Endocrine Reactions During Stress.*

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ALMOST TWO DECADES have passed since the publication of a short note on "A Syndrome Produced by Diverse Nocuous Agents."[1] Since that time, the relationships between the so-called "general adaptation syndrome" or "stress syndrome," and virtually every branch of physiology and clinical medicine have been subjected to study. Those who seek detailed information concerning particular aspects of the stress problem will find a key to the world literature in the monographs[2-10] and yearbooks[11-14] specially devoted to this topic. There, they will also find a survey of the original papers dealing with stress and anesthesia, as well as with such subjects as artificial hibernation, ganglioplegics, steroid anesthesia, etc., which are of more immediate interest to this group. I thought I would fulfill the task you assigned to me better by merely mentioning a few of the most striking facts, more specifically concerned with the relationships between stress, the nervous system and particularly anesthesia, devoting most of my attention to an outline of the stress concept as a whole.

Considerable attention has been given of late to the possible relationships between the so-called "artificial hibernation" (induced by cold and ganglioplegic drugs) and the general adaptation syndrome. As Laborit, the distinguished proponent of artificial hibernation so clearly expressed it, there is no doubt a great field for therapeutic efforts based on the principle of "disconnecting" the various defensive reactions of the vegetative and humoral systems at certain critical times. This is so, for instance, during certain surgical operations, which can best be tolerated if most vital phenomena are inhibited to the minimum compatible with the maintenance of life.

It had long been noted, furthermore, that various steroids, including desoxycorticosterone, cortisone, progesterone and many others, can produce in a variety of animal species (even in primates, such as the rhesus monkey) a state of excitation, followed by deep anesthesia. It has more recently been shown that such steroid anesthesia can also be produced in man.

Several laboratories reported furthermore that the electroshock threshold of experimental animals and their sensitivity to various anesthetics can be affected by corticoids.[14a] Interestingly, when cortisone or cortisol are given in moderate doses as a pretreatment, they tend to shorten the duration of sleep induced by various anesthetics. On the other hand, acute overdosage with cortisone results in nervous depression.[23] Acute overdosage with cortisol hemisuccinate sodium (COLS) caused only sedation, but no actual anesthesia, in rats, even at the highest dose-levels (1000 mg./kg!). However, in themselves

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nearly inactive doses of progesterone, desoxycorticosterone or pentobarbital induced deep anesthesia in rats pretreated with COLS.[14b]

The marked emotional changes (sometimes bordering on psychoses), which may occur in predisposed individuals during treatment with ACTH and cortisone are now too well known to require special discussion.

All these findings make it very probable that endogenous corticoids secreted during stress also have an important influence upon nervous and emotional reactions, as well as upon the course of anesthesia. Conversely, it is now definitely established that nervous stressors (pain, emotions) are particularly conducive to the development of the somatic manifestations of the stress syndrome, so that stress can both cause and be caused by mental reactions.

It may be opportune, therefore, to take stock now, after 20 years of stress research, and present before this group the most fundamental facts which we have learned about the physiopathology of stress.

However, for those not particularly familiar with the subject, it may be well first to give a glossary of the most common technical terms used in this field.

Glossary of Technical Terms and Abbreviations

G-C	=	glucocorticoid (e.g., cortisone, cortisol).
M-C	=	mineralocorticoid (e.g., desoxycorticosterone, aldosterone).
A-C	=	antiphlogistic corticoid (e.g., cortisone, cortisol). Antiphlogistic, glucocorticoid, lympholytic and catabolic activity tends to run parallel in most steroids so far examined.
P-C	=	prophlogistic corticoid (e.g., desoxycorticosterone desoxocortisone). Prophlogistic activity tends to run parallel with mineralocorticoid activity in most compounds so far examined.
DCA	=	desoxycorticosterone acetate.
MAD	=	17-methyl Δ^5-androstene-3β, 17β-diol. (Ordinary methylandrostenediol).
Cortisol	=	hydrocortisone, Kendall's compound "F."
STH	=	somatotrophic hormone or growth hormone of the hypophysis.
STRESS	=	a non-specific deviation from the normal resting state; it is caused by function or damage and stimulates repair.
Non-specific change	=	change which can be produced by many or all agents.
Specific change	=	change which can be produced only by one or few agents.

Precursors of the Stress Concept

EVER SINCE man used the word "disease" he had some, at least subconscious, inkling of the stress concept. The very fact that a single term can be used to denote a great variety of individual maladies, clearly indicates that they have something in common. They possess, as we would now say, some non-specific features which permit us to distinguish disease from the condition of health. Yet, precisely because these manifestations are not characteristic of any one disease, they have received little attention in comparison with the specific ones. They were thought to be of lesser interest for, unlike the latter, they did not help to recognize the "eliciting pathogen" or lend themselves to any effective type of specific therapy.

Nevertheless, several early investigators have attempted to elucidate the mechanisms involved in such non-specific reactions. Since

our knowledge of the nervous system antedates, by far, the development of modern endocrinology, it is understandable that, among the two great integrating systems of the body, the nervous and the hormonal systems, the former was the first to be examined from this point of view. Ricker, Speransky, Reilly, Hoff and many others have gathered important data concerning the role of the nervous system in such non-specific reactions as fever, polymorphonuclear leucocytosis, inflammation, etc. In the domain of what may be called "physiologic stress," W. Cannon's studies helped us to understand the part played by the sympathetic nervous system and its humoral effector substances.

Furthermore, quite independently, a great deal of progress has been made in the study of pituitary and adreno-cortical hormones by chemists, physiologists and clinicians, too numerous to mention by name.

All the knowledge acquired as a result of these early investigations was indispensable for the eventual formulation of the stress-concept, whose leading motive is one of unification. Additional experiments had to be performed, however, to show that the many non-specific responses of individual target organs are closely integrated and actually represent part of a single biologic response, the general adaptation syndrome. These investigations, which will be outlined below, made it evident that the stress pattern of reactions plays an integral part in the most varied physiologic, pathologic and pharmacologic phenomena.

The Concept of Stress

BY A SERIES of experiments on animals it was demonstrated, in 1936, that the organism responds in a stereotypical manner to a variety of widely different factors, such as: infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue or X-irradiation. The specific actions of all these agents are quite different. Their only common feature is that they place the body in a state of general (systemic) stress. Hence, we concluded that the stereotypical response, which is superimposed upon all specific effects, represents the somatic manifestations of non-specific stress itself.

What is non-specific stress? The term had long been used in physics to denote the interaction between a force and the resistance opposed to it. For instance, pressure and tension can put inanimate matter under stress. The above mentioned non-specific response was thought to represent the biologic equivalent of such physical stress. The term has now been quite generally accepted in this sense not only in English, but also in most other languages since attempts to translate "stress" led to much confusion.

The Concept of the General Adaptation Syndrome (G. A. S.)

THE MOST OUTSTANDING manifestations of this stress-response were: adrenocortical enlargement with histologic signs of hyperactivity, thymico-lymphatic involution with certain con-

comitant changes in the blood count (eosinopenia, lymphopenia, polynucleosis) and gastro-intestinal ulcers, often accompanied by other manifestations of damage or shock.

We were struck by the fact that, while during this reaction all the organs of the body show involutional or degenerative changes, the adrenal cortex actually seems to flourish on stress. We suspected this adrenal response to play a useful part in the systemic, non-specific adaptive reaction, which we visualized as a "call to arms" of the body's defense forces and named the "alarm reaction."[1]

Subsequent studies showed that the alarm reaction is but the first stage of a much more prolonged general adaptation syndrome (G-A-S). The latter comprises three distinct stages, namely:

(1) the alarm reaction (A-R), in which adaptation has not yet been acquired,

(2) the stage of resistance (S-R), in which adaptation is optimal,

(3) the stage of exhaustion (S-E), in which the acquired adaptation is lost again.

The Mechanism of the General Adaptation Syndrome (G.A.S.)

In order to elucidate the kinetics of this syndrome we proceeded as follows:

Rats were adrenalectomized and then exposed to stressor agents. This showed us that in the absence of the adrenals, stress can no longer cause thymico-lymphatic involution or characteristic blood count changes.[15]

When adrenalectomized rats were treated with the impure cortical extracts available at that time, it became evident that thymico-lymphatic involution and the typical blood count changes could be produced by adrenal hormones even in the absence of the adrenals. Therefore, these changes were considered to be indirect results of stress mediated by corticoids.[15] [16]

Conversely, the gastro-intestinal ulcers and other manifestations of pure damage or shock were actually more severe in adrenalectomized than in intact animals and could be lessened by treatment with cortical extracts. It was concluded that these lesions are not mediated through the adrenal; in fact, they are actually combated by an adequate adrenocortical response to stressor agents.[15]

What stimulates adrenocortical function during stress? In the course of the next year, we found that among many surgical interventions tried, only hypophysectomy prevents the adrenal response during the alarm reaction. Hence, we concluded that stress stimulates the cortex through an adrenocorticotrophic hormone, now known as ACTH.[17] [18]

Then pure cortical steroids became available, thanks to the classical investigations of Kendall and Reichstein. With these, we could show that administration of mineralo-corticoids or M-Cs (such as desoxycorticosterone) produces experimental replicas of the so-called hypertensive and inflammatory "rheumatic" diseases; notably, nephrosclerosis, hypertension, vascular lesions (especially periarteritis nodosa and hyalin necrosis of arterioles)[19] as well as arthritic changes resembling, in acute experiments, those of rheumatic fever and, after chronic treatment, those of rheumatoid arthritis.[20] Yet, even very high doses of mineralocorticoids did not induce any noteworthy thymico-lymphatic or blood count changes, such as were caused by cortical extracts.

Significantly, exposure of animals to certain non-specific stressor agents (e.g., cold) produced marked adrenocortical enlargement and organ changes very similar to those elicited by the administration of mineralo-corticoids.[21] Still, many investigators doubted that secretion of M-Cs could be involved in the pathogenesis of disease, since the very existence of nature, endogenous M-Cs was questioned. Indeed until quite recently some of the most eminent students of the adrenal gland advocated the "unitarian theory," which held that the gland secretes only one corticoid, so that a derangement in the balance between antagonistic cortical hormones would be impossible. This concept was definitely disproven by the isolation of aldosterone from both the tissue and the venous blood of the adrenals.[22]

Extracts rich in gluco-corticoids or G-Cs (such as cortisol and cortisone), on the other hand, were highly potent in causing thymico-lymphatic involution and in eliciting the characteristic blood count changes of the alarm reaction. They also tended to inhibit the inflammatory "rheumatic like" changes which can be elicited in animals by mineralocorticoids. Thus, in many respects, the two types of corticoid hormones antagonize each other.[2] [16]

Another interesting activity of the corticoids, discovered at about this time, is their singular effect upon the central nervous system of animals. A variety of steroids, among which figured both G-Cs (e.g., cortisone) and M-Cs (e.g., DCA) as well as other steroid hormones, and hormone-metabolites (e.g., pregnanediol, pregnanedione), proved to possess the property of causing a state of great excitation and confusion, followed by marked depression of all reflex activities and, eventually, deep anesthesia.[23] This observation raised the question whether a pronounced increase in the activity of endogenous corticoids could be responsible for certain nervous and emotional accompaniments of exposure to stress. After the introduction of cortisone into clinical therapy, it became evident that, in man, this hormone can also exert a powerful effect upon the central nervous system. In animals, both G-Cs and M-Cs exhibit this effect, hence we shall have to watch for it as soon as patients will be treated with large doses of aldosterone.

The terms "gluco-corticoids" and "mineralo-corticoids" emphasize the salient metabolic actions of these substances; from a clinical point of view, however, their effects upon inflammation are perhaps of even greater interest. Since the gluco-corticoids inhibit inflammation, while the mineralo-corticoids enhance it, the G-Cs may appropriately be called "antiphlogistic corticoids" or "A-Cs" and the M-Cs "prophlogistic corticoids" or "P-Cs," when they are discussed with reference to their effects upon inflammation. It remains to be seen, however, whether G-C and A-C (or M-C and P-C) activities neces-

sarily run parallel in all steroid compounds, including those (like aldosterone) which have not yet been fully examined for these effects.

Inflammatory granulomas, especially those produced in the vicinity of joints by the local application of irritants (e.g., formalin, mustard powder), as well as certain allergic reactions, are likewise aggravated by P-Cs and inhibited by A-Cs. Apparently, the response of the adrenal cortex is most important not only in defense against systemic stress (affecting the whole organism), but also in the manifold topical defense reactions which occur upon exposure to local stress (e.g., bacterial or chemical irritants, response of a "shock organ" to an allergen).[2] [24] These findings helped to formulate the concept of the local adaptation syndrome (L-A-S) to be discussed below.

In this connection, the hormone sensitivity of certain so-called "anaphylactoid inflammatory reactions" is of special interest. Actually, our attention first had been called to a possible relationship between the adrenal cortex and inflammation by an incidental observation on rats, given parenteral injections of egg-white. It was found that the rat is naturally hypersensitive to egg-white, and responds to the intraperitoneal or intravenous administration of this substance by an acute serous inflammation of the paws and snout. This inflammatory response was greatly aggravated in adrenalectomized animals (presumably because they could not defend themselves by the endogenous production of A-Cs). On the other hand, it was prevented by treatment with systemic stressors, directly in proportion to the adreno-cortical enlargement they produced (presumably, as a result of excess A-C secretion.)[18] Subsequently, it could be shown that cortisone and ACTH inhibit, while certain crude anterior pituitary preparations and desoxycorticosterone aggravate this anaphylactoid type of acute inflammation.[26]

Curiously, our crude anterior pituitary extracts also duplicated most of the above mentioned actions of P-Cs upon the cardiovascular system, the blood pressure, the connective tissue (inflammation), and the kidneys.[16] [26] The hypophyseal preparations which we used, were definitely corticotrophic, in that they enlarged the adrenal cortex, but they were particularly rich in the so-called "growth hormone" or somatotrophic hormone (STH). This made it difficult to interpret our early experiments, in which such crude extracts were used, because we were unable to distinguish clearly between the effects of ACTH and STH. However, as soon as we obtained purified ACTH, it became evident that the above mentioned pathogenic actions of the crude anterior pituitary preparations could not be due to their ACTH content, since even the highest tolerable doses of the pure corticotrophic hormone failed to duplicate their predominant P-C effects. On the other hand, overdosage with purified STH caused cardiovascular and renal lesions, virtually identical with those previously observed in animals treated with P-Cs. It was then concluded that, probably, the characteristic actions of our crude anterior pituitary preparations were mainly due to their STH content. It remains to be seen to what extent STH acts indirectly by stimulating the P-C production of the adrenal cortex, or directly by sensitizing the peripheral tissues to P-Cs. Preliminary observations suggest that the last-mentioned mechanism is more important although both may be implicated.[27] This point is not yet settled.

From the internist's point of view, perhaps the most interesting role of STH in the adaptation syndrome is that it can effectively combat catabolism and susceptibility to infections. Animals heavily over-

dosed with ACTH or A-Cs, tend to lose a great deal of weight. Eventually they die, almost always as a result of generalized septicemia, caused by normally saprophytic micro-organisms. In rats, the lung tissue appears to be singularly predisposed to such infections. Under these conditions, adequate doses of STH prevent the loss of body-weight as well as the excessive microbial proliferation.[28] It remains to be seen to what extent these actions of STH will prove to be of value in the management of infections in man, but experiments on rats have already demonstrated the great influence of adaptive hormones upon resistance to the human type of tuberculosis. Normally the rat is virtually resistant to tuberculosis bacilli; it may be rendered sensitive by ACTH or A-Cs and this sensitivity can, in turn, be abolished by STH.[29 30]

Conditioning of Hormone Actions

AS WORK along these lines progressed, it became increasingly more obvious that the activity of the hormones produced during stress depends largely upon a variety of conditioning factors. Both the production of the adaptive hormones and their effect upon individual target organs proved to be greatly influenced by heredity, age, previous exposure to stress, the nutritional state, etc. Thus, for instance, the production of corticotrophic hormone by the pituitary is enhanced by a high-protein diet, while the action of M-Cs upon most target organs is augmented by excess sodium.[16]

Stress itself is perhaps the most effective and most common factor capable of conditioning the actions of adaptive hormones. Thus systemic stress augments the antiphlogistic, lympholytic, catabolic and hyperglycemic actions of A-Cs, while the salient effect of the adaptive hormones, that of modifying the course of inflammation, naturally cannot manifest itself unless some topical stressor first elicited a phlogistic response.

Ingle[31] introduced the concept of the "permissive actions" of corticoids. This term implies that the adrenal hormone does not affect a target of stress itself, although it permits a stressor to act upon it. Furthermore, allegedly the presence or absence of a permissive factor can only allow or disallow a reaction, but is unable to vary its intensity. To illustrate this concept one might compare the production of light by an electric lamp to the biologic reaction and the switch to the permissive factor. The switch cannot produce light, nor regulate the degree of its intensity, but unless it is turned on, the lamp will not function. Correspondingly, the functional signs—generally considered to be characteristic of corticoid overproduction during stress—would not result from any actual increase in corticoid-secretion, but from the extra-adrenal actions of the stressors themselves. The presence of corticoids would be necssary only in a supporting capacity to maintain the vitality and reactivity of tissues.

Actually, it is precisely in the specific and not in the non-specific stress reactions that the corticoids play a purely permissive role of this type. Here they are necessary only to prevent stress and collapse, thus keeping the tissues responsive. For instance, adrenalectomized rats will not respond to injected STH with somatic growth, or to sexual stimulation with mating, without a minimal maintenance corticoid treatment. These reactions are in fact not characteristic of the corticoids and could not be duplicated, in the absence of the specific stimulus, even with the highest doses of corticoids. The characteristic functional signs of A-C overproduction which we see in the alarm reaction (e.g., atrophy of the lymphatic organs, catabolism, inhibition of inflammation) are also impeded by adrenalectomy and restored even by mere maintenance doses of A-Cs in the presence of stress, which sensitizes or conditions the tissues to them. However, unlike specific actions, these non-specific effects can also be duplicated in the absence of any stressor if large doses of A-Cs are given.[14]

The importance of such conditioning influences is particularly striking in the regulation of stress reactions, because, in the final analysis, they are the factors which can actually determine whether exposure to a stressor will be met by a physiologic adaptation syndrome, or cause "diseases of adaptation." Furthermore, in the latter instance, these conditioning factors can even determine

the selective breakdown of one or the other organ. We are led to believe that differences in predisposition, due to such factors, might explain why the same kind of stressor can cause diverse types of diseases of adaptation in different individuals.

Incidentally, it was only on the basis of such experiments that the mechanism through which stress affects the adrenal cortex, could be clarified. We noted that stressors such as formaldehyde, which caused marked adrenal hypertrophy in the normal, but not in the hypophysectomized animal, remained without effect (upon the adrenal), even if the adrenal cortex was prevented from undergoing atrophy by the administration of pituitary extract. The effect of such a drug on the adrenal appears to be an indirect one due to pituitary stimulation.[17]

The Concept of Local Adaptation Syndrome (L-A-S)

It has long been known that many local responses to injury are non-specific; it has been noted, for instance, that a variety of "topical stressors" (burns, microbes, drugs) share the power of producing non-specific tissue damage and/or inflammation. However, it is only recently that the close relationship between the systemic and local types of nonspecific reactions has been more clearly established. While the characteristic response of the body to systemic stress is the G-A-S, characterized by manifold morphologic and functional changes throughout the organism, topical stress elicits a "local adaptation syndrome" (L-A-S), whose principal repercussions are confined to the immediate vicinity of the eliciting injury. They consist, on the one hand, of degeneration, atrophy and necrosis, on the other of inflammation, hypertrophy, hyperplasia, and, under certain conditions, neoplasia.

L-A-S and G-A-S

AT FIRST SIGHT, there appears to be no striking similarity between the systemic and the local reaction type. A patient in traumatic shock furnishes a characteristic example of the G-A-S and, in particular, of its earliest stage, the shock phase of the general alarm reaction. An abscess, formed around a splinter of wood represents a typical example of the L-A-S and, in particular, of its stage of resistance,[1] during which the defensive inflammatory phenomena predominate. On the surface, these two instances of disease reveal no striking similarities and yet, more careful study shows them to be closely related.

The experimental observations which led us to these conclusions have been described elsewhere.[32 33] Let us restate here, however, that, among other things, the G-A-S and the L-A-S are thought to be interrelated because:

(I) both are non-specific reactions, comprising damage and defense;

(II) both are triphasic, with typical signs of "crossed resistance" (or, depending upon the the stressors used, "crossed sensitization"), during the second stage;

(III) both are singularly sensitive to the so-called "adaptive hormones" (ACTH, STH, corticoids);

(IV) if the two reactions develop simultaneously in the same individual, they greatly influence one another; that is, systemic stress markedly alters tissue-reactivity to local stress and vice versa.

The Concept of the Diseases of Adaptation

THUS WE ARRIVED at the conclusion that the pathogenicity of many systemic and local stressor agents depends largely upon the function of the hypophysis-adrenocortical system. The latter may either enhance or inhibit the body's defense reactions against stressors. We think that derailments of this adaptive mechanism are the principal factors in the production of certain maladies which we consider, therefore, to be essentially diseases of adaptation.

It must be kept in mind that such diseases of adaptation do not necessarily become manifest during exposure to stress. This is clearly demonstrated by the observation that temporary overdosage with desoxycorticosterone can initiate a self-sustaining hypertension, which eventually leads to death, long after hormone administration had been discontinued. Here, we speak of "meta-corticoid" lesions.

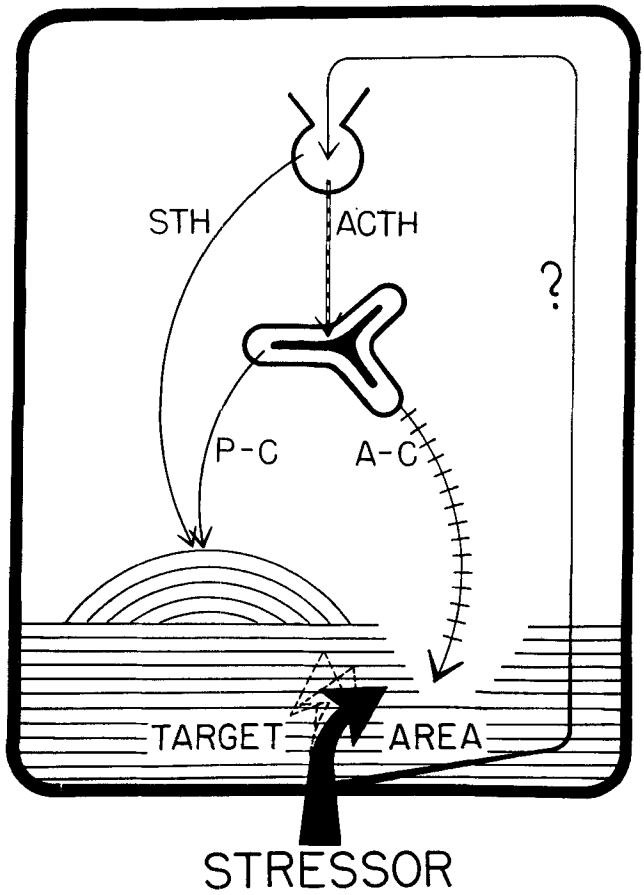
The possibility that a temporary excess of endogenous aldosterone could induce similar delayed maladies deserves serious consideration.

Among the derailments of the G-A-S which may cause disease, the following are particularly important:

(1) An absolute excess or deficiency in the amount of adaptive hormones (e.g., corticoids, ACTH, STH) produced during stress.

(2) An absolute excess or deficiency in the amount of adaptive hormones retained (or fixed) by their peripheral target organs during stress.

(3) A disproportion in the relative secretion (or fixation) during stress, of various antagonistic adaptive hormones (e.g., of ACTH and A-Cs, on the one hand, and of STH and P-Cs, on the other).



(4) Production by stress of metabolic derangements, which abnormally alter the target organ's response to adaptive hormones (through the phenomenon of "conditioning").

(5) Finally, we must not forget that, although the hypophysis-adrenal mechanism plays a prominent role in the G-A-S, other organs which participate in the latter (e.g., nervous system, liver, kidney) may also respond abnormally and become the cause of disease during adaptation to stress.

Summary of Observations

To summarize we might say that all agents which act upon the body or any of its parts exert dual effects:

(1) Specific actions, with which we are not concerned in this review, except insofar as they modify the non-specific actions of the same agents.

(2) Non-specific or stressor effects, whose principal pathways (as far as we know them today) are illustrated in the adjacent drawing.

The stressor acts upon the target (the body or some part of it) directly (thick arrow) and indirectly through the pituitary and adrenal.

Through some unknown pathway (labelled by a question mark), the "first mediator" travels from the directly injured target area to the anterior pituitary. It notifies the latter that a condition of stress exists and thus induces it to discharge ACTH.

It is quite possible that this "first mediator" of hormonal defense is not always the same. In some instances, it may be an adrenaline discharge, in others a liberation of histamine-like toxic tissue metabolites, a nervous impulse or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme).

ACTH stimulates the adrenal cortex to discharge corticoids. Some of these, the prophlogistic corticoids (P-C), stimulate the proliferative ability and reactivity of connective tissue; they enhance the "inflammatory potential." Thus, they help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the pathogenic stressor agent.

However, under ordinary conditions, ACTH stimulates the adrenal glands much more effectively to secrete *antiphlogistic corticoids* (A-C). These inhibit the ability of the body to put up granulomatous barricades in the path of the invader; in fact, they tend to cause involution of connective tissue with a pronounced depression of the inflammatory potential. Thus they open the way to the spreading of infection.

It is not yet known whether ACTH always stimulates the adrenal glands to produce the various corticoids in the same proportions and always with a great predominance of A-Cs. Certain recent experiments[84] suggest that, depending upon conditions, ACTH may cause the predominant secretion of one or the other of the steroid hormones. However, be this as it may, the *somatotrophic* hormone (STH) of the pituitary gland increases the inflammatory potential of connective tissue, very much as the P-Cs do; hence, it can sensitize the target area to the actions of the latter.

It is possible that the hypophysis also secretes some special corticotrophin which induces the adrenal gland to elaborate predominantly P-Cs; indeed, STH itself may possess such effects, but this has not yet been proven. In any event, even if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence can be vastly different, depending upon "conditioning" factors (such as ACTH), which specifically sensitize the target area for one or the other type of corticoid action. Actually, conditioning factors could even alter the response to ACTH of the adrenal cortex itself, so that its cells would produce more A-Cs or P-Cs. Thus, during stress, one or the other type of effect can predominate.

The fundamental reaction-pattern to topical stressors is a local adaptation syndrome with inflammation, to systemic stressors the general adaptation syndrome. Various modifications of these two basic responses constitute the essence of most diseases.

Outlook Suggested by These Observations

PASTEUR, KOCH and their contemporaries introduced the concept of specificity into medicine, a concept which proved to be of the greatest heuristic value up to the present time. Each individual well-defined disease, they held, has its own specific cause. It has been claimed by many that Pasteur failed to recognize the importance of the "terrain," being too preoccupied with the pathogen (micro-organism) itself. His work on induced immunity shows that this is in-

correct. Indeed, allegedly at the end of his life he said: "le germe n'est rien, c'est le terrain qui est tout."

The theory which directed the most fruitful investigations of Pasteur and his followers was that the organism can develop specific adaptive reactions against individual pathogens and that by imitating and complementing these, whenever they are short of optimal, we can treat many of the diseases which are due to specific pathogens.

To our mind, the G-A-S represents, in a sense, the negative counterpart, or mirror image, of this concept. It holds that many diseases have no single cause, no specific pathogen, but are largely due to non-specific stress, and to pathogenic situations which result from inappropriate responses to such non-specific stress.

Our blueprint of the pathways through which stress acts may be partly incorrect; it is certainly quite incomplete. But in it we have a basis for the objective scientific dissection of such time-honoured, but hitherto rather vague, concepts as the role of "reactivity," "constitution and resistance" or "non-specific therapy," in the genesis and treatment of disease.

If we may venture a prediction, we would like to reiterate our opinion that research on stress will be most fruitful if it is guided by the theory that we must learn to imitate—and if necessary to correct and complement—the body's own auto-pharmacologic efforts to combat the stress factor in disease.

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