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THE GENERAL ADAPTATION SYNDROME AND THE DISEASES OF ADAPTATION¹

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DEDICATION

Dedicated to the memory of that great Student of homeostasis, whose life (90b) and work (90a) have been the author's greatest inspiration.

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I. INTRODUCTION

SINCE the first description of the "alarm reaction," a decade ago, many publications have dealt with this phenomenon and with the "general adaptation syndrome," of which it forms a part. It is becoming increasingly more obvious that certain physiologic mechanisms, in which the endocrin system plays a prominent part, help to raise resistance to damage as such, irrespective of the specific nature of the damaging agents. Interest in the general adaptation syndrome has recently received a further impetus as a result of investigations suggesting that some of the most important diseases of human pathology (such as hypertension, nephrosclerosis and the rheumatic diseases) may represent by-products of the endocrine reactions, which are at play in the general adaptation syndrome. It was considered a timely enterprise, therefore, to survey this field now and to supply a guide to the rather scattered and polyglot, pertinent literature. In order to familiarize himself with different points of view, the

reader is also referred to several earlier reviews on the general adaptation syndrome (10, 11, 235, 295, 358, 569, 571, 577, 629, 634, 654).

II. DEFINITION AND TERMINOLOGY

Before entering upon a discussion of a relatively new concept, such as that of the general adaptation syndrome, it is essential to give a clear definition of the subject and the terminology to be used. In some sciences (*e.g.*, mathematics) definitions are unchangeable laws which make a concept what it is; in biology, however, definitions are given merely as concise descriptions of phenomena as they are known at the time, with the view of modifying them as soon as further observations necessitate it. It is with this in mind that the following definitions are presented.

The general adaptation syndrome is the sum of all non-specific, systemic reactions of the body which ensue upon long continued exposure to stress. It is distinct from the specific adaptive reactions, such as the development of the musculature following prolonged physical exercise, the allergic and immunologic phenomena elicited by foreign proteins or micro-organisms, etc. These latter reactions usually endow the body with a great deal of resistance against the particular agent to which it has previously been exposed, but both the manifestations of these adaptive reactions and the resistance which they confer upon the body, are specific to the agent which elicited them.

In the course of our work on the pathologic and biochemical changes elicited by various noxious agents, we were struck by the fact that certain manifestations are always the same, irrespective of the specific nature of the eliciting damaging agent. It is the sum of these non-specific adaptive reactions that is referred to as the "general adaptation syndrome."

It has been found, furthermore, that if an organism is continuously exposed to a certain type of stress, the resulting general adaptation syndrome evolves in three distinct stages, namely, those of the "alarm reaction," the "stage of resistance" and the "stage of exhaustion." Perhaps because historically the alarm reaction was the first to be described, or because of its striking name, it received the greatest attention in the literature. Indeed, some workers fail to distinguish clearly between the alarm reaction and the general adaptation syndrome as a whole. It is especially important, therefore, to emphasize that the former is merely the first stage of the latter.

The alarm reaction is the sum of all non-specific systemic phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted. Some of these phenomena are merely passive and represent signs of damage or "shock," others are signs of active defense against shock. In the case of moderately severe damage, from which recovery is possible, most of the signs of damage become evident

before the signs of defense. Hence, the alarm reaction may in turn be subdivided into two more or less distinct phases: the phase of **shock** and the phase of **counter-shock**. If exposure to damage is not very sudden or if the damaging agent to which the organism is exposed is relatively mild, counter-shock phenomena may become evident without any preceding phase of actual "shock." Unfortunately, no satisfactory definition of shock has as yet been given. In most cases one or the other symptom of shock was singled out as its basic feature and the condition was then defined as one characterized by that symptom (*e.g.*, hypothermia, hypotension, hemoconcentration, capillary permeability, hypochloremia, acidosis, depression of the nervous system, *etc.*). Such definitions are not satisfactory because under certain conditions any one of the so-called "characteristic" symptoms may be in evidence although there is no shock and conversely shock may develop in the absence of one or the other of these symptoms.

It seems more appropriate, therefore, to say that shock is a condition of suddenly developing, intense, systemic (general) damage. This definition, though perhaps not very instructive, is necessarily correct, since it is merely a brief outline of the essential phenomena which induced physicians to coin the term "shock." This latter term always implies a suddenly developing condition, so that damage caused by chronic ailments cannot be thus described. It also implies that the damage is systemic (or general) hence localized lesions, no matter how severe, should not be considered as shock unless they secondarily lead to generalized damage.

Shock may develop in two forms; one is almost instantaneous, the other appears only after a few hours. Some investigators, therefore, distinguish between "**primary**" and "**secondary**" shock. It has been asserted that such a distinction is all the more important, since primary shock is due to nervous stimuli and secondary shock to intoxication with endogenous substances. This is not definitely proven, however, and since even nervous impulses are transmitted by humoral substances, the distinction would not be as sharp as was originally assumed, in any case. Furthermore, even in the case of exposure to damaging agents which lead to fatal shock within less than an hour, the pathologic and biochemical changes may be practically the same as those seen in secondary shock. It is questionable, therefore, whether these two types should be distinguished as essentially different or regarded as an acute and a delayed form of the same process. The recent discovery of counter-shock phenomena may explain cases in which a distinct period of "primary shock" was followed by "secondary shock" after an intermediate period of relative well-being. It is possible that in such cases the intermediate shock-free period is merely the equivalent of the counter-shock phase which later proves insufficient and gives way to fatal shock.

The term **collapse** has often been used as synonymous with primary shock, but here again there is little justification for a special name. Moon (435) summarizes this question as follows: "Collapse designates a sudden failure of the circulation. When this presents, as it usually does, the features embodied in the definition of shock, the terms should be regarded as interchangeable." Allen (14), on the other hand, believes that primary and secondary shock are two entirely different conditions, mainly because the blood-count changes, characteristic of the latter, are usually not found in the former. He expressed the view that "it is questionable whether the name shock should continue to be applied to both." The initial irregularities in the blood count during the first hour of the shock phase of the alarm reaction will be discussed later; suffice it here to say that they are hardly of sufficient significance to justify the distinction between two different types of shock.

The value of the term "shock" has been greatly diminished as a result of the numerous confusing definitions with which it is associated, yet it would be difficult to eradicate it now, although terms such as "**exemia**" (87), "**histotoxicosis**" (14), etc., have been suggested.

More recently, the term "**crush syndrome**" has been introduced to designate a particularly delayed type of general damage which usually follows severe crushing of extensive body regions. It is mainly characterized by renal lesions which appear several days after the eliciting trauma (39, 84, 133a, 158, 168a, 169, 230, 440).

The **stage of resistance** represents the sum of all non-specific systemic reactions elicited by prolonged exposure to stimuli to which the organism has acquired adaptation as a result of continuous exposure. It is characterized by an increased resistance to the particular agent to which the body is exposed and a decreased resistance to other types of stress. Thus the impression is gained that, during the stage of resistance, adaptation to one agent is acquired "at the expense of" resistance to other agents. It is also noteworthy that most morphologic and biochemical changes of the "alarm reaction" disappear during the stage of resistance and indeed in some cases the direction, of the deviations from the normal, is reversed (*e.g.*, hypochloremia during the alarm reaction, hyperchloremia during the stage of resistance).

Finally, the **stage of exhaustion** represents the sum of all non-specific systemic reactions which ultimately develop as the result of very prolonged exposure to stimuli to which adaptation had been developed, but could no longer be maintained.

The characteristics of these three stages are described in Section V., entitled, *Course of the general adaptation syndrome*.

By **specific resistance** we mean that type of inurement which increases

resistance only against the particular type of stress to which the body had been exposed; conversely, **non-specific resistance** designates the ability of the body to withstand stress qualitatively different from that to which it had been adapted.

The term "**adaptation energy**" is used to describe the ability of the organism to acquire resistance to stress.

In connection with the terminology of the general adaptation syndrome, it should be noted that some investigators use the term "alarm reaction" to describe certain nervous phenomena, whose relationship to the general adaptation syndrome has not been fully clarified as yet (332, 693). On the other hand, the "**anamnestic reaction**" is most probably an integral part of the general adaptation syndrome, as we shall see below. It has been defined as "the enhancement of antibody titer which follows the injection of a variety of non-specific substances other than the original antigen" (155).

III. HISTORY OF THE GENERAL ADAPTATION SYNDROME

It is rather instructive to survey the historic development of the alarm reaction concept. The fact that such a common biologic phenomenon as the alarm reaction was not discovered long ago, probably finds its explanation in that previous investigators studied only certain aspects of this problem and failed to recognize that they were dealing with a general reaction in which the object of their particular attention was merely one of a set of correlated symptoms. The most ancient observations along these lines are those on **traumatic shock**, which is now recognized as fundamentally related to toxic, spinal, burn, x-ray and other types of shock—all conditions representing the first phase of the alarm reaction.

In 1911, Bianchi (56, 57) made an observation which may have been the first evidence of the existence of a counter-shock phenomenon. He noted that rabbits receiving intravenous injections of toxic tissue extracts, become more resistant to subsequent injections either of the same or of different organ extracts. This phenomenon was also studied by Champy and Gley (98, 99) who gave it the name "**tachyphylaxis**." Numerous investigators confirmed and extended these observations (190, 467, 501). Almost at the same time, Ancel and his co-workers (24, 344) described similar observations under the name of "**skeptophylaxis**." Both these terms were chosen to imply a rapid defense reaction; tachyphylaxis meaning quick readiness and skeptophylaxis, lightning readiness.

Tzanck and collaborators (3, 450, 643-646) introduced the term "**biophylaxis**" to designate all non-specific defense mechanisms (phagocytosis, inflammation, etc.), exclusive of true immune reactions. These authors limited themselves largely to theoretical considerations and gave so little

factual evidence that it is almost impossible to determine exactly what phenomena they observed. It appears, however, that their concept came very close to what Cannon (89, 90) termed "homeostasis." Lassablière (354) found that injection of such "nutrients" as 40 per cent glucose, rice water, wine, beer, organ extracts, milk, etc., increases the resistance

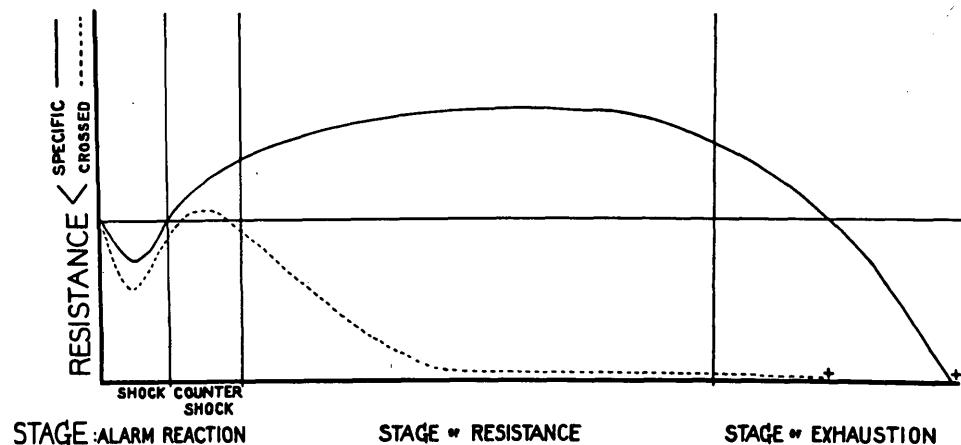


PLATE I. Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during the three stages of the general adaptation syndrome

The progress of time is indicated along the abscissa and the degree of resistance along the ordinate. Note that specific resistance to the agent with which the animal is treated decreases during the shock phase of the alarm reaction and increases during the counter-shock phase, reaching its maximum during the stage of resistance; in the stage of exhaustion, it falls below normal and finally, death ensues. Crossed resistance, to agents other than that with which pretreatment occurred, falls even lower than the specific resistance during the shock phase, rises but slightly during the counter-shock phase and is definitely subnormal in the stage of resistance. This indicates that while resistance to one agent (specific) is acquired by pretreatment with this same agent, resistance to other stimuli (crossed resistance) falls below the normal level (horizontal line).

of mice to cobra venom, a phenomenon which he described as "trophophylaxis."

In 1913, the Belgian histologist Dustin (160, 161) began a series of studies on the effect of certain drugs on nuclear pyknosis and mitotic division. He concluded that certain drugs, which he termed "poisons caryoclasiques," increase the number of pyknoses, especially in the thymus and lymph glands and decreased the number of mitotic figures. He and his followers designate this response "crise caryoclasique" (73, 95, 104, 140, 160a, 162, 242, 243). Later, however, regeneration with an increase in the number of mitoses occurs. More recently, it was concluded that some of

these drugs act more specifically on pyknosis, others on mitosis. It is well to keep in mind, that all so-called "caryoclastic drugs," which the writer had occasion to examine, produced typical signs of the alarm reaction. This has been demonstrated especially clearly (360) for colchicine—one of the most active drugs of this series. It was noted, furthermore, that

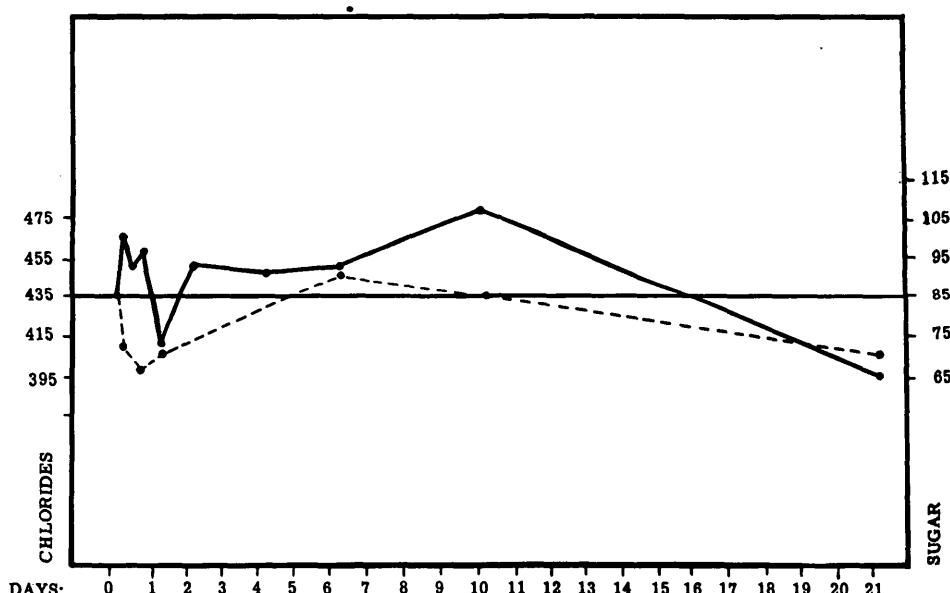


PLATE II. Whole blood chloride and blood sugar changes (expressed in mg. %) in the general adaptation syndrome of rats chronically exposed to cold²

In this experiment, the intensity of the cold was such, that death ensued after 21 days of exposure. The blood chlorides (dotted line) decrease during the first day (alarm reaction) then rise to, or even above normal (stage of resistance) but premortally decline below normal again (stage of exhaustion). The blood sugar changes (solid line) follow essentially the same course, except that during the shock phase (adrenalin hyperglycemia), there is a transitory rise in blood glucose concentration.

waves of pyknosis in the thymus and lymph nodes are produced by all alarming stimuli. This is true not only of drugs but also of spinal and surgical shock, muscular exercise, exposure to cold, etc., so that it appears rather likely that Dustin and his school were studying one phase of the alarm reaction rather than the specific pharmacologic action of a special class of drugs.

² Selye, H. Blood sugar and blood chloride changes in the alarm reaction and during adaptation to various stimuli. *Arch. internat. de pharmacodyn. et de thérap.* 60: 259 (1938).

In 1921, the French physician Widal and his school (684) gave a detailed description of a clinical syndrome which they termed "**crise hémoclasique.**" This was first observed in cases of cold hemoglobinuria and later in many other clinical conditions, such as acute infectious diseases, allergic reactions, etc. The outstanding features of this syndrome are leukopenia, decrease in the refractive index of the serum, decrease in blood-clotting time and in blood pressure. Albuminuria and fever are sometimes also observed, but these are inconstant. Both Widal's reaction and the alarm reaction represent responses to acute, critical situations and it seems likely that there is a close relationship between them. Since the symptoms of the alarm reaction, however, have not as yet been studied sufficiently in man, it is impossible to say whether the two syndromes are actually identical (140a).

The fact that the alarm reaction confers a certain degree of non-specific resistance upon the organism makes it probable that it is also closely related to the so-called "**non-specific therapy**" about which much has been written, but unfortunately, little is known as yet. The relevant literature has repeatedly been reviewed (272, 668-670). It is claimed that administration of certain non-specific damaging substances leads to the production of "metabolites" which increase the resistance of the organism against various diseases ("**Leistungssteigerung und Protoplasmaaktivierung**"). It is probable that these phenomena are closely related to the increase in resistance seen during the above-mentioned "phylactic" reactions and during the counter-shock phase of the alarm reaction.

The "**syndrome polypeptidotoxique**" (372) which develops in acute hepatic insufficiency after burns or trauma and is characterized by an unusually high polypeptide concentration in the blood, evidently also belongs to this group. The extensive protein breakdown characteristic of the shock phase of the alarm reaction is probably the cause of the increase in polypeptides.

Rössle (514-517) was the first to formulate the concept of "**serous inflammation**" (**seröse Entzündung**), which was later elaborated by Eppinger (176) and his school. It is based on the observation that under the influence of various noxious agents the normally low protein concentration of the intercellular fluid rises as a result of migration of plasma into the intercellular spaces. This migration—which is referred to by Eppinger as "albuminuria into the tissues"—is the result of increased capillary permeability. It is accompanied by an increase in the Na, Cl and water content and a decrease in the K and PO₄ content of the tissues. It has been noted (395) that lesions in the intestinal tract, such as are seen in the alarm reaction, may accompany this syndrome in man, an observation which emphasizes the similarity between these two conditions.

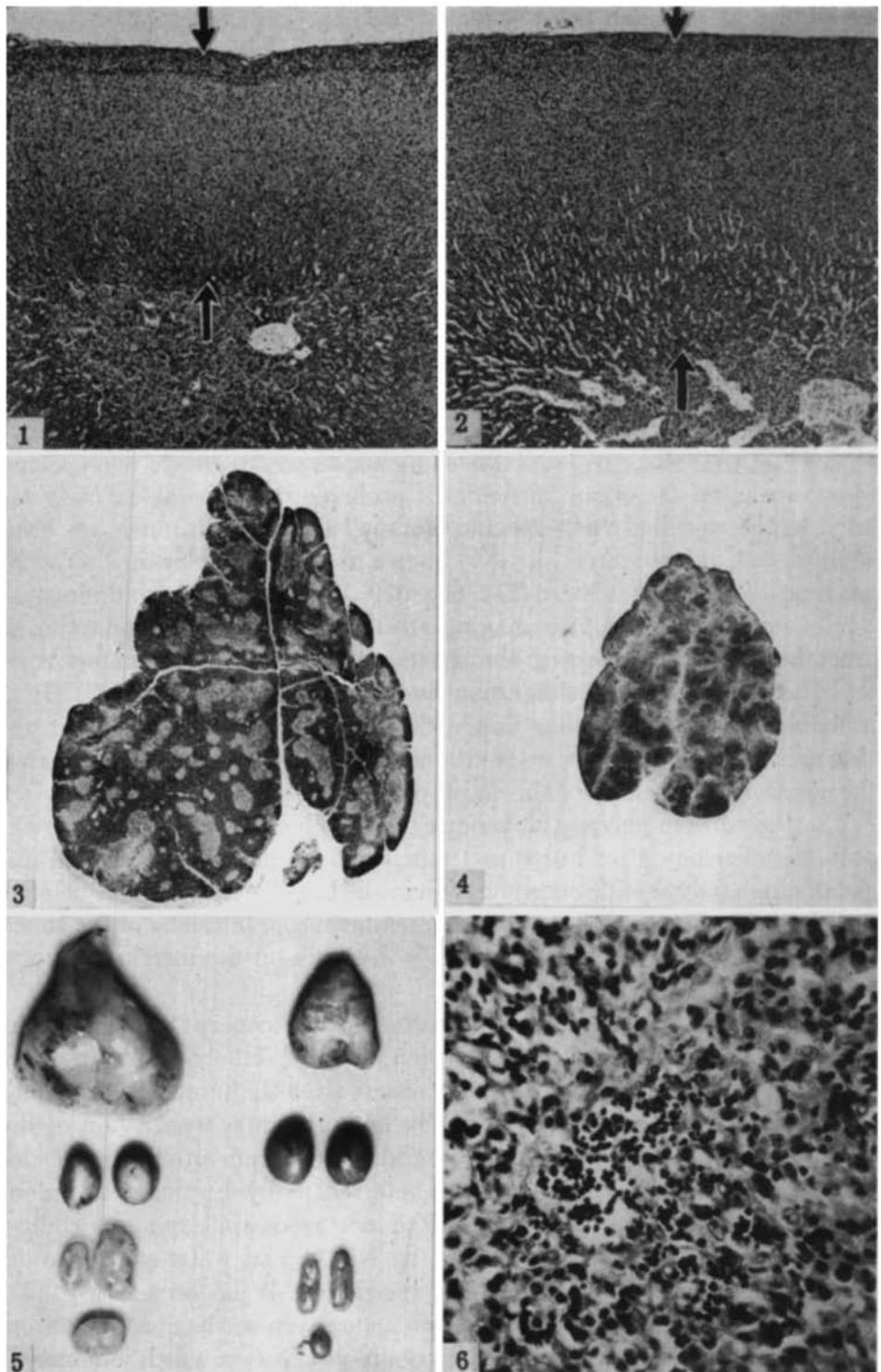


PLATE III. See opposite page for description.

The "Maladie-postopératoire" of Leriche, which has attracted much attention (346, 347), is likewise essentially identical with the shock phase.

The **alarm reaction**, as a clearly defined separate entity, was first described in 1936 (540), when it was realized that in response to a great variety of agents, the organism responds with the same set of symptoms, which—it was concluded—represent "a call to arms" of the body's defense forces. Subsequent work showed that the reaction consists of two more or less distinct phases. The transition between these is not always sharp and some of their manifestations may overlap, but generally speaking, it may be said that the following are characteristic of the first or **shock phase**: tachycardia, decrease in muscular tone and body temperature, formation of gastric and intestinal ulcers, hemoconcentration, anuria, edema formation, decrease in blood chlorides, acidosis, a transitory rise followed by a decrease in blood sugar, leukopenia followed by leukocytosis, and discharge of adrenalin from the adrenal medulla. This phase may last anywhere from

PLATE III. Adrenals and lymphatic organs during the alarm reaction

Fig. 1. Normal adrenal—section through the adrenal cortex of a normal rat. Note width of cortex (delimited by arrows) and clearcut differences between the zona glomerularis and fasciculata.

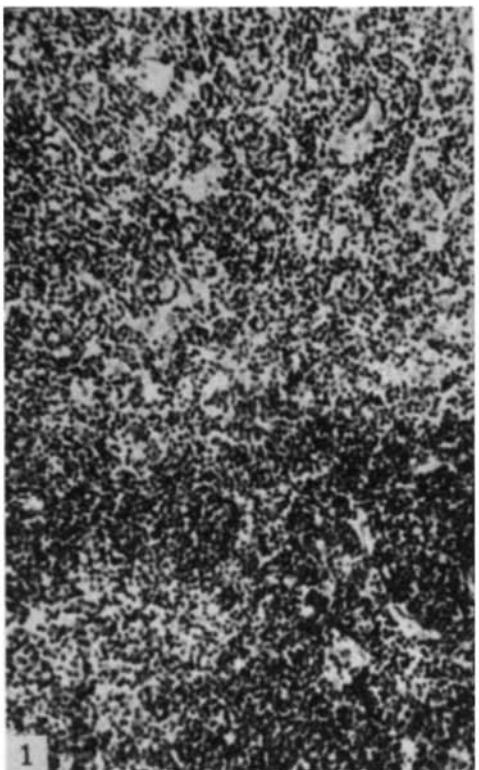
Fig. 2. Adrenal in alarm reaction—section through the adrenal cortex of a rat (similar to that shown in Fig. 1) which received toxic doses of formaldehyde, subcutaneously, during 48 hours. Note greater width of the cortex, whose cells lost their light, lipid ranules. The border between fasciculata and reticularis is no longer distinct.

Fig. 3. Normal thymus—low magnification of a cross-section through the thymus of a normal rat. Note the light medulla and dark cortical areas. The color of the latter is due to the presence of numerous thymocytes.

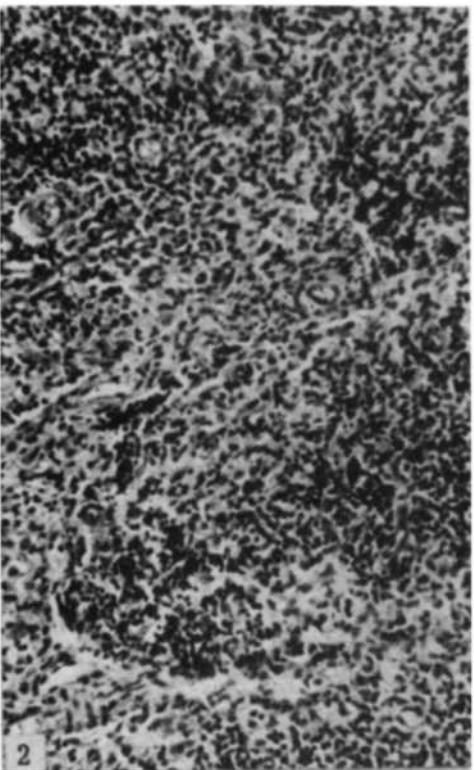
Fig. 4. Thymus in alarm reaction—cross-section through the thymus of a rat (similar to that shown in Fig. 3), which received toxic doses of formaldehyde during 48 hours. Note the "inversion of the thymus pattern," due to depletion of the cortex of thymocytes and migration of thymocyte debris into the medulla.

Fig. 5. Naked eye view of adrenal and lymphatic organs of normal rat and during the alarm reaction—the thymus (top), two adrenals (middle) and three iliac lymph nodes (bottom) of the normal animal (left), whose thymus is shown in Fig. 3, and of the animal during the alarm reaction (right), whose thymus is shown in Fig. 4. Note the marked decrease in thymus and lymph node size as well as the increase in adrenal size, accompanied by loss of cortical lipids (brown macroscopic appearance) in the animal killed during the alarm reaction.

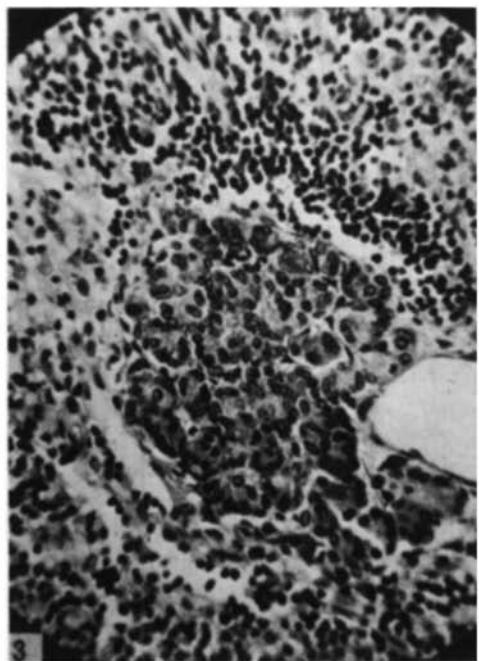
Fig. 6. Thymus in alarm reaction—higher magnification of an area in the medulla of the thymus shown in Fig. 4. Note the well developed epithelioid thymic reticulum with granular, dark thymocyte nuclear debris. These degenerated thymocyte nuclei migrate towards the medulla and are eventually taken up by the thymic lymphatics.



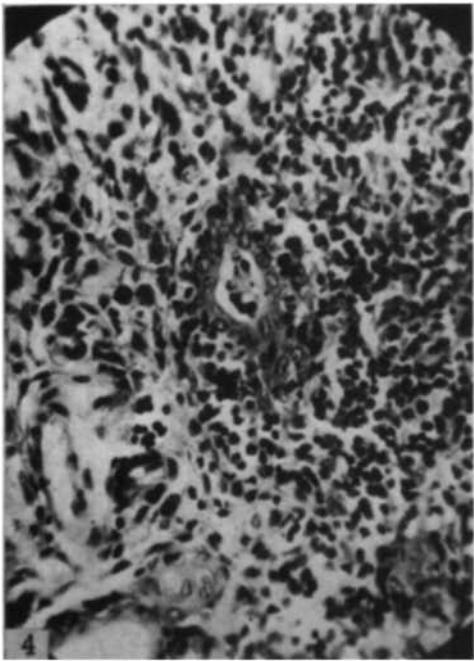
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PLATE IV. See opposite page for description.

a few minutes to 24 hours, depending on the intensity of the damage inflicted, but unless the termination is fatal, it is always followed by the **counter shock phase**. The latter is characterized by: an enlargement of the adrenal cortex whose cells show signs of increased activity, acute involution of the thymus and other lymphatic organs and a reversal of most signs characteristic of the shock phase. Thus, there is blood dilution and increase in blood volume, increase in blood sugar and blood chlorides, alkalo-sis, diuresis, and often a rise in body temperature.

If treatment with the alarming stimulus is continued the counter shock phase gradually merges into the **stage of resistance**, during which most of the morphologic lesions regress and specific resistance (to the eliciting stimulus) reaches its peak.

Finally it was found that even a perfectly adapted organism cannot indefinitely maintain itself in the stage of resistance. If exposure to abnormal conditions continues adaptation wears out, the lesions characteristic of the alarm reaction (involution of lymphatic structures, adrenal enlargement, gastrointestinal ulcers) reappear and the **stage of exhaustion** develops during which further resistance becomes impossible (312, 542, 543, 557, 577). These observations, which will be described in detail later (see *Course of the general adaptation syndrome*), led to the conception that any non-specific noxious agent which causes sudden, general, systemic damage elicits the shock phase of the alarm reaction, probably because it liberates toxic metabolites from the tissues. The theory was proposed that if the damage is not too severe and hence permits survival, the damaging agent (perhaps through a hypothetical toxic metabolite produced under its influence) acts on the anterior lobe of the pituitary and stimulates it to dis-

PLATE IV. Thymus during the alarm reaction

Fig. 1. Normal thymus—medium magnification of an area from the thymus shown in Plate III, Fig. 3. Note the numerous and regular thymocyte nuclei in the cortical region (lower part of field) and the equally regular but less numerous thymocyte nuclei in the medulla (upper part of field).

Fig. 2. Thymus in alarm reaction—medium magnification of an area from the thymus shown in Plate III, Fig. 4. Note proliferation of epithelioid thymic reticulum and granular or dust-like debris of degenerated thymocyte nuclei.

Fig. 3. Thymus in alarm réaction—high magnification of an area from the thymus shown in Fig. 2. Note parathyroid-like cell accumulation within the proliferating epithelioid reticulum of the thymus. Surrounding it, there are pyknotic thymocyte nuclei.

Fig. 4. Thymus in alarm reaction—higher magnification of an area from the thymus shown in Fig. 2. Note the cyst-like, epithelioid formation in the center, which may be a dilated Hassall body. Surrounding it there are pyknotic thymocyte nuclei. Pyknosis of the thymocytes and proliferation of the epithelioid elements in the reticulum are particularly characteristic of the alarm reaction.

charge adrenotropic hormone. This in turn stimulates the adrenal cortex to produce an excess of corticoid hormones, which help to raise the resistance of the body and elicit the characteristic counter-shock phenomena (e.g., involution of the lymphatic organs). All essential tenets of this theory have since been confirmed by a variety of experimental technics, and this original interpretation still represents the most commonly accepted view.

Except for the interpretation of "shock," the clinical importance of the

	Normals	Formal-dehyde	Adre-nalin	Cold	Surgical Shock	Exercise
RATS						
Total white cell count	13,034	25,264	22,700	22,800	25,800	24,600
Polymorphs	35	76	71	78	84	64
Small Lympho.	58	17	24	14	11	31
Large Lympho.	7	7	5	8	5	5
MICE						
Total white cell count	8,832	18,540	20,010	13,300	17,540	16,800
Polymorphs	38	69	68	68	63	58
Small Lympho.	56	25	26	26	31	33
Large Lympho.	6	6	6	6	6	9

PLATE V. Average white cell count in alarm reactions, produced by various stimuli³

Note that both in the rat and in the mouse the total white cell count rises during alarm reactions produced by various damaging agents. This is entirely due to an increase in the number of polymorphonuclear leukocytes and is accompanied by a sharp decrease in the percentage of small lymphocytes. The large lymphocyte count is not significantly affected.

general adaptation syndrome did not become evident, however, until quite recently, when it was shown that, under special experimental conditions, exposure to non-specific damaging agents (e.g., cold) causes hypertension and nephrosclerosis in animals (574). This hypertension and nephrosclerosis was found to be accompanied by an enlargement of the adrenal cortex and the question arose whether the increased production of corticotrophic hormones during the general adaptation syndrome could be the pathogenic agent involved. Further experiments showed that pure synthetic desoxy-corticosterone acetate (592, 605) as well as anterior pituitary extracts (576) are particularly active in eliciting nephrosclerosis and hypertension

³ Harlow, C. M., and H. Selye. The blood picture in the alarm reaction. *Proc. Soc. Exper. Biol. & Med.* 36: 141 (1937).

in animals; these changes are not infrequently accompanied by myocardial lesions and arthritides, similar to those seen in patients with rheumatic fever. As we shall see later, there is still some doubt concerning the intimate mechanism through which non-specific damaging agents and hormonal preparations cause the above-mentioned experimental diseases. The fact remains, however, that all experimental observations are most readily compatible with the view that during the general adaptation syndrome, certain hormones of the anterior pituitary and adrenal cortex are produced in excessive amounts in order to increase resistance; this defensive endocrine response is valuable in as much as it facilitates adaptation to stress (*e.g.*, infections, intoxications, nervous commotions, cold, *etc.*), but the resulting endogenous hormone overdosage may become the cause of certain cardiovascular, renal and joint diseases. Thus developed the concept that many of the most common maladies of man are "**diseases of adaptation**," that is to say, the by-products of abnormal adaptive reactions to stress (577).

IV. THE ALARMING STIMULI

By definition any agent capable of producing an alarm reaction is an "alarming stimulus." It is well to realize, however, that agents causing merely local damage, which require no general adaptive adjustment (*e.g.*, amputation of limbs), are relatively mild alarming stimuli, while exposure to even moderate cold, solar or roentgen radiation, muscular exercise, etc., which evoke intense adaptive responses, produces very severe alarm reaction symptoms. It should be emphasized, furthermore, that the alarm reaction is not necessarily a pathologic phenomenon. In the case of mild alarm reactions there is no "shock" in the ordinary sense of the word. Slight hyperglycemia, tachycardia and leukocytosis may be the only detectable symptoms and there is a continuous series of transitional steps between the definitely physiologic adaptive processes to the stress and strain of everyday life, and the most severe alarm reactions which cause death during the "shock phase."

The systemic effects caused by exposure to a variety of alarming stimuli have frequently been reviewed. Perusal of the relevant publications re-emphasizes the great similarity between the response of the organism to such a variety of alarming stimuli as: **traumatic shock** (52, 87, 339, 347, 435, 536, 542, 545), **obstetric shock** (412, 521, 607, 617, 618), "gravity shock" (112), **muscular exercise** (502, 545, 563, 621), **infectious diseases** (304, 502), **hemorrhage** (191), **nervous shock** (304, 545), **exposure to cold** (488, 502, 608), **temporary blood vessel occlusion** (13, 14, 290-292, 687), **reduced oxygen tension** (146, 231, 629), **burns** (177, 195b, 273), **drugs** (138,

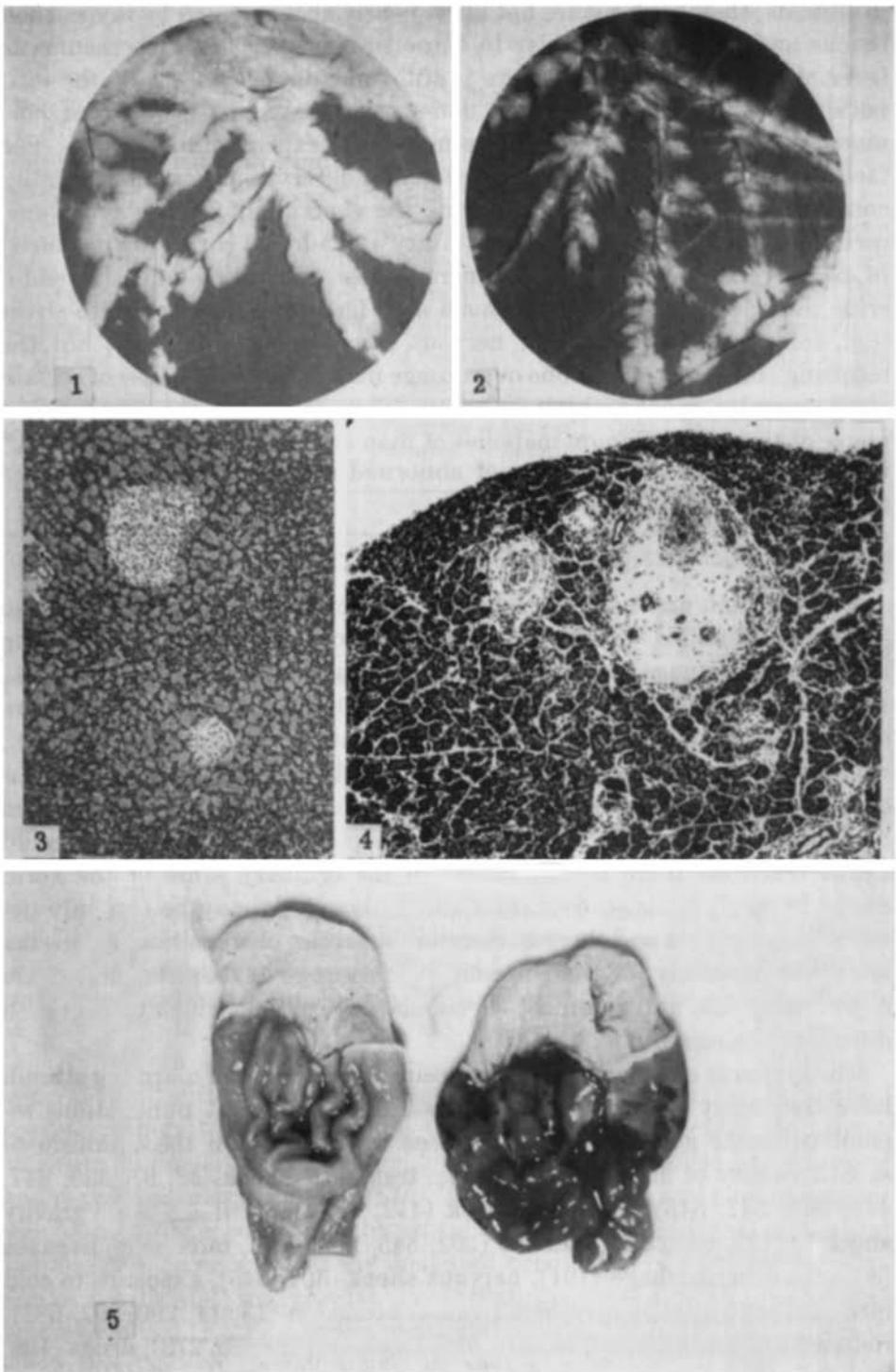


PLATE VI. See opposite page for explanation.

401, 502, 545), bacterial toxins (464), x-rays or radium rays (173, 361, 438, 439, 493, 494, 502, 537) and solar rays (480).

A few alarming stimuli deserve special consideration. Thus, it is noteworthy that **colchicine**, a typical caryoclastic drug, is, according to Leblond and Segal (360), the most active alarming stimulus yet described. It is also of interest that if given in sufficiently high doses, natural and synthetic **folliculoids** ("estrogens") are capable of producing an alarm reaction (473, 566, 596). As will be seen later, **muscular exercise** differs from all other known alarming stimuli in that it causes remarkably little shock and very pronounced counter-shock phenomena. It has been claimed that, in contradistinction to traumatic shock, the blood concentration diminishes in **spinal shock** (443). Henderson (265) remarked that "the only significance which the latter observation bears for the problem of traumatic shock is the additional evidence which it affords that traumatic and spinal shock are two totally distinct conditions." These conclusions were later disproven, since it was found that spinal shock produces all the characteristic signs of the shock phase, including hemoconcentration; the blood dilution referred to above, appears only during the counter-shock phase, so that spinal shock may also be regarded as an alarming stimulus (539). Purely **functional nervous commotions** (rage, fear) may act as strong alarming

PLATE VI. Pancreas and stomach during the general adaptation syndrome

Fig. 1. Normal pancreas—macroscopic view of the pancreas of a normal rat.

Fig. 2. Pancreas in alarm reaction—macroscopic view of the pancreas of a rat similar to that shown in Fig. 1 but having received toxic doses of atropine. Note the distinctly visible white Langerhans' islets along the blood vessels. The pancreatic lobules are atrophic and translucent.

Fig. 3. Pancreas in alarm reaction—section through the pancreas of a rat, in which an alarm reaction was produced by excessive, forced muscular exercise. Note that acinar tissue remains normal only in a halo-like area around the two Langerhans' islets. Here, it contains numerous (eosinophilic) secretory granules. The remaining acinar tissue shows no sign of secretion and is atrophic. (Selye, H. Studies on adaptation. *Endocrinology*. 21: 169 (1937)).

Fig. 4. Pancreas in experimental periarteritis nodosa—the lesion was produced by desoxycorticosterone acetate overdosage in the rat. Note marked hyalinization of the perivascular connective tissue, with round-cell infiltration, presumably, a late stage of periarteritis nodosa in which scar formation has become prominent.

Fig. 5. Normal stomach (left) with proventriculus in the upper and gastric mucosa in the lower part of the field.

Stomach in alarm reaction (right) produced by transsection of the spinal cord, below the 7th vertebra in a rat killed 19 hours after the intervention. Note that the proventriculus remains unchanged, but the gastric mucosa is hyperemic and contains numerous deep ulcers covered with dark blood clots.

stimuli (542) but since the same is true of deep anesthesia, there is no reason to assume that the functional integrity of the nervous system is essential for the development of the alarm reaction (569). Even **fasting** must be regarded as a typical, though rather slowly acting, alarming stimulus, since it elicits such characteristic symptoms as adrenal enlargement, thymus atrophy, hypochloremia, hypoglycemia followed by hyperglycemia, hemoconcentration and gastrointestinal erosions (567).

After what has been said above, it is hardly necessary to insist further upon the non-specific nature of the alarm reaction. It is noteworthy, however, that many lesions which had previously been thought to be due to the specific action of certain stimuli, have now been recognized as manifestations of the resulting alarm reaction. To give but a few characteristic examples, many of the changes produced by **x-rays** (362), **protamine** (655), the so-called "critical period" following **parabiosis** (120), **fever** caused by ultra-high frequency radio emanations (50), **anoxia** (146, 351, 355), **spinal cord transection** (207) and the injection of "**menstrual toxin**" (614), **burns** (232) are no longer considered to be specific lesions but are now interpreted as manifestations of alarm reactions produced by these damaging agents.

Finally, it should be kept in mind that any alarming stimulus—if it is given in a dosage compatible with the maintenance of life and for a sufficiently prolonged period—is capable of eliciting the other two stages of the adaptation syndrome as well. In this connection it is interesting that a certain degree of adaptation can be acquired even to the shock-producing action of mechanical trauma (458, 639).

V. COURSE OF THE GENERAL ADAPTATION SYNDROME

The reader is also referred to the sections on *Definition and terminology* and *History of the general adaptation syndrome*, where he will find brief sketches of the sequence in which the principal manifestations develop during the general adaptation syndrome.

A. Functional changes

Probably the most important functional change, which occurs in the course of the general adaptation syndrome, is the change in **resistance** to damaging agents. It has been found that if an animal is continuously treated with the same, sublethal, daily dose of one alarming stimulus, its resistance to an additional minimum lethal dose of that same stimulus decreases during the shock phase and gradually returns to, or above normal, in the counter-shock phase of the alarm reaction. During the subsequent stage of resistance, a considerable amount of specific adaptation to this same alarming stimulus becomes evident; yet if exposure is continued

over a period of many weeks or months, eventually this acquired adaptation breaks down. Apparently, even a fully inured organism cannot indefinitely maintain its adaptation when continuously exposed to a great amount of stress. It is this observation which led to the concept of "adaptation energy." Apparently, under the influence of continuous adaptive work, the adaptability or "adaptation energy" of the organism is eventually exhausted. The time at which this breakdown of adaptation occurs, is referred to as the "stage of exhaustion."

The non-specific resistance is likewise characteristically influenced by the general adaptation syndrome. That is to say, while an animal acquires resistance to a certain agent, its resistance to other agents is also altered. During the shock phase the non-specific resistance decreases, even more than the specific resistance. In the counter-shock phase, on the other hand, there is an increase in the ability of the animal to withstand various types of stress, not only that to which it had been previously exposed. Yet this "non-specific" or "crossed-resistance," is never as great as the specific resistance to the particular agent with which the alarm reaction had been produced.

There are many observations which can best be interpreted as examples of "crossed-resistance." Thus, the appendicitis-like changes elicited by certain very acute alarming stimuli may be prevented by pretreatment with the same or different agents (310). Similarly the lung edema, normally produced by adrenalin, is prevented in animals in which an alarm reaction had previously been elicited either by adrenalin or by other agents (*e.g.*, exercise, exposure to cold, surgical interventions, or formaldehyde injections) (552, 561). The anaphylactic shock, produced by re-injection of protein into sensitized guinea-pigs, is likewise inhibited during the counter-shock phase of an alarm reaction evoked by a variety of agents (236a, 310, 311). Karády and his associates (309) noted, furthermore, that during the alarm reaction the water output is diminished but if during the course of an alarm reaction produced by any stimulus, the same or any other stimulus is given, the second stimulus not only fails to cause water retention but actually increases urine output. These findings are in good accord with the assumption that two alarm reactions cannot be elicited in rapid succession, and that an alarm reaction produced by one stimulus raises the resistance of the organism both against this stimulus and against any other alarming agent." Several other instances of such an increase in general resistance have been described (374, 551). Certain types of non-specific resistance, which were presumed to result from desensitization to histamine, are now also considered as examples of non-specific tolerance due to the development of an alarm reaction (677).

It should be emphasized, however, that it is extremely difficult in any

one case to prove that "crossed-resistance" is a direct result of the general adaptation syndrome. Undoubtedly, there are other mechanisms which may induce "crossed-resistance." Thus severe injury to the liver from uranium nitrate may lead to the formation of an atypical hepatic epithelium which is resistant to chloroform (390). The "crossed-resistance," resulting from the general adaptation syndrome is, on the other hand, probably due to the excessive production of adrenal corticoid hormones, which are known to raise resistance to stress. With our present day methods, it is rather difficult to ascertain the causative mechanism in many instances of crossed-resistance.

While during, and immediately following the counter-shock phase, non-specific resistance is increased, the reverse is true during the "stage of resistance." In other words, in animals which have acquired a high degree of specific adaptation against a certain damaging agent as a result of prolonged treatment with it, resistance against other agents is greatly decreased; this presumably means that adaptability or "adaptation energy" is consumed for resistance against one agent (312, 313, 404, 406, 409, 556).

A particularly interesting new aspect of non-specific resistance has been discovered recently by Dougherty *et al.* (155). These investigators found that in mice toxic agents (such as benzene and potassium arsenite) liberate antibodies from lymphocytes, but only in the presence of the adrenals. The authors believe that such alarming stimuli cause the pituitary to produce excessive amounts of adrenocorticotropic hormones, which in turn induce the adrenal cortex to elaborate an excess of corticoids. The latter, through their well known ability to induce involution of the lymphatic organs, liberate the antibodies from lymphatic tissue. This hormonal mechanism was further elucidated by experiments indicating that purified adrenocorticotropic hormones or adrenal cortex extracts have the same effect upon lymphocytes and antibodies as alarming stimuli. The observations suggest that the alarm reaction may play an important role even in the serologic type of immunity. It has also been claimed (63a) that "the lymphatic tissue acts as a mesenchymal reserve in the simple and immune, local and generalized reactions by furnishing large numbers of lymphocytes which readily turn into macrophages."

The **blood clotting time** shows a pronounced decrease during the alarm reaction (403) and fibrin formation is markedly accelerated (130). This is in accord with clinical observations, indicating that following surgical operations, the platelet count rises (347) while the clotting time decreases. Perhaps the frequent occurrence of thromboses after operations (224) and burns (273) may be due to these changes. Following x-ray treatment, the clotting time also decreases (466). The "**bleeding time**" is likewise shortened by exposure to damaging agents and although the mechanism of this

change is not clear as yet, increased corticoid production has been considered to be of possible importance (648, 649, 650). According to Ungar (651a) the spleen releases a special hormone-like principle, "splenin," under the influence of corticoids elaborated as a result of increased adrenotropic hormone production during the alarm reaction. This splenin is held responsible for the reduction of bleeding time. After very serious surgical interventions, however, the blood platelets may disintegrate (334).

The **blood pressure** rises for a short period immediately after exposure to alarming stimuli. This is probably due to the emergency secretion of adrenalin and has been observed following many types of interventions. After this transitory rise, a period of pronounced hypotension follows, with an eventual return to or above normal during the counter-shock phase. This response has been studied, especially during surgical shock (347, 531). Conversely, during the stage of resistance there is a tendency to develop hypertension and nephrosclerosis—especially under certain experimental conditions, to be discussed below.

The **absorption** of various substances, which usually do not pass through the intestinal epithelium in significant quantities, may be greatly increased during the alarm reaction, perhaps because of the intestinal erosions. This has been demonstrated for such compounds as adrenalin and histamine (553).

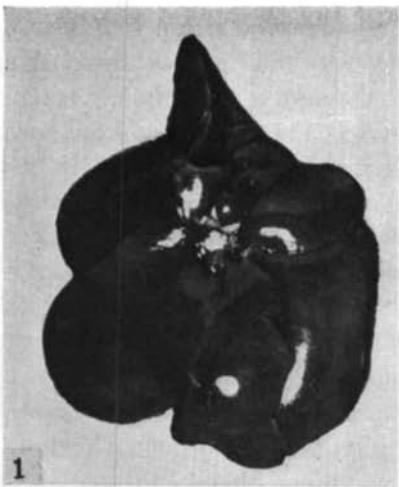
Other functional changes are not very conspicuous except for the tachycardia, sweating, peripheral vasoconstriction and mental stupor characteristic of the shock phase (435) and the total immobility of the pupil occasionally seen after severe trauma (342).

B. Metabolic changes

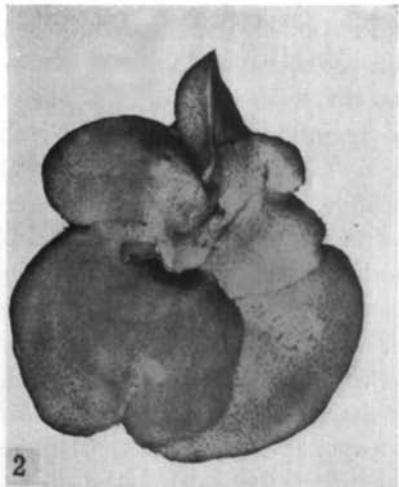
The **body temperature** decreases during the shock phase of the alarm reaction (126) and this is particularly obvious in adrenalectomized animals (554). In man, hypothermia is seen after traumas (435), burns (273) and other shock-producing agents, while fever is probably a counter-shock phenomenon.

The **basal metabolism** is decreased by x-ray treatment, while the respiratory quotient rises (305). Systematic animal experiments, performed specifically with the view of determining the effect of the general adaptation syndrome upon the basal metabolic rate, revealed that a variety of alarming stimuli (drugs, surgical interventions, etc.) cause a decrease during the shock phase but during the counter-shock phase, the basal metabolic rate returns to normal in spite of continued treatment (682).

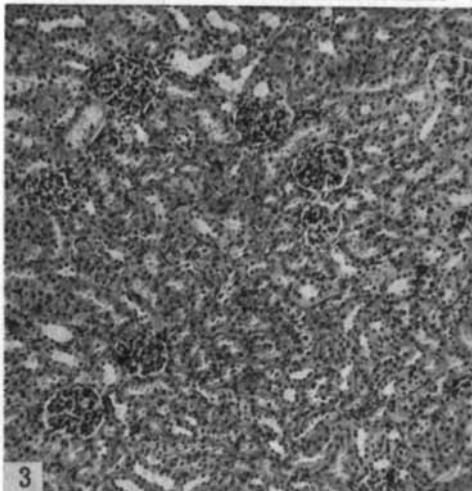
It is of interest in this connection that experiments on sea urchin eggs showed, contrary to expectations, that exposure to damaging agents increases the tissue metabolism; only extremely severe, almost fatal, damage



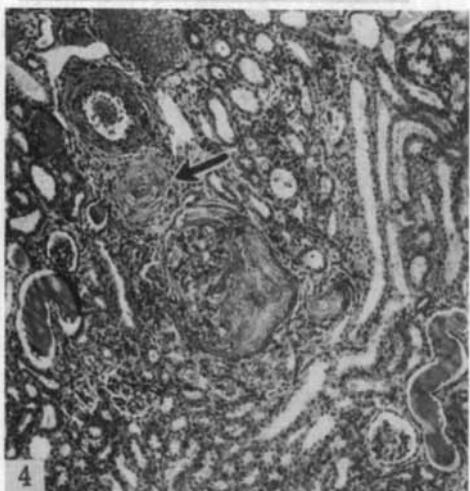
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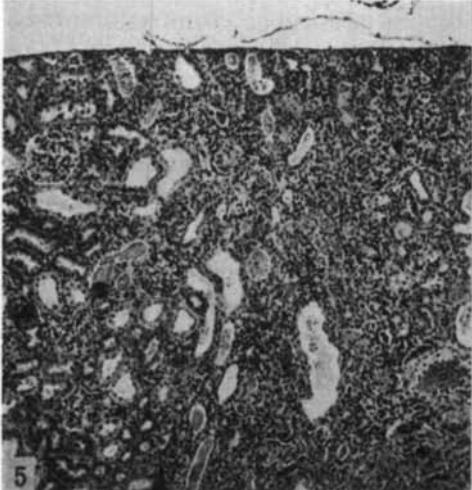
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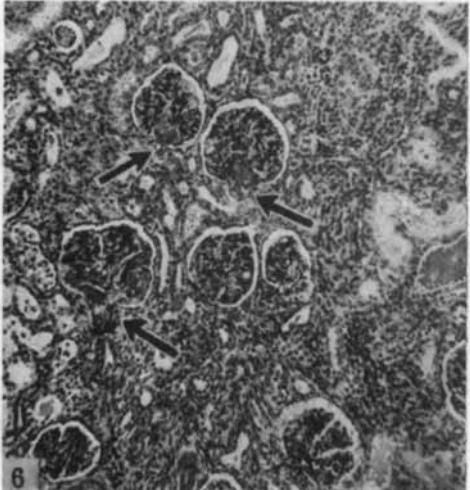
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PLATE VII. See opposite page for explanation.

results in a decrease. On the other hand, if sea urchin eggs are previously treated with one type of a damaging agent and subsequently exposed to another type, this second exposure tends to cause a sharp decline in tissue metabolism (74). This may be another example of the decrease in non-specific resistance at a time when specific resistance became high as a result of pre-treatment.

The general adaptation syndrome exerts a very marked effect upon **carbohydrate metabolism**. The blood sugar rises immediately following exposure to an alarming stimulus ("emergency hyperglycemia"). This rise may still be evident during the peak of the shock phase, especially if the reaction is elicited by abdominal interventions. Later, however, the blood sugar falls, often considerably below the normal level, and especially in fasted animals pronounced hypoglycemia may become evident. With the development of counter-shock phenomena, the blood sugar rises again and may reach hyperglycemic levels even if no food is given (109, 408, 409, 555, 557, 564).

This response is essentially the same, no matter what alarming stimulus is used, but when the stimulus has a specific effect on blood sugar, this is superimposed on that of the alarm reaction. Thus, if the reaction is elicited by muscular exercise, the hyperglycemic peaks are relatively low and the

PLATE VII. Liver and kidney during the general adaptation syndrome

Fig. 1. Normal liver—naked-eye view of the liver of a normal rat.

Fig. 2. Liver in alarm reaction—naked-eye view of the liver in a rat in which an alarm reaction was elicited by exposure to cold. Note the light color of the hepatic parenchyma due to marked fatty infiltration. Formation of fatty livers is a comparatively uncommon accompaniment of the alarm reaction.

Fig. 3. Normal kidney—medium magnification of a section through the kidney of a normal rat.

Fig. 4. Experimental nephrosclerosis produced by desoxycorticosterone acetate overdosage in the rat. Note greatly enlarged glomerulus with transudation of hyaline material into the capsular space and dilated convoluted tubules, many of which contain hyaline casts. A medium sized arteriole (arrow) shows hyaline necrosis of its walls.

Fig. 5. Experimental renal infarct produced by desoxycorticosterone overdosage in the rat. Note sclerosed infarct area (right) and comparatively normal renal tissue (left). (Figs. 3, 4 and 5 taken from Selye and Pentz: Pathogenetical correlations between periarteritis nodosa, renal hypertension and rheumatic lesions. *Canad. M.A.J.*, 49: 264 (1943)).

Fig. 6. Experimental nephrosclerosis produced with desoxycorticosterone acetate in the monkey. Note that the afferent arterioles of several glomeruli are almost completely hyalinized (arrows) and many of the dilated tubules contain hyaline casts.

hypoglycemia is especially pronounced, because much glucose is utilized for the muscular work (563).

In cases of traumatic shock in man, the initial hyperglycemia is very pronounced and prolonged (17, 30, 130, 347, 373, 508, 524, 652) though in some cases the hypoglycemic phase is also well-marked (328). Simultaneously with this rise in blood sugar, the glycogen content of the liver diminishes (343). In men performing very strenuous muscular exercise it was found that (490) a transitory initial rise is followed by a decrease in blood sugar. Similar glycemic responses have been noted during the "acute malignant or toxic syndrome" of infants (189) following burns (273, 625), x-rays (173, 330, 493) and numerous other damaging agents (380, 619).

Masson (404-406) summarizes his investigations, concerning the variations of the blood sugar during the general adaptation syndrome, as follows:

"In rats continuously treated with various damaging agents (exposure to cold, forced muscular exercise, formaldehyde injections), there develops an initial period of hypoglycemia (alarm reaction) followed by a second period of hyperglycemia after a certain degree of adaptation is acquired (stage of resistance). This confirms previous work along these lines indicating that during adaptation to damaging agents certain biochemical changes develop which appear to be entirely independent of the specific nature of the damage and are apparently corollaries of adaptation as such.

"During the alarm reaction, after 24 hours' treatment with the above-mentioned damaging agents, a small and perhaps insignificant decrease in the hypoglycemic action of insulin was noted. This was accompanied by a marked increase in the hyperglycemic action of adrenalin and orally-administered glucose.

"During the stage of resistance, after nine days' of treatment, the hypoglycemic action of insulin and the alimentary hyperglycemic response were considerably increased, while the adrenalin sensitivity showed rather irregular changes.

"Comparison of these findings with the existing data concerning the action of acute and chronic damage on the glycemic response to insulin, adrenalin and glucose, shows that changes in the response to these agents cannot be regarded as specific pharmacological actions without considering the possibility that they may merely be the result of adaptation to the non-specific damaging effect of such agents."

In human beings a mild—and rather inconstant—decrease in glucose tolerance was observed under the influence of chronic intermittent anoxia (80).

In rats temporary application of clamps to the limbs decreases the glycogen deposition in the liver following carbohydrate ingestion, and even insulin fails to improve glycogen storage under these conditions (250a).

In connection with the changes in carbohydrate metabolism, characteristic of the stage of resistance, the following observations are of special interest. Contrary to most other damaging agents, exposure to low atmospheric pressure, increases the glycogen content of the liver and that, even in the fasting animal. A rise in the fasting glycogen levels of the liver may also be obtained by treatment with the so-called "carbohydrate ac-

tive" corticoids. There is good evidence to suggest that adaptation to low atmospheric pressure causes the adrenal cortex to produce an excess of such corticoids which are responsible for the rise in liver glycogen during anoxia. Thus the adrenal cortex hypertrophies under the influence of low atmospheric pressure and adrenalectomized rats show no rise in liver glycogen when kept in a condition of anoxia (181—183, 351). All these observations are in agreement with our concept of adrenal response during the general adaptation syndrome. Low atmospheric pressure depresses sugar utilization and—as does any other alarming agent—stimulates the endogenous production of corticoids. It is not unreasonable to assume, therefore, that under the influence of carbohydrate active corticoids, a large amount of protein is transformed into sugar and that the latter—not being adequately utilized in anoxia—is deposited as glycogen in the liver. The fact that adrenalectomized animals treated with sub-glycotropic amounts of corticoids also show an increase in liver glycogen during anoxia (351), is not incompatible with our view, since the factor of decreased sugar utilization would still be operative in them. Perhaps the exceptionally high blood sugar values seen in thyroidectomized animals during the general adaptation syndrome (562) could be explained on a similar basis by assuming that in the absence of thyroid hormone, sugar utilization is also impeded, yet gluconeogenesis from protein is increased, just as in intact animals, as a result of excess corticoid formation. It is more difficult to understand why the "diabetogenic" action of folliculoids—which is inhibited by adrenalectomy—reappears in corticoid-treated, adrenalectomized animals (295, 299). It is possible, of course (but by no means proven), that the folliculoids could also inhibit sugar utilization.

In connection with what has been said above, concerning the rise in tissue metabolism under the influence of non-specific damaging agents, it is noteworthy that some (424), though not all (411) investigators, believe that during the process of inflammation, protein catabolic processes and gluconeogenesis increase within the area of damage. Severe trauma to one limb results in a pronounced fall in the glucose concentration of the venous blood coming from that limb as compared with the arterial going to it (585); this likewise supports the view that damaged tissues need more than the normal amount of sugar. Hence, increased gluconeogenesis, due to increased formation of carbohydrate active corticoids, is probably a beneficial response to trauma and likely to raise resistance to it. It is not unlikely that the aggravation of diabetes by infections and other types of incidental stress, may be due to a temporary, defensive, overproduction of carbohydrate active corticoids.

The lactic acid content of the blood increases rapidly following x-ray treatment (261, 301, 329) but it has not been definitely established as yet

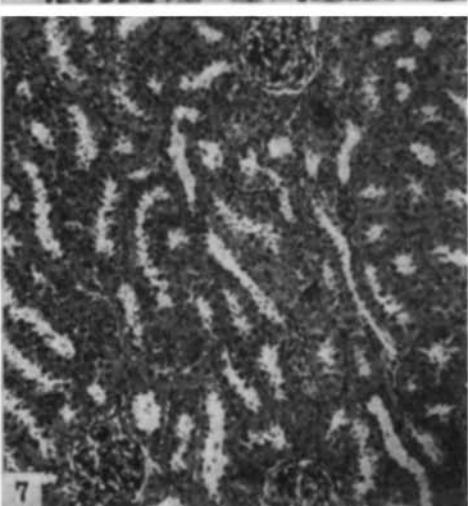
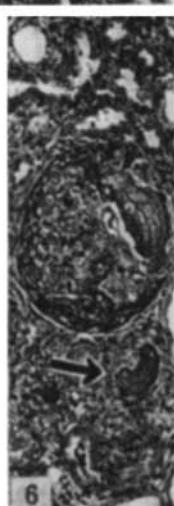
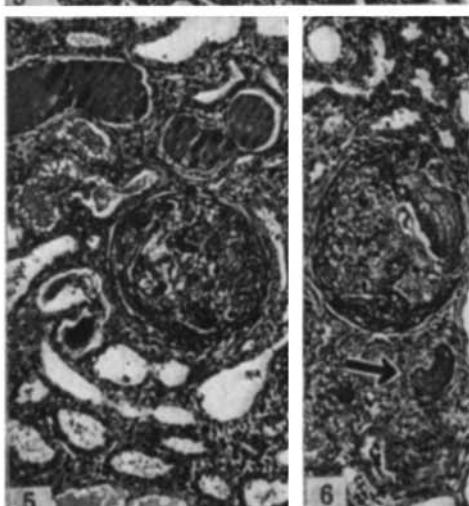
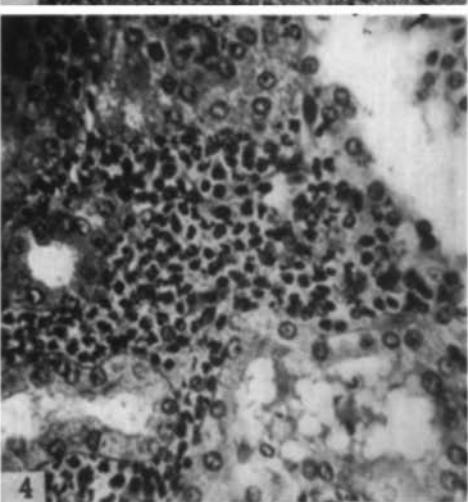
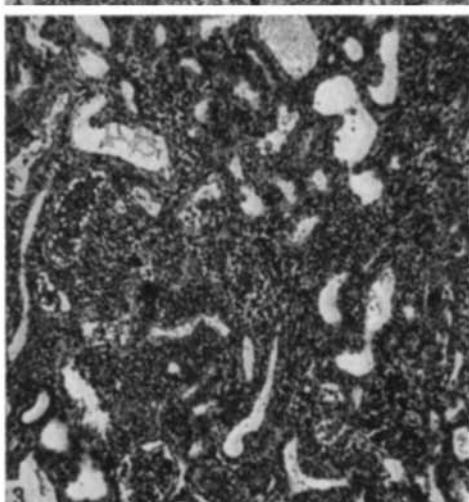
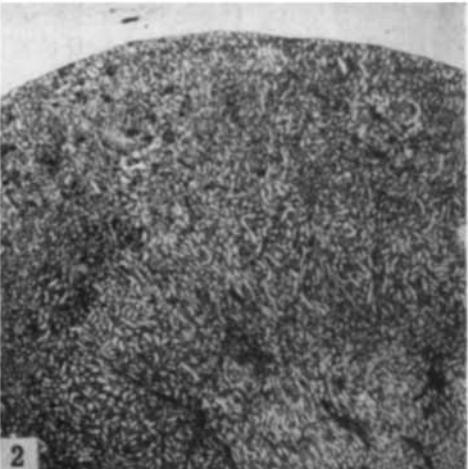
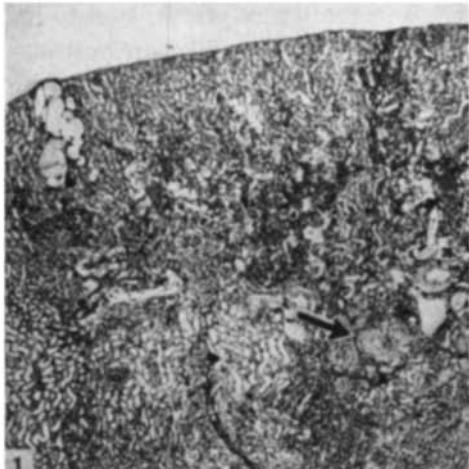


PLATE VIII. See opposite page for description.

whether this is due to an alarm reaction. It is also relevant to mention that the blood sugar, blood pyruvic acid, as well as the blood and muscle lactic acid rise following exposure to mechanical trauma in non-adapted animals, while in animals adapted to traumatic injuries these changes are comparatively mild or absent (451).

The **lipid metabolism** is likewise affected, since marked lipid deposits may suddenly appear in the liver during the course of the alarm reaction (203, 363, 567). Exposure to low oxygen tension also increases the fat content of the liver (100). At the same time, the fat tissue itself involutes so that it appears possible that the fat is merely transferred from the fat cells into the liver. The total blood lipids decrease following such stimuli as exposure to low atmospheric pressure (388).

A decrease in the **cholesterol** content of the blood has been noticed after strenuous exercise (490), x-ray treatment (308, 328, 413, 466, 493, 506), in "toxic infants" (189), following massive hemorrhages (71), traumatic shock (33), etc. However, the serum cholesterol may remain normal even

PLATE VIII. Hormonally produced renal lesion similar to those occurring in diseases of adaptation

Fig. 1. Experimental nephrosclerosis produced with desoxycorticosterone acetate in the rat. Note numerous distended tubules, some filled with hyaline casts. The arrow points to an enlarged hyalinized glomerulus.

Fig. 2. Prevention of nephrosclerosis by NH₄Cl—The rat whose kidney is shown here, was treated with desoxycorticosterone acetate in the same manner as that whose kidney is represented in Fig. 1, however, it was simultaneously given NH₄Cl solution to drink. Note absence of pathologic changes. (Selye, Hall and Rowley: Prevention of experimental nephrosclerosis with ammonium chloride. *Lancet*. 248: 301 (1945)).

Fig. 3. Experimental interstitial nephritis produced with lyophilized anterior pituitary substance in a rat receiving a high NaCl intake. Note leukocytes between the tubules.

Fig. 4. Experimental interstitial nephritis—higher power view of inflammatory cells between tubules of the kidney shown in Fig. 3.

Fig. 5. Experimental nephrosclerosis produced with lyophilized anterior pituitary material and high NaCl intake in the rat. Note greatly dilated tubules, some with casts and transudation of hyaline material into the capsular space.

Fig. 6. Experimental nephrosclerosis—another area of the kidney shown in Fig. 5. Note hyalinization of afferent arteriole, near its junction with glomerulus (arrow), enormously enlarged glomerulus with transudation of hyaline material into the capsular space.

Fig. 7. Prevention of experimental nephrosclerosis with NH₄Cl—The rat whose kidney is shown here, was treated in the same manner as that whose kidney is represented in Figs. 3-6, however, it was simultaneously given NH₄Cl solution to drink. Compare size of glomeruli and note that pathologic changes are completely prevented. (Figs. 3-7 taken from Hall and Selye: Prevention of the nephrosclerosis usually induced by anterior pituitary extract. *Rev. Canad. de Biol.* 4: 197 (1945)).

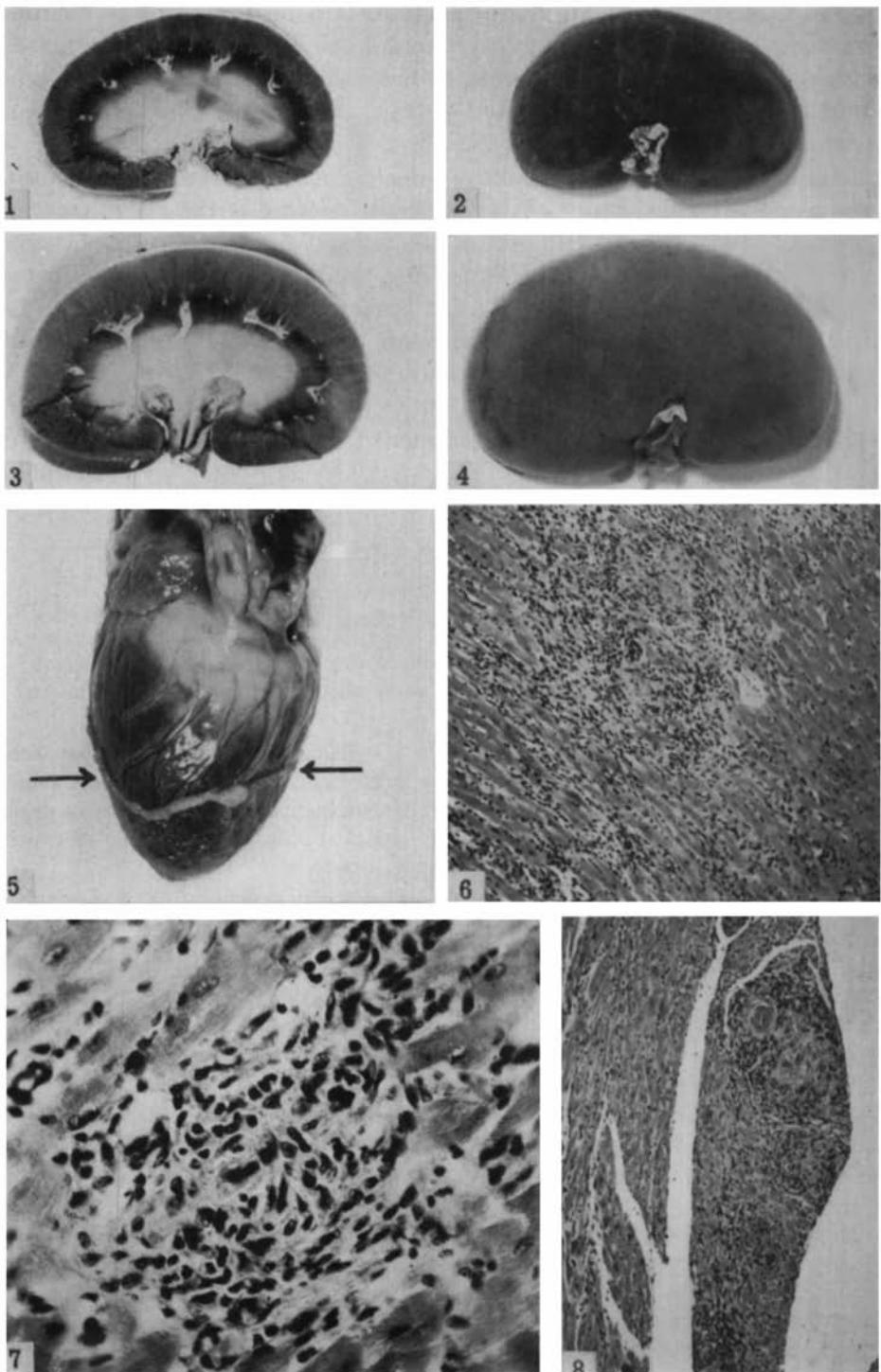


PLATE IX. See opposite page for description.

after exposure to alarming agents sufficiently severe to deplete the adrenal cholesterol stores (366, 522d).

The **ketone bodies** of the blood increase following x-ray treatment (685), excessive muscular exercise (690) and numerous other alarming stimuli.

Nitrogen metabolism is severely deranged during the alarm reaction. In the rat there is a pronounced increase in blood N.P.N. which reaches a peak during the later part of the shock phase (527). This may explain the increase in total N.P.N. and uric acid which was noted in man as a result of excessive muscular exercise (490). In burns (173), x-ray shock (493) and surgical shock (451) the N.P.N. is likewise increased (163, 520). The same is true of the blood urea (347, 352), the blood amino acids (46, 332a) and

PLATE IX. Hormonally produced renal and cardiac lesions similar to those occurring in diseases of adaptation

Fig. 1. Normal kidney—cross section through normal kidney of a female dog (final body weight 19 lbs.) which acted as a control for Figs. 3 and 4.

Fig. 2. Normal kidney—surface view of kidney shown in Fig. 1.

Fig. 3. Experimental nephrosclerosis—cross section through kidney of a female dog (final body weight 19 lbs.) treated with anterior lobe extract, desoxycorticosterone acetate and thyroxin for 10 weeks. As explained in the text, thyroxin augments the nephrotoxic action of both anterior lobe and corticoid preparations. Note great increase in renal size, mainly due to cortical enlargement. The organ is reminiscent of the "large white kidney" of human pathology.

Fig. 4. Experimental nephrosclerosis—surface of the kidney shown in Fig. 3. Note "flea bitten" appearance due to numerous glomerular hemorrhages. These were histologically confirmed and microscopic examination also showed signs of typical nephrosclerosis.

Fig. 5. Experimental fibrinous pericarditis produced with desoxycorticosterone acetate and NaCl treatment in the dog by giving daily subcutaneous injections of 20 mg. of desoxycorticosterone acetate for seven weeks and then 2% NaCl solution to drink *ad lib.* The animal died within 48 hours of the NaCl administration, with an enormous amount (36 cc.) of pericardial transudate containing excessive quantities of K, Na, Cl and fibrin. The fibrinous coating was rolled down towards the apex (arrow).

Fig. 6. Myocarditic (Aschoff?) nodule produced by desoxycorticosterone overdosage in the rat. Note granuloma tissue between otherwise normal myocardial fibers.

Fig. 7. Myocarditic (Aschoff?) nodule—high magnification of a nodule similar to that shown in Fig. 6. Note several slightly basophilic, polymorphonuclear giant cells (Aschoff cells?) with characteristic fringy cell borders.

Fig. 8. Myocarditic nodules (Aschoff?) in subendocardial layer of a papillary muscle—produced in the rat by treatment with desoxycorticosterone acetate and NaCl. Note characteristic excentric location of the (partially hyalinized) blood vessel in this nodule. The center of the nodule consists of hyalinized material, in which several giant cells are detectable. (Figs. 6-8, after Selye and Pentz: Pathogenetical correlations between periarteritis nodosa, renal hypertension and rheumatic lesions. *Canad. M. A. J.* 49: 264 (1943)).

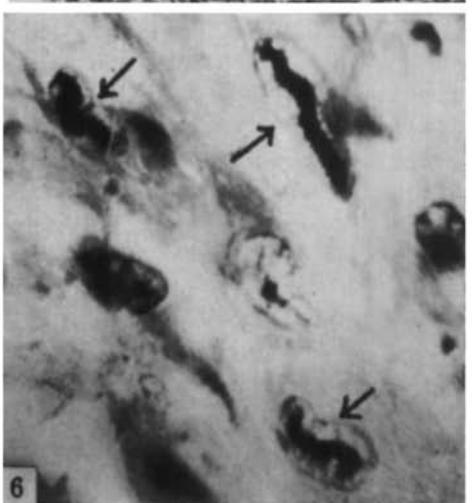
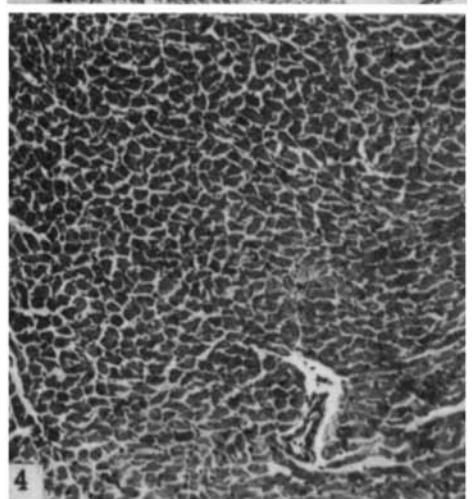
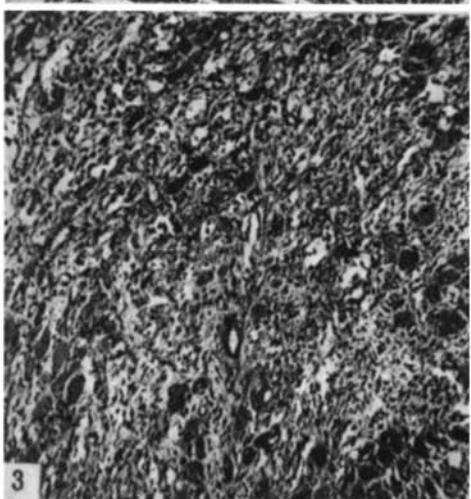
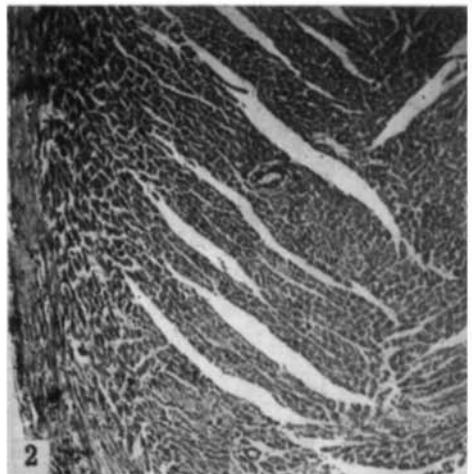
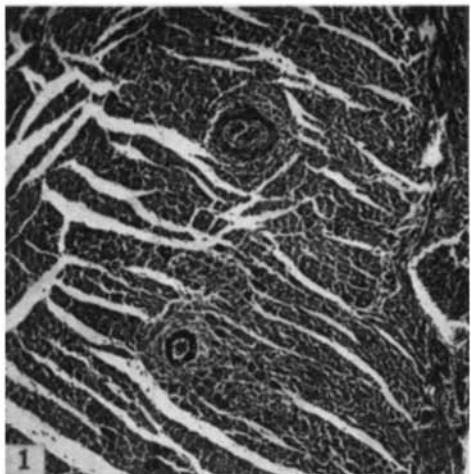


PLATE X. See opposite page for description.

the blood polypeptides (117, 347, 352, 379). The nitrogen balance becomes markedly negative during the alarm reaction (12, 78, 232). Most probably all these changes are due to the marked catabolic effect of the shock phase.

The urinary elimination of creatine is greatly augmented during an alarm reaction produced by cold, exercise, or formaldehyde, but continued treatment with these same agents has no such effect after the symptoms of the alarm reaction vanish. From this J. S. L. Browne and his associates (79) concluded that the creatinuria observed in many acute conditions is probably due to the resulting alarm reaction.

The globulin content of the blood increases at the expense of its albumin content after burns (273), traumatic shock (347), etc. It is rather probable that a significant fraction of the protein catabolites, which appear in the blood during the alarm reaction, originates in the lymphatic organs as a result of the lymph tissue-destroying property of excess corticoids (573). This was made especially probable for the γ -globulin fraction (155, 156).

The protein catabolic reaction seen during the first phase of the general adaptation syndrome may also have some bearing on the so-called "Donaggio inhibition." The latter is probably due to sudden increase in blood

PLATE X. Hormonally produced vascular lesions similar to those occurring during diseases of adaptation

Fig. 1. Periarteritis nodosa of the cardiac vessels produced with lyophilized anterior pituitary material in a rat receiving 1% NaCl to drink. Note dark ring of subintimal hyalinization in one small artery (lower part of field) and inflammatory infiltration of the walls in the other (upper part of field).

Fig. 2. Prevention of myocardial periarteritis nodosa by NH₄Cl—The animal whose cardiac muscle is shown in this picture, received the same treatment as was given to the animal illustrated in Fig. 1, but in addition, 1% NH₄Cl was added to the drinking water. Note complete absence of pathologic changes.

Fig. 3. Experimental myocarditis produced by lyophilized anterior pituitary material in a rat receiving 1% NaCl to drink. Note almost complete degeneration of myocardial fibers and their replacement by a fibrous granuloma tissue. The area probably corresponds to one of the many myocardial infarcts which develop under such experimental conditions, due to periarteritis nodosa of the cardiac vessels.

Fig. 4. Prevention of experimental myocardial lesions by NH₄Cl—The rat whose myocardium is shown here received the same treatment as that illustrated in Fig. 3, but in addition, 1% NH₄Cl was added to the drinking water. Note complete absence of pathologic changes.

Fig. 5. "Caterpillar cells" formed in a myocardial nodule of a rat treated with lophilized anterior pituitary material and receiving 1% NaCl to drink (indicated by arrows).

Fig. 6. "Caterpillar cells"—oil immersion view of an area of Fig. 5. Note two typical "caterpillar cells" with their nuclear chromatin arranged in the characteristic fashion (indicated by arrows).

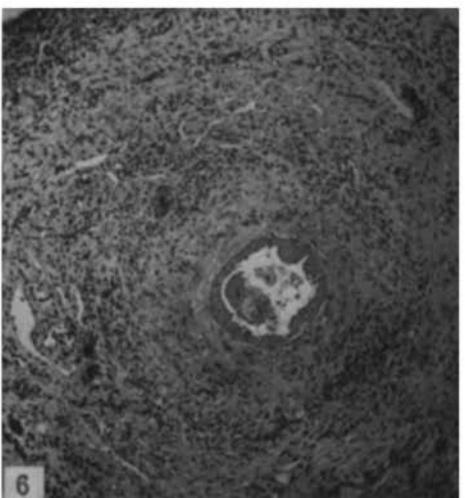
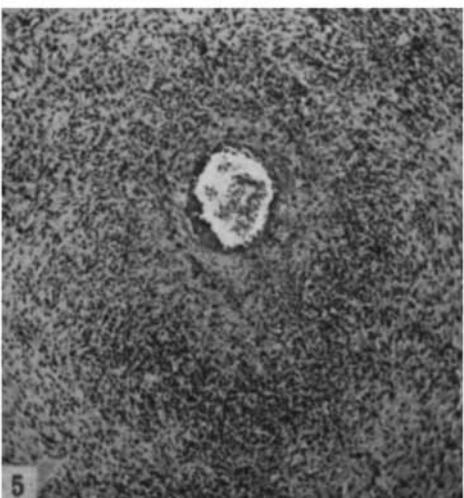
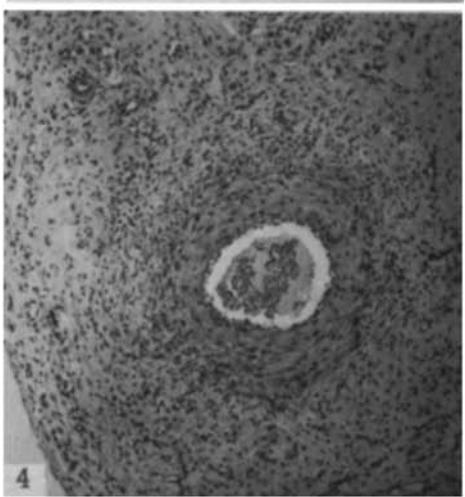
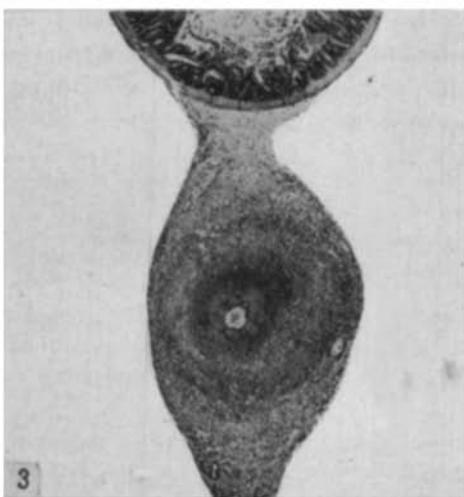
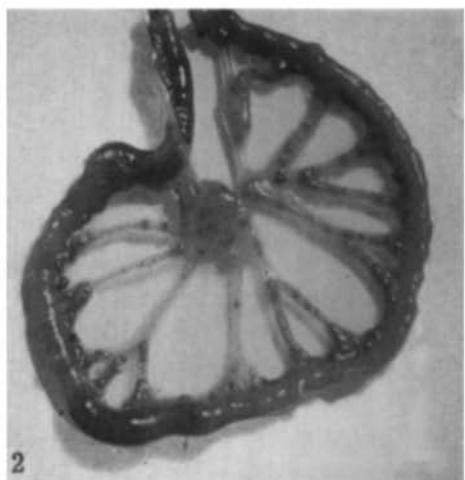
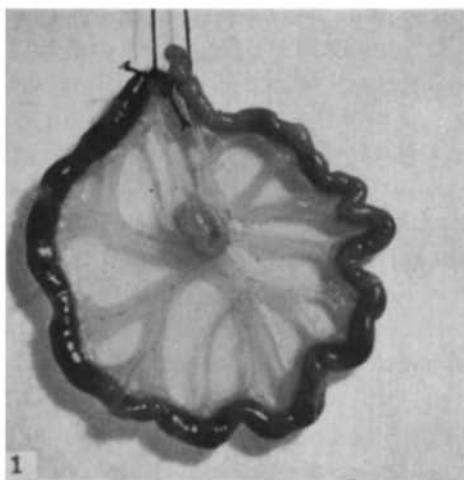


PLATE XI. See opposite page for description.

polypeptides and has been considered an index of non-specific damage, following various types of acute diseases and muscular fatigue; hence, it is sometimes also referred to as a fatigue reaction or "Ermüdungsreaktion" (228).

A pronounced decrease in blood **chlorides** is one of the most constant changes of the shock phase. It gives way to marked hyperchloremia during the counter-shock phase (408, 555, 557). The chloride concentration decreases, particularly in the red cells and less markedly in the plasma (312, 313). The excretion of chlorides is diminished during the alarm reaction (79) so that the fall in blood chlorides cannot be attributed to a loss through the urine. This receives further support through the observation that bilateral nephrectomy fails to prevent this hypochloremia. The chloride content of the tissues also decreases, with the exception of the muscles and the brain, in which it usually increases considerably above the normal level (569). This increase does not account, however, for the decrease in blood chlorides and probably at least a considerable part of them, as well as the organ chlorides, are excreted into the pleural and peri-

PLATE XI. Hormonally produced vascular lesions similar to those occurring in diseases of adaptation

Fig. 1. Normal mesenteric vessels—macroscopic view of a normal small intestinal loop of a rat. Note thin and regular mesenteric vessels.

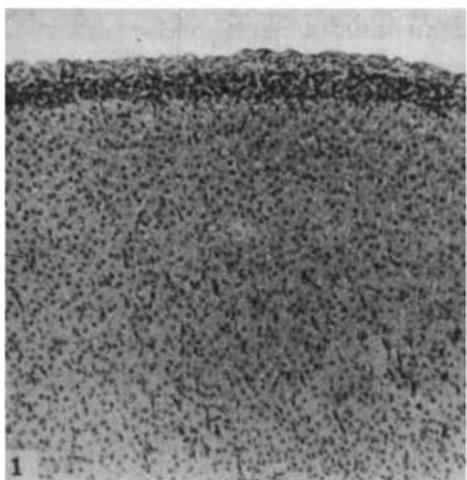
Fig. 2. Mesenteric periarteritis nodosa—macroscopic view of a small intestinal loop of a rat chronically treated with desoxycorticosterone acetate. Note numerous bead-like, periarteritis nodosa nodules along the mesenteric vessels.

Fig. 3. Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat. Low magnification of a section through mesenteric insertion on intestinal wall. Note thickening and infiltration of the transversely sectioned mesenteric arteries.

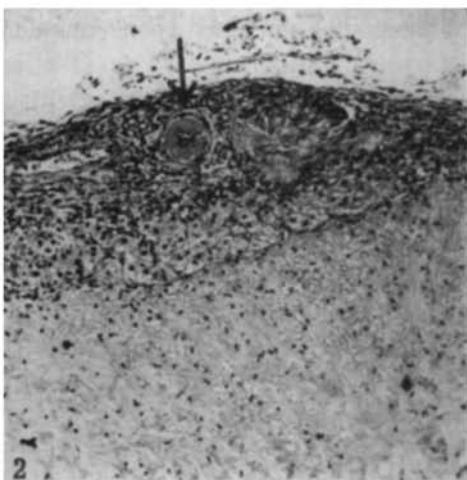
Fig. 4. Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat. Transverse section through mesenteric artery, showing first stages of periarteritis nodosa. Medium magnification. Note deposition of a thin layer of hyaline material, underneath the somewhat irregular endothelial surface. The structure of the muscular coat is still well-preserved but the adventitia shows some inflammatory infiltration.

Fig. 5. Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat. Somewhat more advanced stage of the same process as shown in Fig. 4. Note almost complete destruction of the endothelium with deposition of a fairly thick layer of hyalinized fibrin-like material on the vascular wall. The structure of the vessel is almost unrecognizable owing to heavy infiltration with leukocytes, many of which are eosinophilic. Some giant cells are also detectable. (Same magnification as Fig. 4.)

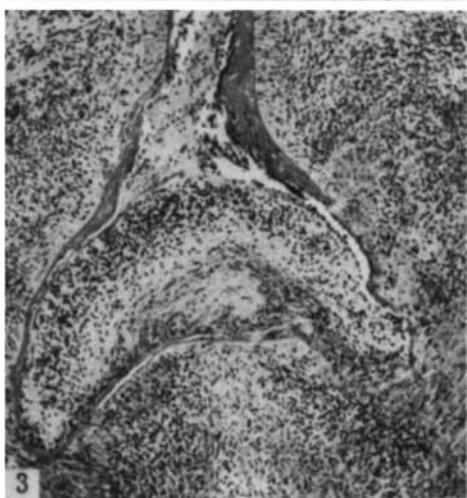
Fig. 6. Mesenteric periarteritis nodosa produced by desoxycorticosterone overdosage in the rat. Transverse section through mesenteric artery, showing final stages of periarteritis nodosa. Note thick layer of hyalinized fibrin, lining the vascular lumen. The vessel walls have undergone partial necrosis and hence, appear somewhat homogeneous. (Same magnification as Figs. 4 and 5.)



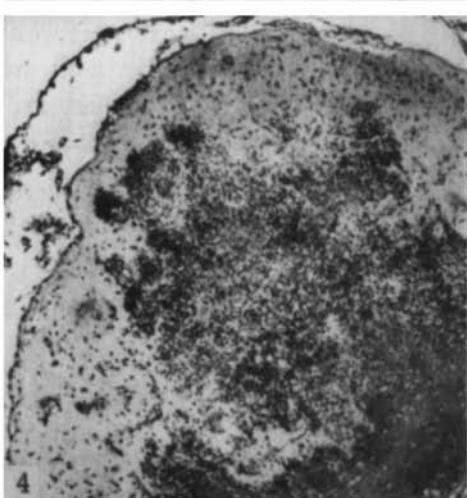
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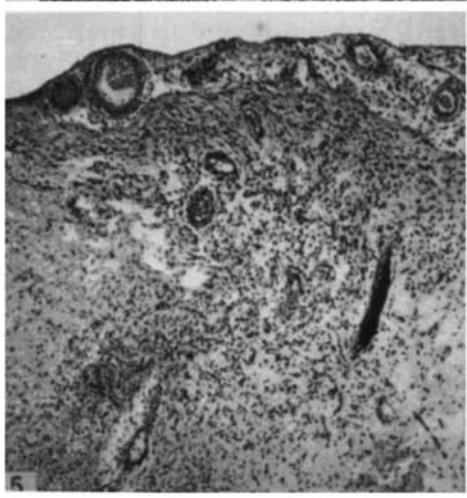
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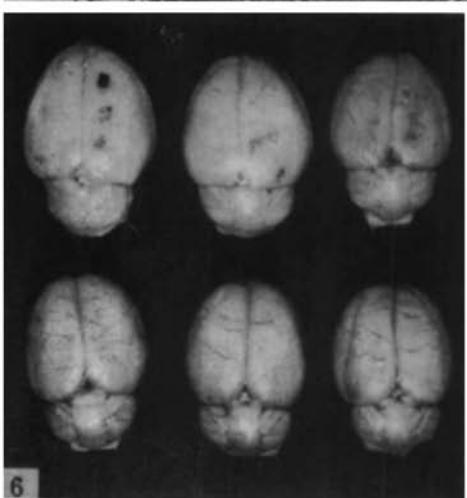
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PLATE XII. See opposite page for description.

toneal transudates or, if the reaction is produced by trauma, into the traumatized area. This view is in accord with the observation (365) that traumatized muscle tissue is especially rich in chlorides. The high chloride concentration in the subcutaneous edema of the injection region in animals, in which an alarm reaction is produced by formalin, is also in agreement with this concept (539). The hypochloremia observed in cases of surgical shock (96, 345, 347, 352, 504), ileus (652), "toxic infants" (189), burns (273) and other types of shock in man, may readily be explained on the same basis. In this respect, excessive muscular exercise again occupies a special position, inasmuch as, contrary to most other agents, it causes an almost immediate hyperchloremia (557, 563). Perhaps this is due to the fact that counter-shock phenomena are especially readily elicited by this very physiologic type of an alarming stimulus. More recently it was found that "gravity shock" (seen in rabbits suspended by their ears)

PLATE XII. Hormonally produced vascular lesions similar to those occurring in diseases of adaptation

Fig. 1. Normal adrenal—suprarenal cortex of a rat (control for Fig. 2).

Fig. 2. Periarteritis nodosa of the adrenal vessels produced by chronic overdosage with an alkaline anterior lobe extract and administration of 1% NaCl instead of drinking water. Note the subintimal hyalinization of the arteriole in the capsule (arrow) and the inflammatory infiltration around it. The adrenal cortex is almost completely necrotic, due to interference with its blood supply. Only a thin layer of subcapsular cells remain. It will be recalled that unlike desoxycorticosterone, anterior lobe extracts do not tend to produce widespread periarteritis nodosa but usually affect only the vessels of the heart and adrenal cortex.

Fig. 3. Thrombus formed at the bifurcation of a mesenteric artery, following desoxycorticosterone overdosage in the rat. Note thick layer of fibrin which lines the vessel wall and a U-shaped thrombus which almost completely occludes the lumen. The thrombus consists mainly of fibrin, platelets and leukocytes (this, as well as Figs. 1-6 of Plate IX, after Selye and Pentz: Pathogenetical correlations between periarteritis nodosa, renal hypertension and rheumatic lesions. *Canad. M. A. J.* 49: 264 (1943)).

Fig. 4. Brain hemorrhages secondary to periarteritis nodosa, following desoxycorticosterone overdosage in the rat. Note extensive hemorrhage underneath the cerebral cortex.

Fig. 5. Periarteritis nodosa of the brain vessels produced by chronic desoxycorticosterone overdosage in the rat. Section through the brain, showing hyalinization of some arterioles on the surface of the cerebral hemisphere. Note also tissue edema and perivascular round cell infiltration.

Fig. 6. Brain hemorrhages produced by periarteritis nodosa of the cerebral vessels, following desoxycorticosterone overdosage in the rat. Macroscopic view of three brains with hemorrhagic patches, due to periarteritis nodosa of the surface vessels (top row) and three normal brains of untreated control rats (bottom row). Note the rather characteristic arrangement of the hemorrhages along a sagittal, paramedian line.

causes no change, or a slight fall, in plasma chlorides accompanied by an increase in red cell chlorides (15).

It appears very probable that the fall in blood chlorides is accompanied by a corresponding decrease in blood **sodium**, especially since such a decrease has been repeatedly observed in cases of shock (273). Anoxia may cause a temporary rise in the urinary elimination of sodium, followed by a compensatory fall during the counter-shock phase (83a).

The **potassium** concentration of the blood rises during the shock phase in burns (273), ileus (302), exposure to cold (386), traumatic shock (108, 451), muscular exercise (195), acute infectious diseases (455, 622), nervous stimulation (223), etc. After trauma there may also be a loss of tissue potassium (108) and an increased excretion of potassium through the urine (119). Anoxia also tends to raise urinary potassium excretion and this is followed by potassium retention in the counter-shock phase (83a). It is most probable that the hyperpotassemia, which according to Kendall and Ingle (325) is one of the most important changes in the alarm reaction, is due to the discharge of potassium from the tissues into the blood. In vitro, studies indicate that tissue slices also lose potassium under the influence of various "stimulating" or "damaging agents" (75).

The **phosphate** content of the blood is increased during the shock phase and later tends to decrease, even to a point below normal (410). The hyperphosphatemia of the shock phase may be due to the liberation of phosphorus from catabolized tissues (108). The phosphatemic curve, as described above, agrees with that observed following massive hemorrhages (457), asphyxia (456), traumatic shock (451), "gravity shock" (15), deep anesthesia (397), muscular exercise (247, 481), and histamine injections (97). During recovery from shock there is phosphaturia (15).

The **blood volume** is greatly decreased in animals during the shock phase but rises above normal during the counter-shock phase (312, 313). While the decrease in blood volume during shock caused by trauma (62, 269, 347, 435, 436), x-rays (173, 438), burns (348), etc., is well known to clinicians, the secondary blood dilution of the counter-shock phase has not as yet been adequately studied in man.

Diuresis is diminished in the shock phase but rises above normal during or immediately after the counter-shock phase (79, 83a, 285, 286, 309).

The **blood pH** has not been studied as yet with the view of determining its variations throughout the adaptation syndrome but clinical evidence at hand indicates that in surgical shock (91, 115, 263-265, 347), burns (273), gas gangrene (695), "gravity shock" (15), deep anesthesia (136) and other conditions capable of eliciting the shock phase, marked acidosis occurs. The observation that the acute acidosis produced by radium and x-ray treatment or peptone injections is followed by an alkaline wave

(248, 276, 338, 340, 341, 493, 658) makes it very likely, however, that the acidosis of the shock phase is reversed during the counter-shock phase.

Enzymatic activities probably play a prominent role in the catabolic phenomena which occur during the alarm reaction (651a). Thus it was found that following a burn or trauma to a dog's extremity, the peptidase activity rises abruptly in the lymph draining from the affected area. In the calf and rat an increase in this enzymatic activity of the serum has consistently been found following a burn (695a). The view has repeatedly been expressed that injured tissue produces proteolytic enzymes (424a, 430a) and studies on fibrinolytic enzymes lead to the view "that pathological syndromes associated with cellular injury, from any cause whatsoever, might be the effect of the release of toxic by-products of proteolysis from the action of this enzyme (616a)."

The effects of the general adaptation syndrome on **hormone metabolism** will be discussed in the section dealing with the endocrine theory of the syndrome.

C. Pathologic anatomy

One of the most important morphologic changes in the alarm reaction is the enlargement of the **adrenal cortex**. Its individual cells hypertrophy and discharge their lipid granules. This has been considered a sign of increased endocrine activity. True hyperplasia is usually less pronounced. These changes take several hours to develop and, as a rule, do not reach their peak until counter-shock phenomena are evident (545). The adrenal changes, and especially the rather characteristic lipid distribution pattern in the cortex during the three stages of the adaptation syndrome, have repeatedly been described (129, 131, 152, 698). The cholesterol content of the adrenal cortex rapidly decreases under the influence of alarming stimuli (366, 522d). It appears that the cortical hypertrophy and lipid loss of the alarm reaction subside quite regularly during the stage of resistance but reappear during the stage of exhaustion.

The chromaffin granules of the medulla are discharged within a few minutes after exposure to an "alarming stimulus," and the medullary cells become vacuolized. In certain extremely acute cases, adrenal hemorrhages and bilateral necrosis of the medulla were observed. This is noteworthy because it may explain why the adrenal medulla is so often predisposed to become the site of blood-borne infections (545). It will be seen later that in addition to these morphologic changes there is a great deal of other evidence showing that the adrenals play an important part during the alarm reaction and secrete adrenalin immediately after exposure, even before the shock phase is evident, while corticoid secretion is a counter-shock phenomenon.

The adrenal changes are essentially the same, irrespective of the alarming stimulus used, and have been observed in the rat (541, 543, 545), in the rabbit (402) and in the guinea-pig (203). Previously, these lesions have often been described as the specific result of burns (195b, 273), infectious diseases (9, 29, 141, 398, 448, 478, 518, 635, 636), intoxication with various drugs (147, 394, 523, 678), bacterial toxins (464), x-rays (214, 282, 482), ultra-violet rays (237), etc. Now it is increasingly recognized, however, that the cortical hypertrophy occasioned by the alarm reaction is responsi-

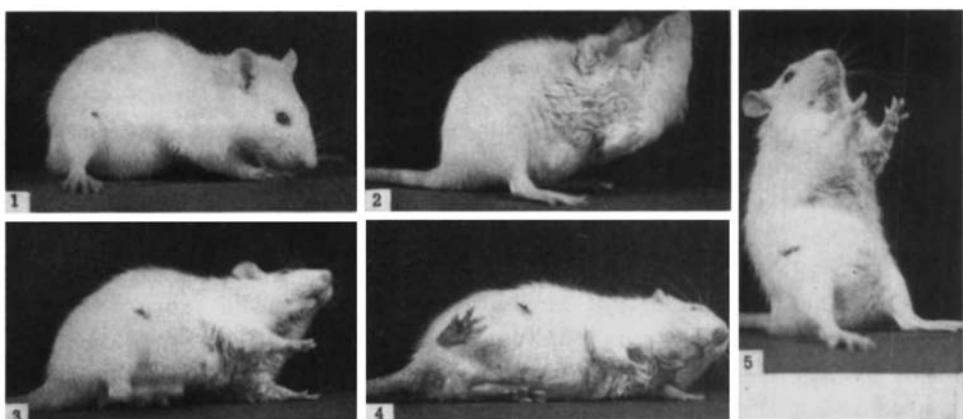


PLATE XIII. Motor disturbances due to periarteritis nodosa of the brain

Fig. 1. Desoxycorticosterone treated rat with periarteritis nodosa of the brain, shown during rest between two spells.

Figs. 2 and 3. Same rat shown during successive stages of a typical clonic spell with rotation of the shoulder girdle and head towards the left.

Fig. 4. Final stage of the same attack, with animal rolling over completely to the left.

Fig. 5. Another similarly treated rat in which the nature of the clonus is such that the entire front part of the body is thrown back during each attack. These spells are characteristic of cerebral hemorrhages due to experimental periarteritis nodosa of the brain. (Figs. 4, 5 and 6 of Plate XII and all Figs. of this plate, after Selye, Beland and Sylvester (581)).

ble for the adrenal enlargement which ensues after exposure to such diverse stimuli as forced muscular exercise (294), cold (152), fever caused by ultra-high frequency radio emanations (50), anoxia (131, 146), treatment with various drugs (152), x-rays (362), transection of the spinal cord (207), toxic tissue extracts (441) and other damaging agents (271).

There is still insufficient evidence to evaluate the changes in the ascorbic acid content of the adrenal during the general adaptation syndrome (441).

The thymus also shows very conspicuous changes during the alarm reaction, inasmuch as it undergoes acute "accidental involution" which becomes most pronounced during the counter-shock phase when the adrenal cortex reaches its maximum development. This loss of thymus weight is preceded by histologic signs of nuclear pyknosis with consequent complete dissolution of the thymocytes. Large macrophages engulf the dead thymus cells and carry them away through the lymphatics. At the same time the thymic reticulum reverts to its original epithelial type, inasmuch as its cells become roundish or polygonal and rich in cytoplasm. They often form massive cell-nests, resembling parathyroid tissue, new Hassal bodies or colloid-filled vesicles similar to those of the thyroid. When involution is most acute, the entire organ is distended with jelly-like edema (202, 361, 541-543, 545). During the acute stage the thymic changes are identical with those seen in the so-called "caryoclastic crisis." It is noteworthy that an increase in the mitotic figures is but rarely seen in the thymocytes during the alarm reaction, while it appears to be fairly frequent after treatment with certain "caryoclastic drugs" such as arsenic (293). It is possible, however, that this is merely the result of differences in dosage. As in the case of the adrenal response, the thymus and lymphnode involution occasioned by exposure to damaging agents, is now generally recognized as due to the alarm reaction mechanism and not to the specific effects of the agents used. This has been demonstrated in recent years for such stimuli as transection of the spinal cord (207), cold (496) and anoxia (146).

The lymphnodes, the spleen and other lymphatic organs are almost as markedly affected as the thymus, although they do not involute quite as rapidly nor is their involution as completely prevented by adrenalectomy (202, 541-543, 545). Similar changes have been seen following burns in the lymphnodes and tonsils of man (273). If the circulating blood volume is increased by intravenous infusions of saline, subsequent exposure to alarming stimuli may lead to the transformation of the ordinary lymphnodes into hemolymphnodes (589).

The pancreas likewise undergoes acute involution during the alarm reaction. This affects mainly the acinar tissue whose cells discharge their zymogen granules, decrease in size, and may even become necrotic. Only in the immediate vicinity of the islets does the excretory parenchyma retain its normal appearance. As a result of this change, the organ, which is usually firm and of a white color, becomes very soft, translucent, and grayish or pink. In some cases, the individual Langerhans islets with their surrounding "halos" of relatively normal parenchyma become readily visible to the naked eye. The islets themselves often show an increased number of nuclear pyknoes, but in some cases the impression is gained that active new formation of islet tissue occurs from the small ducts or

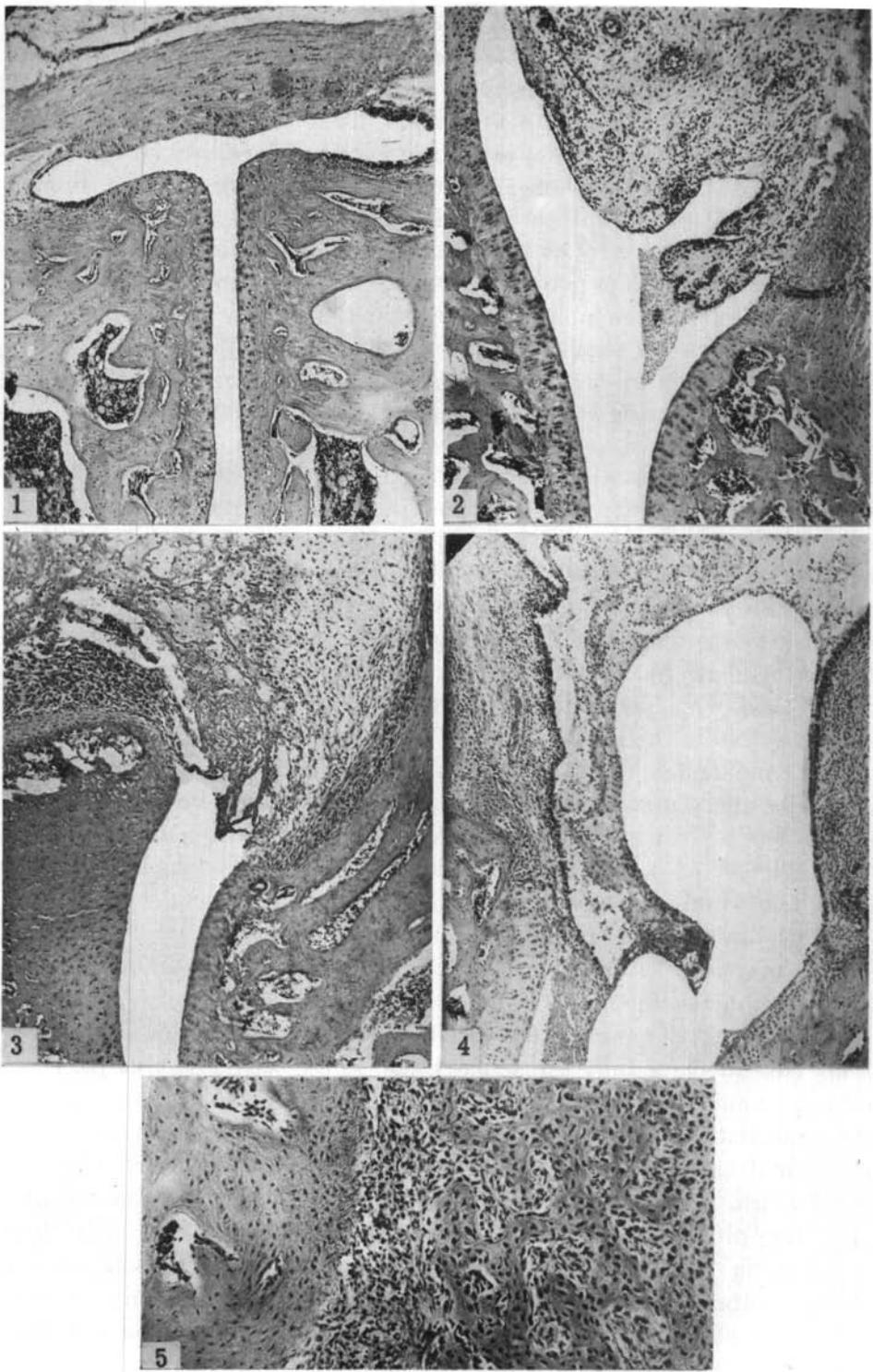


PLATE XIV. See opposite page for description.

that several islets unite into one "giant islet" (545). This acute involution cannot be regarded merely as the result of generalized tissue breakdown, intended to supply the organism with large amounts of nutritive material, since during the latter stages of the counter-shock phase the pancreas resumes its normal appearance even if no food is administered throughout the experiment. Such a temporary involution during the shock phase with subsequent restoration from endogenous sources is difficult to understand unless it is assumed that the pancreas contains especially readily available or valuable substances which are of particular use during an emergency.

Richardson and Young (500) noted that their "pancreatropic" pituitary extract causes changes in the Langerhans islets which bear some resemblance to those seen during the alarm reaction, but they emphasized that these changes are not identical and probably quite unrelated. Similarly, Sergeyeva (606) observed discharge of zymogen granules from the axinus cells following vagus stimulation or choline administration. Here again, "halos" of unexhausted acinus cells remained in evidence only in the immediate vicinity of the islets. The author claimed that in spite of the striking resemblance to the lesions characteristic of the alarm reaction, these changes are specific. It would be difficult, however, to prove the specificity of this change in any particular instance, since a great many other drugs, such as atropine (26), guanidine derivatives (144), etc., have been found to produce similar lesions. It is probable that the acute pancreatitis seen after burns (273) and certain cases of acute pancreatic necrosis have a similar etiology.

The anterior lobe of the hypophysis often shows degranulation, especially of the eosinophils, and sometimes marked waves of nuclear pyknosis. The borderline between anterior and posterior lobe may become rather irregular, with signs of "basophilic invasion" (545) but these changes are inconstant. More recently it has been found that in the rat, hypertrophy and

PLATE XIV. Hormonal production of arthritis

Fig. 1. Normal metatarsal joint of a rat. Control for subsequent figures.

Fig. 2. Acute arthritis produced by desoxycorticosterone overdosage in the rat. Note edematous, synovial membrane and exudate in metatarsal joint cavity.

Fig. 3. Necrotizing arthritis and periarthritis produced by desoxycorticosterone overdosage in the rat. Note hyaline necrosis of the synovial membrane and cellular infiltration of the connective tissue around the joint. The joint surface itself is normal.

Fig. 4. Arthritis produced by treatment with alkaline anterior pituitary extract. Note edema and round-cell infiltration of the synovial membrane with some necrotic material projecting into the metatarsal joint cavity.

Fig. 5. Newly formed periarticular bone in the metatarsal region of a rat treated with alkaline anterior pituitary extract.

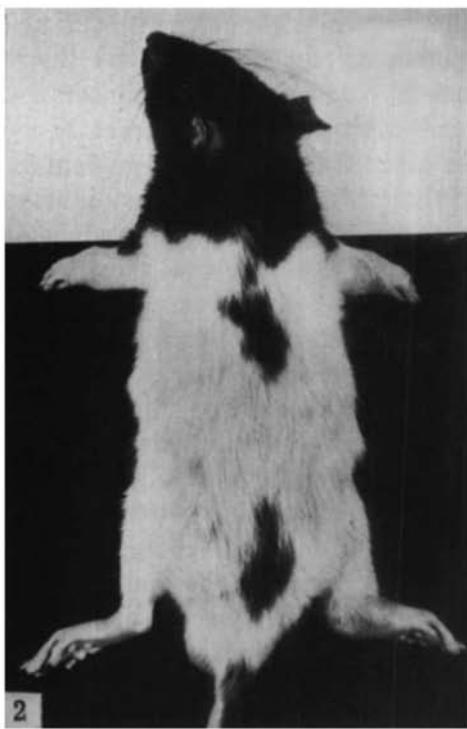
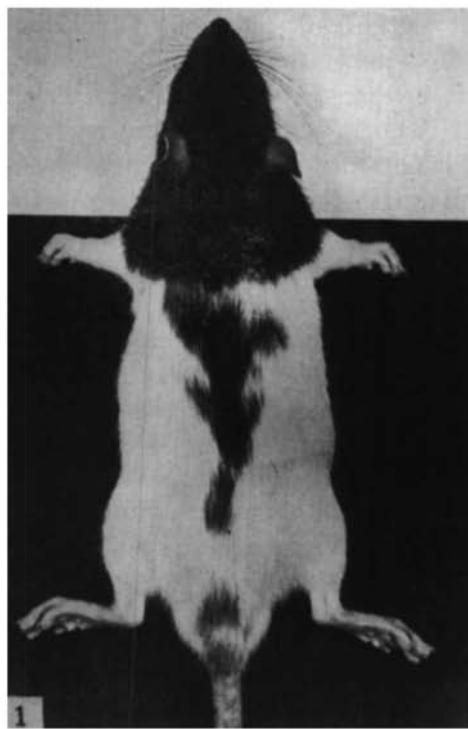


PLATE XV. See opposite page for description.

hyperplasia of the anterior lobe basophils is induced by such diverse agents as experimental nephritis, bilateral ligature of the ureters, injection of 10% HCl, ligature of the internal jugular veins, or injection of hypertonic fluids into the cerebral ventricles. It was concluded that "probably in all these instances, the pituitary changes are due to the same mechanism and constitute a form of the general adaptation syndrome to intensely damaging agents, as described by Selye" (269a). Further studies concerning histologic changes in the hypophysis during adaptation to stress would be most desirable since there is convincing physiologic evidence to show that this gland plays a very important rôle in the general adaptation syndrome (See section on "Theories concerning the general adaptation syndrome").

The **thyroid** may display signs of atrophy and involution during the early stages and sometimes this is followed by a second phase of hyperplasia. Perhaps the latter has something to do with the thyroid-stimulating effect of various non-specific substances, such as casein, tissue extracts, etc., (545) and the development of Graves' disease following sudden stress. Means (421) gave a table in his book on the thyroid in which he demonstrated the similarity between thyrotoxicosis and the alarm reaction, but these inter-relations will have to be studied in more detail before they can be fully understood.

The **gonads** of both sexes undergo atrophy during the general adaptation syndrome. This has been interpreted as due to a "shift" in the hormone production of the pituitary which in times of emergency produces more of such vitally necessary hormones as the adrenotropic principle at the expense of its gonadotropic hormone output (58a, 146, 200, 350, 547, 565).

The **blood count** shows very characteristic changes during the alarm reaction. There is a pronounced increase in the total white cell count due to neutrophilic leukocytosis with relative lymphopenia. These changes are particularly obvious in the counter-shock phase and may be preceded by leukopenia during the shock phase, especially if the damage is severe. Animals in which the leukopenia persists for an unduly long period are

PLATE XV. Hormonal production of arthritis

Fig. 1. Normal rat, control for Fig. 2.

Fig. 2. Inflammation of metatarsal joints in two front paws and right hind paw of a rat chronically treated with anterior pituitary extract.

Fig. 3. Arthritis in both hind paws of a rat chronically treated with anterior pituitary extract.

Fig. 4. Acute arthritis in the tarsal and metatarsal joints of the left hind paw in a rat chronically treated with anterior pituitary extract. Compare with the corresponding right hind foot, which in this case, was not affected.

usually irritable and succumb without showing any signs of counter-shock (130, 133, 254). This non-specific leukocytosis may be preceded by a decrease and followed by an increase in eosinophils (132, 133). Boyd and his associates (72) claimed that in rabbits in which an alarm reaction was produced by hemorrhage, no leukocytosis developed and concluded that this change is not characteristic of the alarm reaction. The table given in their paper, however, indicates an increase in the total leukocyte count from the normal of 8450 to 12,000 in 24 hours.

In the light of these observations, the leukocytosis observed by previous investigators following muscular exercise (28, 170, 178, 239, 533), treatment with various drugs (23, 65, 85, 471), tissue extracts (464, 526), bacterial toxins (464), exposure to cold (175, 303, 519), operative procedures (347, 532), infections (145, 186-188, 279), anaphylaxis (58, 666, 672, 683), burns (273, 348), ultraviolet rays (660) and x-rays (493) can hardly be regarded as the specific effect of these agents and is much more probably due to the alarm reaction produced by them. It is interesting that many of the above-mentioned authors emphasized that in cases of severe damage, leukopenia may precede or replace the leukocytosis. Recently Dougherty *et al.* (155) brought forth important evidence showing that the lymphopenia elicited by alarming stimuli is produced through the same pituitary-adrenal cortex mechanism which is responsible for the thymus and lymphatic tissue involution during the alarm reaction. Perhaps some of the leukopenias produced by infections and intoxications (625b) may also be explained on this basis.

The red cell count and the hematocrit values show a marked increase during the alarm reaction, especially during the shock phase. This may be preceded by a transient decrease (132, 133, 312) and is frequently accompanied by reticulocytosis (130, 133). Among all the alarming stimuli so far studied, only muscular exercise caused an almost immediate and persistent decrease in the red cell count, which was but rarely preceded by a transitory rise during the peak of the shock phase (133, 312, 563). This blood dilution must be regarded as a specific effect of exercise, but even this stimulus leads to the usual typical non-specific leukocytosis (133). The blood-diluting effect of strenuous exercise has also been seen in man (426).

Gastro-intestinal ulcers are likewise characteristic of the shock phase. They are most frequently seen in the stomach and small intestine and are usually accompanied by more or less massive hemorrhages into the intestinal lumen (541, 543, 545). They are evidently signs of damage and occur even more readily than usual in adrenalectomized animals which are unable to develop well-marked counter-shock phenomena. These ulcers are probably comparable to the acute gastro-intestinal erosions which are so

frequently observed during shock in man where they account for the dark coffee-colored vomitus seen under such conditions. They often develop following burns ("Curling's ulcer") (273) or intense emotional excitement (e.g., "air-raid ulcers") (575), etc. An excellent description of emotional changes in the human gastric mucosa (including the formation of erosions) was made on a patient with a gastric fistula (692). In animals similar changes occur after exposure to intense solar radiation (480), low oxygen tension (231), x-rays (362), spinal cord transection (207, 545, 597), head injuries (633) or any other intense alarming stimulus. The healing of the gastric ulcers is very rapid and usually far advanced 24 hours following exposure to damaging agents (128). This change is always accompanied by other symptoms of the alarm reaction.

* In cases of particularly acute and severe damage, that part of the cecum which in the rat corresponds to the human appendix may be specifically affected and show marked hemorrhagic edema similar to that observed during the first stages of acute appendicitis. It has been concluded that perhaps certain cases of acute appendicitis in man may also be due to similar systemic, rather than local causes. Since some investigators believe that the liberation of a histamine-like metabolite from the tissues may be the basic cause of shock symptoms, it is of particular interest that intravenous administration of histamine proved especially effective in eliciting such acute appendicular lesions (544, 546).

Hyperemia of the lungs, often accompanied by edema and even acute pneumonia, may also occur during the alarm reaction but these changes are not constant. At the same time, pleural transudates are often observed which are especially pronounced if the alarm reaction is produced by peritoneal interventions (541, 543). It appears probable that the pneumonia observed following x-rays (173), intense solar radiation (480), burns, intestinal obstruction, surgical trauma (435) and toxic doses of various drugs (435, 561), etc., are also merely signs of the alarm reaction rather than specific changes. It is not clear, however, whether the acute lung edema produced by anoxia, is a manifestation of the alarm reaction; although like most manifestations of the latter, it is more severe and more frequent in fasting than in fed animals (357, 359).

The liver often shows only signs of cloudy swelling and a decrease in size, which may partly be accounted for by the decrease in blood volume (545). It may, however, show more extensive atrophy and degenerative changes with focal necroses sometimes accompanied by intense fatty infiltration (203, 567) which Leblond *et al.* (362, 363) consider to be typical of the alarm reaction.

The kidneys show no very obvious changes during the alarm reaction. Occasionally there may be cloudy swelling and some albuminuria, or even

hemoglobinuria, but this is by no means constant (545). Conversely, during the stage of resistance and the stage of exhaustion of the general adaptation syndrome, nephrosclerosis or even acute nephritis occurs, especially in animals sensitized by unilateral nephrectomy and a high sodium intake. These renal changes are accompanied by a malignant type of hypertension, proteinuria and sometimes, widespread periarteritis nodosa with cardiac nodules which resemble the Aschoff bodies of rheumatic fever. Apparently not all alarming stimuli are equally capable of eliciting this syndrome; exposure to cold being most effective in this respect (574). These lesions are essentially identical with those produced by overdosage with crude anterior lobe extracts or desoxycorticosterone acetate, hence it was thought that a deranged hormonal adaptive mechanism to strain may be the cause of the corresponding maladies in man. (See also chapter on *Clinical implications of the general adaptation syndrome*, especially for discussion of cardiovascular changes).

The crystalline lens of the eye shows pronounced cloudiness in cases of sublethal shock, during the first phase of the alarm reaction but if the animal recovers, the lens clears up again (545). The fact that these changes in the lens are truly non-specific is further corroborated by the observation that in animals, they may be elicited by exposure to cold (545), anoxia (44), various types of narcotics (32) and adrenalin overdosage (627, 628). During the dehydration of diabetic coma they occur also in man (356).

VI. FACTORS INFLUENCING THE COURSE OF THE GENERAL ADAPTATION SYNDROME

One of the most important factors influencing the course of the general adaptation syndrome is the **stage of adaptation** of the organism at the time when it is confronted with an alarming stimulus. Thus, immediately following an alarm reaction, produced by one evocative agent, neither this nor any other such stimulus can elicit this reaction again. On the other hand, when a high degree of adaptation has been acquired to one agent (the "stage of resistance" of the general adaptation syndrome), exposure to a different stimulus finds the organism particularly irritable, so that it responds with a marked shock phase (313, 374-376, 409, 556). Besides the previously-mentioned examples of loss of adaptability to new conditions during the stage of resistance elicited by one particular, alarming stimulus, many additional, illustrative instances could be mentioned. Thus, it was found that mice, highly adapted to ultraviolet rays, become exceedingly sensitive to acetonitril (174); morphine addicts who have developed a great tolerance to this drug are hyper-reactors in the "cold-pressor test" (274) etc. Other examples given earlier in this review indicate that during the counter-shock phase of the alarm reaction both specific and non-specific

resistance tends to rise above normal. Unfortunately, however, as we have said above, so many factors influence resistance that it is almost impossible to ascertain in any specific case whether a change in resistance is solely due to the development of a general adaptation syndrome.

After **adrenalectomy** (542, 545, 601) or **hypophysectomy** (542, 545) the shock phase is particularly severe, the counter-shock phase negligible or absent. Even relatively mild alarming stimuli such as the folliculoid hormones cause severe shock phase symptoms in the absence of the adrenals or the pituitary (566, 596).

The hypoglycemia is particularly marked and the hyperglycemic peaks are negligible if present in adrenalectomized (554) and hypophysectomized (588) animals. This is probably due to the fact that in hypophysectomized or adrenalectomized animals glucose is not readily produced from endogenous sources.

Exposure to non-specific damage also causes particularly marked hypochloremia which is not followed by a second hyperchloremic counter-shock phase in adrenalectomized animals. It is noteworthy, furthermore, that in the absence of the adrenals, the hyperchloremic response peculiar to muscular exercise is reversed to the hypochloremic type common to all other alarming stimuli (554).

The lipid deposition in the liver, occasionally seen during the alarm reaction, is prevented by adrenalectomy (362, 363).

The thymus, and to a lesser extent, the other lymphatic organs, fail to involute in adrenalectomized (155, 156, 200, 284, 360, 361, 542, 624) or hypophysectomized (201, 542, 545) rats, although all other signs of the alarm reaction are particularly severe in such animals. Even the well-known x-ray atrophy of the thymus and other lymphatic organs is prevented by adrenalectomy unless huge doses are administered (680) or the rays are applied directly to the thymus (361, 362). Regeneration of the thymus after x-ray exposure is accelerated by adrenalectomy (241a). The low resistance of patients suffering from *status thymicolymphaticus* is brought to mind by these observations, since in this disease, enlargement of the thymus and adrenal hypoplasia are combined with particular sensitivity to sudden stress.

Corticoid hormone treatment produces thymus involution even in adrenalectomized or hypophysectomized animals and simultaneously improves their resistance to alarming stimuli; however, larger doses are required for this than for the mere maintenance of life (284, 286, 542, 545, 601). Adrenalin is ineffective in causing thymus involution after adrenalectomy (542).

It should be mentioned in this connection that estrone, estradiol, testosterone (242a, 525, 596) and diethylstilbestrol (598), *i.e.*, compounds with

male or female sex hormone activity, are also capable of producing thymus involution even in the adrenalectomized animal. Since the adrenal cortex contains both folliculoids and testoids it is not impossible that secretion of such steroids could also play some part in the production of thymus involution during the alarm reaction.

The characteristic lymphocytopenia of the alarm reaction is prevented by adrenalectomy (175). Unlike adrenalectomy **castration** does not protect the thymus against "accidental involution" due to alarming stimuli (695b).

It is rather curious that in **thyroidectomized** animals the blood sugar shows a particularly marked and persistent rise following exposure to alarming stimuli and after prolonged fasting the hyperglycemia of the counter-shock phase develops very rapidly in them (562). This is all the more surprising since in intact, fasted animals the hypoglycemia seen during the latter stages of the shock phase is particularly pronounced (564). Thyroidectomy also increases the severity of the hypochloremic phase and reverts the abnormal hyperchloremic response of muscular exercise to the hypochloremic type common to all other alarming stimuli (562).

Most investigators agree that **adrenalin** exerts no important beneficial effect in shock although it may temporarily raise the blood pressure (14, 438). The same is probably true of vasopressor **posterior lobe extracts** (4, 53).

Some workers, who probably used unsuitable hormone preparations, or otherwise unfavorable experimental conditions, concluded that in the normal (not adrenal deficient) individual, **corticoids** are entirely ineffective in combatting shock and allied conditions (14, 51, 148, 165, 168, 196, 209, 288, 289, 296, 318-321, 336, 382, 438, 470, 509, 630). We found, however, that at least under certain conditions, these hormones can prevent shock and facilitate the development of counter-shock phenomena thus increasing resistance even in the non-adrenalectomized animal (583, 584, 587). It is possible that some types of damage are better combatted with salt-active and others with sugar-active corticoids; our first efforts to demonstrate that corticoid treatment can raise resistance above normal in the non-adrenalectomized animal indicated, however, that in general cortical extracts and pure carbohydrate-active corticoids (with oxygen on carbon atom 11) are more efficient in this respect than are the salt-active corticoids (such as desoxycorticosterone). Since the appearance of these first publications the question has received a great deal of attention and it was claimed that corticoid hormones can increase the resistance of intact animals not only to traumatic shock (349, 460, 462, 675) but also to a variety of other alarming stimuli such as excessive muscular exercise (54, 335), colchicine (106, 107), peptone shock (297), intraperitoneal injection of hypertonic glucose solution (498), KCl (383, 442, 642), water intoxication (220, 221),

GENERAL ADAPTATION SYNDROME									
Third	Second	First	Stage of Alarm Reaction		Stage of Counter-shock		Name	Stage	
Stage of Exhaustion	Stage of Resistance	Stage of Resistance	↑	↓	↑	↓	Blood Vessels *		
Nephrosclerosis	Nephrosclerosis	Periarteritis nodosa	↑	↑	↑	↑	Heart *		
Periarteritis nodosa	Fibrous (Aschoff?) nodules	Fibrous (Aschoff?) nodules	↓	↓	↓	↓	Body Weight		
			↓	↑	↑	↑	Blood Volume		
			↓	↓	↑	↑	Diuresis		
			↓	↓	↓	↓	Blood Sugar		
			↓	↓	↑	↑	Blood Chlorides		
			↓	↓	↑	↑	Blood N.P.N.		
			↓	↓	↑	↑	Specific Resistance		
			↓	↓	↑	↑	Crossed Tolerance		
			↓	↓	↑	↑	Size Adrenal Cortex		
			↓	↓	↑	↑	Lipids		
			↓	↓	↑	↑	Thymus & Lymph Tis.		
			↓	↓	↑	↑	Polys. Leucocyte Count		
			↓	↓	↑	↑	Erosions Gastroint. Tract		
			↓	↓	↑	↑	Erosions & Ulcers		
			↓	↓	↑	↑	Gonads		

Explanation of Symbols: ↑ = Increased } ↓ = Decreased } magnitude of change indicated by size of arrow.

↔ = Normal unchanged.

* = The changes in these organs are dependent upon a high Na intake.

? = No conclusive data published on this subject.

PLATE XVI. Nomenclature and symptomatology of the general adaptation syndrome

Schematic representation of the most prominent morphologic and metabolic changes during the general adaptation syndrome and the diseases of adaptation.

histamine (42, 474), intestinal distention (197), menstrual toxin(616), microbial toxins and infections (6, 114, 218, 326, 396, 486, 612), partial hepatectomy (584), anoxia (27, 637), heat (67, 391, 529), veronal (171), toxic tissue extracts (503) and perhaps even the type of shock produced after temporary occlusion of large vascular territories (69, 70, 314, 315, 509, 530).

In clinical medicine the beneficial effect of corticoids is more difficult to prove, at least with the type of preparation now available. However, many investigators consider such treatment desirable in combatting shock although most clinicians agree that it should not replace but merely complement the other established therapeutic procedures, such as blood transfusion (76, 94, 166, 252, 258, 262, 352, 353, 384, 412, 420, 483, 689).

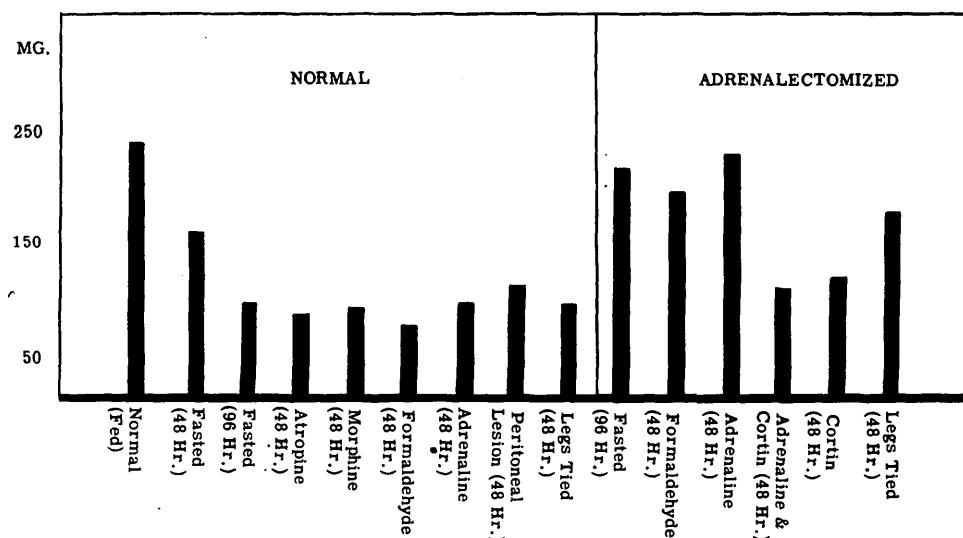


PLATE XVII. Prevention by adrenalectomy of thymus atrophy, normally seen during alarm reaction in the rat⁴

It will be noted that in the intact animal, various non-specific damaging agents, including prolonged fasting, cause involution of the thymus while adrenalectomy prevents this reaction. Among the agents studied here, only cortical extracts caused thymus involution after adrenalectomy. All animals (except the first group which acted as a control) were fasted throughout the experiment and the length of the exposure is indicated in brackets, with each group.

In patients corticoids have also been claimed to be beneficial in the treatment of celiac disease (5, 16, 283, 337, 454, 463, 534, 620), hemoconcentration due to ether anesthesia (417, 489), acute confusion during typhoid fever or the puerperium (280, 661), various acute infections, especially typhoid fever and diphtheria (31, 38, 41, 48, 49, 54, 76, 149, 199, 229, 241, 244, 245, 268, 298, 393, 399, 400, 425, 453, 475, 609, 662), psychoses (377, 378), exhaustion due to fever therapy (164), burns (172, 233, 253, 268, 465,

⁴ The black areas indicate the weight of the thymus under various experimental conditions and have been obtained from averages of large groups of rats. Slightly modified after: Selye, H. Thymus and adrenals in the response of the organism to injuries and intoxications, *Brit. J. Exper. Path.* 17: 234 (1936).

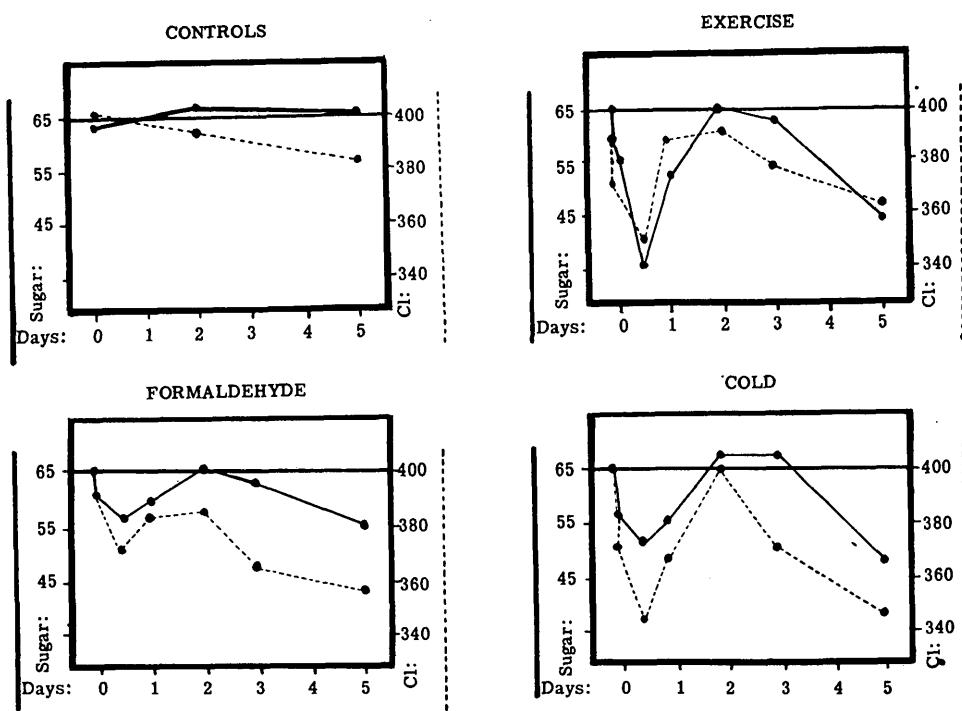


PLATE XVIII. Whole blood chloride and blood sugar changes in adrenalectomized rats, during the general adaptation syndrome⁵

Note that in the adrenalectomized animals, the initial hyperglycemia of the alarm reaction fails to develop while the hypoglycemic phase is particularly pronounced. The entire general adaptation syndrome is "telescoped" into a brief five-day period but three stages are still distinguishable. The first (alarm reaction) is characterized by hypoglycemia and hypochloremia, the second (stage of resistance) by a return of these values to normal and the third (stage of exhaustion) by a second period of hypoglycemia and hypochloremia; this third stage ends in the death of the animal.

499, 689), allergy (684a, 684b), premature infants (25), "fetal shock" (47), tuberculosis (49, 102, 103, 535), damage due to heat (528, 529), cold (234, 331) or x-rays (671), etc., (101, 392, 667).

In connection with the low power of desoxycorticosterone to combat acute damage, it should be kept in mind that most actions of this compound tend to develop slowly and that animals chronically pre-treated with it develop a pronounced "compensatory atrophy" of the adrenal cortex. Such animals whose adrenal cortex has involuted under the influence of desoxycorticosterone pre-treatment can show a slight enlargement of the adrenal cortex when exposed to alarming stimuli, but this enlarge-

⁵ Selye, H. Blood sugar and chloride changes in adrenalectomized rats during adaptation to various stimuli. *Proc. Soc. Exper. Biol. & Med.* 38: 728 (1938).

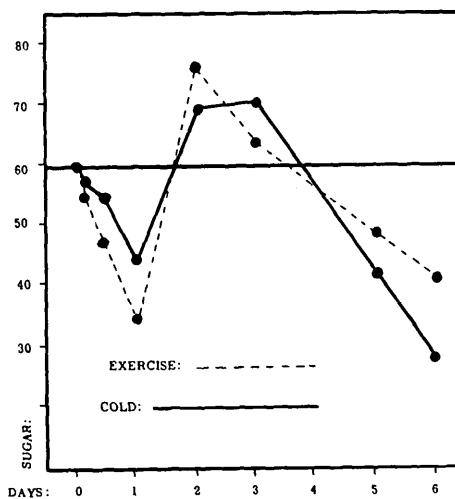


PLATE XIX. Blood sugar changes in hypophysectomized rats during the general adaptation syndrome produced by exercise or cold⁶

Note that hypophysectomy likewise decreases adaptability so that the general adaptation syndrome is "telescoped" into a brief six-day period under the conditions of this experiment; yet the three stages are again clearly distinguishable: hypoglycemia, during the alarm reaction, return slightly above normal during the stage of resistance and secondary hypoglycemia during the stage of exhaustion. The greatly shortened stage of resistance in the adrenalectomized (Plate XVIII) and hypophysectomized (this Plate) animal clearly show that adrenal and hypophyseal hormones are not indispensable for adaptation but they prolong the period during which resistance, to uniform and continuous exposure, is possible.

ment is subnormal and functionally inadequate. Probably after compensatory atrophy the adrenal cortex is comparatively ineffective in producing the large amounts of sugar-active corticoids required during the alarm reaction and hence, animals so pre-treated respond to damage somewhat like adrenalectomized animals and exhibit low general resistance and marked hypoglycemia during stress (150, 153, 294, 383, 570, 586, 587). This is probably due to the inhibitory effect that corticoids have on the formation of adrenotropic hormone by the pituitary. It is well established that excess production of the latter hormone is essential for the cortical enlargement seen in the general adaptation syndrome, since in hypophysectomized animals the cortex does not undergo hypertrophy under stress (214, 294, 542, 596) even if it is maintained by daily treatment with adrenotropic hormone (582). It is noteworthy, however, that unlike in mammals,

⁶ Selye, H., and V. G. Foglia. Blood sugar changes in hypophysectomized rats during adaptation to various stimuli. *Proc. Soc. Exper. Biol. & Med.* 39: 222 (1938).

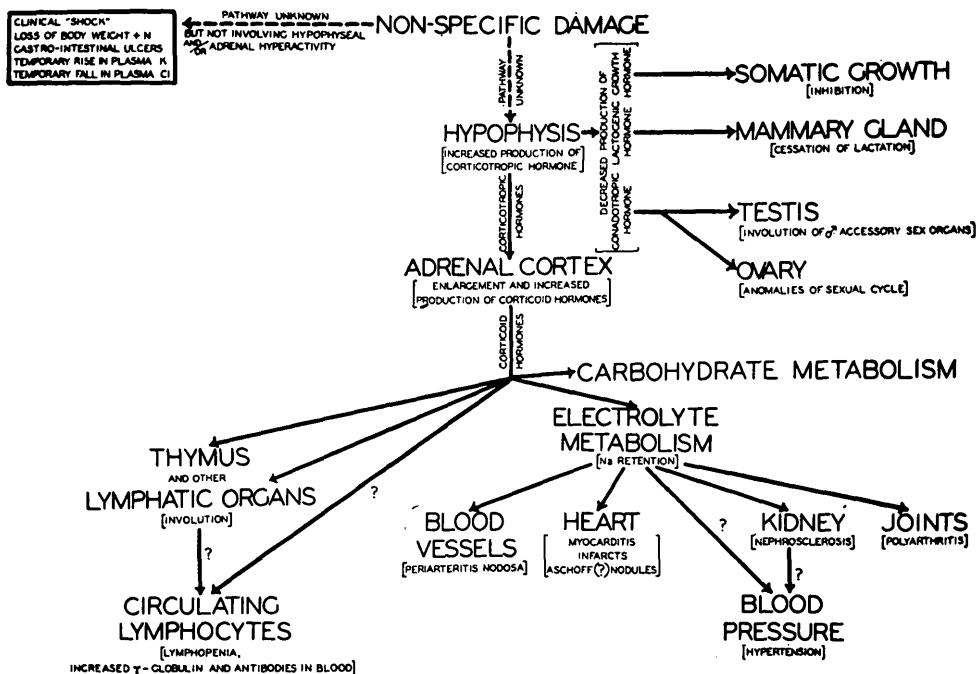


PLATE XX. Functional interrelations during the general adaptation syndrome

Schematized drawing indicating that non-specific damage causes clinical shock, loss of body weight and nitrogen, gastro-intestinal ulcers, temporary rise in plasma potassium with fall in plasma Cl, through unknown pathways (nervous stimulus?, deficiency?, toxic metabolites?) but manifestly not through the stimulation of the hypophyseo-adrenal mechanism. This is proven by the fact that the above manifestations are not prevented either by hypophysectomy or by adrenalectomy; they even tend to be more severe in the absence of either or both of these glands.

Non-specific damage, again through unknown pathways, also acts upon the hypophysis and causes it to increase corticotropic hormone production at the expense of a decreased elaboration of gonadotropic, lactogenic and growth hormones. The resulting corticotropic hormone excess causes enlargement of the adrenal cortex with signs of increased corticoid hormone production. These corticoids in turn cause changes in the carbohydrate (sugar active corticoids) and electrolyte metabolism (salt-active corticoids) as well as atrophy of the thymus and the other lymphatic organs. It is probable that the cardiovascular, renal, blood pressure and arthritic changes are secondary to the disturbances in electrolyte metabolism since their production and prevention are largely dependent upon the salt intake. The changes in γ -globulin, on the other hand, appear to be secondary to the effect of corticoids upon the thymic lymphatic apparatus.

We do not know as yet, whether the hypertension is secondary to the nephrosclerosis or whether it is a direct result of the disturbance in electrolyte metabolism caused by the corticoids. Similarly, it is not quite clear, as yet, whether corticoids destroy the circulating lymphocytes directly, or whether they influence the lymphocyte count merely by diminishing lymphocyte formation in the lymphatic organs. Probably both these mechanisms are operative.

in the pigeon the cortex responds to alarming stimuli even after hypophysectomy (429, 430).

Anterior pituitary extracts may help to counteract the protein catabolic effects of non-specific damage (118) and purified corticotropic preparations share to some extent the power of cortical extracts to raise resistance to alarming stimuli (460, 462, 498).

Testosterone and other testoid compounds with marked nitrogen-retaining ability may also help to combat the protein catabolic action of non-specific damaging agents (2, 12, 37, 495, 623). It is thought that the protein catabolism occasioned by excess corticoids is inhibited by the protein anabolic or nitrogen-retaining effect of the testoids.

The beneficial action of blood or saline **transfusions** has been established in carefully controlled animal experiments (14) as well as by general clinical experience. Both corticoid administration and transfusions are physiologic types of treatment, inasmuch as they imitate the phenomena of counter shock.

Dietary measures are of particular importance in influencing the course of the general adaptation syndrome. Thus, it was found that feeding or even intravenous injection of glucose can selectively prevent gastric ulcer formation in rats in which an alarm reaction is produced by spinal cord transection, exposure to cold, etc., (597). In these acute experiments the other manifestations of the alarm reaction (thymus and lymph node involution, adrenal enlargement, etc.) were not influenced by the glucose treatment, so that a certain dissociation of the manifestations of the reaction was accomplished.

As we shall see later, the experimental "diseases of adaptation" are likewise considerably influenced by the diet, irrespective of whether they are produced by chronic exposure to damage (*e.g.*, cold) or stimulated by hormone (desoxycorticosterone, anterior pituitary extract) overdosage. Thus, we have found that a high intake of sodium and diets rich in protein but poor in carbohydrates, greatly facilitate the production of these diseases, while "acid ash" diets, as well as food poor in sodium and protein but rich in carbohydrate, protect against them.

If an equi-caloric amount of fat is substituted for carbohydrate, there is no change in the ability of the diet to influence the production (by lyophilized anterior pituitary or desoxycorticosterone acetate) of the diseases of adaptation in the rat. Hence, we concluded that the low protein and not the high carbohydrate content of the protective diets was the cause of their efficacy. Experiments are now under way to determine whether all proteins are equally active or whether individual proteins, polypeptides or amino acids are responsible for increasing sensitivity to

the actions of corticoids and corticotropic hormones. In any case the mechanism through which high carbohydrate, low protein diets protect against the "diseases of adaptation" is rather complex. Our experiments, on the rat, indicate that not only the actions of the corticoids on peripheral organs (*e.g.*, heart and kidney) but even the adrenal stimulating effect of corticotropins is augmented by high protein diets. Hence we conclude that such diets enhance the production of the diseases of adaptation at two different steps in their pathogenesis; they augment the efficacy of both corticotropin and of corticoid steroids. This fact should also be taken into account in bio-assays for these activities.

The fact that some agents may selectively inhibit the development of one particular manifestation helps to explain that not all the lesions characteristic of the general adaptation syndrome are proportionately developed in every individual instance.

Fasting is particularly effective in increasing sensitivity to alarming stimuli. In fasted animals, protein catabolism, gastric ulcer formation, involution of the thymus and lymph nodes as well as the hypoglycemic phase of the alarm reaction are especially prominent and the adrenal cortex undergoes particularly rapid and intense hypertrophy (355, 542, 545, 564). This is hardly surprising if we remember that protein catabolic actions are especially deleterious in the absence of exogenous food supplies with which the tissues could be repaired.

The importance of **nervous disturbances** has often been suspected; yet comparatively little evidence has come forward to prove that the nervous system plays a prominent rôle in regulating the course of the general adaptation syndrome. It is well known, of course, that extensive surgical interventions on the nervous system will in themselves cause an alarm reaction (*e.g.*, hypothalamic injuries, spinal cord transection), but this is not unexpected since such interventions, just as any other type of damage, act as alarming agents. On the other hand, it was found that the general systemic effects (gastro-intestinal ulceration, pleural effusions, ascites, hemoconcentration, etc.) of thermal trauma to one hind leg, were essentially the same in intact and in spinal cats (306, 307).

Analgesic drugs are of definite value in combatting various types of shock but they must be given in moderate doses. Otherwise they prove stronger alarming stimuli than the pain and emotion which they combat (438, 492, 539). It has been noted, furthermore, that animals under ether anesthesia appear to be more resistant to shock produced by traumatizing an artificially-perfused, enervated limb, than more deeply anesthetized animals under chloralose anesthesia (381). Some promising preliminary experiments have been performed to prove that transection of the pituitary

stalk modifies the rate of thyrotropic hormone production in response to certain emergency situations (142), but further work along these lines will be necessary to determine exactly what part is played by nervous connections in conducting stimuli to the pituitary and thus modifying adrenotropic hormone production. It has been claimed that denervation of the carotid sinus combats shock by increasing the endogenous production of corticoids (364), but the evidence is inconclusive.

The commonly practised method of combatting shock by **heat**, with the view of maintaining the body temperature at a normal level, has been claimed to be not only useless, but actually harmful, in well-controlled animal experiments (14). In the event of an alarm reaction produced by transection of the spinal cord, however, the resulting drop in body temperature appears to represent the major shock-producing factor. This has been proven by experiments in which the body temperature of spinal cord transected animals was maintained by placing them in warm surroundings. Under such conditions the manifestations of the alarm reaction were greatly inhibited or completely prevented (126, 127, 207).

Partial kidney insufficiency produced by **unilateral nephrectomy** sensitizes animals to the development of nephrosclerosis, nephritis, hypertension and periarteritis nodosa, following chronic exposure to damaging agents, such as cold (574, 577).

The administration of excessive quantities of **sodium chloride** further sensitizes the body in this respect, while **acidifying salts** (*e.g.* ammonium chloride) tend to prevent such changes (574). It is noteworthy that the same agents which increase sensitivity to this type of non-specific damage (partial nephrectomy, NaCl), also sensitize animals to desoxycorticosterone and anterior pituitary extract, while conversely, the agents (acidifying salts) which inhibit the toxic manifestations of these hormones are also beneficial in preventing hypertension, renal and cardiovascular lesions following exposure to non-specific damage (251, 599). Preliminary observations suggest that Na restriction (246a) or treatment with NH₄Cl are also beneficial in patients with renal hypertension (530a). These observations give further support to the concept, according to which the corresponding diseases of clinical medicine are due to the endogenous overdosage with hormones of this type, presumably elaborated for defensive purposes.

Probably many **other factors** exert some influence on the development of the general adaptation syndrome but all these can hardly be discussed here in detail. Suffice it to mention, for example, that sodium succinate injections appear to exert some beneficial influence upon traumatic shock (445) and that climatic and weather conditions are also of importance for the development of the general adaptation syndrome (476).

VII. THEORETIC INTERPRETATION OF THE GENERAL ADAPTATION SYNDROME

In discussing the theories proposed to explain the various manifestations of the general adaptation syndrome it is well to separate the theories on shock from those dealing with the other phases of this syndrome.

A. Theories concerning the shock phase

The greatest problem in interpreting the manifestations of shock is to explain why so many different agents lead to essentially the same syndrome and how an injury to a limited part of the body can effect the entire organism. Innumerable theories have been proposed in an effort to explain these two basic facts. It is not within the scope of this review to discuss all these in detail and the following brief summary is only given as a key to the relevant literature.

1. Impaired circulation

Moon (435, 437) defined the shock phase as follows: "Shock is a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, decreased cardiac output (reduced volume flow) and by increased concentration of the blood." Although this definition is widely accepted, it is not valid in every case, since among other things it excludes spinal shock, which is generally considered to result from vaso-motor paralysis and yet leads to the typical morphologic and chemical changes characteristic of shock (545). It also excludes shock resulting from excessive muscular exercise, which is often accompanied by a decrease in the red cell count (563). Allen (14) observed, furthermore, that in cases of severe experimental traumatic shock, "transfusions of blood or plasma no longer suffice to save life, even though the corpuscle count is kept at a normal or reduced level and all indications point to normal or increased blood volume together with adequate propulsion of the blood. Theories which regard these as the determining factors in shock are thus invalidated."

It has been claimed that capillary permeability is increased in all known types of shock be this as it may, the capillaries are extremely sensitive to damaging agents and tend to become permeable as a result of local or general disturbances, hence this symptom is hardly a suitable basis for a definition; it is no more characteristic than any other sign of damage (e.g., muscular weakness, pallor, etc.). Increased capillary permeability is also present during the agonal stage of chronic diseases, which is not generally considered to be "shock."

2. Dehydration and hemoconcentration

This theory is rather similar to that mentioned above. It is based on the assumption that the symptoms of the shock phase are primarily due to de-

hydration resulting from increased capillary permeability with consequent loss of plasma, especially into the damaged area (14, 43, 60-63, 137, 138, 256, 269, 435, 613). As mentioned above, the extremely sensitive endothelial cells of the capillaries readily become permeable under the influence of damage, but shock ensues even if the resulting hemoconcentration is prevented by transfusion or—as in shock due to hemorrhage—if no hemoconcentration occurs. Furthermore, not every type of increased capillary permeability leads to shock. This theory also fails to explain what makes the capillaries permeable in cases of spinal, muscular exercise or psychic shock in which there is no direct interference with the endothelial cells.

3. Endogenous intoxication

Most workers believe that toxic metabolites which are released from the damaged tissues into the blood stream are the mediators between the injured area and the rest of the body. In the light of the alarm reaction concept, it becomes evident that even if we accept this, there must be a second mediator which causes the tissues to release a toxic metabolite, since not only direct injury to tissues (burns, trauma, etc.), but any intervention necessitating adaptation (nervous lesions, cold, muscular exercise, etc.) elicits an alarm reaction with an initial shock phase. It is probable that this link in the chain of events is not always the same; in the case of nervous shock it may be a nervous stimulus, in decreased oxygen tension the anoxia and in cases of toxic shock the injected poison itself, which causes the cells to release shock-producing metabolites.

Among the hypothetical shock-producing metabolites, histamine has received particular attention even since Abel and Kubota (1) expressed the view that its liberation from traumatized tissues is the fundamental cause of wound shock. Many investigators have discussed this theory as a possible interpretation of shock caused by trauma (14, 35, 36, 86, 122, 124, 277, 300, 531, 610, 652), burns (34, 45, 192, 216, 217, 255, 277, 447, 688), cold (281, 608), peptone (123, 192, 194, 260), snake venoms (179, 180, 192, 193, 322, 323), bee venom (192), microbial toxins (192, 324), intestinal occlusion (8), allergy (684a, 684b) and numerous other damaging agents (493, 647, 696). Although Rose and Browne (510) found a decrease in blood histamine during shock, others (387, 651) expressed the opinion that in the final analysis, histamine liberation from the tissues may be the basic cause of the alarm reaction syndrome, irrespective of the evocative agent. The writer (545, 550) also considered this possibility but emphasized that there is no irrefutable evidence to support it and that numerous other metabolites might be invoked with almost equal justification. Among these metabolites are **adenosin derivatives** (697), **acetylcholine** (545), the "**Früh-gift**" of Freund (215), the **leukotaxin** and **necrosin** of Menkin (424a) and **vasoconstrictor substances** (468, 469).

Kendall and Ingle (325) rejected the histamine theory of the alarm reaction, favoring the concept that **potassium** may be the shock-producing metabolite, since as they say: "In all the conditions given by Selye as suitable to produce the 'alarm reaction,' there is a rise in the concentration of potassium in the serum." It is possible, however, to raise serum K without eliciting an alarm reaction and animals which developed hypopotassemia due to desoxycorticosterone overdosage are especially prone to develop the shock phase (539).

Various more or less exactly defined **other toxic metabolites** have been considered (24a, 55, 66, 212, 239a, 273, 317, 385, 419, 428, 440a, 631, 638, 688) but none of these theories have received sufficient support to be acceptable.

The possibility of **enterogenic intoxication** should also be kept in mind in certain cases, since owing to gastrointestinal ulcer formation toxic substances are readily absorbed from the gut during the alarm reaction (553). It is interesting in this connection that the anoxia at high altitude is claimed to increase the permeability of the gastrointestinal tract, thus predisposing to food allergy (30a). It must be remembered, however, that shock can also develop in eviscerated animals.

4. Nervous disturbance

The possibility that nervous factors may play a rôle in eliciting the symptoms of the shock phase (116, 273) has briefly been discussed above in the sections on *Collapse* and *Factors influencing the course of the general adaptation syndrome*, (e.g., spinal cord transection, severance of the pituitary stalk, etc.).

There is some evidence which would suggest that many, if not all the manifestations of the general adaptation syndrome, are due to **conditioned reflexes**. Thus, it was found that the tachycardia elicited by adrenalin in the dog can subsequently be produced even by the injection of saline solution when a conditioned reflex to injection has already been established (626). Although this example is somewhat far-fetched, the fact remains that certain manifestations of the general adaptation syndrome, which are dependent upon pretreatment or training, could be based upon the development of conditioned reflexes.

It has also been claimed, with more or less justification, that the **vegetative nervous system** may play a prominent rôle, namely that an over-stimulation of the sympathetic division could be the cause of shock (208, 640, 641) but this did not remain uncontested (198). Yet, perhaps certain manifestations of the alarm reaction may be selectively mediated by nerves. Thus, it is claimed that vagotomy, adrenal denervation and spinal cord transection exert a pronounced effect on the glycemic response to alarming stimuli (225-227). It is well known furthermore, that sympathet-

tomy interferes with many adaptive reactions and prevents adrenalin liberation in emergencies (90a).

The fact that strong nervous stimuli can act as alarming agents (e.g., rage, spinal cord transection) has repeatedly been mentioned in the course of this review and hardly requires much further discussion. Shock caused by intestinal obstruction has often been considered to depend largely upon nervous irritation (198, 270, 632). It was found, however, that preliminary exclusion of the extrinsic nerve supply of the gastrointestinal tract does not influence the survival time of cats in which shock was produced by obstruction of the intestines (198).

Fear has also been regarded as a possible causative factor in shock, by increasing the output of adrenalin and producing vasoconstriction with increased capillary permeability, hemoconcentration and secondary fall of blood pressure (88, 208, 210). Neurogenic shock has been produced by carotid sinus stimulation (even in the anesthetized dog) but this probably has little bearing upon shock in man since similar conditions would hardly arise (477). Experiments planned to prove that **anesthesia alleviates shock** have yielded very contradictory results, probably because deep anesthesia in itself can be an alarming stimulus (63). To make anesthesia a useful shock-preventing agent, care must be taken that its own alarming effect be less pronounced than that of the nervous stimulus which it is supposed to counteract (381, 438, 492, 539).

5. Distributed thermoregulation

It is a well-known fact that in severe shock the mechanism of thermoregulation is disturbed and the body temperature falls. Furthermore, exposure to excessive cold can produce shock-like symptoms by depressing the body temperature (545). It is true that the alarm reaction symptoms produced by transection of the spinal cord, can to some extent be prevented by maintaining the body temperature (126, 127). However, exposure to excessive heat may also lead to shock-like symptoms, although the body temperature arises (542) and it is common clinical experience that in patients, suffering from trauma or burns, shock is not necessarily prevented by maintaining the body temperature on a normal level.

6. Hypochloremia

The **hypochloremia**, which many investigators regard as characteristic of shock, is absent when muscular exercise is the evocative agent (557, 563). This is particularly true of the reputedly typical decrease in red cell chlorides (312, 313). Furthermore, marked hypochloremia may be elicited (e.g., by desoxycorticosterone overdosage), without any shock symptoms.

7. The theory of "leukopoietic substances"

Among the individual manifestations of the alarm reaction, the leukocytosis has received particular attention. Numerous investigators expressed

the view that metabolites, liberated during the shock phase, stimulate leukocyte formation, since at this time the blood acquires the property of increasing the leukocyte count in normal animals (81-83, 92, 139, 446). Such leukocytosis-producing metabolites have been termed "neutrophilins" (18-23, 275, 444), leukotaxin (424a) or "leukopoietins" (40). Other investigators postulate the existence of a special leukocyte center in the brain (64, 260, 278, 449, 511-513, 522, 653).

Beer (40) united these two theories by assuming that the leukocytosis is produced through stimuli exciting the leukocyte center which, in turn causes liberation of leukopoietic substances. On the other hand, Feenders (191) was unable to demonstrate any leukopoietic effect with the blood of animals taken at the peak of the leukopoietic reaction. Investigations attempting to determine whether transection of the spinal cord, splenectomy, or thyroidectomy prevents the leukocytic reaction yielded contradictory results (20, 22, 23, 275, 452, 471).

Blockade of the reticulo-endothelial system does not interfere with the effect of the alarm reaction on the leucocyte count (186, 188).

The recent discovery that corticotropic anterior lobe extracts and corticoid adrenal hormones have a pronounced effect upon the white cell picture during the general adaptation syndrome will be discussed below in connection with the endocrine theories.

8. The deficiency theory

In discussing the many previous theoretical interpretations of the shock phase, we have pointed out that they may explain certain instances of shock, but there are other types which cannot be interpreted by them. This led us to consider the possibility that shock may not always be caused by the same mechanism. It is true that much weighty evidence has been brought forward in favor of one or the other formulation of the intoxication theory, but it is perhaps profitable also to consider the possibility that shock symptoms may be caused by deficiency in certain metabolites rather than by the presence of excessive amounts of them. All the classical experimental arrangements, quoted to prove the toxic theory, are equally applicable to the deficiency theory. For instance, the fact that shock following occlusion of a vascular territory by a tourniquet occurs only after re-establishment of the circulation, can equally well be interpreted as due to intoxication of the organism by metabolites which come from the damaged tissues or by loss of vitally-important substances from the general circulation into the area of damage.

In some instances, it is indubitably a deficiency that causes shock-like symptoms. Thus, we have been able to produce typical shock by partial hepatectomy (584), a condition in which no tissue remaining in the body is directly lesioned nor is there any damaging substance introduced into the

organism. In this instance, just as in the case of shock due to anoxemia or hypoglycemia, it is the lack of something rather than an excess of toxic metabolites that was the primary cause of shock and cellular injury, although secondarily this lack may have led to the formation of toxic substances. It is conceivable that lack of certain substances necessary for shock defense plays a part in many if not all types of shock. The interpretation of the shock phase as one of "relative adrenal insufficiency" (502, 545, 587) is essentially one application of this deficiency theory.

The previously-quoted experiments (151, 585), showing that much blood sugar disappears during circulation through a traumatized limb, might also be interpreted on the basis of the deficiency theory. Increased glucose combustion in the damaged tissue would probably require the presence of large quantities of substances (*e.g.*, co-enzymes), which are necessary for glucose utilization and by attracting these into the area of damage, the body may become deficient in them.

Attention should also be called to the fact that among the previously-mentioned interpretations, the theory of hypochloremia and the theory of dehydration also represent modified types of the deficiency theory. Incidentally, there is no proof that it is actually water loss into the damaged tissues that is of importance. Compression treatment of crush injuries of limbs has proven quite effective in clinical and experimental medicine and this cannot always be entirely attributed to the prevention of water loss into the damaged tissue. The possibility that other important blood constituents are lost into the tissues has likewise been considered (316, 472).

9. Other theories of shock

Among the numerous other theories proposed to explain shock, suffice it to mention those of **acapnia** (265, 267), **fat embolism** (59, 246, 484, 485, 664), **acidosis** (249, 250, 333, 389, 418) and **constriction of the hepatic vessels** (416). More recently (185), it has been suggested that at least in cases of shock caused by burns, **cardiac lesions** are responsible for the general damage. However, none of these latter theories have received much support.

B. Theories concerning the entire general adaptation syndrome

1. The hypothesis of adaptation energy

The observation that resistance is increased during the counter-shock phase of the alarm reaction intimated that the "adaptability" of the organism is mobilized in some way. On the other hand, following prolonged treatment with an alarming stimulus, that is, during the "resistant stage" of the general adaptation syndrome, when the organism has acquired a high degree of adaptation to the agent to which it had been exposed, it becomes especially irresistant and unable to adapt itself to other damaging agents.

This seemed to signify that the body possesses only a limited amount of "adaptability" or "adaptation energy" which is consumed while the adaptation is acquired to a certain agent, so that less of it is available for resistance against other agents. This concept is also supported by the observation that continued treatment with the same agent (which originally caused an alarm reaction and to which the organism later became adapted), eventually becomes damaging again ("stage of exhaustion" of the general adaptation syndrome). It would be extremely difficult to explain the loss of an already acquired adaptation without assuming that, due to continued use, all the available adaptation energy of the organism had been exhausted (231, 427, 556, 558-560, 568). The extensive and painstaking studies of Sundstroem and Michaels (629) on adaptation to anoxia, led them—quite independently—to a concept very similar to ours. They also found that adaptation proceeds, in three stages [1) "pre-adaptive," 2), "adapted" and 3) "postadapted"], that it depends upon a defensive hyperactivity of the adrenal cortex and that it terminates in a final break-down, reminiscent of cortical insufficiency. It is likewise worth mentioning in this connection that Gause's (222) studies, concerning the relation of adaptability to adaptation led him to conclude that "the stronger the initial inherent adaptation, the weaker is the adaptability, and vice versa. This conclusion follows from observations on unicellular organisms, but it was shown to agree well with the data obtained in the work with other animals."

To quote but one possible application of this hypothesis to contemporary clinical medicine, we may call attention to the fact that aviators, who have had to adapt themselves to work under nervous tension at a high altitude, often break down following a period of apparently complete inurement. The period of breakdown is characterized, among other things, by gastrointestinal disturbances and other manifestations reminiscent of the "stage of exhaustion" of the general adaptation syndrome. In such cases, it has been customary to speak of exhaustion of the "nervous energy reserve" (663).

Of course, it must be admitted that the adaptation energy hypothesis does not even attempt to explain the pathogenic mechanism responsible for the development of the various manifestations of the general adaptation syndrome. It is offered merely as a working hypothesis which may help to visualize the fact that adaptation to a multiplicity of agents occurs in three distinct stages.

2. Theories concerning functional (mainly hormonal) interrelations

The functional interrelations between the various organs affected by the general adaptation syndrome, are still far from being clearly understood. It has long been suspected, however, that hormones play an important

rôle in adaptive processes (4a, 163a, 390a, 522a), and considerable progress has been made along these lines since the first publication on the alarm reaction appeared nearly ten years ago. It would be premature to outline a hypothesis attempting to interpret all manifestations of the adaptation syndrome. There is practically no information as yet concerning certain links in the chain of events, but some interrelations have been proven beyond doubt and others have at least been made extremely probable by experimentation. At this stage it is best not to lean too heavily upon any preconceived theoretical concept, but as a working hypothesis it may be useful to outline those correlations which are in best accord with the facts observed. (For a more detailed description of the observations cited in support of our hypothesis, the reader is referred to foregoing sections of this review.)

It must be admitted, at the outset, that we do not know as yet through what pathways non-specific damage evokes the clinical manifestations of "shock." Loss of body weight (due at least partly to increased protein catabolism and tissue destruction), the formation of gastro-intestinal ulcers, a temporary rise in plasma potassium and a temporary fall in plasma chloride as well as other purely **retrogressive or catabolic manifestations** (disturbance of thermoregulation, blood circulation, etc.) are all characteristic of the "shock phase." The various theories, which attempt to explain how a comparatively localized injury can influence the entire body, and produce all these changes, during shock (intoxication, deficiency, etc.) have been discussed in the previous section. We do not feel that any of these theories are adequately proven and hence, we shall not dwell any longer on the possible pathways through which non-specific damaging agents might elicit the shock syndrome. It is of great theoretical importance, however, to keep in mind that whatever this pathway might be, it does not require the integrity of the hypophyseoadrenal system. It will be remembered that all these destructive, or detrimental, changes of the shock phase can be elicited in hypophysectomized or adrenalectomized animals and indeed tend to be much more severe in the absence of either or both of these glands. This is noteworthy because a series of other changes characteristic of the general adaptation syndrome—especially those which presumably are of a defensive nature—depend upon the integrity of the hypophysis and the adrenal cortex.

The **hypophysis** probably occupies the most important, central position in the constructive or defense reactions which are essential for resistance and adaptation to non-specific damage. There is good evidence to show that under such influences, the hypophysis produces increased amounts of **corticotropic hormones** since in hypophysectomized animals, the adrenal cortex shows no signs of hypertrophy or increased functional activity (the

apparently exceptional behavior of birds has been mentioned above) (545). We have considered the possibility that any type of alarming stimulus may cause a condition of "relative adrenal cortical insufficiency" and that the increased corticotropic hormone production might be viewed as a type of compensatory hypertrophy such as that seen after partial adrenalectomy (545). Other investigators (522c, 634) essentially concur with this view. Our interpretation received additional support from the many observations showing that in animals overdosed with corticoids, the response of the adrenal cortex to alarming stimuli is subnormal presumably because of deficient corticotropic hormone production.

It has been claimed that during the alarm reaction an excess of corticotrophic hormone can actually be demonstrated in the blood (651); however, because of the unusual bioassay method employed, this work requires confirmation.

Teleologically speaking, increased corticotropic hormone production is a useful reaction to stress since it augments the corticoid hormone production of the adrenals and thus raises non-specific resistance.

On the other hand, while the pituitary is actively engaged in increased corticotropic hormone production it is apparently less capable of elaborating **growth hormone, prolactin and gonadotropic hormones** ("shift in hormone production") (269a, 582) hence, during the general adaptation syndrome, somatic growth, milk secretion (in lactating animals) and the development of the gonads are inhibited. In the male there is an involution of the spermatogenic epithelium and of the Leydig cells with a consequent atrophy of the accessory sex organs (due to decreased testoid hormone production). In the female there are abnormalities in the development of the follicles and corpora lutea which may lead to disturbances in the sexual cycle (amenstrual ovulation, anovular menstruation, etc.).

There is ample evidence (see page 153 in section on *Pathologic anatomy*) that the **adrenal cortex** is enlarged and shows histologic signs of increased activity, especially during the alarm reaction phase of the general adaptation syndrome. During the stage of resistance, these changes become less obvious; during the stage of exhaustion there is a second period of marked adrenal enlargement which may or may not be accompanied by an overproduction of corticoid substances.

There can hardly be any doubt that at least during, and immediately after the alarm reaction stage, the enlargement of the adrenal is accompanied by a pronounced increase in **corticoid hormone** production. It was found that, in patients following operations, burns and other types of exposure to alarming stimuli, the corticoid activity of the urine rises considerably above normal (77, 232, 656, 657, 673, 674). It has also been claimed that the increased diuresis noted in aviators, at high altitude may

be the result of increased cortical hormone secretion, since the corticoids are known to have diuretic properties (479). It should be pointed out, however, that this interpretation has not been proven as yet.

The adrenal cortex is also a site of **17-ketosteroid and testoid hormone** production and hence it appeared of some interest to establish whether this function of the cortical cells is also influenced by alarming stimuli. In general it may be said that most relevant investigations are in accord with the assumption that immediately following exposure to an alarming stimulus, the 17-ketosteroid, and testoid excretion in the urine rises for a brief period and then declines to subnormal levels (113, 204-206, 213, 287, 623). These observations suggest that under the immediate influence of an alarming agent perhaps the 17-ketosteroid and testoid compounds present in the adrenal cortex are eliminated with the corticoids, but later, during the stage of resistance, the adrenal cortex produces only or at least predominantly, corticoid compounds ("shift in hormone production"). For this reason, and since the gonads become inactive (lack of gonadotropic hormone secretion), it is understandable that the 17-ketosteroid and testoid production and elimination is subnormal during the later stages of the general adaptation syndrome.

Albert (7) examined the possible testoid and folliculoid hormone production by the adrenals during the alarm reaction. He found that "in gonadectomized animals treated with 10% formalin solution there occurred a marked hypertrophy of the adrenal glands but no significant change in the size of the accessory sex organs (vaginal smears and preputial glands in the female; seminal vesicles and prostate in the male)." From this he concluded "that the adrenal cortical hypertrophy so characteristic of the alarm reaction, is not accompanied by increased sex hormone production."

It is known that certain pituitary corticotropic preparations can selectively stimulate the testoid production of the adrenal cortex and that the production of sugar-active and salt-active corticoids is not always proportionate. Hence, it appears very probable that there are three different corticotropic principles which stimulate the testoid, salt-active corticoid and sugar-active corticoid hormone production of the adrenal respectively (576). Apparently during the general adaptation syndrome only the production of the latter two is increased.

It has often been argued that if resistance during the alarm reaction were really dependent, to any great extent, upon increased corticoid hormone production, the treatment of shock-like conditions with corticoids should give more satisfactory results than have so far been obtained. In this connection it is of interest to note that even the basic corticoid hormone production of the adrenal is apparently enormous in comparison with the

amount of corticoid substance that has usually been administered for therapeutic purposes. Thus bioassays performed on the venous blood of adrenals indicate that "the average output of one suprarenal gland, per min., per kg. body weight, was equivalent to 0.6 gm. of suprarenal tissue" . . . "the potency of 1 ml. suprarenal plasma was at least several times, occasionally 10-12 times, as high as the activity obtained by extraction of 1 gm. of gland" (659). There is very convincing evidence that, in combatting damage during the alarm reaction, the sugar-active corticoids are much more effective than the salt-active (583, 587). Indeed, there is some doubt whether salt-active corticoids are of any value except in very special cases (KCl intoxication, dehydration, etc.). Since commercial preparations of sugar-active corticoids are often impure, and not as yet readily available, it is not surprising that, up to the present, it has rarely been possible to improve markedly upon the natural performance of the adrenal cortex.

It is noteworthy that the increased production of corticoids is especially important during the alarm reaction phase of the general adaptation syndrome. Adrenalectomized animals need much larger than maintenance doses of corticoids to withstand sudden stress (anoxia, muscular exercise, cold) (601) but after adaptation to a damaging agent, they usually tolerate it on maintenance doses of corticoids (351, 548, 551, 659).

Non-adapted, adrenalectomized animals fail to develop a normal counter-shock phase and hence, it has been concluded that corticoids play an important rôle in the development of counter-shock phenomena. Some recovery from the shock phase is seen, yet, even in adrenalectomized animals if the alarm reaction is not too severe. It is noteworthy, however, that in the case of chronic exposure even to mild stress, adrenalectomized animals can maintain themselves in the stage of resistance only for a very short period before exhaustion and death supervene. Hence, it must be concluded that although corticoids facilitate the process of adaptation, and delay the onset of exhaustion, they are not entirely indispensable for inurement (548, 551, 554).

The **chromaffin system** has been shown to play a prominent rôle only during the first few minutes of the alarm reaction when the blood pressure and the blood sugar show their transitory rise. It is questionable whether it is of great importance at any other time during the course of the general adaptation syndrome. It has been claimed that the discharge of chromaffin granules which occurs during the shock phase may be secondary to dehydration, since it can sometimes be prevented by maintaining the blood volume with infusions (209, 211). Animal experiments indicate that shock is not connected either with exhaustion (491) or with excess activity (487) of the sympathin and adrenalin-producing system.

The excess corticoid hormones (produced by the adrenal cortex, under

the influence of corticotropic hormones) cause a number of secondary changes, especially in the lymphatic organs, the antibody titer, carbohydrate metabolism, electrolyte metabolism, the cardiovascular system and the kidney which can now be considered individually.

The thymus and lymphatic organs involute under the influence of alarming stimuli in the intact animal but this involution is inhibited by adrenalectomy or hypophysectomy (542, 545). The thymus involution caused by corticotropic pituitary extracts is directly related to the adrenal enlargement (459) and corticotropic extracts, which cause marked thymus and lymphnode involution in the intact or hypophysectomized animal, have no such effect following adrenalectomy (611). On the other hand, corticoids induce thymus and lymphnode involution even in hypophysectomized or adrenalectomized animals and hence, it is reasonable to assume that their action is not mediated through the hypophysis or adrenal cortex.

It may be mentioned incidentally that some workers hoped to clarify the rôle of the thymus in the alarm reaction by examining the effect of thymectomy upon the survival of adrenalectomized rats but these investigations yielded no positive data (538).

The transitory lymphopenia and polymorphonuclear leukocytosis, characteristic of the alarm reaction, have been reproduced in experimental animals by purified corticotropic pituitary extracts (497). The latter also depress the lymphocyte count in thoracic duct lymph (497a). On the other hand, the changes in the white cell count induced by alarming stimuli are not as constantly and characteristically inhibited by adrenalectomy as is the involution of the thymus and of the other lymphatic organs (130). It is somewhat uncertain, therefore, whether the circulating leukocytes are as strictly under adrenal control as the thymocytes.

Recently, several interesting facts came to light which indicate that the alarm reaction may also have an important influence upon serologic immune reactions. It has been found that lymphocytes of normal rabbits contain a globulin identical with the normal serum γ -globulin which is important for antibody formation (681). Furthermore, "labelled globulin" (antibody protein) has been demonstrated in lymphocytes isolated from the lymphoid tissue of immunized mice (154). The presence of immune bodies in lymphocytes has also been confirmed in the immunized rabbit (257). All these observations suggest that the lymphatic organs play an important rôle in immune reactions. It has been noted, furthermore, that corticotropic hormone secretion accelerates the rate of release of antibodies from the lymphoid tissue of immunized rabbits (157) and that alarming stimuli enhance the antibody titer in the sera of previously immunized animals (92). Finally, it is claimed that the enhancement of antibody titer, produced by alarming stimuli, can also be elicited by corticotropic pitui-

tary extracts and adrenal cortical extracts, but not by desoxycorticosterone acetate. Cortical extracts, but not corticotropic extracts, are effective in this respect, even in the adrenalectomized animals. From these experiments it was concluded that "adrenal cortical mediation is essential for the control of the release of antibody from lymphocytes" (155).

The above-mentioned investigations make it very probable that the general adaptation syndrome influences serologic immunity. This may shed some light upon the observation that during the counter-shock phase of the alarm reaction anaphylactic phenomena are inhibited (310, 311).

The theoretic interpretation of the changes in **carbohydrate metabolism**, which occur during the general adaptation syndrome, has already been discussed in the section "Metabolic changes." Suffice it to recall here firstly that the changes in carbohydrate metabolism elicited by certain alarming stimuli (anoxia, folliculoids) and by corticotropic anterior pituitary extracts are inhibited by adrenalectomy; secondly that the sugar-active corticoids [*e.g.*, corticosterone, dehydrocorticosterone, but not the salt-active corticoids (desoxycorticosterone)],⁷ exert a pronounced effect upon carbohydrate metabolism; and thirdly that animals whose adrenal cortex is inactivated by hypophysectomy, adrenalectomy or "compensatory atrophy" (due to prolonged desoxycorticosterone overdosage) exhibit a great tendency to develop fatal hypoglycemia under the influence of alarming stimuli. All these observations suggest that the need for sugar is increased during the alarm reaction and hence an increased secretion of sugar-active corticoids is essential for resistance to stress. This increased sugar-active corticoid production may lead to hyperglycemia, increased glycogen deposition in tissues and occasionally even to glycosuria, if experimental conditions are such that sugar utilization is impeded (anoxia, thyroidectomy?). It is not impossible that certain types of clinical diabetes—especially those in whose etiology continued stress and strain appears to play a rôle—may have their origin in this type of hormonal derangement, rather than in a primary pancreatic failure.

The prominent changes in **electrolyte metabolism**, seen during the general adaptation syndrome, have also been discussed; see page 144, the section, *Metabolic changes*. In clinical shock, hypochloremia and a rise in plasma potassium are outstanding. These are reminiscent of the hypochloremia and potassium of adrenal insufficiency and were partly responsible for the interpretation of the shock phase as a type of "relative adrenal cortical insufficiency."

It is known that overdosage with salt-active corticoids (*e.g.*, desoxy-

⁷ In all our experiments, discussed in this review, desoxycorticosterone was administered in the form of its acetate.

corticosterone) causes sodium retention accompanied by hypochloremia and hypopotassemia. It has been claimed that the cardiovascular and renal changes produced by chronic overdosage with desoxycorticosterone are secondary to the hypopotassemia induced by this compound (134, 135, 159). We disagree with this view since in our experience the maintenance of normal blood potassium levels through oral administration of excess KCl failed to prevent these lesions in animals receiving excessive amounts of desoxycorticosterone (407, 599). It appears more probable that the salt-active corticoids produce organ changes by virtue of their sodium retaining property. This interpretation is supported by the observation that animals kept on a high NaCl intake are particularly sensitive to the toxic effects of desoxycorticosterone (599, 602). On the other hand, the so-called "acidifying salts" (ammonium sulphate, ammonium chloride, ammonium nitrate and calcium chloride) protect against this steroid (595, 599) and the possibility has been considered that this may be due to their ability to bind sodium and facilitate its excretion. Interestingly, the life-maintaining action (tested on adrenalectomized rats) of desoxycorticosterone is not significantly influenced by ammonium chloride (603).

For the understanding of the hormonal interrelations during the general adaptation syndrome, it is of fundamental importance to elucidate through what mechanism overdosage with salt-active corticoids produces organ changes. It will be recalled that desoxycorticosterone (especially when given to animals on a high sodium diet) produces **vascular lesions** identical with those seen in periarteritis nodosa (581, 593, 600), **hypertension** (577, 593), **myocardial** (592) and **joint lesions** similar to those observed in acute rheumatic fever (605), **nephrosclerosis** (572, 577, 591-593) and sometimes acute **nephritis** (539). It was obvious to consider the possibility that the diseases of man which are thus imitated by desoxycorticosterone overdosage might arise as a result of an excessive production of endogenous salt-active **corticoids**. In this sense, these lesions would have to be interpreted as "diseases of adaptation."

There is a good deal of evidence in favor of this interpretation, inasmuch as the above-mentioned diseases have long been known to occur following sudden or chronic exposure to stress (infections, cold, nervous strain, etc.). All these are conditions which elicit the adaptation syndrome and increase corticoid hormone production. It is not inconceivable, therefore, that the defensive production of corticoids—while useful in raising the resistance of the body to stress—would have certain detrimental side-effects due to the inherent toxicity of the corticoids. Such a defense reaction which, at least partly, defeats its own purpose, is not without precedent in experimental pathology. It is known that certain essentially useful immunologic defense reactions are responsible for serum sickness and anaphylaxis, both of which

conditions are definitely detrimental. Even in endocrinology we have examples of defense reactions which elicit harmful side-effects. Thus in the case of renal disease, the blood phosphate may rise to dangerous levels and in order to compensate for this, the parathyroids produce an excess of parathyroid hormone through which the blood phosphate level is restored towards normal. This is obviously a useful defense reaction but its consequence is that under the influence of excessive endogenous parathyroid hormone osteitis fibrosa-like changes develop in the skeleton and "renal rickets" results. It is possible that the diseases of adaptation are the consequences of a similar derailed or excessive adaptive reaction on the part of the adrenal cortex which under certain conditions of strain may produce disproportionate and excessive amounts of salt-active corticoids.

Subsequent work showed that overdosage with crude **anterior lobe extracts** can produce the same organ lesions as desoxycorticosterone (576) and the changes produced by these extracts are likewise most readily obtained in animals receiving a high NaCl intake and are effectively inhibited by the administration of acidifying salts (*e.g.*, ammonium chloride) (251). Therefore it is possible that the anterior lobe extract acts through its corticotropic hormones upon the adrenal and causes it to release an excessive amount of salt-active corticoids. These in turn would produce the same overdosage symptoms as are elicited by injection of desoxycorticosterone itself.

Notably, however, desoxycorticosterone administered to hypophysectomized animals fails to depress the blood chlorides (579) and causes little or no morphologic lesions in the cardiovascular system, the kidney or the joints (594). This observation raises the possibility that a hypophyseal principle may produce the "diseases of adaptation" directly and not through the intermediary of the adrenal cortex. It is indeed not inconceivable that even desoxycorticosterone acts only through the intermediary of the pituitary rather than vice versa. Yet preliminary experiments (590) indicate that in adrenalectomized animals (kept on maintenance doses of adrenal cortical extract), hypophyseal preparations do not elicit the usual organ changes.

In connection with experiments on hypophysectomized or adrenalectomized animals, it must be kept in mind, however, that it is difficult to maintain these on diets high in sodium and protein but low in carbohydrate content. On the other hand—as mentioned above—high carbohydrate diets in themselves suffice to give protection against the production of cardiovascular and renal changes by either desoxycorticosterone or anterior pituitary preparations. Hence, it is difficult to form a definite opinion concerning the causative hormonal mechanism and it must be admitted that the morphologic changes characteristic of overdosage with either des-

oxycorticosterone or anterior lobe extracts may be due to any of the following endocrine interactions:

- a. Both desoxycorticosterone and anterior lobe extracts may act upon the target organs (cardiovascular system, kidney, etc.) directly and independently of each other.
- b. The anterior lobe preparation may, through adrenotropic hormone, cause the adrenal cortex to produce desoxycorticosterone-like substances, which alone would have a direct action upon the target organs.
- c. Conversely, desoxycorticosterone may act upon the pituitary and cause it to secrete a substance directly affecting the target organs involved.
- d. Both anterior pituitary and adrenal corticoid hormones may have to act simultaneously upon the target organs, the lesions produced in the latter being the result of a synergistic action between corticoids and anterior lobe hormones.

Among these various possibilities, "b" is, *a priori*, most probable since there are many other examples proving the common occurrence of this type of mechanism. Thus, the thymus atrophy in the alarm reaction is proven to result from the liberation by the pituitary of adrenotropic hormone, which in turn causes the adrenal cortex to secrete thymus involution-producing corticoids. Similarly, the nervous stimulus of copulation causes progestational transformation in the endometrium because it stimulates the pituitary to secrete an excess of gonadotropic hormones, which in turn act upon the endometrium through the corpus luteum hormone.

Our most recent experiments show that in adrenalectomized rats maintained on a threshold dose of cortical extract, it is impossible to produce nephrosclerosis or myocarditis with anterior pituitary preparations. Since under otherwise similar conditions, nonadrenalectomized controls develop marked nephrosclerosis and cardiac lesions, it appears justified to conclude that the action of the anterior lobe principles is mediated through the adrenal cortex.

Be this as it may, the production of the "diseases of adaptation" with hypophyseal extracts furnished additional proof against the theory that these diseases are secondary to the depression of blood potassium occasioned by the salt-active corticoids, as our hypophyseal preparations did not depress the blood potassium and yet produced the typical organic lesions. These experiments are in accord, however, with the view that sodium retention plays a rôle in the pathogenesis of these lesions, since administration of excess NaCl facilitates their production both by pituitary and by corticoid preparations.

The possibility that the thyroid may play an important part in the development of the diseases of adaptation must also be considered. The fact that hypophsectomy inhibits the nephrosclerotic (and allied) actions of

desoxycorticosterone could, at least partly, be due to thyroid inactivation, especially since thyroideectomy has a similar effect and the nephrosclerotic potency of anterior pituitary extract is also diminished in the absence of the thyroid gland (251, 259). Conversely, thyroxin treatment sensitizes the rat to the nephrosclerotic action of both desoxycorticosterone and anterior hypophyseal preparations (580, 604). All these observations indicate that although the thyroid is perhaps not indispensable for the production of nephrosclerosis and allied phenomena, its hormone facilitates their development.

No definite interpretation can as yet be offered as regards the pathogenesis of the hypertension seen during the resistance phase of the general adaptation syndrome, but the following theoretical considerations should be kept in mind. Salt-active corticoids and anterior pituitary preparations elicit hypertension accompanied by the same organ changes (in kidney, heart vessels, *etc.*) as those associated with the rise in blood pressure induced by non-specific damage. Experimental work has shown furthermore, that the adrenal cortex plays an essential rôle in the production of hypertensinogen probably by stimulating its elaboration in the liver. The presence of the adrenals or desoxycorticosterone treatment are indispensable for the maintenance of the normal hypertensinogen level in rats (219). It is possible that the pituitary and corticoid hormones act upon blood pressure directly through this mechanism and that the renal changes are independent or are secondary to the high blood pressure. The fact that chronic hypertension elicited in rats by other means does not result in similar renal changes (143) speaks against this latter interpretation. It is not impossible, therefore, that the renal changes are primary and that the blood pressure is raised through the intermediary of pressor principles released by the pathologic kidney tissue.

VIII. CLINICAL IMPLICATIONS OF THE GENERAL ADAPTATION SYNDROME

Adaptation to our surroundings is one of the most important physiologic reactions in life; one might even go so far as to say that the capacity of adjustment to external stimuli is the most characteristic feature of live matter (549). It is hardly surprising, therefore, that some of the most important and most frequent diseases of man appear to be diseases of adaptation. There is increasingly more evidence to show that the diseases of adaptation play the same important rôle in pathology as the general adaptation syndrome in physiology. The observations reported in the previous sections of this review, indicate that some of these diseases (*e.g.*, the clinical syndrome of "shock," the gastro-intestinal ulcers, *etc.*) are merely signs of damage due to lack of adaptation, while others (*e.g.*, hypertension, peri-

arteritis nodosa, nephrosclerosis) are the result of abnormal or excessive adaptive reactions to our environment. We called attention to some of the errors which found their way into pharmacology, bacteriology and other branches of experimental medicine, because of the impression that if a certain change appears consistently, following treatment with a certain agent (a drug, a microbial infection, exposure to abnormal temperatures, etc.) this change is specifically—and perhaps even directly—caused by that agent. If, in such instances, further experimental work reveals that a number of agents can elicit the same change, the task of interpreting the observations appears to be insurmountably difficult and confusion ensues.

There are many similar examples in clinical medicine. For instance, such conditions as nephritis, rheumatic fever or acute gastric ulcers, in some instances indubitably occurred as the result of an acute infection but in other instances they could, with an equal degree of certainty, be traced to an exposure to intense cold, an intoxication or an emotional stimulus. If we assume that certain lesions are produced by the response of the body to damage as such, rather than to one specific pathogenic agent, the difficulty of interpreting the comparatively uniform response to divers agents is no longer insuperable.

Perhaps the strongest argument against this type of reasoning is the fact that the same degree of damage or stress does not necessarily always elicit the same response; even lesions which are manifestly not the specific result of one particular pathogenic agent, may be more prone to occur following exposure to one or the other type of damage. To give but one example, nephritis may be caused by a variety of micro-organisms, by exposure to cold or by treatment with various drugs but it is particularly frequent in patients suffering from staphylococcus infection with tonsillitis, scarlet fever or sepsis. This does not mean that the pathogenic agent of nephritis is a staphylococcus in the sense in which the pathogenic agent of tuberculosis is the tuberculosis bacillus. It merely means that staphylococcus infection elicits a somatic response which produces especially favorable conditions for the development of nephritis. Furthermore, we have seen that numerous factors can specifically sensitize or desensitize the body to one or the other manifestation of the general adaptation syndrome. Thus we have seen that sodium chloride sensitizes, while ammonium chloride desensitizes the kidney to the nephrosclerotic action of cold; glucose administration desensitizes while exposure to cold sensitizes the gastric mucosa to the ulcer-producing effect of spinal cord transection. The dissociation of symptoms, resulting from such selective sensitization or desensitization to one particular lesion, helps to understand that the same degree of stress or damage does not always result in the same symptomatology.

It would be tempting to survey all the diseases of unknown etiology from

this new point of view and to examine whether those among them which apparently can be caused by a variety of agents, belong to the category of the diseases of adaptation. Unfortunately, at the present time, we know far too little about the intricate mechanism of the adaptation syndrome to make such a systematic study profitable. It may be of some value, however, to call attention to a few apparently relevant diseases and cite pertinent literature which suggests that they have some relation to the general adaptation syndrome.

Nephrosclerosis and **hypertension** can most probably be regarded as diseases of adaptation when they occur as a result of continuous exposure to stress and strain (574). As explained above, they may be produced through the intermediary of the hypophyseo-adrenal cortical hormone mechanism. This final common pathway could explain that so many different types of strain may lead to the same end-result.

The fact that hypertension (676) and angina pectoris (184) may be elicited by purely emotional stimuli in man, should also be kept in mind in this connection.

It is noteworthy furthermore that Na restriction (246a) and high carbohydrate diets (324a) have repeatedly proved of benefit in the spontaneous renal hypertension of man.

The lipid and especially the cholesterol content of the adrenals is usually very high in cases of hypertension and chronic renal disease (63b, 99a, 99b, 195a, 293a, 332c, 333a, 333b, 678), however, as a rule, the cortex is not markedly enlarged. It is true that some investigators claim to have found hypertrophy and hyperplasia of the adrenal cortex, sometimes with an unusually high incidence of adenomas, in hypertensive patients (451a, 503a, 513a, 522b) but others state that these are no more frequent in hypertensive than in normotensive patients (79a, 142a).

It is perhaps significant that the 17-ketosteroid excretion is markedly lower in hypertensive than in normotensive subjects (79a). This may represent another instance of the previously mentioned "shift" in the hormone production of the adrenal cortex. While this gland produces excessive amounts of corticoids, it may not be able to elaborate the normal quantity of testoids.

It is of interest that in a patient with established hypertension, subsequent development of Addison's disease caused a fall in blood pressure, which remained unchanged by sodium chloride treatment but returned to the original hypertensive level under the influence of desoxycorticosterone. It was concluded that "the adrenal cortex may be important for the development or maintenance of essential hypertension in man" (473a). Some workers (632a) even ascribe the hypotensive effect of various toxic substances and infections to an impairment in adrenal cortical function.

The various forms of **nephritis** have always puzzled pathologists because they appear following—and probably as a result of—such diverse, noxious agents as tonsillitis, colds, scarlet fever, influenza, other infectious diseases, exposure to cold, pregnancy, intoxication with various drugs and allergic conditions (369). In experimental medicine, the similarity of the renal lesions produced by a diversity of agents, has also been discussed and Christian (105) “ . . . emphasized the non-specificity of lesions observed in the glomerulus of the kidney and offered this non-specificity as an explanation of many similarities in the signs and symptoms of renal disease.” Here again the assumption of a common hypophyseo-adrenal defense mechanism against damage would facilitate the understanding of the fact that such diverse stimuli can produce the same renal change.

The etiology of acute **rheumatic fever** has been discussed by pathologists for more than 100 years. Recently, it has been more and more customary to consider the condition an infectious disease caused by a specific type of microorganism. Yet Lichtwitz (370) introduces his book on rheumatic fever with the sentence “Rheumatic fever is a non-infectious disease.” He believes it to be caused by sensitization to antigens, protein in nature, which in most cases are products of micro-organisms. However, he is forced to admit that in the rheumatic individual, reactivation of the process can be brought about not only by the specific antigen but by a variety of non-specific factors; “thus fatigue, a chill, an adventitious infection, a slight injury, a touch of indigestion, a mental upset, or increased bodily activity may cause the rheumatic to relapse from quiescent into an acute febrile state.” In animals, cardiovascular lesions of the rheumatic type were produced by “anaphylactic hypersensitivity” to protein (499a).

It has been claimed that even rheumatoid arthritis can be elicited by a purely emotional stimulus (111).

The main problem is again to find the common pathway which could explain the similarity of the lesions produced by such a diversity of agents. Acceptance of the hypophyseo-adrenal theory does not necessitate abandonment of other interpretations. It merely implies that such agents as cold, bacteria, serologic disturbances, etc., have so influenced the hypophyseo-adrenal defense mechanism that an excessive amount of the salt-active corticoid hormones is elaborated whenever an individual is exposed to a particular type of stress and that the rheumatic attack is the result of such a derailed defense mechanism.

Periarteritis nodosa is another condition which has been produced experimentally by overdosage with anterior lobe or corticoid hormones. This vascular lesion frequently occurs in combination with pituitary or adrenal changes (30b, 206a, 372a, 488a) and in patients who previously suffered from rheumatic fever and it is often accompanied by hypertension. There

is evidence, furthermore, that in man periarteritis nodosa can be the consequence of exposure to a variety of non-specific damaging agents (600). Even in animal experiments it was possible to reproduce this condition by mere exposure to such non-specific damage as cold (574). It is rather likely, therefore, that periarteritis nodosa likewise belongs to the so-called diseases of adaptation (577).

There probably also are close relations between the so-called focal necrosis of the adrenal cortex, the **Waterhouse-Friderichsen syndrome** and the diseases of adaptation. It has been emphasized that the focal necrosis of the adrenal cortex often represents "a replica in miniature of the adrenal changes seen in the Waterhouse-Friderichsen syndrome" and that they appear to be caused by such a diversity of etiologic factors as infection, toxemia, endocrine factors and allergy (431). Since animal experiments showed that exposure to particularly severe types of stress may cause necrotic lesions in the adrenals (see above) it appears quite probable that in man changes of this type are also due to an excessive stimulation of the adrenal cortex which results in a final breakdown. This view receives support from observations showing that the cortical lesions in the Waterhouse-Friderichsen syndrome are suggestive of exhaustion and that corticoid hormones are beneficial in this condition (486a, 625a).

There is some reason to believe that **eclampsia** may likewise belong to this group of diseases. Thus, Smith and Smith (614) were struck by the similarity of the organ changes noted in experimental animals treated with "menstrual toxin" and those characteristic of the alarm reaction. These authors found, furthermore, that treatment with adrenal cortical extract is beneficial in patients suffering from eclampsia (a condition which they believe to be caused by a similar "toxin"). They concluded, "that the adrenal cortical exhaustion may play a part in the alarming rapidity with which clinical manifestations may increase in severity in the pre-eclamptic patient. Up to a certain point, overactivity of the adrenal cortex may combat the 'toxin' as in the first stages of the 'alarm reaction' . . ." The histologic similarity between the glomerular lesions seen in eclampsia and those reproduced by a variety of other non-specific agents has also been noted (105).

Gastro-intestinal ulcers, especially the acute gastric erosions and duodenal ulcers (Curling's ulcer), often noted in association with extensive burns, almost certainly also belong to this group of lesions. It is noteworthy that following burns, intestinal ulcerations occur in conjunction with adrenal hemorrhages and with renal changes similar to those produced by acute overdosage with hypophyseal or corticoid hormones (177). Furthermore, numerous non-specific damaging agents have been shown to produce gastric ulcers both in animals and in man (597). Even purely emo-

tional stimulation may result in the formation of peptic ulcers in man (433, 691). It is almost certain, therefore, that acute gastric ulcers are part of the adaptation syndrome but there is no adequate proof as yet which would permit us to classify chronic gastric ulcers into this category.

It has already been mentioned that **appendicitis-like** changes may be produced in animals by exposure to very acute alarming stimuli (546). The appendix contains a great deal of lymphatic tissue and as we have repeatedly stated, the lymphatic organs are particularly sensitive to non-specific damage because the corticoids liberated during the general adaptation syndrome cause the lymphocytes to disintegrate. This may perhaps also explain the not uncommon development of appendicitis in patients suffering from a variety of contagious diseases (236).

The acute tonsillitis so often noted after exposure to cold following burns, radiation damage and other types of non-specific injuries may perhaps also find its explanation in a similar phenomenon. It is quite conceivable that the lymphatic organs undergo acute involution as a result of a defensive corticoid hormone production and that micro-organisms settle secondarily within the damaged lymphatic tissue, because the latter form a particularly favorable medium for microbial development.

Many other lesions bear some resemblance to the diseases of adaptation, but their connections with the latter have not as yet been the subject of special investigation. Among these we may mention the so-called "**post-operative focal necrosis of arteries**" (327), the so-called "**diffuse collagen disease**" (332b), **fibrositis** (613a), the fibrinoid necrosis and periarteritis nodosa-like changes in the vessels and heart muscles of experimental animals treated with serum (422), the "**shock disease**" which is often epidemic among the snowshoe hare (240) and perhaps even some of the types of the so-called "**effort syndrome**" (238, 367, 694).

It remains to be proven whether abnormal adaptive processes play a rôle in the production of metabolic diseases such as **thyrotoxicosis** (421a, 432) or **diabetes mellitus** (371, 615) when they occur following purely emotional stimuli.

In connection with this latter disease, a number of interesting problems come to mind. We noted in our animal experiments with crude anterior pituitary extracts that the healing of the inflammatory reactions around the injection sites was much improved by the same high carbohydrate diets which also antagonized the toxic effects of the pituitary extract upon the kidney and the cardiovascular system. Could it be that in diabetes, impaired wound healing is due to a failure of carbohydrate utilization by the tissues? In this event, administration of carbohydrates, plus insulin, to diabetics would improve wound healing through that same mechanism which appears to be operative in our experimental rats, namely, by making

more glucose available for tissue repair. Could it be, furthermore, that the gradually decreasing incidence of cardiovascular and renal complications in diabetes is due to the now popular treatment with insulin and diets containing adequate amounts of carbohydrates which facilitate glucose utilization? All these are still unsolved problems, but questions of sufficient practical importance to deserve systematic experimental analysis.

The connections between **Cushing's syndrome** and the adaptation syndrome have been studied in detail by Albright (10). He emphasized that the excessive production of corticoids as well as the resulting changes in sugar and electrolyte metabolism in Cushing's syndrome are very reminiscent of those seen in the general adaptation syndrome. This is particularly true of those cases in which the serum potassium and chloride levels are below normal (110, 686). It is significant, furthermore, that Cushing's syndrome is often conducive to nephrosclerosis and hypertension, that is, changes which are experimentally produced by anterior lobe or corticoid hormones. These observations suggest that in Cushing's disease, we have a condition closely related to the diseases of adaptation but differing from the latter in that the hormonal imbalance is the primary cause of disease, not the consequence of adaptation to exogenous damage.

Even certain types of **Simmonds' disease** may be related to the disease of adaptation. Thus, certain instances of hypopituitarism, developing after pregnancy, were ascribed to "exhaustion" of the anterior lobe, due to increased demands during gestation (167). This relationship is still very problematic although it must be admitted that increased demands for excess anterior lobe hormone production during stress may, under certain conditions, cause a breakdown of pituitary tissue.

A close relationship between the general adaptation syndrome and **allergy** has often been suspected, especially since the liberation of histamine-like, toxic metabolites has been considered to play an important role in the pathogenesis of both these conditions. The extensive studies of Williams (684a, 684b) led him to the following conclusion: "I have suggested that physical allergy is a perversion of a normal physiologic reaction, the alarm reaction of Selye. Since I have shown that the hormones of the adrenal cortex can relieve the symptoms of physical allergy and these hormones control the permeability of cell membranes and electrolyte and water metabolism, and since intact adrenal function is necessary for the alarm reaction to take place, I feel that good, indirect evidence, that physical allergy is an alteration of this normal mechanism, is at hand."

It is evident from what we said above, that some of the diseases mentioned in this section are by no means proven to be diseases of adaptation. They are listed here merely in order to call attention to their possible connections with the general adaptation syndrome. For other diseases, how-

ever (*e.g.*, hypertension, nephrosclerosis, periarteritis nodosa), we feel that there is strong evidence to show that they are probably due to abnormal adaptive processes. If this theory proves correct, it follows that some of the most common fatal diseases of man are due to a breakdown of the hormonal adaptation mechanism.

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