) rather than a deficiency of some vitally important blood constituent which is "used up" during any kind of biologic activity.

It was always tacitly assumed that, whatever it may be, the first mediator is blood-borne rather than relayed through afferent nerves. This view appeared to receive confirmation from our first experiments, in which we showed that if one limb of an experimental animal is amputated (under appropriate anesthesia) and then only the main arteries and veins are reconnected by catheters, a burn applied to the severed, and hence totally denervated, extremity still causes manifestations of stress in the body, to which it is now connected only by the bloodstream. Yet similar experiments performed subsequently on dogs in which all structures were transected at the mid-thigh level, leaving only the femoral artery and vein and the sciatic nerve intact, showed that burns applied to the isolated leg increased corticoid secretion into the adrenal vein, whereas this was not the case after severance of the nerve. From this it was concluded that "there is no evidence for the production in the wounded area of a substance which stimulates the pituitary-adrenal axis."

On the other hand, recent observations on parabiotically united rats showed that if one partner is restrained on a mobile cart which its twin can pull about, stress ulcers of the stomach develop in both twins. These findings were interpreted to indicate a blood-borne "transmittal of restraint-induced gastric ulcers by parabiosis"; however, it may be assumed that in the experiments both partners were under considerable stress.

It is somewhat disappointing that forty years after the first description of the alarm reaction—despite all that we have learned about the subsequent mediation of the stress response through the hypothalamus-pituitary-adrenal and the sympathetic nervous systems—we still know virtually nothing about the nature of the first mediator.

All future studies along these lines should take into account that, despite the stereotyped nature of the stress response itself, we have no reason to believe that the first mediator is necessarily always an excess or a lack of a single substance, or the result of nervous arousal. It must be remembered that nervous stimuli are certainly dispensable, since stress occurs under deep anesthesia or after deafferentation of the hypothalamus in mammals, as well as in lower forms of life that have no nervous system. It is quite conceivable that a stereotyped stress reaction can be produced through the most diverse means merely by deranging the homeostasis of biologic systems, which are notoriously labile. In this event, stress could be compared with fatigue or energy consumption, which likewise are nonspecific responses to any demand, be it pleasant or unpleasant. Also, like stress, fatigue or energy utilization may be localized in any region of the body, or generalized throughout more or less diffuse organ systems.

The First Mediator

(See also our earlier stress monographs, p. xiii)

Selye, H.: "Further evidence in support of the alarm reaction theory of adrenal insufficiency." *Am. J. Physiol.* **119**: 400-401 (1937). 68,414/37

Brief description of observations which "lead us to assume that the liberation from the tissues of certain toxic metabolites with histamine-like pharmacological effect is the primary cause both of the alarm reaction and of adrenal insufficiency."

Guillemin, R., Fortier, C.: "Role of histamine in the hypothalamo-hypophyseal response to stress." *Trans. N.Y. Acad. Sci.* **15**: 138-140 (1953). B80,534/53

In rats pretreated with Phenergan and exposed to various "neurotropic" (sound, restraint) or "systemic" (cold, histamine) stressors, only histamine became incapable of causing an adrenal ascorbic acid discharge. "These results do not support the view that histamine may be an important factor and, in no way, an indispensable link in hypothalamo-pituitary alteration due to neurotropic stress." They also show that histamine cannot be the only humoral agent responsible for pituitary stimulation during stress.

Egdahl, R. H.: "Pituitary-adrenal response following trauma to the isolated leg." *Surgery* **46**: 9-21 (1959). D96,659/59

In dogs, all leg structures were transected at the midthigh level, leaving only the femoral artery and vein and the sciatic nerve intact. Burns applied to the isolated leg increased corticoid secretion into the cannulated adrenal vein only as long as the nerve supply remained intact. "The adrenocortical stimulation which follows severe burns or operative trauma is dependent exclusively upon peripheral nervous impulses. There is no evidence for the production in the wounded area of a substance which stimulates the pituitary-adrenal axis."

Mach, W. J., Mach, C.: "Biogenese und Chemismus der 'first mediators of stress.' Vorläufige Mitteilung" (Biogenesis and chemistry of the "first mediators of stress." Preliminary report). *Ärzt. Forsch. [II]* **13**: 101 (1959). C78,761/59

Preliminary observations suggesting that there is no single "first mediator" of stress, but rather a group of substances which are probably anionic polycondensates containing various cyclic compounds.

Rose, K. D., Maca, R., Pace, D. M.: "Sterol synthesis by cells cultured on serum from heat-stressed chickens." *Proc. Soc. Exp. Biol. Med.* **108**: 282-285 (1961).

D89,507/61

"Young chickens subjected to heat stress at 102°F for 24 hours elaborate a stress factor into their blood stream. When serum from these animals is used as an adjuvant in a serum-balanced salt solution medium, cells grown on this medium accumulate large numbers of small lipid droplets within their cytoplasm." Possibly, this factor may account for the hypercholesterolemia characteristic of stress in vivo.

Jayle, M. F.: "Rôle du métabolisme des glycoprotéines dans la biogénèse de l'athérosclérose. Concept sur le 'syndrome général de l'agression'" (Role of the metabolism of glycoproteins in the biogenesis of atherosclerosis. Concept of the "general stress syndrome"). *Ann. Thér.* **14**: 11-22 (1963).

G63,439/63

Under various stress conditions, the plasma levels of fibrinogen and of the glycoproteins haptoglobin and seromucoid are characteristically increased; this may play an important part in stress-induced atherosclerosis. The common denominator of the diseases of adaptation and of stress responses may be a rise in these compounds which might thus correspond to the "first mediator." This interpretation might act as a valid focal point of Selye's "unitary concept" although the claims concerning the central role of the pituitary-adrenal axis are rejected.

Seidel, W., Lorenz, W., Doenicke, A., Mann, G., Uhlig, R., Rohde, H.: "Histaminfreisetzung beim Menschen und Stressulkus-Pathogenese" (Histamine liberation in man and the pathogenesis of stress ulcers). *Z. Gastroenterol.* **11**: 297-300 (1973).

J24,571/73

In man, the plasma histamine content rises under the influence of various stressors and may play an important role in the pathogenesis of stress ulcers.

Tran, T. A., Gregg, R. V.: "Transmittal of restraint-induced gastric ulcers by parabiosis in rats." *Gastroenterology* **66**: 63-68 (1974).

J9,758/74

Induction of gastric ulcers "in the parabiotic mate of a restrained rat implicates a humoral factor in the etiology" of this lesion. "One rat of a parabiosed pair was restrained

for 28 or 30 hr on a mobile cart which its unrestrained mate was free to pull about. All restrained animals showed gastric ulceration, and 15 of 17 unrestrained mates also devel-

oped gastric ulceration" (28 refs.). [It may be assumed, however, that the control animal was also under considerable stress under such conditions (H.S.).]

GENERAL ADAPTATION SYNDROME (G.A.S.) VS. LOCAL ADAPTATION SYNDROME (L.A.S.)

Whereas the G.A.S. is the general or systemic response to a stressor, the L.A.S. represents its local, or topical, equivalent. Obviously, nonspecific demands for adaptation may be limited to certain regions of the body (for example, inflammation, wound healing), but both specificity and localization are relative concepts: demands may be more, or less, specific in the type of response that they require, or the region of the body that they affect. Thus, not only limited topical responses to diverse agents, but even nonspecific reactions primarily limited to certain systems (cardiovascular, nervous, RES), may be regarded as examples of an L.A.S.

In all these cases, the L.A.S. may cause a G.A.S. Thus, a nonspecific local inflammatory response may mobilize the hypothalamus-adrenal-pituitary axis for systemic defense if the demands are of sufficient intensity to require general adaptive reactions. This same is true even if the L.A.S. selectively affects not a circumscribed body system, but the CNS, the immune system, or any other anatomically widespread, but functionally separable and delimited entity.

To take one of the most carefully studied examples of such interactions: an L.A.S. produced by local inflammation (such as a granuloma pouch) will result in a triphasic nonspecific L.A.S. If mild, this will remain largely topical, but if sufficiently intense, it will cause systemic stress phenomena. Conversely, the G.A.S., with its associated discharge of stress hormones (particularly glucocorticoids), will act back upon the L.A.S. and inhibit the inflammatory response. The pain induced by topical injury in the region of an L.A.S. will likewise have systemic manifestations and induce a G.A.S. which, in turn, can alter the pain threshold. Indeed, if a highly specific and quite localized stimulus is of sufficient intensity to affect the whole organism, it may also produce a G.A.S. (for example, intense white light affecting the retina or a particular sound acting upon the ear). However, in such cases a specific agent, and not the L.A.S., represents the cause of a G.A.S.

General Adaptation Syndrome (G.A.S.) vs. Local Adaptation Syndrome (L.A.S.)

(See also our earlier stress monographs, p. xiii)

Hardy, J. D., Goodell, H., Wolff, H. G.: "Studies on pain: measurement of the threshold for an alarm reaction in man and its relation to pain perception." *Science* **93**: 439-440 (1941). B26,756/41

In man a thermal stimulus that evokes a just perceptible change in skin resistance is considered to be the equivalent of a local

alarm reaction probably elicited by pain. "The threshold level of the alarm reaction appeared to be related to the emotional state of the subject at the time. The administration of an analgesic agent such as acetylsalicylic acid when large areas were exposed raised the alarm reaction threshold to the pain threshold, and in the case of alcohol, higher than the pain threshold."

Selye, H.: "The local adaptation syndrome (L-A-S)." *Proc. 19th Int. Physiol. Congr.*, p. 750. Montreal, 1953. B79,918/53

The similarity of the L.A.S. to the triphasic G.A.S. (illustrated in rats by the use of the granuloma pouch technique) is emphasized by the fact that, in the pouch, "the first stage of this response is initiated by phenomena of cell degeneration and necrosis. These are immediately followed by the typical manifestations of acute inflammation. The second stage is characterized by chronic inflammatory changes, while during the third stage, cellular degeneration and necrosis again become prominent." The L.A.S., like the G.A.S., is nonspecific in its causation but quite typical in its manifestations. Furthermore, a severe L.A.S. can initiate a G.A.S., and the G.A.S. can inhibit the L.A.S., primarily through excess secretion of glucocorticoids.

Selye, H.: "The part of inflammation in the local adaptation syndrome." *Rev. Can. Biol.* **12**: 155-176 (1953). A97,423/53

Description of the L.A.S. and its relation to the G.A.S. Both are nonspecific reactions comprising damage and defense; they are triphasic, with typical signs of "cross resistance" and "cross sensitization" during the second stage; both are singularly sensitive to "adaptive hormones" (ACTH, STH, corticoids); and if they develop simultaneously in the same individual, they greatly influence one another.

Selye, H.: "Sensitization of individual vascular territories to the antiphlogistic effect of hydrocortisone. An example of 'selective conditioning.'" *Circ. Res.* **2**: 53-59 (1954). B83,630/54

In rats, ligation of one iliac artery causes a latent circulatory disturbance, after which intraperitoneal dextran induces severe anaphylactoid edema only in the other extremities. Cortisol likewise inhibits this response most markedly in the region with diminished blood supply. On the other hand, a stronger irritant such as croton oil causes necrosis with surrounding inflammation especially in the vasoligated extremity. "It is tentatively assumed that both vasoligation and hydrocortisone facilitate the breakdown of tissue by croton oil; the irritation of the resulting necrotic tissue being then added to that of the injected irritant, inflammation is stimulated to such an extent that the circulatory disturbance and the hormone fail to inhibit it."

Selye, H.: "Nonspecific resistance." *Ergeb. Allg. Pathol. Pathol. Anat.* **41**: 208-241 (1961). C95,972/61

In a review on nonspecific resistance, special attention is given to the prevention of inflammatory changes and aggravation of necrosis in the L.A.S. by the concurrent production of the G.A.S. (85 refs.).

Selye, H.: "Interactions between systemic and local stress." *Br. Med. J.* May 22, 1954, pp. 1167-1170. B90,618/54

"Using the granuloma-pouch technique, it was shown that, depending upon circumstances, systemic stress can either inhibit or aggravate the topical damage caused by exposure of a limited tissue area to a pathogen—for example, a chemical irritant, such as croton oil.

"The antiphlogistic effect of stress is not merely due to increased secretion of cortisol-like hormones, since it is also observed in adrenalectomized animals maintained on (in themselves inactive) threshold doses of injected cortisol.

"The aggravation of topical tissue injury by systemic stress also depends only in part upon endogenously produced adrenal hormones; it is abolished by complete adrenalectomy, but not if suitable substitution therapy with antiphlogistic corticoids (cortisone, cortisol) is given.

"Both these effects of systemic stress upon topical tissue reactions can be delayed, becoming manifest only after the systemic stressor has ceased to act."

Selye, H., Tuchweber, B., Gabbiani, G.: "Prevention of cutaneous calciphylaxis by topical stress." *Arch. Dermatol.* **87**: 566-574 (1963). D40,219/63

"A variety of agents such as distilled water, mechanical trauma (pinching the skin with a hemostat), formaldehyde, croton oil, or histamine liberators (e.g., compound 48/80, polymyxin) selectively inhibit skin calcification at the point where they are applied within the challenged area. Histologic studies show a relationship between this form of skin calcification, the distribution of mast cells, and the deposition of iron."

Funk, G. A., Jensen, M. M.: "Influence of stress on granuloma formation." *Proc. Soc. Exp. Biol. Med.* **124**: 653-655 (1967). F77,633/67

"Mice subjected to sound stress or a combination of avoidance-learning stress and sound stress showed a highly significant decrease in their ability to produce foreign body granulomas against subcutaneously-implanted cotton pellets."

Machida, T.: "Luteinization of ovaries under stressful conditions in persistent-estrous rats bearing hypothalamic lesions." *Endocrinol. Jap.* **18**: 427-431 (1971). H49,947/71

In rats bearing a croton oil granuloma pouch, persistent vaginal cornification and corpus luteum formation occurred if the medial preoptic area was destroyed. When both the medial preoptic area and the suprachiasmatic nuclei were destroyed, persistent estrus likewise developed, but without corpora lutea. These and other findings "suggest that the preoptic-suprachiasmatic region of the hypothalamus, especially the suprachiasmatic nuclei, is involved in luteinization of ovaries in persistent-estrous rats following exposure to stressful stimuli."

Balint, G. A.: "Examination of the inflammatory effect of ricin with special reference to the endogenous corticosteroid

mobilisation." *Toxicology* **1**: 329-336 (1973).

J10,650/73

The topical arthritis produced by injection of ricin into the hind foot pad of the rat shows the phlogistic potency of the substance. When injected intraperitoneally, it increases plasma corticoids and causes degranulation of the adrenals with inhibition of the anaphylactoid edema induced by dextran in the same animal.

Balasz, T.: "Development of tissue resistance to toxic effects of chemicals." *Toxicology* **2**: 247-255 (1974). J13,976/74

Review and personal observation on the development of topical tissue resistance following repeated systemic treatment with drugs having a topical damaging effect. This phenomenon represents an instance of cross-resistance presumably related to the G.A.S. (32 refs.).

CONDITIONING

In stress research, we understand by "conditioning" merely the establishment of conditions necessary for an agent to act. It can be positive if the conditions permit an action, or negative if they prevent it. Positive conditioning by corticoids has also been referred to as a "permissive" action. The concept is by no means limited to the establishment of conditioned reflexes, although it includes these together with any other nervous, chemical or physical factors that affect the body's reactivity.

Probably the first clearcut demonstration of conditioning in this sense was carried out in 1941. At that time, it was shown that adrenalectomized rats respond to the stressor effect of trauma with hypo-, rather than with the usual hyperglycemia. Active adrenocortical extracts (synthetic glucocorticoids were not yet readily available) restored the blood sugar level of the adrenalectomized animals but caused no hyperglycemia at the dose levels used. However, such substitution therapy permitted trauma again to elicit the usual stress hyperglycemia, at the same time raising shock resistance. It was concluded that the metabolic changes of stress are dependent upon amounts of corticoids that are, in themselves, ineffective. During the subsequent three decades, innumerable additional examples of such positive conditioning by corticoids and other agents were demonstrated. Yet it was many years before it became generally understood that conditioning is not always positive, and certainly is not limited to corticoids. In fact, the entire concept of "pluricausal diseases" is based upon the realization that certain morbid changes are not produced by one agent but by the simultaneous activity of conditioning and evocative factors.

In view of the many misunderstandings generated by the pertinent publications, this topic will be discussed in detail in the following abstract section. It should be emphasized here, however, that excess corticoids, produced as a consequence of stress, can also produce changes by themselves, under ordinary circumstances, without the simultaneous agency of unusual conditioning factors.

Conditioning

(See also our earlier stress monographs, p. xiii)

Selye, H., Dosne, C.: "Influence of traumatic shock on blood sugar of adrenalectomized rats treated with adrenal cortical extract." *Proc. Soc. Exp. Biol. Med.* **48**: 532-535 (1941). A37,037/41

In adrenalectomized rats, trauma failed to cause the usual hyperglycemia of stress. Active corticoid extracts restored the low blood sugar of adrenalectomized animals to normal, but at the doses used, they did not raise it above this level, nor did they elicit hyperglycemia in intact controls. However, if these extracts were administered to adrenalectomized rats during stress induced by trauma, a significant hyperglycemia resulted and shock resistance was raised simultaneously. Manifestly, the metabolic changes of stress are, in themselves, dependent upon ineffective amounts of corticoids. [This is probably the first experimental observation supporting the concept of "conditioning" or "permissive" actions of corticoids (H.S.).]

Ingle, D. J., Ward, E. O., Kuizenga, M. H.: "The relationship of the adrenal glands to changes in urinary non-protein nitrogen following multiple fractures in the force-fed rat." *Am. J. Physiol.* **149**: 510-515 (1947).

B4,742/47

In adrenalectomized rats, multiple bone fractures caused no rise in urinary nitrogen excretion unless the animals were treated with maintenance doses of adrenal cortical extract (cortin). In untraumatized, adrenalectomized rats, cortin actually diminished nitrogen excretion. "The negative nitrogen balance which characteristically develops following fractures may require the presence of the adrenal cortical hormones but is not caused specifically by the increase in secretion of the cortical hormones which occurs during stress." [This is the type of experiment that subsequently led Ingle to coin the term "permissive action" for what had previously been known as positive conditioning (H.S.).]

Skelton, F. R.: "On certain factors conditioning the action of the pituitary-adrenal system." In: Christman, R. C., *Pituitary-Adrenal Function*, pp. 39-48. Washington: American Association Advancement Science, 1950.

B45,085/50

Ingle, D. J., Nezamis, J. E.: "Effect of stress upon glycosuria of force-fed depa-

creatized and of adrenalectomized-depancreas-
tized rats." *Am. J. Physiol.* **162**: 1-4 (1950).

B49,683/50

In mildly diabetic rats, some of which were adrenalectomized and treated with maintenance amounts of cortical extract to sustain preadrenalectomy levels of glycosuria, stress (formalin) decreased sugar excretion, especially after adrenalectomy. [This is an example of a "permissive action" of corticoids, since adrenalectomized, untreated rats did not exhibit this effect (H.S.).]

Ingle, D. J.: "The functional interrelationship of the anterior pituitary and the adrenal cortex." *Ann. Intern. Med.* **35**: 652-672 (1951).

B65,287/51

Review of numerous earlier experiments by the author which shows that corticoids sensitize for various effects of diverse agents without being independently responsible for the changes. The author describes this "permissive" action which we previously designated as "conditioning."

Engel, F. L.: "The significance of the metabolic changes during shock." *Ann. N. Y. Acad. Sci.* **55**: 381-393 (1952).

B74,810/52

Review of the literature and personal observations showing that many metabolic actions characteristic of the G.A.S. are due to the conditioning (or "permissive") effects of corticoids upon responses to stress. As early as 1941, it was shown by Selye and Dosne that the typical hyperglycemia of traumatic shock in rats is replaced by hypoglycemia after adrenalectomy but hyperglycemia can be restored by glucocorticoid extracts in doses which by themselves do not influence the blood sugar of untraumatized adrenalectomized animals (64 refs.).

Ingle, D. J.: "The role of the adrenal cortex in homeostasis." *J. Endocrinol.* **8**: xxiii-xxvii (1952).

B75,214/52

Review suggesting that "the adrenal hormones play a 'permissive' rather than causative role in certain diseases and in certain metabolic responses to stress." The many observations of undoubtedly conclusive experiments that support this interpretation show that even large doses of corticoids produce few pathologic lesions by themselves, but they do facilitate the effects of various pathogens. [A phenomenon which had previously been described as the "conditioning action" of hormones (H.S.).]

Selye, H., Jacot, B.: "On the effect of various steriods upon the extra-adrenal thy-

molytic action of ACTH." *Acta Endocrinol.* (Kbh.) **9:** 333-336 (1952). B62,780/52

In adrenalectomized and orchidectomized rats, the thymolytic action of cortisone is greatly enhanced by simultaneous administration of ACTH, which has no such effect under similar conditions if given in combination with DOC or estradiol. Apparently, the thymolytic action of cortisone is augmented (conditioned) by ACTH, which has no direct effect on the thymus.

Ingle, D. J.: "The role of the adrenal cortex in homeostasis." In: Yoffey, J. M., *The Suprarenal Cortex*, pp. 177-189. London: Butterworths 1953. B83,030/53

Recapitulation of the author's earlier experiments indicating that, during stress, adrenalectomized rats maintained on a fixed amount of cortical extract may show signs of adrenal deficiency because of increased corticoid requirements. "There is no doubt that the presence of the adrenal cortical hormones is essential for the overt manifestation of such diseases as diabetes mellitus, hypertension, prostatic cancer, etc. It may be possible to explain much of the evidence which Selye offers in support of his hypothesis in terms of the 'permissibility' of cortical hormone action."

Engel, F. L.: "The adrenal cortex and the metabolic response to stress." *J. Clin. Endocrinol.* **15:** 1555-1558 (1953).

B88,627/53

Theoretical discussion on the relative merits of the "permissive" and "conditioning" roles of corticoids in stress reactions. These are practically indistinguishable from each other but appear to be more important than the direct effects of these hormones upon the tissues.

Engel, F. L.: "General concepts of adrenocortical function in relation to the response to stress." *Psychosom. Med.* **15:** 565-571 (1953). B88,336/53

Review of the literature on the G.A.S. in relation to the role of conditioning factors in determining responses to corticoids. Some authors emphasize conditioning, others the direct action of corticoids. "In all likelihood, the truth probably lies somewhere in between these two views, with the adrenal and stress responses being so inextricably interwoven and interdependent as to be essentially inseparable" (31 refs.).

Burns, T. W., Engel, F. L., Viau, A., Scott, J. L. Jr., Hollingsworth, D. R., Werk, E.:

"Studies on the interdependent effects of stress and the adrenal cortex on carbohydrate metabolism in man." *J. Clin. Invest.* **32:** 781-791 (1953). B84,911/53

Observations on the effect of cortisone during stress, as well as after insulin or glucose administration, "are considered to be compatible with the concept that there is an interaction between stress and adrenal hormone in modifying carbohydrate metabolism. They are not reconcilable with the view that the metabolic alterations during stress are direct consequences of adrenal cortical hypersecretion."

Selye, H.: "'Conditioning' versus 'permissive' actions of hormones." *J. Clin. Endocrinol. Metab.* **14:** 122-127 (1954) (12 refs.).

B86,400/54

Review of the earlier literature which led the author to the concept that the main action of corticoids is not their direct effect upon the target organ, but their ability to "condition" tissues to respond to stimuli, and that, conversely, the action of specific stimuli is altered by corticoids. Such conditioning increases or decreases stress responses. The term "permissive" is also acceptable, but only for what we have called "positive conditioning," that is, when a response is made possible as a result of corticoid actions. The principle of conditioning (first formulated in 1936) has been repeatedly illustrated by many experimental examples and is summarized in Figure 23 (p. 1144).

Ingle, D. J.: "Permissibility of hormone action. A review." *Acta Endocrinol.* (Kbh.) **17:** 172-186 (1954). C789/54

Review of experimental observations that leads the author to the conclusion that "the conditions under which the term permissive is applied are as follows: 1. The metabolic response to a stimulus occurs in the presence of an endocrine organ. 2. The response fails to become overt when the organ is removed and no replacement therapy is given. 3. The response is again elicited by an appropriate stimulus when a steady intake of hormone is substituted for an endocrine organ." Although earlier experiments have led to the designation of these same observations as "humoral conditioning," this is not considered a valid reason for replacing "humoral" with "permissive."

Ingle, D. J.: "Permissive action of hormones." *J. Clin. Endocrinol. Metab.* **14:** 1272-1274 (1954). B98,701/54

Arguments in favor of replacing the term

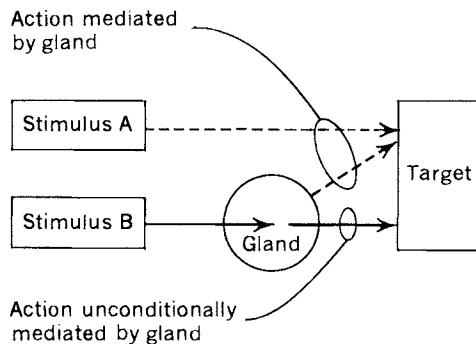


Figure 23. Conditional and unconditional actions of stimuli, the effects of which depend upon an endocrine gland. Supposing a stimulus acts on a target organ in the presence, but not in the absence of an endocrine gland, two possibilities exist: *A.* the stimulus acts directly on the target organ, but only if the latter is maintained in a responsive condition by constant hormonal impulses, which it receives from the gland (interrupted lines), *B.* the stimulus has no direct effect upon the target, but merely induces the gland to release a hormone which, in turn, acts upon the target (solid lines). (Reproduced from *J. Clin. Endocrinol. Metab.* 14 (1954) by permission of the J B Lippincott Company.)

"conditioning" by "permissive." Reconsideration of published data leads the author to the conclusion that "Selye and I agree that the word 'permissive' is not adequately descriptive of the facts. I prefer the term 'supporting,' but neither it nor any other word that has been suggested has quite the desired connotation. Selye suggests the term 'conditioning' on the grounds that the presence of hormone is one of a pattern of conditions under which the response will occur." However, the view that "extra-adrenal mechanisms may require the presence of the cortical hormones to support normal responsiveness, is in my opinion not weakened by evidence that the extent of response can also be modified by a change in titer of these hormones."

Selye, H.: "Sensitization of individual vascular territories to the antiphlogistic effect of hydrocortisone. An example of 'selective conditioning.'" *Circ. Res.* 2: 53-59 (1954).

B83,630/54

In rats, ligation of one iliac artery causes a latent circulatory disturbance, after which dextran ip induces severe anaphylactoid edema only in the other extremities. Cortisol likewise inhibits this response most markedly in the region with diminished blood supply. On the other hand, a stronger irritant such as croton oil causes necrosis with surrounding inflammation, especially in the vasoligated extremity. "It is tentatively assumed that both vasoligation and hydrocortisone facil-

tate the breakdown of tissue by croton oil; the irritation of the resulting necrotic tissue being then added to that of the injected irritant, inflammation is stimulated to such an extent that the circulatory disturbance and the hormone fail to inhibit it."

Selye, H.: "Selective alteration of certain ACTH and glucocorticoid effects by androstan derivatives." *Metabolism* 4: 403-415 (1955).

C2,007/55

In rats, "the actions of ACTH upon its primary target, the adrenal, can be altered, both quantitatively (inhibition of hypertrophy) and qualitatively (formation of hyaline-cell inclusions), by concurrent treatment with certain androstan derivatives (MAD, methyltestosterone, testosterone). These same steroids can also alter the pattern of the peripheral changes produced by ACTH in its ultimate targets. Some effects of ACTH treatment (catabolism) are diminished, while others are enhanced (preputial gland stimulation) and yet others may remain essentially unaltered (antiphlogistic, thymolytic effects), in the same animal." Thus, one hormone can selectively condition certain targets for the actions of another.

Ingle, D. J.: "The role of the adrenal cortex in homeostasis." *Pediatrics* 17: 407-413 (1956).

C13,045/56

Several types of experiments on rats show that "at least some responses to stress occur full-blown in adrenalectomized animals

given normalizing doses of cortical hormones, although the response does not become overt in the animal with adrenal insufficiency. This can be regarded as an example of the permissive or supporting role of hormones." Alternatively, tissue responsiveness to corticoids may be augmented by stressors. Hence, the "diseases of adaptation" may not be the direct effect of adrenocortical dysfunction (20 refs.).

Ingle, D.: "Current status of adrenocortical research." *Am. Sci.* **47**: 413-426 (1959).

D41,791/59

In rats, excess sodium chloride intake can elicit hypertension, but concurrent treatment with corticoids greatly accelerates its development. "This is the basis for my claim that the primary cause of pathology in the Selye experiments is the trouble the animal is having with electrolytes: the sodium-retaining steroids play a 'conditioning' role—to use Selye's word—when they are present."

Ingle, D. J., Ingle, D. J.: "The relationship of the adrenal glands to diseases of adaptation." *Acta Endocrinol. (Kbh.)* **50** Supp.: 89-92 (1960). C92,395/60

Recapitulation of the authors' experiments on the permissive conditioning action of glucocorticoids. The production of diseases of adaptation by excess corticoid secretion during stress is questioned on the basis of the assumption that, in stress, more corticoids are utilized for resistance, which is also why Cushingoid symptoms do not occur. Still, the authors admit that some symptoms of corticoid excess are evident during stress. They conclude that "suppression of some but not all symptoms of hypercorticalism by stressors may be related to the well known fact that the need of the organism for cortical hormones is greatly increased by severe stress." [It is difficult to see how removal of excess corticoids by increased utilization could selectively annul only some of their effects (H.S.).]

Ingle, D. J.: "The effect of some stressors on steroid diabetes in the rat." *Diabetes* **9**: 394-395 (1960). C94,537/60

Several stressors (tumor implant, restraint, formaldehyde) suppress the glycosuria caused by large doses of cortisone in force-fed rats. [Here the concept of "permissive" actions is not invoked (H.S.).]

Ingle, D. J.: "The relationship of adrenal cortex functions to disease." *Am. J. Proctol.* **12**: 245-252 (1961). D12,583/61

Detailed discussion on the importance of conditioning (permissive effect) in stress-induced ulcerations (25 refs.).

Corson, S. A.: "Neuroendocrine and behavioral response patterns to psychologic stress and the problem of the target tissue in cerebrovisceral pathology." *Ann. N. Y. Acad. Sci.* **125**: 890-918 (1966). G36,865/66

Review of the technical literature on the conditioning factors determining the particular target tissue which will respond to physiologic or psychologic stressors.

Selye, H.: "Pluricausal diseases." *Exp. Med. Surg.* **24**: 191-209 (1966).

G32,043/66

The pluricausal diseases are divided into "conditioned lesions," in which the action of the primary pathogen is merely enhanced or diminished by the conditioner, and "synthetic lesions," in which appropriate combinations of the most diverse, and in themselves ineffective, potential pathogens produce identical lesions. These possibilities are schematically illustrated in Figure 24 (p. 1146).

Selye, H.: "Malattie da cause molteplici" (Pluricausal diseases). *Osped. Ital. Chir.* **16**: 375-399 (1967). G46,780/67

Italian translation of the English article.

Stevenson, I.: "Single physical symptoms as residues of an earlier response to stress." *Ann. Intern. Med.* **70**: 1231-1237 (1969).

J22,514/69

"Single physical symptoms often persist after a general reaction to stress and after the other symptoms of the general reaction have subsided.... Factors influencing the persistence and location of one symptom after a general reaction to stress form only one group of the relevant causal factors in these disorders" (15 refs.).

Hinkle, L. E. Jr.: "The concept of 'stress' in the biological and social sciences." *Sci. Med. & Man* **1**: 31-48 (1973).

J10,855/73

A review of the history of the stress concept and the diseases of adaptation. Accumulated evidence "has confirmed that a large proportion of the manifestations of disease are produced by reaction of the host and not directly by the 'causal agents' of disease, and that the components of the host's reactions are not in themselves 'specific' to any given 'causal agent'; it has confirmed that reactions of people to other people, or to the social environment may in-

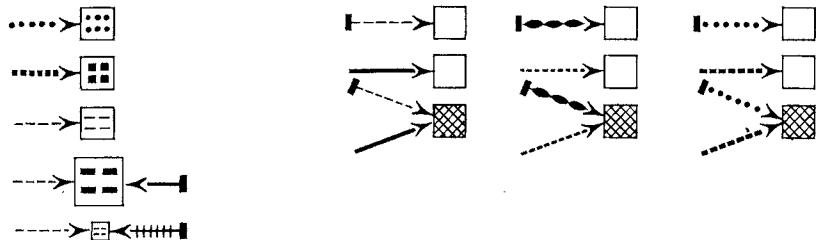


Figure 24. Left. *Conditioned lesions*. Each agent produces different lesions whose development is readily suppressed or aggravated (without being qualitatively altered) by conditioning factors. Right. *Synthetic lesions*. Identical prototypes of lesions are elicited by several combinations of in themselves inactive, essentially different agents. (Reproduced from *Exp. Med. Surg.* 24 (1966) by permission of Brooklyn Medical Press.)

fluence any physiological process or any disease." Yet the author doubts that the stress concept can provide an adequate explanation for these phenomena. He feels that "one who undertakes to criticize a theory such as the theory of stress, and to indicate that it may be inadequate today, is fortunately not required to put forward a new theory to replace it. Possibly no new theory is needed." On the other hand, the importance of conditioning factors which make stress pathogenic is clearly recognized by the statement: "One will, indeed, see hard

working, striving, impatient men who drop dead suddenly at the end of a hard day's work. If one performs population studies on a prospective basis, one is likely to find that this occurs most frequently among middle-aged and elderly men who are hyperlipidemic, who have elevated blood pressures, who have a long history of smoking cigarettes, and who have evidence of disorders of their cardiac conduction systems; and it will be very rare, indeed, that such a sudden death will be found in a healthy young woman who has none of these conditions."

THE THREE PHASES OF THE G.A.S., ADAPTATION ENERGY, AGING

The triphasic nature of the G.A.S., the concept of adaptation energy, and the theory of aging are so closely interdependent that it is most convenient to discuss them conjointly here.

Both the G.A.S. and the L.A.S. evolve in *three stages*: the alarm reaction, the stage of resistance and the stage of exhaustion. When the concept was first developed, we adopted this terminology because it seemed that the first stage represents a call to arms of the organism's defensive forces; this gradually leads to resistance when adaptation to the evocative stressor is acquired; but eventually the ability to resist is exhausted and death ensues. In the systemic form of this reaction (G.A.S.), the first manifestations to be observed during the alarm reaction are: catabolism of tissues

(with loss of body weight), pronounced thymic lymphatic involution, signs of adrenal hyperactivity (loss of lipid secretion granules from the cortex and of chromaffin material from the medulla, with hyperemia and mitotic proliferation), acute gastrointestinal erosions (which subsequently became known as stress ulcers), eosinopenia, lymphopenia and polynuclear leukocytosis.

During the stage of resistance of the G.A.S. all these changes disappear or become much less pronounced, notwithstanding continued treatment with the same dose of the evocative stressor. However, despite adequate caloric intake and an apparently perfect adaptation, resistance is eventually exhausted, and changes very similar to those of the alarm reaction reappear.

The objective manifestations of the L.A.S. likewise develop in three stages: the local alarm reaction is mainly characterized by degeneration, necrosis and/or atrophy as well as acute inflammation, hypertrophy and hyperplasia of the topically-injured area; this is followed by chronic inflammation, hypertrophy and hyperplasia of tissues at the site of irritation; and eventually there is degeneration, necrosis and/or atrophy owing to local tissue breakdown, corresponding to the local stage of exhaustion.

Most of our work on the L.A.S. was performed with the granuloma pouch technique. This lends itself particularly well to the demonstration of the local triphasic reaction. The wall of the inflammatory pouch is at first acutely damaged and inflamed, but under continued irritation it becomes sclerotic and extremely resistant to local irritation; finally, if the topical stressor is sufficiently severe, tissue breakdown results in the eventual perforation of the pouch wall and evacuation of the exudate and irritant.

Both the G.A.S. and the L.A.S. are essentially nonspecific: they can be provoked by a great variety of agents although they act respectively on the whole body or on one part of it. A good deal has been learned about the mechanism that ensures the local or systemic mobilization of defense forces, followed by the acquisition of resistance; but we know little about the causes of systemic or local exhaustion.

The maxim, "The length of life depends inversely on the rate of living," or in more popular terms, "The candle of life does not last long if you burn it at both ends," was accepted on empirical evidence much before the G.A.S. concept could have been clearly formulated. The phenomenon referred to is reminiscent of *aging* and fatigue, but we can only speculate upon its mechanism. We have all noticed that, like an inanimate machine, a living organism (or any part of it) shows wear and tear as a consequence of continuous demands upon it. But wear and tear cannot be wholly responsible for the aging process, since despite uninterrupted exposure to a stressor, at least partial adaptation can be maintained for a long time. Possibly, most of the innumerable reactions involved in adaptation are reversible, leading to soluble end-products that can be metabolized or excreted, thereby assuring recovery. However, a small percentage of these reactions may produce metabolites (possibly in the form of virtually insoluble precipitates of calcium deposits, cross-linked proteins, amyloid or "aging pigments") that may represent some of the wastes of life. Their accumulation in the cells and intercellular spaces increasingly interferes with normal function, leading eventually to death.

Normal immune function decreases with age, while autoimmunity increases. The latter observation is interesting both because of its interpretation of aging as being caused by the accumulation of undesirable waste products (here antigen = antibody complexes), and because both systemic stress and aging result in thymic lymphatic involution. Neonatal thymectomy produces changes characteristic of premature aging.

This interpretation appears to be compatible with the observation that, following

comparatively short exposure to stressors, simple rest will result in near-complete recovery, perhaps because most of the chemical wastes of short-term stress can be metabolized or excreted. However, after a whole lifetime of adaptation to the countless demands of homeostasis under constantly changing conditions, the destruction and elimination of wastes can no longer keep pace with their accumulation, probably representing what we usually consider to be tissue aging.

This concept is also quite consonant with the view that actually we have two types of *adaptation energy*: one superficial, readily accessible in times of need, but also quickly exhausted; the other deep-seated, more slowly mobilized and virtually irreplaceable. During the alarm reaction, we can call upon immediately accessible superficial adaptation energy, but of this we have only small amounts that are rapidly used up unless the demand is sufficiently mild to allow time for the mobilization of deep-seated adaptation energy and transition to the stage of resistance. Yet even this form of adaptation is not limitless, and eventually leads to exhaustion. This final stage is characterized by local tissue necrosis in the L.A.S., and in the G.A.S. by premature death if the organism is faced with fatally severe stressors, or by death at the end of a normal lifespan under ordinary conditions.

In the light of these considerations the L.A.S. and G.A.S. could be considered, respectively, as the topical and systemic telescoped equivalents of a normal lifespan. As time passes, the excessive sensitivity and adaptability of childhood is followed by the lesser responsiveness, but greater resistance, of adulthood and eventually by tissue breakdown and degeneration, with loss of adaptability, and death.

In closing this speculative section, let us call attention to the phenomena of cross-resistance and cross-adaptation, which have already been considered in describing responses to two or more simultaneously-applied stressor agents. Truly nonspecific adaptive phenomena can usually lead to cross resistance against nonspecific effects of other stressors; but if the demands made by one agent are excessive, the exhaustion of adaptation energy necessarily diminishes the ability to activate additional adaptive resources.

The concept of adaptation energy is necessarily vague, since we have no way of identifying it directly and must rely upon resistance itself to estimate its quantity. However, if we attempt to express these same thoughts in more precise chemical terms as "the accumulation of damaging waste products," we are more likely to arrive at an objective indicator of adaptability, adaptation energy meaning the ability to get rid of these wastes that, in the final analysis, may be the cause of local or systemic exhaustion in the L.A.S. and G.A.S., as well as of the phenomenon of aging.

These interpretations would also appear to be applicable to various forms of experimental progeria and premature aging, such as those induced by x-irradiation or chronic vitamin D overdosage, which undoubtedly lead to insoluble metabolic wastes, such as protein metabolites or calcium deposits.

The Three Phases of the G.A.S., Adaptation Energy, Aging

(See also our earlier stress monographs, p. xiii)

Pearl, R.: *The Biology of Death*. Philadelphia: J. B. Lippincott, 1922.

E295/22

Enunciation of hypothesis that "the length of life depends inversely on the rate of living."

Selye, H.: "Thymus and adrenals in the response of the organism to injuries and intoxications." *Br. J. Exp. Pathol.* 17: 234-248 (1936). 36,032/36

First detailed description of the "alarm reaction," characterized by adrenocortical enlargement with acute loss of lipids, thymic-lymphatic atrophy and loss of body weight. The response appears to be elicited by any damaging agent (surgical injuries, exposure to cold, restraint, fasting for forty-eight hours or more, large doses of atropine, morphine, formaldehyde, or EP). Adrenalectomy and, to a lesser extent, hypophysectomy prevent the thymus involution. "The changes caused by a drug when it is given for the first time will subside later in spite of the continued administration of this drug" but greatly shorten survival. Perhaps the adrenal enlargement, loss of body weight and the other manifestations of the alarm reaction enable the organism "to meet critical situations more efficiently."

Dosne, C., Dalton, A. J.: "Changes in the lipid content of the adrenal gland of the rat under conditions of activity and rest." *Anat. Rec.* **80**: 211-217 (1941). 81,198/41

In rats, treatment with various stressors (cold, formaldehyde) causes an initial hypertrophy and lipid loss from the adrenal cortex during the alarm reaction. This is followed by lipid storage during the resistance stage and a second period of lipid loss during the stage of exhaustion of the G.A.S.

Reid, D. D.: "Some measures of the effect of operational stress on bomber crews." *Air Ministry, A.P.* **3139**, pp. 245-258. London: HMSO, 1947. B27,155/47

Reid, D. D.: "Fluctuations in navigator performance during operational sorties." *Air Ministry, A.P.* **3139**, pp. 321-329. London: HMSO, 1947. B27,164/47

Pilots making repeated sorties over Germany during World War II showed an initial intense anticipatory anxiety with steady deterioration in efficiency on the outward journey, particularly over the enemy coast and on approaching the target. This was maximal in the phase of heavy enemy fighter opposition and persisted as long as the aircraft was over enemy territory. Following numerous sorties, neurotic manifestations and breakdown eventually occurred.

Nigeon-Dureuil, M., Rabinowicz, M., Rahandraha, T., Ratsimamanga, A. R.: "Signification des variations pondérales et biochimiques transitoires de l'hypophyse, de la surrénale et du thymus, au cours d'un stimulus continu de moyenne intensité, le froid à 6°" (Significance of the transitory ponderal

and biochemical variations of the hypophysis, adrenal, and thymus during exposure to a continuous stimulus of moderate intensity, cold at 6°). *C.R. Soc. Biol. (Paris)* **146**: 370-377 (1952). B75,131/52

In rats exposed to moderate cold, the various manifestations of the G.A.S. show periodic fluctuations, probably due to successive discharges and storage of hormones. The thymus allegedly can store corticoids and thereby provide an additional reserve. [The authors promised subsequent papers in which these concepts would be further elaborated (H.S.).]

Selye, H.: "The part of inflammation in the local adaptation syndrome." *Rev. Can. Biol.* **12**: 155-176 (1953). A97,423/53

Description of the L.A.S. and its relation to the G.A.S. Both are nonspecific reactions comprising damage and defense; they are triphasic with typical signs of "cross resistance" and "cross sensitization" during the second stage; both are singularly sensitive to "adaptive hormones" (ACTH, STH, corticoids); and if they develop simultaneously in the same individual, they greatly influence one another. The characteristics of the three phases in the L.A.S. are illustrated by Figure 25 (p. 1150).

Selye, H.: "The 'critical period' in the development of inflammation." *Acta Physiol. Lat. Am.* **3**: 188-193 (1953). B85,700/53

In rats with granuloma pouches, pretreatment of a circumscribed area with a threshold dose of an irritant causes topical resistance to subsequent administration of an otherwise fully effective dose of the same agent. This corresponds to the phase of resistance of the L.A.S.

Flückiger, E., Verzár, F.: "Überdauern der Adaptation an niedrigen atmosphärischen Druck, nachgewiesen an der Wärmeregulation" (Body temperature regulation indicating retained adaptation under reduced oxygen tension). *Helv. Physiol. Pharmacol. Acta* **11**: 67-72 (1953). B92,392/53

In rats exposed to reduced oxygen tension, the body temperature drops but returns to normal after three to four days. "This 'retained adaptation' is not dependent on the presence of the adrenals. The phenomenon can also be seen in adrenalectomized rats kept alive with corticoids."

Perlman, R. M.: "The aging syndrome." *J. Am. Geriatr. Soc.* **2**: 123-219 (1954). C34,471/54

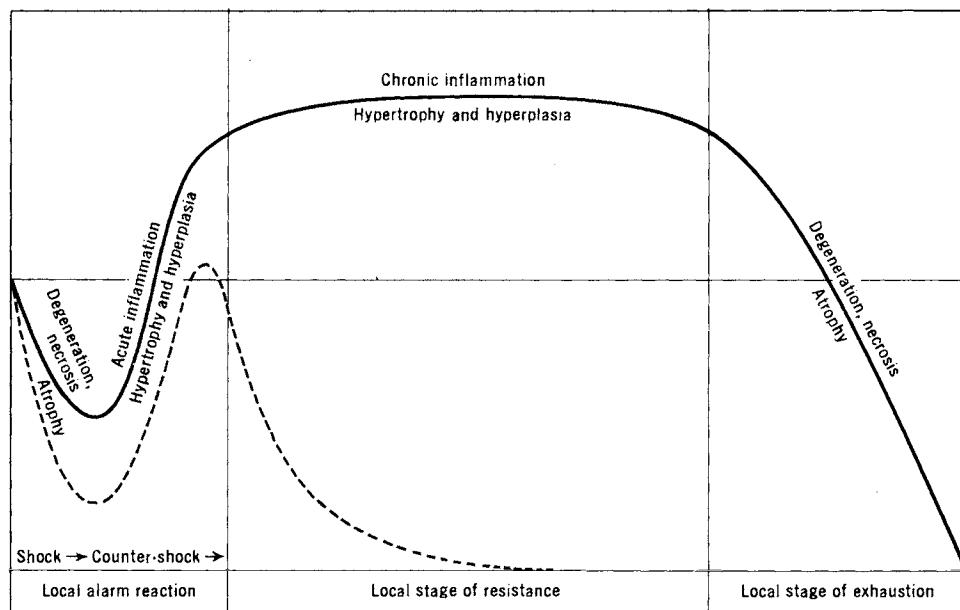


Figure 25. Typical changes in morphologic structure and topical resistance, as they occur during the three stages of the L.A.S. The heavy line represents "specific resistance," the interrupted line, "cross-resistance." (Reproduced from *Rev. Can. Biol.* 12 (1953) by permission.)

"Data are furnished to develop the thesis that aging in man is, essentially, a disease syndrome arising out of the struggle between environmental stress versus biologic resistance and relative adaptation to the effects of stressor agents."

Selye, H.: "Stress and disease." *Geriatrics* 10: 253-261 (1955). B98,390/55

Kountz, W. B., Kheim, T., Ackermann, P. G., Toro, G.: "Nutritional deficiency due to age and physiologic stress; its control by food and hormones." *J. Am. Geriatr. Soc.* 4: 1005-1020 (1956). J25,131/56

Jones, H. B.: "A special consideration of the aging process, disease, and life expectancy." *Adv. Biol. Med. Phys.* 4: 281-337 (1956). J22,383/56

Still, J. W.: "Physiology. The physiology of aging—a research approach." *J. Wash. Acad. Sci.* 48: 224-229 (1958).

G62,259/58

Emphasis upon similarities between the three phases of the G.A.S. and the three stages of life. The response to stress, and particularly the duration of the resistance phase, is characteristically shortened in the aged.

Curtis, H. J., Gebhard, K. L.: "Peaceful uses of atomic energy." *Proc. 2nd Int. Conf.* 22: 53 (1959). J11,912/59

In mice, chronic treatment with nitrogen mustard, bacterial toxins, turpentine or other stressors did not detectably shorten lifespan.

Selye, H., Prioreschi, P.: "Stress theory of aging." In: Shock, N. W., *Aging. Some Social and Biological Aspects*, No. 65, pp. 261-272. Washington: American Association Advancement Science, 1960. C76,248/60

Theoretical discussion of the relationship between aging and the exhaustion phase of the G.A.S. in the case of systemic stress, and that of the L.A.S. in the case of topical chronic stress. Premature aging of the entire organism occurs upon long continued exposure to severe stress, as in concentration camp survivors. As examples of local aging, the gradual disintegration of granuloma pouches exposed to strong local irritants and the disintegration of the "central cords" in tissue scaffolding tubes unable to rid themselves of accumulating wastes are mentioned. "The life span of an individual seems to depend on two factors: the quantity of adaptation energy that he receives at birth and the rate at which he spends it." [The concept of

accumulating "chemical scars" in the form of waste products that increasingly interfere with normal function by their mere presence is only hinted at in this first paper (H.S.).]

Geschickter, C. F., O'Malley, W. E., Rubacky, E. P.: "A hypersensitivity phenomenon produced by stress: the 'negative phase' reaction." *Am. J. Clin. Pathol.* **34**: 1-8 (1960). C88,483/60

Various stressors inhibit the anaphylactoid reaction produced by egg white in the rat, but this may be followed by a "negative phase" of hypersensitivity. "Although the 'negative phase' is similar to Selye's exhaustion stage of the general adaptation syndrome, it differs by being a more acute, frequent, and repetitive occurrence, and of a lesser degree of severity than that observed with exhaustion."

Kinsell, L. W.: "Physiologic aging and radiologic life-shortening." *Fed. Proc.* **20**: 14-21 (1961). D12,597/61

Critical review of the literature on the induction of artificial aging by ionizing radiations, and its relation to natural aging. "There would appear to be no question that radiation, in common with many other physical agents, if used in sufficient amount, can produce in any cell, tissue, or organ a state in which catabolism goes on at a greater rate than anabolism." It remains to be seen, however, whether such changes are comparable to physiologic aging. On the other hand, "the stress of a life in which the threat of sudden death is ever present must certainly influence the aging process" (99 refs.).

Platner, W. S.: "The effect of stress on the aging process." *Mo. Med.* **58**: 373-376 (1961). D6,730/61

Trujillo, T. T., Spalding, J. F., Langham, W. H.: "A study of radiation-induced aging: response of irradiated and nonirradiated mice to cold stress." *Radiation Res.* **16**: 144-150 (1962). D24,525/62

In mice, resistance to standard "cold stress" showed a linear decrease with age. The same reaction was obtained after x-irradiation. "The radiation-induced effect was considered similar to life shortening by natural aging."

Selye, H.: *Stress und Altern* (Stress and aging), p. 20. Bremen: Angelsachsen-Verlag, 1962. D26,079/62

Review of the author's earlier observations on the relationship between stress and aging.

Curtis, H. J.: "Biological mechanisms underlying the aging process." *Science* **141**: 686-694 (1963). E24,424/63

In mice, exposure to x-rays or temporary treatment with mercury produced premature aging and death, but a number of other chemical stressors, though severe, did not noticeably shorten life expectancy under the conditions prevailing in these experiments. Hence the author doubts that stress, as such, invariably reduces lifespan.

Curtis, H. J.: "Cellular processes involved in aging." *Fed. Proc.* **23**: 662-667 (1964). F13,382/64

Review of the author's earlier experiments showing that a variety of stressors, such as nitrogen mustard, typhoid toxin, typhoid toxoid, tetanus toxin, subcutaneous turpentine and so on, administered chronically up to three times a week, did not significantly shorten the life expectancy of mice. "Attempts to obtain evidence for the wear and tear theory have all shown that a generalized stress is not necessarily life shortening. This does not mean that a specific stress agent causing irreparable damage to one organ might not result in a reduced life expectancy. For example, in mercury poisoning the kidney is irreparably damaged but the animal does not die for some time. In this case a 'weak link' is created and will be the first to break as the aging process advances."

Rotondo, G.: "Sull'impiego dell'acido adenosintrifosforico e della cocarbossilasi in piloti affetti da lieve o iniziale fatica di volo" (The use of ATP and cocarboxylase in pilots suffering from light or initial flying fatigue). *Riv. Méd. Aeronaut. Spaz.* **27**: 176-192 (1964). G19,344/64

Flying fatigue in jet pilots is ascribed to the exhaustion of adaptation energy. It is beneficially influenced by combined treatment with ATP and cocarboxylase (19 refs.).

Paré, W. P.: "Premature aging as a function of long-term environmental stress." *J. Genet. Psychol.* **104**: 185-191 (1964). G41,960/64

A review on the relationship between stress and aging revealed that the BMR decreases with old age, whereas the prostate undergoes hypertrophy. In experiments on rats chronically exposed to stressors (sound, electric shocks), aging (defined in terms of BMR and prostatic hypertrophy) was in fact accelerated. The animals also showed eosinopenia and lymphopenia. It was concluded

that "an animal's environment may 'require' or 'cause' adaptive responses that produce irreversible damage and hence shorten life span. A concept such as 'normal' aging may be misleading since aging cannot be represented as a unitary concept. Aging is the cumulative effect of responses made by biological systems as these systems adapt themselves to environmental stressors" (21 refs.).

Guth, P. H., Mendick, R.: "The effect of chronic restraint stress on gastric ulceration in the rat." *Gastroenterology* **46**: 285-286 (1964). G18,489/64

Restraint is very useful for producing experimental ulcers in the rat, but after a certain time adaptation occurs, and the ulcerogenic effect of this stressor diminishes during the phase of resistance.

Ordy, J. M., Rolsten, C., Samorajski, T., Collins, R. L.: "Environmental stress and biological ageing." *Nature* **204**: 724-727 (1964). F26,091/64

Fridrich, R.: "Die Auswirkungen von Kombinationsschäden auf den bestrahlten Organismus" (The effects of combined stress on the irradiated organism). *Strahlentherapie* **124**: 302-307 (1964). G19,723/64

In mice, production of stress by traumatic injuries (removal of part of the omentum) forty-eight hours before or after x-irradiation offers considerable protection. This type of increased resistance is ascribed to the stressor effect of pituitary-adrenocortical mobilization, since it can be blocked by morphine or barbiturates which inhibit hypothalamic reactivity (40 refs.).

Paré, W. P.: "The effect of chronic environmental stress on premature aging in the rat." *J. Gerontol.* **20**: 78-84 (1965). F31,169/65

From experiments on rats exposed to repeated electroshock and then tested for muscular fatigability or thermic contraction of tail tendon fibers, it was concluded that "the stress-induced changes in swimming speed and collagen contraction were valid signs of aging, since they were irreversible."

Vecsei-Weisz, P., Kemény, V., Harangozo, M.: "Further investigations concerning functional changes in the adrenal cortex at the resistance stage of the general adaptation syndrome." *Acta Physiol. Acad. Sci. Hung.* **27**: 265-273 (1965). G34,303/65

"The resistance stage of the general adaptation syndrome has been evoked in rats by

the repeated administration of formalin, and the resulting functional changes were studied by the in vitro incubation of surviving adrenal slices. The aldosterone production was found to be augmented, the corticosterone production unaltered. After adding a progesterone precursor to the incubation medium the rate of production of corticosterone and aldosterone increased. The increase in aldosterone production after formalin treatment was equal to that in the controls. The increase in corticosterone synthesis was more pronounced in formalin-treated animals."

Ouellette, R., Perrault, H. J., Dugal, L. P.: "Effet du froid sur le testicule endocrinien: chronologie des événements" (Effect of cold on the endocrine testis: chronology of events). *Rev. Can. Biol.* **24**: 7-21 (1965).

F42,194/65

In male rats, "a time study of the response of the sexual accessories reveals the succession of events as distinct phases related to the duration of the stress and reminiscent of the three stages of the General Adaptation Syndrome."

Gray, R. M., Baker, J. M., Kesler, J. P., Newman, W. R. E.: "Stress and health in later maturity." *J. Gerontol.* **20**: 65-68 (1965).

F31,165/65

Statistical studies showed that, among elderly people, those "who had experienced the most stress during the past ten years also had the poorest health scores. In addition, the data revealed that the severely disabled persons had significantly higher stress scores than did non-disabled older persons, which indicated that they had experienced more stress than the non-disabled."

Tintera, J. W.: "Stabilizing homeostasis in the recovered alcoholic through endocrine therapy: evaluation of the hypoglycemia factor." *J. Am. Geriatr. Soc.* **14**: 126-150 (1966).

F62,090/66

People genetically predisposed to alcoholism have evidence of hypocorticoidism and hypoglycemia. "By the continued use of alcohol the organism as a whole goes through the stages of alarm reaction, resistance, and eventually exhaustion." [The data are not subject to statistical evaluation (H.S.).]

Sobel, H.: "Stress and environmental factors in aging." *Psychosomatics* **8** No. 4, Sect. 2: 21-27 (1967).

F87,136/67

Ordy, J. M., Samorajski, T., Zeman, W., Curtis, H. J.: "Interaction effects of environ-

mental stress and deutron irradiation of the brain on mortality and longevity of C57BL/10 mice." *Proc. Soc. Exp. Biol. Med.* **126**: 184-190 (1967). F90,270/67

"Contrary to expectation, stress resulted in a significant decrease in mortality and a longer life span of both the non-irradiated and brain-irradiated mice." These findings are "consistent with evolutionary theories of natural selection and survival of multicellular populations under fluctuating environmental conditions." [A certain amount of stress is undoubtedly beneficial but, depending upon its kind and quantity, the reverse is undoubtedly also true. Protection against irradiation could be ascribed to cross-resistance (H.S.).]

Lang, C. M.: "Effects of psychic stress on atherosclerosis in the squirrel monkey (*Saimiri sciureus*)."*Proc. Soc. Exp. Biol. Med.* **126**: 30-34 (1967). F90,255/67

About two years of exposure to restraint, alone or combined with conditioned avoidance, accelerated the development of atherosclerosis, increased urinary 17-KS excretion and raised serum cholesterol.

Rahe, R. H., McKean, J. D. Jr., Arthur, R. J.: "A longitudinal study of lifechange and illness patterns."*J. Psychosom. Res.* **10**: 355-366 (1967). D88,215/67

A close relationship was found between stresses (as judged by the LCU questionnaire) and the frequency of disease, especially psychiatric illness, among U.S. Navy personnel.

Stark, E., Fachet, J., Makara, G. B., Mihály, K.: "An attempt to explain differences in the hypophyseal-adrenocortical response to repeated stressful stimuli by their dependence on differences in pathways."*Acta Med. Acad. Sci. Hung.* **25**: 251-260 (1968). G63,921/68

In rats, "certain non-specific stimuli that raise the plasma corticosterone level when administered on a single occasion fail to raise it when administered repeatedly whereas others raise it independently of the number of administrations. It is suggested that stressor agents reach the CRF-secreting hypothalamic cells by different pathways, and that the CRF-activating mechanism of some stressors does adapt itself to repeated stimuli, that of others does not."

Paré, W. P.: "Effect of duration of environmental stress on stomach ulceration and

adrenal ascorbic acid."*Psychol. Rep.* **23**: 683-688 (1968). J19,594/68

In rats repeatedly exposed to electroshock over a twenty-four day period, adrenal ascorbic acid showed an initial decline, followed by a rise far above normal by the end of the experiment [corresponding to the stage of adaptation (H.S.)]. In these animals, which were not deprived of food or water, gastric lesions developed only irregularly.

Glass, D. C., Singer, J. E., Friedman, L. N.: "Psychic cost of adaptation to an environmental stressor."*J. Pers. Soc. Psychol.* **12**: 200-210 (1969). G67,952/69

"Among a group of college females, the work of adapting to unpredictable, in contrast to predictable, noise resulted in lowered tolerance for frustration and in impaired performance efficiency after termination of the noise." These findings are compatible with the theory of adaptation energy depletion, but there is still no precise concept of what is being diminished.

Hodges, J. R., Mitchley, S.: "The effect of 'training' on the release of corticotrophin in response to minor stressful procedures in the rat."*J. Endocrinol.* **47**: 253-254 (1970). H26,814/70

Martin, M. S., Martin, F., Lambert, R.: "Effet de l'habituation sur la sensibilité du rat à l'ulcère de contrainte" (Effect of habituation on the sensitivity of the rat to restraint ulcer).*C.R. Soc. Biol. (Paris)* **164**: 826-828 (1970). H33,491/70

Rahe, R. H., Mahan, J. L. Jr., Arthur, R. J.: "Prediction of near-future health change from subjects' preceding life changes."*J. Psychosom. Res.* **14**: 401-406 (1970). J14,839/70

On the basis of the LCU questionnaire, it was possible to predict illness frequency among U.S. Navy personnel on three combat cruises, thus confirming the many earlier retrospective studies documenting the association between a subject's life stress and illness rate. "The finding, then, that the life change and subsequent illness hypothesis held up in the prospective test is perhaps more impressive when it is realized these experiments dealt with a very restricted portion of the spectrum of stress and disease" (23 refs.).

Selye, H.: "Stress and aging."*J. Am. Geriatr. Soc.* **18**: 669-680 (1970). G70,439/70

Brief review of data suggesting that the

phenomenon of aging may be due to the cumulative effect of repeated exposure to stress conducive to irreversible "chemical scars" in organs.

Árvay, A., Takács, I., Ladányi, P., Balogh, A., Benkő, K.: "The effect of intensive nervous stimulation on certain physico-chemical properties of rat tail tendon and uterus collagen." *Gerontologia* **17**: 157-169 (1971).

J16,955/71

The physico-chemical properties of rat tail tendon (quantity of labile hydroxyproline, changes in thermo-isometric tension) and uterine collagen during biologic aging and exposure to various stressors are essentially similar. These and EM studies led the authors to suggest that "long-lasting intensive stress, therefore, produced changes of such a degree and character which exceeded the physiological changes characteristic of and accompanying biological ageing."

Hall, D. A.: "The use of stress as a tool in gerontological research." *Age and Ageing* **1**: 141-145 (1972).

G93,666/72

"In the author's opinion, whatever phenomenon is observed, the results obtained under conditions of stress may well bear a closer relationship to the normal ageing condition than do determinations made under the rather specialized resting conditions in which such parameters are normally measured."

Bellamy, D.: "The thymus in relation to problems of cellular growth and ageing." *Gerontologia* **19**: 162-184 (1973).

J11,032/73

The thymus involution occurring during stress was compared to that of old age, but a causal connection between the two could not be established.

Damon, A., Roen, J. L.: "Aging in the Solomon islands and the United States: test of Pearl's hypothesis." *Hum. Biol.* **45**: 683-693 (1973).

J9,933/73

Pearl's hypothesis that "the length of life depends inversely on the rate of living" has been tested in Americans and Solomon Islanders, using the resting pulse rate as an index of "the rate of living." On this basis, it is concluded that "although the present evidence is equivocal at best, Pearl's hypothesis deserves further investigation in man, with appropriate measures of pace and duration of life." [Graying of hair was used as an indicator of physiologic aging. It is questionable whether resting pulse rates are accurate indices of the stress of life, and

graying of hair hardly reflects physiologic aging (H.S.).]

Everitt, A. V.: "The hypothalamic-pituitary control of ageing and age-related pathology." *Exp. Gerontol.* **8**: 265-277 (1973).

J8,461/73

Although aging is primarily under genetic control, the speed of its development may be influenced by hormones secreted under stress (about 100 refs.). [A review without additional new data (H.S.).]

Yanase, M.: "A study on the role of brain for the establishment of adaptation to the repeated immobilization stress. II. A role of the limbic-midbrain system in the repeated immobilization stress." *J. Physiol. Soc. Jap.* **35**: 171-178 (1973) (Japanese).

J17,716/73

In rabbits, ACTH release following repeated restraint diminished as a consequence of adaptation. This was not found after sectioning of the fornix. "Therefore, hippocampal inhibition of ACTH release is considered to correlate with the inhibition of ACTH release under the repeated stress, and hippocampus may play an important role in the establishment of adaptation to the stress."

Mikulaj, L., Kvetňanský, R., Murgaš, K.: "Changes in adrenal response during intermittent and repeated stress." *Rev. Czech. Med.* **20**: 162-169 (1974).

J16,273/74

In rats the initial marked corticosterone secretion was significantly diminished after twenty to forty-two days of repeated stress (restraint, formaldehyde). On the other hand, the adrenal medulla gradually increased its ability to release catecholamines as adaptation developed.

Welch, B. L., Brown, D. G., Welch, A. S., Lin, D. C.: "Isolation, restrictive confinement or crowding of rats for one year. I. Weight, nucleic acids and protein of brain regions." *Brain Res.* **75**: 71-84 (1974).

J14,176/74

Rats living for one year under stressful conditions of isolation or crowding have a diminished DNA content in their telencephalon. The authors suggest the tentative working hypothesis that "stress or high levels of environmental stimulation may accelerate the natural aging-associated loss of neurons from the brain."

Goldstein, A. L., Hooper, J. A., Schulof, R. S., Cohen, G. H., Thurman, G. B., Mc-

Daniel, M. C., White, A., Dardenne, M.: "Thymosin and the immunopathology of aging." *Fed. Proc.* **33**: 2053-2056 (1974).

H92,570/74

Thymosin, a low molecular weight acidic polypeptide isolated from thymus tissue, is probably a hormone. Its blood concentration is high in young and low in old people. Probably, the thymus, through secretion of thymosin and perhaps other hormones, can act at a distance and influence the function and development of lymphoid cells involved in cell-mediated immunity; thereby it participates in the aging process.

Grosch, H.: "Psychovegetative Störungen bei Erschöpfungszuständen" (Psychovegetative disturbances caused by exhaustion). *Med. Welt* **25**: 310-311 (1974).

H85,385/74

Review of empirical findings concerning the eventual onset of exhaustion in patients exposed to the stress of long-lasting organic diseases.

Yunis, E. J., Greenberg, L. J.: "Immunopathology of aging." *Fed. Proc.* **33**: 2017-2019 (1974).

H92,566/74

A review of the literature suggests that thymic involution and cellular immune dysfunction may influence the pathogenesis of aging, while its etiology requires a genetically programmed system involving genes linked to immune response loci.

Walford, R. L.: "Immunologic theory of aging: current status." *Fed. Proc.* **33**: 2020-2027 (1974).

H92,567/74

Normal immune function decreases, whereas autoimmunity increases with age. Alterations in thymus function may play an important role in regulating the immunopathology of aging (106 refs.).

Good, R. A., Yunis, E.: "Association of autoimmunity, immunodeficiency and aging in man, rabbits, and mice." *Fed. Proc.* **33**: 2040-2050 (1974).

H92,568/74

A review of the literature and personal observations suggesting that primary immunodeficiency diseases of man, as well as those produced by neonatal thymectomy and the ones that develop during aging in experimental animals, are all accompanied by several autoimmune phenomena and frequently by amyloidosis. Thus, antigens or organisms otherwise forbidden access to the body can penetrate or persist, abnormally stimulating residual immunologic systems (78 refs.).

Teague, P. O.: "Spontaneous autoimmu-

nity and involution of the lymphoid system." *Fed. Proc.* **33**: 2051-2052 (1974).

H92,569/74

In mice, neonatal thymectomy elicits changes reminiscent of premature aging. "Immunization of autoimmune strain mice with nuclear antigens is followed by anti-nuclear antibody production in older but not younger animals. Treatment of animals already producing this autoantibody with thymocytes results in disappearance of autoantibody and inhibits induction of antinuclear antibody by immunization. Thymectomy of young adults resulted in accelerated appearance of antinuclear antibodies in autoimmune strains. Aged mice of autoimmune strains were found to be deficient in T-lymphocyte function by several parameters as compared to syngeneic young mice. Aged mice of a strain lacking autoimmune potential did not show this decline. Thymectomy of young adults was shown to be followed by a severe impairment in T-lymphocyte function."

Tharp, G. D., Buuck, R. J.: "Adrenal adaptation to chronic exercise." *J. Appl. Physiol.* **37**: 720-722 (1974).

J18,803/74

Observations on rats chronically forced to exercise led the authors to the conclusion that "part of the diminished in vivo corticosterone release occurring with training is due to adaptation of the adrenal gland to ACTH stimulation."

Amster, L. E., Krauss, H. H.: "The relationship between life crises and mental deterioration in old age." *Int. J. Aging Hum. Dev.* **5** (I): 51-55 (1974).

J24,302/74

Busse, E. W.: "Criteria for determination of premature aging attributed to prisoner-of-war status." *J.A.M.A.* **231**: 521 (1975).

H98,500/75

"Secondary aging refers to changes resulting from stress, trauma, and infection (all factors in combat and internment)." The life expectancy of POWs after release may be normal or increased, depending upon circumstances during internment.

Warren, S., Chute, R. N., Porter, M. W.: "The effect of parabiosis on life-span of rats stressed by radiation." *J. Gerontol.* **30**: 15-21 (1975).

J19,637/75

Rose, R. M., Hurst, M. W.: "Plasma cortisol and growth hormone responses to intravenous catheterization." *J. Hum. Stress* **1**: 22-36 (1975).

H97,894/75

In patients, the first catheterization tended to produce parallel rises in plasma STH and cortisol, but the STH responses were much more variable. In general, the findings "suggest a definite endocrine adaptation to catheterization by the second or third hour of the experience."

Selye, H., Tuchweber, B.: "Stress in relation to aging and disease." In: Everitt, A. and Burgess, A., *Hypothalamus, Pituitary and Aging*. In press. Springfield, Ill.: Charles C Thomas. G70,417/

Chapter emphasizing the influence of stress upon life expectancy.

STRESS AND FATIGUE

We touched upon the phenomenon of fatigue in the preceding section on adaptation energy, as well as in the section on Occupations (Aerospace) which deals with flying fatigue. A great deal of empirical information has been accumulated in relation to fatigue caused by diverse occupations, athletic activities and so on. There can be no doubt that fatigue is one of the consequences of systemic stress, but its mechanism is still too incompletely understood to justify detailed discussion here.

The syndrome of "pernicious fatigue," present on arising, then relieved, but recurring during the afternoon and again relieved in the evening, has been "conceived as a common physiologic reaction to stress," and without much evidence ascribed to hypoglycemia.

Fatigue, like stress, can be general or local, affecting the entire body or only one part, for example, the CNS or the muscular system.

Stress and Fatigue

(See also our earlier stress monographs, p. xiii)

Bartley, S. H., Chute, E.: *Fatigue and Impairment in Man* (Foreword by A. C. Ivy), p. 429. New York and London: McGraw-Hill, 1947. B34,753/47

Monograph on various types of specific organ system impairments and general fatigue. A wealth of empirical information without any reference to the stress concept.

Drew, G. C.: *Fatigue*. London: Flying Personnel Research Committee, Air Ministry, No. 488, 1951. E10,663/51

Floyd, W. F., Welford, A. T.: *Symposium on Fatigue*, p. 196. London: H K Lewis, 1953. B86,075/53

Proceedings of a symposium in which numerous specialists discussed the criteria, measurement and mechanism of fatigue. Several sections deal with the relationship between physical and mental fatigue in stress.

[No special attempt has been made to estimate stress by objective indices (H.S.).]

Brouha, L.: "Fatigue—measuring and reducing it." *Adv. Management* 19: 9-19 (1954). B92,375/54

Discussion of fatigue in relation to stress in industry.

Bartley, S. H.: "Fatigue and inadequacy." *Physiol. Rev.* 37: 301-333 (1957). C39,912/57

Review of neural, hormonal, dietary and stressor effects on various types of fatigue affecting different functions (174 refs.).

Wachholder, K.: "Müdigkeit ein allgemeines Stress-Symptom infolge der Ausschüttung von ACTH?" (Is fatigue, a general stress symptom, caused by ACTH release?). *Int. Z. Physiol. Einschl. Arbeitsphysiol.* 16: 361-364 (1957). C39,970/57

About 50 percent of the patients who received a large dose of ACTH developed a feeling of generalized fatigue, whereas 30

percent reacted by becoming refreshed and alert. Apparently, there are individual differences in responsiveness, but ACTH discharged during stress may be responsible for the associated changes in mood.

Bugard, P.: *La Fatigue* (Fatigue), p. 308. Paris: Masson, 1960. C79,049/60

Somewhat technical discussion on the somatic and psychic manifestations of fatigue with reference to the G.A.S.

Jaffe, D. S.: "Fatigue states. Asthenic reactions." In: Cantor, P. D., *Traumatic Medicine and Surgery for the Attorney*, pp. 22-34. Washington: Butterworths, 1962.

E10,309/62

A chapter in an encyclopedia on legal medicine, concerning the relationship between stress and fatigue, especially in industry or after trauma.

Bartley, S. H.: *Fatigue. Mechanism and Management*, p. 96. Springfield, Ill.: Charles C Thomas, 1965. E5,041/65

Monograph on the causes of fatigue and the chemical changes associated with it. A special section deals with the participation of the G.A.S. (63 refs.).

Edholm, O. G., Bacharack, A. L. (eds.): *The Physiology of Human Survival*, p. 581. New York and London: Academic Press, 1965. E6,283/65

A monograph on human reactions to various stressors such as heat, cold, anoxia, high altitudes, compression and decompression, nutritional damage, sleep deprivation, monotony, fatigue, emotional arousal and muscular exercise. Each chapter is written by a specialist in the field, and numerous references indicate the difference between specific defense mechanisms and the stressor effect of the agents used.

Mohler, S. R.: "Fatigue in aviation activities." *Aerosp. Med.* 37: 722-732 (1966).

J10,968/66

Review of the literature on the factors that influence physical and mental fatigue during very prolonged or difficult flight tasks, with special reference to the role of stress. There are also definite recommendations for measures to combat flight fatigue (105 refs.).

Albeaux-Fernet, M., Bellot, L., Canet, L., Deribreux, J., Gelinet, M., Romani, J. D.: "Fatigue et glandes endocrines" (Fatigue

and the endocrine glands). *Ann. Endocrinol.* (Paris) 19: 192-202 (1967).

F80,821/67

Kamchatnov, V. P.: "Effect of working in red light on development of fatigue." *Ind. Med. Surg.* 38: 445-447 (1969).

J15,917/69

"Persons working in red light show a sharp decrease in working ability compared with persons working in normal lighting, and this may evidently explain their greater proneness to fatigue."

Grim, P. F.: "Relaxation therapies and neurosis: a central fatigue interpretation." *Psychosomatics* 13: 363-370 (1972).

J15,998/72

General review of the relationship between stress, neurosis and fatigue (56 refs.).

Asmussen, E.: "Fatigue and physiological capacity for work." *Wk. Environ. Health* 10: 1-8 (1973).

H80,369/73

Review of the metabolic consequences of physical and mental fatigue, with special reference to blood FFA and energy stores (14 refs.). [The relationships to stress are not discussed (H.S.).]

Cameron, C.: "A theory of fatigue." *Ergonomics* 16: 633-648 (1973).

J8,264/73

Review on fatigue in various occupations, with special reference to its participation in stress and in the diseases of adaptation.

Bugard, P.: *Stress, Fatigue et Dépression. (L'Homme et les Agressions de la Vie Quotidienne)* (Stress, fatigue, and depression. Man and the aggressions of daily life), Vol. 1, p. 294; Vol. 2, p. 302. Paris: Doin Edit., 1974.

E10,487/74

Kaye, P. L.: "Pernicious' fatigue. Identification, pathogenesis, and treatment." *Behav. Neuropsychiatry* 5: 24-29 (1974).

H88,050/74

Description of a type of "pernicious fatigue" that has a clearly diurnal cycle: present on arising, then relieved; recurring in the afternoon and again relieved in the evening. One manifestation of this syndrome is an overactivity of the autonomic, particularly the vagal, system with periods of dizziness, weakness, headaches and a general feeling of misery and anxiety. Frequently, there are flat glucose tolerance curves among these patients, but this is regarded as a symptom,

not a cause of the malady. Atropine is recommended to relieve the manifestations. The syndrome of pernicious fatigue has often been ascribed to low blood sugar, and an organization called "Hypoglycemia Foundation" exists (allegedly with a twenty-five

hundred-physician membership), but according to the author its claims and methods of treatment are entirely unjustified. "The syndrome is best conceived as a common physiologic reaction to stress." Ten case reports are presented (7 refs.).

VARIOUS OTHER THEORIES

It will not be necessary to discuss the many other theories proposed for the explanation of the G.A.S., since none of them have been clearly substantiated. The publications abstracted on the following pages call attention to the possible roles played by various not previously mentioned *organs, enzymes, RNA, cAMP, toxic substances* (especially bacterial endotoxins absorbed from the intestinal tract), and concepts based on *systems models* of stress.

Various Other Theories

(See also our earlier stress monographs, p. xiii)

Kidney. Gupta, D. das, Giroud, C. J. P.: "Experimental aminonucleoside nephrosis. (I): Action of cortisone on aldosterone and corticosterone production." *Proc. Soc. Exp. Biol. Med.* **98**: 334-339 (1958).

C55,024/58

In rats with nephrosis induced by puromycin aminonucleoside, aldosterone production is increased.

Ganong, W. F., Alpert, L. C., Lee, T. C.: "ACTH and the regulation of adrenocortical secretion." *N. Engl. J. Med.* **290**: 1006-1011 (1974).

H85,990/74

Excellent and very succinct review on factors regulating corticoid production. Aldosterone release occurs in the glomerulosa which, unlike the fasciculata and reticularis, undergoes no atrophy following glucocorticoid overdosage. Aldosterone secretion by the glomerulosa, on the other hand, is stimulated by angiotensin, and this effect is not prevented by corticoid-induced adrenocortical atrophy.

Liver. Tyler, F. H., Schmidt, C. D., Eik-Nes, K., Brown, H., Samuels, L. T.: "The role of the liver and the adrenal in producing elevated plasma 17-hydroxycorticosteroid levels in surgery." *J. Clin. Invest.* **33**: 1516-1523 (1954).

B99,414/54

Metabolic studies in man suggest that "the

increased plasma levels of 17-hydroxycorticosteroid after surgery are the result of both increased adrenal secretion of these steroids and impaired hepatic removal."

Yates, F. E., Urquhart, J., Herbst, A. L.: "Impairment of the enzymatic inactivation of adrenal cortical hormones following passive venous congestion of the liver." *Am. J. Physiol.* **194**: 65-71 (1958).

C56,413/58

In rats, venous congestion of the liver severely impairs enzymatic reduction of ring A in DOC, cortisone and cortisol. The same is probably true for aldosterone. "Secondary aldosteronism of congestive heart failure may be accounted for in part by this enzymatic lesion."

Dougherty, T. F., Berliner, D. L.: "The effect of stress and ACTH on the metabolism of hydrocortisone in the liver." In: Brauer, R. W., *Liver Function*, pp. 416-417. Washington: American Institute Biological Sciences, 1958.

J11,223/58

In vitro and in vivo experiments on mice show that ACTH inhibits the steroid-conjugating capacity of the liver. This reduces the rate of excretion and increases the blood steroid level.

Bohus, B., Endrőczi, E.: "The effect of endogenous diminution of corticosteroid level on pituitary-adrenocortical function." *Acta Physiol. Acad. Sci. Hung.* **25**: 351-358 (1964).

G33,534/64

In anesthetized dogs, connection of the

adrenal vein with the hepatic portal circulation led to a rapid increase in the corticoid concentration of the adrenal vein blood. Morphine prevented this elevation. Presumably, "the plasma corticosteroid level increases the pituitary-adrenocortical activity through a hormonal feed-back mechanism."

Yates, F. E.: "Contributions of the liver to steady-state performance and transient responses of the adrenal cortical system." *Fed. Proc.* **24**: 723-730 (1965). F41,048/65

Review of data concerning the part played by the liver in maintaining blood corticoid levels during stress (34 refs.).

Lempert, B. L., Sheikman, M. B., Petrova, T. S., Zaslavskaya, M. G.: "Corticosteroid response to stress in experimental toxic hepatitis." *Biull. Èksp. Biol. Med.* **71** No. 4: 21-24 (1971) (Russian). Engl. trans.: *Bull. Exp. Biol. Med.* **71**: 367-369 (1971).

J21,619/71

In rats stressed by restraint, the rise in plasma 11-OHCS was inhibited by toxic hepatitis induced by carbon tetrachloride. The decrease in adrenocortical responsiveness "may to some extent explain the lowering of the nonspecific resistance of the animal to various pathogenic agents in diseases accompanied by lesions of the liver parenchyma."

Enzymes. Yuwiler, A., Geller, E., Schapiro, S.: "Effect of neonatal corticoids on tryptophan pyrrolase and brain serotonin." In: Németh, S., *Hormones, Metabolism and Stress. Recent Progress and Perspectives*, pp. 215-228. Bratislava: Slovak Academy of Sciences, 1973. E10,470/73

In newborn rats a single injection of cortisol induces tryptophan pyrrolase, retards body growth and diminishes the 5-HT content of the brain. These results are discussed in relation to the function of tryptophan pyrrolase in stress.

RNA, DNA. Arimura, A., Bowers, C. Y., Schally, A. V., Saito, M., Miller, M. C.: "Effect of corticotropin-releasing factor, dexamethasone and actinomycin D on the release of ACTH from rat pituitaries in vivo and in vitro." *Endocrinology* **85**: 300-311 (1969). H15,815/69

Comparative in vivo and in vitro studies in rats led the authors to conclude that: "1) dexamethasone suppresses the action of CRF at the pituitary level, 2) this dexamethasone blockade does not develop immediately, 3) dexamethasone-blockade of CRF requires a

process which involves DNA-dependent RNA synthesis, and 4) the process of ACTH release by CRF does not require RNA synthesis" (34 refs.).

cAMP. Fleischer, N., Donald, R. A., Butcher, R. W.: "Involvement of adenosine 3',5'-monophosphate in release of ACTH." *Am. J. Physiol.* **217**: 1287-1291 (1969).

H18,307/69

Experiments with theophylline, vasopressin and methylxanthine (which influence cAMP activities), as well as determinations of cAMP in the pituitaries of intact or adrenalectomized animals, "strongly support the hypothesis that cyclic AMP is involved in the release of ACTH by rat pituitary tissue in vitro."

Birmingham, M. K.: "Stress in the test tube. Effects of ACTH and adenosine-3', 5'-monophosphate (cyclic AMP) on corticosteroid and lactic acid production in vitro." *Can. Psychiatr. Assoc. J.* **15**: 635-640 (1970).

G80,312/70

Paul, M. I., Květnanský, R., Cramer, H., Silbergeld, S., Kopin, I. J.: "Immobilization stress induced changes in adrenocortical and medullary cyclic AMP content in the rat." *Endocrinology* **88**: 338-344 (1971).

H35,409/71

Fortier, C., Labrie, F.: "Regulation of secretion." In: Berson, S. A. and Valow, R. S., *Peptide Hormones*, pp. 383-391. Amsterdam: North-Holland, 1973. J12,062/73

Review on the regulation of pituitary hormone secretion, with a separate section excellently summarizing available data on the role of cAMP as a mediator of the action of releasing factors upon the adenohypophysis.

Fortier, C.: "New frontiers in neuroendocrinology." In: Mogenson, G. J. and Calaresu, F. R., *Stevenson Memorial Volume on The Limbic System*. Toronto: University of Toronto Press. In press. J12,064/

A review on the origin and nature of various releasing factors, with special reference to a cAMP-dependent protein kinase initiating the synthesis and discharge of adenohypophyseal hormones. "The general concept that extracellular homeostasis is but an extension of intracellular homeostasis" becomes increasingly evident.

Various Toxic Substances (see also First Mediator). Selye, H.: "The prevention of

adrenalin lung edema by the alarm reaction." *Am. J. Physiol.* **122**: 347-351 (1938).

A7,154/38

In rats, an alarm reaction produced by EP, formaldehyde, cold, forced exercise or surgical trauma enhances resistance to the lung edema elicited by subsequent intravenous injection of EP. "This observation invalidates the possibility that the alarm reaction increases resistance only because it delays the absorption of toxic agents into the blood stream." The pulmonary edema normally produced in rats given large amounts of sodium chloride intravenously after bilateral nephrectomy can be prevented by an alarm reaction (forced exercise). This is a good example of cross-resistance.

Selye, H.: "The effect of the alarm reaction on the absorption of toxic substances from the gastro-intestinal tract." *J. Pharmacol. Exp. Ther.* **64**: 138-145 (1938).

A8,052/38

In rats, EP or histamine (which are normally not absorbed to any significant extent from the intestinal tract) readily enter the bloodstream when given orally during an alarm reaction produced by muscular exercise or cold. "It is concluded that the increased absorption of toxic substances, such as are usually present in the alimentary tract, probably plays an important part in the causation of the general damage resulting from various non-specific noxious agents."

Rosoff, C. B., Goldman, H.: "Effect of the intestinal bacterial flora on acute gastric stress ulceration." *Gastroenterology* **55**: 212-222 (1968).

G60,200/68

In rats, polymyxin B offers significant protection against acute stress ulcers elicited by restraint, probably because this nonabsorbable antibiotic reduces the coliform bacteria in the intestine. "This change in the flora results in a decrease in the motor tone of the stomach and cecum, and in the volume and concentration of gastric acid produced in response to the stress of immobilization. The protection offered by the coliform-poor state is eliminated when endotoxin is given to antibiotic-treated animals." Conversely, systemic administration of endotoxin increases both gastric acid and stress ulcers. "It is suggested that, under the conditions induced by stress, detoxification mechanisms suffer and permit absorbed bacterial products to reach the systemic circulation and stimulate the hypothalamus."

Nagler, A. L., Levenson, S. M.: "The nature of the toxic material in the blood of rats subjected to irreversible hemorrhagic shock." *Circ. Shock* **1**: 251-264 (1974).

J19,533/74

In rats exposed to hemorrhagic shock, there appeared a passively-transferable lethal factor in the plasma that caused death when transfused into animals in mild, reversible shock.

Walker, R. I.: "Endotoxin and stress." *Lancet* August 31, 1974, pp. 527-528.

H84,663/74

Review of earlier data on the possibly inadequate elimination of endotoxins entering the portal circulation during shock. Endotoxin was found in liver homogenates of mice stressed by x-irradiation or anoxia. It was probably derived from the intestine. "These findings should prompt consideration of aseptic endotoxin in patients undergoing various situations involving prolonged stress and those who, because of poor nutrition and/or poor general state of health, may not be able to maintain normal homoeostasis between the intestinal endotoxin pool and the body."

Gans, H., Matsumoto, K.: "The escape of endotoxin from the intestine." *Surg. Gynecol. Obstet.* **139**: 395-402 (1974).

H90,517/74

Many earlier investigators believed that the increased absorption of microbes or microbial toxins could be largely responsible for the development of shock during severe stress. By use of lead acetate-sensitized rats (which are very responsive to endotoxins), it could be shown that the absorption of bacterial endotoxins from the intestine is greatly augmented during osmotic, shock (57 refs.).

Filkins, J. P.: "Blood endotoxin detoxification after trauma and endotoxemia." *Physiologist* **17**: 221 (1974).

H89,896/74

In lead-sensitized rats, the endotoxin-detoxifying ability of liver homogenates was greatly increased twenty-four hours after trauma. Possibly, "a detoxifying protein is elaborated incident to trauma or endotoxemia; it may play an important role in host-defense against shock pathogenesis."

Mathematical Models. Urquhart, J., Li, C. C.: "Dynamic testing and modeling of adrenocortical secretory function." *Ann. N.Y. Acad. Sci.* **156**: 756-778 (1969).

H10,877/69

A review of the available literature that lends itself to the construction of models representing the various factors that regulate ACTH secretion and actions. Most of the work was performed on perfused canine adrenal glands subjected to several temporal patterns of stimulation by ACTH. [Such models can incorporate all known factors that influence adrenocortical secretion (chemical composition of the blood, blood flow, nervous stimuli, genetic elements, chronologic sequence of all stimulants, etc.) but of course, *in vivo*, the number of modifying circumstances is virtually infinite. Hence these models must necessarily be restricted to a description of known stimuli and modifying circumstances, the sequence of intermediates in biosynthesis and biodegradation of hormones, and the limited number of other variables which can be established only under highly specific conditions; thus, they have little predictive value when compared to data amenable to programming in a computer (H.S.).]

Stear, E. B., Kadish, A. H. (eds.): *Hormonal Control Systems* (Proc. Symp. Rancho Santa Fe, Calif., 1967), p. 304. New York: American Elsevier, 1969. E10,611/69

Proceedings of a symposium on biologic control systems, with contributions by various experts on the regulation of corticoid secretion. Special attempts have been made to develop mathematical models that lend themselves to computer simulation. The principal advantage of such systems is described as follows: "Computer simulations (models) of biological systems require that the static and dynamic characteristics of all the pertinent components and processes of the systems be identified and quantitatively specified; computer models are truly functional—they can change state with the flow of time, and therefore they expose the incompleteness of knowledge."

Yates, F. E., Brennan, R. D.: "Study of the mammalian adrenal glucocorticoid system by computer simulating." In: Stear, E. B. and Kadish, A. H., *Hormonal Control Systems* (Proc. Symp. Rancho Santa Fe, Calif., 1967), pp. 20-87. New York: American Elsevier, 1969. J12,012/69

Mathematical interpretation of biologic data led to an attempt at computer simulation (model) of the factors influencing glucocorticoid secretion.

Rashevsky, N.: "A note on the mathemati-

cal theory of the effect of nervous stress on coronary thrombosis." *Bull. Math. Biophys.* 31: 403-416 (1969). J23,247/69

Urquhart, J., Krall, R. L., Li, C. C.: "Adrenocortical secretory function—communications and control aspects." *Automatica* 6: 193-205 (1970). J11,823/70

After reviewing their observations on the stimulation of corticoid secretion by ACTH in the canine adrenal, the authors "have developed a seventh order state variable model of this process in terms of current knowledge about the mechanisms of cortisol biosynthesis. The modeling plays a dual heuristic role: (1) at the very least, it provides a phenomenological description of adrenocortical secretory function for use in larger models of pituitary-adrenal control mechanisms, and (2) it is an aid in evaluating postulated mechanisms by which ACTH acts on the kinetic parameters of cortisol biosynthesis."

Green, J. F., Miller, N. C.: "A model describing the response of the circulatory system to acceleration stress." *Ann. Biomed. Eng.* 1: 455-467 (1973). J10,890/73

"A mathematical model of the circulatory system based on the principles of venous return is described and applied to the condition of acceleration stress."

Papaikonomou, E.: *Biocybernetics, Bio-systems Analysis and the Pituitary Adrenal System*, p. 334. Purmerend: Nooy's Drukkerij, 1974. E10,437/74

A monograph that combines insight and wit in applying the principles of systems analysis strategy and biocybernetics to the study of the pituitary-adrenocortical apparatus in relation to the G.A.S. Sayers' hypothesis about the activation of ACTH secretion by a negative feedback due to increased utilization of glucocorticoids during stress was not supported by subsequent experiments. It was replaced by the theory of Yates that stress activates a controller of the system in the hypothalamus. Then Smelik provided evidence of an integral controller of the system with a derivative controller sensitive to negative rates of change of blood glucocorticoids. It is essential in studies concerning the regulation of corticoid secretion to consider the ACTH concentration of the blood, and the blood flow, as separate input variables, and to distinguish between the effect of free and protein-bound corticoids. A diagram summarizing the author's concept will be found on p. 1106.

Yates, F. E., Maran, J. W.: "Stimulation and inhibition of adrenocorticotropin release." In: Greep, R. O. and Astwood, E. B., *Handbook of Physiology. Section 7. Endocrinology*, Vol. 4, Part 2, pp. 367-404. Washington, D.C.: American Physiological Society, 1974. E10,758/74

General review of interactions in the hypothalamo-pituitary-adrenocortical system during stress with an attempt to summarize it in

the mathematical model presented in Figure 26.

Lumsden, D. P.: "Towards a systems model of stress: feedback from an anthropological study of the impact of Ghana's Volta river project." In: Sarason, I. and Spielberger, C., *Dimensions of Anxiety and Stress*. (In press). J15,030/

An attempt to present a model of stress as an open system, based mainly on anthro-

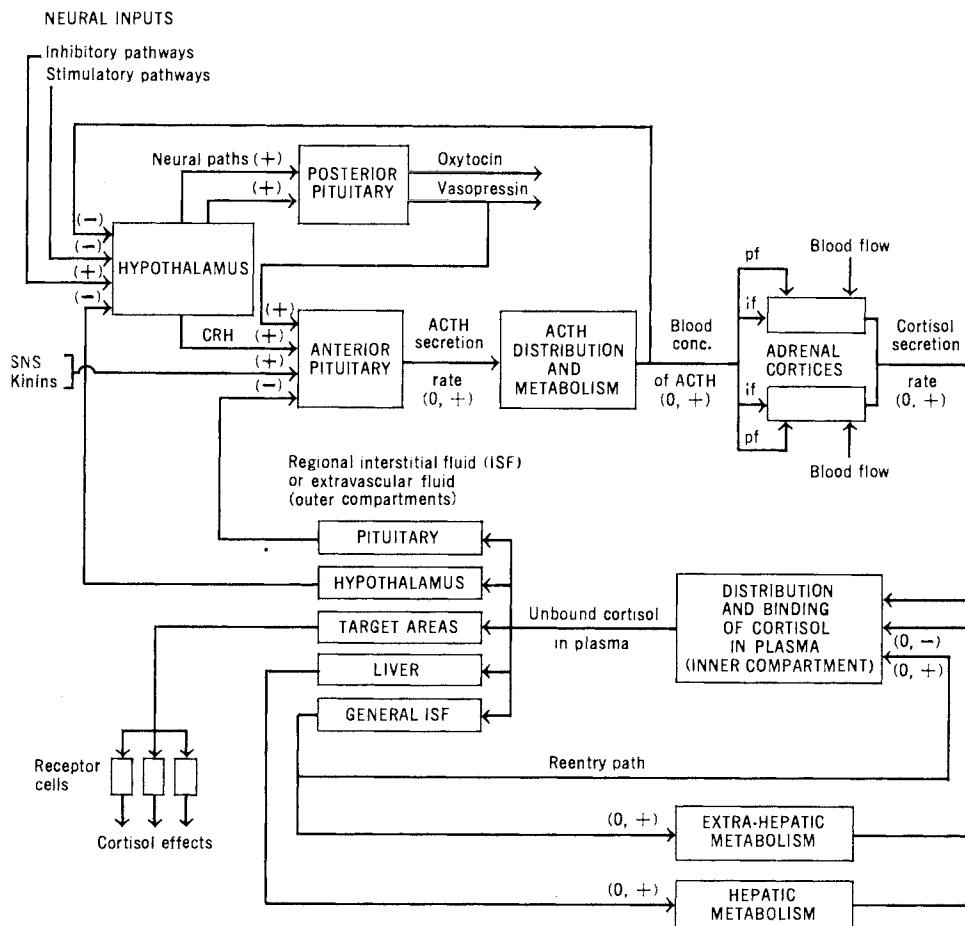


Figure 26. Complete block diagram of adrenal glucocorticoid control system. If, input forcing of adrenal by ACTH; pf, parametric forcing of adrenal (hypertrophic effect) caused by ACTH over a longer time period. Parametric effect of changes in adrenal blood flow is also indicated. The designators 0,+ and 0,- indicate that signals in pathways are restricted in values (e.g., there are no negative masses or frequencies and removal processes or inhibitors are negative in effects. Sign restrictions described in Dallman and Yates, *Ann. N.Y. Acad. Sci.* **156**: 696-721/1969. (Reproduced from *Handbook of Physiology* (1974), Section 7. Endocrinology, Fig. 8, p. 386, by permission of F. E. Yates and J. W. Maran and the American Physiological Society.)

pologic studies within the frame of Ghana's Volta river project (about 100 refs.).

Varia. Tuttle, E.: "Intracellular biochemical adaptation process therapy theory." *Rev. Gastroenterol.* **20:** 893-912 (1953).

J12,184/53

Highly speculative review on the mechanism of the G.A.S. (84 refs.).

Briggs, F. N., Munson, P. L.: "Studies on the mechanism of stimulation of ACTH secretion with the aid of morphine as a blocking agent." *Endocrinology* **57:** 205-219 (1955).

C7,791/55

In rats, morphine blocked ACTH secretion induced by various stressors (histamine, EP, vasopressin, laparotomy) or unilateral adrenalectomy, whereas these stimuli were effective in anesthetized controls. The action of exogenous ACTH was not blocked by morphine, showing that the drug fails to interfere directly with the response of the adrenal cortex.

Goldstein, M. S., Ramey, E. R.: "Non-endocrine aspects of stress." *Perspect. Biol. Med.* **1:** 33-47 (1957).

C61,319/57

While the importance of the G.A.S. (and particularly of the pituitary-adrenocortical axis) in adaptation is recognized, the non-endocrine aspects of stress responses are considered to be equally indispensable and are described in detail.

Dedichen, J., Laland, P., Laland, S. G.: "The effect of material prepared from ox blood on cold stress in mice." *Acta Pathol. Microbiol. Scand.* **58:** 219-224 (1963).

E22,664/63

High molecular material prepared from ox blood after exposure to stress significantly reduces the mortality of cold-stressed mice. "It is suggested that the material is related to a hypothetical resistance factor mentioned in the work of Raškova and Vaneček."

Wilder, J.: *Stimulus and Response. The Law of Initial Value*, p. 352. Bristol: John Wright & Sons, 1967.

E630/67

Monograph on the law of initial value, which states that the higher the initial value of some physiologic parameter (blood pressure, pulse rate), the more pronounced is its tendency to decrease and the smaller its tendency to rise under the influence of various agents. Numerous observations are mentioned which indicate that this law plays an important role in determining variable courses of changes characteristic of the G.A.S. (843 refs.).

Marqués-Sala, R., Cochs-Cristia, J., Cabarcas-Gafarot, E.: "El fenómeno de la excitación celular predepresiva y la homeostasis" (The predepressive cellular excitation phenomenon and homeostasis). *Folia Clin. Int.* (Barcelona) **21:** 513-521 (1971).

G87,001/71

Highly speculative article relating the G.A.S. to variations in energy regulation.

Chernukh, A. M., Gorizontova, M. P., Alexeyev, O. V.: "The mechanism of participation of the mast cells in regulation of the vascular permeability." *Biochem. Exp. Biol.* **11:** 105-110 (1974).

H96,177/74

In rats, restraint causes degranulation of mast cells with liberation of histamine, 5-HT and heparin. These substances may have a role in the mechanism of vascular reactions during stress.

Terjung, R. L., Baldwin, K. M., Winder, W. W., Holloszy, J. O.: "Glycogen repletion in different types of muscle and in liver after exhausting exercise." *Am. J. Physiol.* **226:** 1387-1391 (1974).

H88,009/74

Study of various factors influencing glycogen metabolism in different organs of rats exposed to the stress of intense muscular exercise.

Strasser, H.: "Technisch-physiologische Aspekte der Beziehung Stress-Strain. Eine modell-theoretische Betrachtung" (Technical-physiologic aspects of the relationship between stress and strain. A heuristic model). *Arbeitsmed. Sozialmed. Präventivmed.* **9:** 212-217 (1974).

J18,267/74

VII. VARIOUS OTHER RELATED TOPICS

LEGAL IMPLICATIONS

Stress as a cause of disease has often been invoked in the courts to support the cases of plaintiffs who developed various illnesses following exposure to unusual demands for adaptation, especially at work or in concentration camps. Pertinent data that may be useful to the attorney will be found in the sections dealing with the corresponding stressors, such as noise, magnetism, vibration, shift work, aerospace, travel, ATC activities, industry (particularly mining), trauma and so on.

Of course it must be realized that stress is rarely the sole cause of any disease; yet it may play a role in almost all maladies, especially those discussed in the section Diseases of Adaptation (such as hypertension, cardiac accidents, neuropsychiatric disorders, peptic ulcers, sudden death of unknown cause, and even diabetes, asthma, menstrual disturbances or impotence).

The most important thing to remember in the evaluation of such cases is that diseases of stress are always pluricausal, in that they depend on both the stressor and the conditioning circumstances (genetic predisposition, previous illness, antecedent surgical operations, diet). It is evident that in all such lawsuits, if the defendant is found to be responsible for exposing the plaintiff to undue stressors, the main problem is to determine the relative parts played by stress and by conditioning factors respectively. This can never be accomplished with absolute quantitative accuracy, since neither the stressor effects nor the conditioning factors can be measured precisely. Yet a fairly close approximation of the defendant's share in the responsibility has often been possible when the attorneys have based their case on well-supported data in the medical literature, evaluated in collaboration with competent physicians.

It is not within the scope of this treatise, nor the field of competence of its author, to discuss the topic of jurisprudence adequately, but a few points that have often been raised in connection with the legal implications of stress might be enumerated briefly.

1. Both physical and emotional stressors can cause illness.
2. A great variety of diseases and disabilities may be precipitated by stress, even those not usually considered to be diseases of adaptation. As previously stated, in every person the weakest, most predisposed organ system will break down under the general demand of adaptation to stress, as the weakest link breaks in a chain exposed to mechanical stress.
3. The "survivor syndrome" of previous concentration camp inmates has clearly demonstrated that stress can induce delayed manifestations long after the stressor has ceased to act. This is especially true of psychologic disturbances or of psychogenic so-

matic lesions. Indeed, it has been argued that even the offspring of concentration camp inmates may be damaged, because they are brought up by parents with permanently warped mental attitudes. Although these delayed effects have been studied mainly on the large available population of concentration camp survivors, the conclusions presumably are applicable to persons exposed to other stressors of equal severity and duration.

4. Stress undoubtedly increases accident proneness (for example, in industry, driving, aerospace, travel, ATC work and combat).

5. Acting as a witness, judge, attorney or juror can in itself be extremely stressful and can influence performance in sensitive individuals.

These are a few of the most striking facts that emerge from the study of the pertinent literature, but their evaluation in the light of the laws of each country must be left up to legal experts.

Legal Implications

(See also our earlier stress monographs, p. xiii)

Introna, F.: "Richerche sperimentalali sulla patologia da ultrasuoni" (Experimental research on the pathology of ultrasound). *Med. Leg. e Assicur.* 1: 13-42 (1953).

C4,806/53

In guinea pigs exposed to ultrasound, morphologic changes occur in various tissues, particularly in the mesenchyma, similar to those "described by Selye in the condition of stress." In view of the occupational exposure of some people to ultrasound, these findings have medico-legal significance.

Selye, H.: "Notes on the medico-legal implications of the stress concept with special reference to status thymicolymphaticus." *J. Forens. Med.* 1: 231-239 (1954).

B84,940/54

Brief note on the application of the stress concept in legal medicine. Special attention is given to sudden death and status thymicolymphaticus.

Sigler, L. H.: "Cardiac disability and death caused by strains: problem in workmen's compensation." *J.A.M.A.* 154: 294-299 (1954).

B89,752/54

Morris, R. E.: "Witness performance under stress: a sociological approach." *J. Soc. Issues* 13 No. 2: 17-22 (1957).

J9,878/57
General discussion of the stressor effect of acting as a legal witness. No reference is made to the somatic aspects of the G.A.S.

Rosch, P. J.: "Stress. Its relationship with illness." In: Cantor, P. D., *Traumatic Medicine and Surgery for the Attorney*, Vol. 3,

pp. 261-361. Washington: Butterworths, 1960.

E10,310/60

Very detailed chapter on stress in an encyclopedia on legal medicine, with special reference to the interests of the attorney.

Petit, A. G., Champeix, J., Petit, G.: "Les problèmes médico-légaux dans la survie d'après les études anatomo-histologiques et biologiques récentes" (Medico-legal problems in survival according to recent anatomo-histologic and biologic studies). *Ann. Méd. Lég.* 40 No. 5: 444-458 (1960).

D12,909/60

Review of the role played by the G.A.S. in legal medicine.

Sparkman, D. R.: "Trauma or strain and heart disease. Causal relationship." *Calif. Med.* 94: 72-76 (1961).

D1,913/61

To clarify the problems of the cardiac patient under workmen's compensation laws, a special committee of the Washington State Heart Association stated that a "causal relationship of trauma to heart disease may exist under the following circumstances: Sudden death from acute coronary disease (or coronary occlusion with myocardial infarction, or acute coronary insufficiency) in which symptoms develop during the course of or immediately following exertion or strain that is both excessive and unusual for the particular individual concerned; this exertion or strain may be either physical or emotional." In the years 1950-59, 77 percent of the claims for cardiac damage made in the state of Washington were for myocardial infarction or acute coronary insufficiency following unusual effort. Since CHD is progressive, it is difficult to ascertain when a given

stress at work may have contributed to an eventual infarct. Data on steps taken by several states concerning a causal relationship of stress to heart disease are reviewed (20 refs.).

Jaffe, D. S.: "Fatigue states. Asthenic reactions." In: Cantor, P. D., *Traumatic Medicine and Surgery for the Attorney*, Vol. 6, pp. 22-34. Washington: Butterworths, 1962.

E10,309/62

A chapter in an encyclopedia on legal medicine concerning the relationship between stress and fatigue, especially in industry or after trauma.

Bruni, B.: "Anamnesi psicologica del diabete. Sui rapporti tra alterazioni psicoemotive e inizio del diabete" (Psychologic history of the diabetic. On the relation between psychomotor alterations and the beginning of diabetes). *Minerva Med.* 54: 3516-3524 (1963).

E36,698/63

Discussion of the pathogenic importance of "acute emotional stress" in diabetes, with special reference to its legal implications.

Lyon, E.: "Das peptische Geschwür, eine Stresskrankheit der Verfolgten (Neue Gesichtspunkte für die Begutachtung)" (Peptic ulcer as a stress disease of the persecuted [New viewpoints on testimony]). *Med. Klin.* 58: 1514-1517 (1963).

E27,706/63

In concentration camp survivors, stress ulcers are particularly common, and this has been recognized even in legal testimony.

Mari, E., Mari-Rizzatti, E.: "Latest observations on the subject of carbon monoxide poisoning and general adaptation syndrome." *Minerva Med.* 84: 162-167 (1964).

J23,794/64

Schattenfroh, C.: "Das Stress-Ulcus, Klinik und Begutachtung" (Stress ulcer, clinical aspects and expert opinion). *Chirurg.* 37: 338-343 (1966).

G42,453/66

Voigt, J.: "Adrenal lesions in medico-legal autopsies." *J. Forens. Med.* 13: 3-15 (1966).

G42,472/66

Larcan, A.: "Stress et diabète" (Stress and diabetes). *Agressologie* 7: 447-458 (1966).

F75,116/66

Meticulous collection of literature on the aggravation of preexistent, and the production of previously undetected, diabetes by a variety of stressors. This finding may have

legal implications, as it may constitute a basis for awarding compensation.

"The survivor syndrome: concentration camp effects." *Sciences* 8: 32-37 (1968).

F94,111/68

Review of the "survivor syndrome" based on observations by various physicians who examined a large number of former concentration camp inmates. Both the acute and the delayed manifestations are described with respect to somatic and psychic damage. An important pathogenic factor, "survivor guilt, persists long after relatives have died because the survivor unconsciously identifies with the aggressor."

Olla, G.: "Considerazioni sul lavoro usurante (Con particolare riferimento ai riflessi in campo assicurativo)" (Wear-and-tear type work [with special reference to its repercussions in the insurance field]). *Folia Med.* (Napoli) 52: 81-93 (1969).

J20,757/69

Discussion of justifiable insurance claims for excessive work requirements in industry.

Baeyer, W. von: "Psychiatrisches Gutachten über Fragen der Glaubwürdigkeit und Erinnerungszuverlässigkeit bei der Beurteilung von Zeugenaussagen rassistisch Verfolgter, die weit zurückliegenden Extrembelastungen ausgesetzt waren" (Expert psychiatric opinion on the problem of credibility and recall reliability evaluation in testimonies of racially persecuted witnesses who were exposed to extreme stress in their distant past). *Nervenarzt* 41: 83-89 (1970).

J21,703/70

Hoppe, K. D.: "The aftermath of Nazi persecution reflected in recent psychiatric literature." *Int. Psychiatr. Clin.* 8: 169-204 (1971).

J20,184/71

Review of the literature (including medico-legal problems of compensation) in relation to Nazi persecution (195 refs.).

Fischer, H.: "Vitiligo als Verfolgungsschaden" (Vitiligo as sequelae of persecution). *Berufsdermatosen* 19: 317-324 (1971).

J21,408/71

Zimmerly, J. G., Oleniewski, W. A.: "Mental anguish as an element of damages in malpractice cases." *Maryland Med. J.* 22: 37-39 (1973).

J20,207/73

Medico-legal aspects of malpractice as they affect physician and patient.

Oleniewski, W. A., Zimmerly, J. G.: "Mental anguish claims in medical malprac-

tice cases." *Postgrad. Med.* **53**: 131-132 (1973).
J19,728/73

Arnold, L. C.: "Diabetes and trauma." *Med. Trial Tech. Q.* **20**: 89-98 (1973).
J23,506/73

Arguments for and against the concept that diabetes can be produced or aggravated by stress.

Selye, H.: "Stress and the nation's health." *Court Rev.* **13**: 22-30 (1973). J4,242/73

Review on stress presented for the legal profession.

Luff, K., Karger, J. von: "Zur Frage der Verhaltenskontrolle von Kraftfahrern nach Verkehrsunfällen unter Berücksichtigung des Schuldmasses" (Behavioral self-control of drivers following road accidents with reference to the degree of guilt). *Beitr. Gerichtl. Med.* **31**: 18-21 (1973). J17,717/73

The stressor effect of automobile accidents may lead to an immediate disturbance of decision-making conducive to flight from

the scene of an accident. The legal implications in German courts are described.

Freeman, Z.: "The effect of stress on the heart." *Med. J. Aust.* **1**: 87-90 (1974).
J10,829/74

Review of the literature on stress-induced heart disease, with special reference to its medico-legal implications.

Holzmann, H., Hoede, N., Krapp, R.: "Gutachterliche Probleme bei der Beurteilung der Psoriasis" (Problems of expert opinion in the assessment of psoriasis). *Z. Hautkr.* **49**: 493-496 (1974). J20,840/74

Psoriasis may occur as a disease of adaptation during the postconcentration camp survivor syndrome. The medical and legal implications of this observation are discussed.

Silen, W.: "Stress ulcers." *Med. Trial Tech. Q.* **20**: 254-266 (1974). J23,293/74

General characterization of stress ulcers, mainly for the benefit of attorneys.

PHILOSOPHIC IMPLICATIONS

The philosophic and particularly the behavioral implications of research on the somatic and mental consequences of the stress and G.A.S. concepts have stimulated a great deal of work, not only by professional philosophers and behavioral scientists, but also by theologians, writers of fiction and nonfiction, paleontologists, motion picture and television producers, painters, and recently, even choreographers. My own thoughts on this subject were stated most concisely in *Stress Without Distress*, with a short summary on pp. 32-34 of this book.

As Dubos has so poignantly put it, human life is shaped by three classes of determinants: (1) the genetic code, (2) adaptation to environmental sources, and (3) the ability to choose among alternatives.

Actually these three factors are all interdependent, in that our genetic makeup determines the type of responsiveness to environmental stimuli and the ability to choose among possible alternatives.

A clear distinction between the specific and the nonspecific, as well as an awareness of the fundamental fact that specificity is always relative (with an infinite range between the two extremes of total specificity and total nonspecificity), are by no means limited to medicine and physiology. Our whole philosophy of life, and especially the justification of our behavior, must take these factors into consideration. It has been a most stimulating experience to attempt the development of a code of behavior based exclusively on natural laws, particularly those regulating efficient homeostasis. There appears to be a great similarity between the laws governing the maintenance of a healthy equilibrium, and those assisting us to achieve the satisfaction of success in reaching whatever goal we consider worthwhile, both on the somatic and on the mental

level. Of course, our efforts represent only a beginning; much more work is needed to develop the applications of a natural code of behavior to the innumerable problems encountered during a normal lifespan. However, we have identified a few examples of clearcut similarities between the somatic behavior of a person on the cellular and molecular level on the one hand, and his efficient aim-oriented attitude toward the challenges of his environment (including his society) on the other. Even this beginning offers hope to replace superstition, and blind faith in allegedly infallible authorities, by guidelines based on scientific research subject to objective verification.

Philosophic Implications

(See also our earlier stress monographs, p. xiii)

Mace, C. A.: "Homeostasis, needs and values." *Br. J. Psychol.* **44**: 200-210 (1953).

J13,303/53

Philosophic considerations on the nature of stress and homeostasis.

Stagner, R.: "Homeostasis: corruptions or misconceptions? A reply." *Psychol. Rev.* **61**: 205-208 (1954). D75,941/54

Philosophic considerations on the relationship between homeostasis and the G.A.S.

Belgium, D.: *Why Did It Happen To Me?*, p. 110. Minneapolis: Augsburg, 1960.

C91,719/60

Monograph on theology with an extensive chapter on "sin and stress," based mainly on observations reported in *The Stress of Life*.

Lippman, H. E.: "Stress, the adaptation mechanism, and the metamorphic evolution of the vertebrates." *J. Natl. Med. Assoc.* **53**: 582-592 (1961). D16,106/61

Detailed dissertation on the roles of stress and the G.A.S. in the evolution of the species, based largely on paleontologic data.

Selye, H.: "Stress: the wear and tear of life." *Think* **27**: 20-32 (1961).

C87,657/61

Popular outline of the "philosophy of gratitude" as applied to daily life.

Bharucha-Reid, R. P.: "The internal modulating system and stress: a neurophysiological model." *J. Gen. Psychol.* **66**: 147-158 (1962). J13,890/62

Selye, H.: "Creative health for all Canadians." *Health* (Toronto) **31**: 14-15 (1963).

E24,123/63

First attempt to formulate a code of behavior based upon natural laws, particularly the results of stress research.

Mason, J.: "Don't eliminate tension." *Bus. Management* August 1964, pp. 37-38.

J17,432/64

On the basis of speculative considerations on the effect of stress upon the body, the author concludes that "a reasonable number of anxieties and personal conflicts are often good for employees."

Farber, S. M., Mustacchi, P., Wilson, R. H. L. (eds.): *Man Under Stress*, p. 173. Berkeley and Los Angeles: University of California Press, 1964. E4,227/64

Proceedings of a symposium organized by the University of California. A group of physicians, surgeons and basic research men (among them Brock Chisholm, René Dubos, Seymour Farber, Stanley Sarnoff, Hans Selye and Paul Dudley White) discussed the various aspects of stress, particularly in relation to the philosophy of life, social environment, cardiovascular disease, space medicine and so on. Most of the speakers refrained from highly technical discussions, but key references to scientific papers are given.

Arangüena-García-Inés, C.: "El médico neohipocrático y la conducta del hombre ante el stress" (The neohippocratic physician and the behavior of man in relation to stress). *Folia Clin. Int. (Barc.)* **17**: 27-32 (1967).

J22,402/67

The author develops an entirely new philosophic interpretation of disease on the basis of the stress concept.

Reeves, R. B. Jr.: "What happens to the patient's religion?" *Delaware Med. J.* **45**: 40-43 (1973). J19,880/73

A pastor describes his experience in the change of the religious feelings of patients in hospitals. "We are dismayed by our own humanity, unable to accept our creatureliness as proper to our being, unable to love ourselves. This, of all the stresses a patient may suffer, can be the most disturbing."

Laszlo, E.: *Introduction to Systems Philos-*

ophy, p. 328. New York, San Francisco and London: Harper & Row, 1973. E10,096/73

Selye, H.: "Stress without distress in teamwork." *Viewpoint* November 1973.

J4,207/73

Brief outline of the behavioral lessons derived from the stress concept as applied to daily problems. Essentially a preview of the points developed in *Stress Without Distress*.

Leyhausen, P.: "The biological basis of ethics and morality." *Sci. Med. Man* 1: 215-235 (1974). J19,699/74

A biologic approach to the understanding of ethics (what we mean when we term something good or bad) and morality (what to do about something that is good or bad). The naturalists called "peristostable" those characteristics which developed in every case, even under the most diverse conditions, and "peristolabile" those characteristics which varied more readily, depending upon postnatal influences. "In other words, there never was any question of characteristics or traits being developed by genes alone," as environmental factors were always considered to be vital conditions. Altruistic behavior is one of the favorite examples of the anti-Darwinist critique; to substantiate a biologic basis for moral and ethical behavior, "we must first show that evolution in some ways and certain cases rewards sacrifice, including self-sacrifice, and that this fact neither directly contravenes the principle of the 'survival of the fittest' nor is excluded by it." Even refraining from suicide is an act of altruism if we consider our lives a liability we owe to God and/or society. If, in schools of fish, some swim at the periphery where they are most exposed to attack, this protects those in the central core through what the author considers "altruism." Certain instincts are used only once in a lifetime; they are called "templates" for the whole series of possible life events, and are kept in a state of readiness. Such "Innate Releasing Mechanisms" represent an a priori code of conduct. These and other considerations lead the author to outline a biologic basis for ethics and morality, but no effort is made to translate this into a prescriptive code of behavior in daily life.

Maston, J. W.: "The integrative approach in medicine. Implications of neuroendocrine mechanisms." *Perspect. Biol. Med.* 17: 333-347 (1974). H87,007/74

Discussion of the relative merits of "inte-

grative" and "analytical" approaches to exploring the stress response. Special emphasis is placed upon the facts that, at least in higher animals, the characteristic pituitary-adrenal responses are largely affected by CNS stimuli, and that the stressor effect of each agent is only relatively nonspecific since it is influenced by various responses characteristic of individual agents and conditioning factors.

Selye, H.: "Stress and distress. The first preview of a forthcoming book on how you and your patients can master stress." *Physicians World* 2 No. 3: 25-28 (1974).

J4,239/74

Brief, popular summary of *Stress Without Distress*, with special emphasis upon the behavioral implications of stress research and an attempt to formulate a code of ethics based exclusively on natural laws.

Dubos, R.: "Homeostasis, illness, and biological creativity." *Lahey Clin. Found. Bull.* 23: 94-100 (1974). J17,042/74

Excellent lecture on homeostatic reactions regulating man's somatic and mental behavior in health and disease. Human life is shaped by three classes of determinants: (1) the genetic code, (2) adaptation to environmental forces and (3) the ability to choose among alternatives.

Institutes, Laboratories, and Societies Primarily or Exclusively Devoted to Stress Research

American Academy of Stress Disorders (Dr. R. R. Grayson)

103 West Main Street
Saint Charles, Ill. 60174
U.S.A.

Community Studies on Environmental Stress Research Unit

University College Dublin (Dr. John Cullen)
Department of Psychiatry
Earlsfort Terrace
Dublin
Ireland

Institute of Environmental Stress University of California (Dr. Steven M. Horvath)

Santa Barbara, Calif. 93106
U.S.A.

Institute of Experimental Medicine and Surgery

University of Montreal (Dr. Hans Selye)
 P.O. Box 6128
 Montreal 101, P.Q.
 Canada

Instituto de Investigaciones "Hans Selye"
 Hospital de Ferrocarriles de México
 Mexico City
 Mexico

Laboratory for Clinical Stress Research
 Karolinska Institutet (Dr. Lennart Levi)
 S-104 01 Stockholm 60
 Sweden

Military Stress Laboratory
 Department of the Army (Dr. Wayne O. Evans)
 U.S. Army Research Institute of Environmental Medicine
 Natick, Mass. 01760
 U.S.A.

Multiple Stress Research Group
 Boeing Company (Dr. Robert Dean)
 Seattle, Wash.
 U.S.A.

Naval Medical Research Institute
 National Naval Medical Center (Dr. E. Hardenbergh)
 Bethesda, Md. 20014
 U.S.A.

Stress and Hypertension Clinics Dispensary
 U.S. Naval Gun Factory (Dr. Daniel C. Lipman)
 Washington, D.C.
 U.S.A.

Stress Medicine Division
 Naval Health Research Center (Dr. Richard H. Rahe)
 San Diego, Calif. 92152
 U.S.A.

Stress Physiology Laboratory
 University of Iowa (Dr. Carl V. Gisolfi)
 Iowa City, Iowa 52242
 U.S.A.

Stress Research Section
 U.S. Department of Health, Education, and Welfare
 Public Health Service (Dr. William H. Kroes)
 Center for Disease Control
 National Institute for Occupational Safety and Health
 U.S. Post Office and Courthouse
 Cincinnati, Ohio 45202
 U.S.A.

Stress Transformation Centers, Ltd.
 78 East 79th Street (Adam Crane, Josh Reynolds)
 New York, N.Y. 10021
 U.S.A.

Stress Unit
 Hospital Aeronáutico
 Ministry of Defense
 Buenos Aires
 Argentina

Tokyo Stress Research
 (Dr. Naoharu Fujii)
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 Japan

EPILOGUE

At the end of this treatise I would like to present in retrospect some general thoughts that have occurred to me during the long labor of writing this work.

First, it may be useful to point out for those who see the finished product that it represents forty years of work, which began in 1935 when we performed the first primitive experiments published the following year in a brief letter to the editor of *Nature*. In the years since then I have spared no time or effort in my untiring drive to clarify the role of nonspecific reactions affecting living beings in health and disease. I have written quite a number of reviews and smaller monographs on the subject, always postponing the task of the "grand synthesis" until I had more evidence and understood the subject better. However, there seems to be no natural endpoint in sight. I keep on learning more and more, but I am afraid that my ability to learn and understand begins to lag behind both the explosive growth of information to be dealt with and my own capacities of evaluation.

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Today, at the age of 68 I feel that the best service I can render to those interested in my favorite subject, stress, is to coordinate and compile what I know as best I can, before I lose the strength to undertake such a gigantic task. Now that the concepts of stress and of the diseases of adaptation are clearly defined, I think it is important to give a panoramic overview of the subject, for with the tremendous increase in data it becomes increasingly difficult to retain the proper perspective. As in all correlative subjects—such as understanding of the nervous system, intermediate metabolism or endocrine activity—even the most profound study of one restricted area is meaningless if its manifold interactions with other parts are neglected. Many specialists know a great deal about individual aspects of stress research, but few (if any) generalists are still capable of seeing the field as a whole. Even if some subjects had to be merely catalogued with little or no interpretation, it is better to have a manageable synopsis, no matter how imperfect, than to possess no general overview at all.

Only by carefully compiling a data inventory, a veritable encyclopedia of stress research, can this holistic approach be attempted. It is for this reason that I collected every publication that we could trace through the literature and every bit of information that we managed to obtain by personal research. Of the 110,000 references in my documentation service I have selected about 7 percent, either because they dealt with fundamental problems or themselves provided key bibliographies that would help the reader find virtually anything pertaining to stress in medicine, biochemistry, or daily life that he might choose to pursue further.

Fortunately, I have had a very large staff of excellent coworkers to assist me both with the laboratory and the bibliographic research required for compiling this encyclopedia; yet in order to maintain a unified perspective, I wrote every line of it myself. I know that many chapters could have been presented much better had I delegated them to experts in each respective topic, but then we would have ended up with yet another of those monumental, disjointed handbooks or proceedings of symposia on stress, in which some topics are repeated or overemphasized, others overlooked. Probably the time is not far away when volumes of this scope can no longer be written by any one author (in fact it occurred to me in my more pessimistic moments, while involved in this task, that perhaps that time had already arrived), but at any rate, I have attempted to present a balanced picture of my topic.

As I approach the end of my career I do not regret having had to sacrifice virtually my whole private life to accomplish this task, nor even, to be honest, the hardships I had to inflict upon my many coworkers who—some enthusiastically, some by necessity—helped me with my effort, which certainly could not have been achieved without them. The occasional doubt and remorse that I must admit to having experienced has left no permanent scar, for as I said in the introductory outline, I do believe in “altruistic egoism,” in trying “to earn thy neighbor’s love”—meaning the love of most neighbors, even at the unavoidable expense of irritating a few. I have spent my life guided by these principles, and as far as possible, have tried to encourage my coworkers to do likewise. Scientific objectivity demands, of course, that I admit to being somewhat prejudiced by four decades of one-sided activity, but at the end of this labor I still believe that I could not have used either my own time or that of my associates any better by doing something else. At the present period of history, stress in health and disease is medically, sociologically and philosophically the most meaningful subject for humanity that I can think of.

I am considering with my editors the possibility of writing a second edition or annual addenda as time goes by, if this work proves to be successful as a guide to future stress

research. Indeed, it may be necessary, owing to advances in stress research and the deterioration of one of its guardians, to use the present monograph merely as a basis for a more detailed encyclopedia to be written later, in which the advantage of a single coordinating author would have to be sacrificed in favor of an editor assigning each section to a more qualified specialist.

Meanwhile, let me conclude by expressing the hope that, even as it stands, uneven in workmanship and incomplete, this treatise will, at least for some time to come, help investigators find their way through the mass of information that has accumulated on the role of stress in health and disease.

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SUBJECT INDEX

In this index, an arrow is used to indicate the effect of one agent upon another. For example, ACTH → inflammation indicates the effect of ACTH upon inflammation; blood vessels ← corticoids indicates the effect of corticoids upon blood vessels. The symbol + is employed when two or more agents act conjointly (for example, electricity + adrenalectomy). Only such simple signs are used. Letters or numerals identifying structural details of chemical compounds do not determine the placement of the entry (for example, γ-aminobutyric acid is entered under A, 5-HT under H, and so on).

It would defeat the purpose of indexing if we were to place *stress* as the keyword with each entry. Therefore, entries are indexed as factors concerned with stress. Boldface numerals refer to principal discussions of a subject. Figures relating to a particular topic are indexed by their number followed (in parentheses) by the number of the page on which they appear.

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