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The Physiopathology of Stress

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The physiopathology of the stress syndrome is described, with special reference to participation of the endocrine system in stress reactions. Also outlined is the mechanism through which "adaptive hormones" are produced during stress, and the way in which these hormones participate in producing and preventing nonendocrine diseases.

HANS SELYE

MORE than two decades have passed since the description of "a syndrome produced by diverse nocuous agents," and the time has come for re-evaluation. The literature on this reaction type, which is now known as the general adaptation syndrome (G.A.S.) or stress syndrome, has been reviewed in several extensive reference books,[1,2] as well as in a simplified synopsis.[3] We may limit ourselves, therefore, to reassessing the basic concepts and to reporting on that newest and to my mind most practical phase in this line of research, the production and prevention of stress-induced cardiac necroses.

What Is Stress?

Like health, disease or life itself, stress is difficult to define in precise terms. I have attempted elsewhere[3] to formulate a rather precise definition of what should be called stress; for practical purposes it will suffice to say that *stress is the consequence of the rate of wear and tear in a biologic system.* This system may be the organism as a whole (systemic stress) or one of its parts (topical stress). The visible manifestations of the former constitute the general adaptation syndrome, while those of the latter are known as the local adaptation syndrome (L.A.S.). The general adaptation syndrome, like the local adaptation syndrome, is a triphasic reaction, which evolves through an acute phase, the alarm reaction, to the stage of resistance, and finally ends in the stage of exhaustion. In the general adaptation syndrome, the manifestations of these three stages are systemic, that is, not limited to the area primarily affected. Thus, after a localized burn the reaction spreads throughout the body,

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resulting in stimulation of the hypothalamus and increased ACTH and corticoid secretion. All these manifestations are remote, mediate consequences of the local stress situation. It is particularly striking that these manifold systemic manifestations are largely independent of the specific nature of the stressor—trauma, infection, x-rays or nervous stimuli—that induces the stress situation. In the area primarily affected, there is also a triphasic nonspecific reaction; however, its manifestations—cell proliferation, inflammation, necrosis—are limited to that region of the body which is directly influenced by the stressor.

Since stress is a general manifestation of vital activity, it often has been confused with somewhat related but still essentially different aspects of life from which it must be strictly distinguished.

Stress is not necessarily a pathologic phenomenon. Any kind of physiologic activity, such as locomotion, heart beat, respiration or glandular secretion, produces some kind of wear and tear. Complete freedom from stress never occurs in living beings.

Stress is not identical with aging. The phenomena of aging depend on the accumulated results of life's wear and tear, not on its rate at any one moment. The rate of wear and tear is high in an active child and low in an elderly person at rest.

Stress is not identical with the metabolic rate. Fuel consumption and heat production do not necessarily parallel wear and tear in living organisms any more than they do in inanimate machines.

How Nonspecific Is the Stress Reaction?

The stress syndrome is nonspecific only as regards its causation, not its form. It is nonspecific in the sense that essentially the same type of response can be caused by a variety of essentially different stressors such as cold, heat, trauma or infection. On the other hand, it is quite specific as regards its appearance, in that it selectively affects certain organs in the body. For example, it induces secretion of ACTH by the pituitary gland and secretion of corticoids by the adrenal glands.

Role of Pituitary-adrenocortical Axis

Because hypophysectomy and adrenalectomy, with subsequent substitution therapy, happened to be useful technics in our first attempts to identify the common pathways through which various stressors act on distant organs, we have given special attention to the pituitary-adrenal axis since first describing the general adaptation syndrome. However, many manifestations of systemic and local stress can still develop when these glands are absent, and it is abundantly evident that both the humoral and the nervous systems play important roles as coordinators of activity during stress.

Hormonal Conditioning

Hormones participate in many physiologic and pathologic reactions which they do not actually produce. All biologic reactions depend not only on the evocative stimulus, but also on other factors which determine reactivity. In pharmacology these modifying effects are variously described by such terms as sensitization, desensitization, blockade, reversal of effects, summation and potentialization. As a generic term for these types of interaction, we recommend the designation "humoral conditioning."[1,2]

About 20 years ago we became aware of the important role played by the internal secretions in determining tissue reactivity. At that time, we found that hormones can enable various stimuli to produce reactions that would not occur unconditionally, that is, without the aid of a special hormonal sensitization.[4] In endocrinology this phenomenon came to assume special importance, because it altered certain fundamental concepts. Previously it had been thought that if an agent acts on a target only in the presence of an endocrine gland, its effect must be mediated through that gland and must be due to increased secretion of hormones. The discovery of the conditioning effect of hormones showed that this is not necessarily the case; often the endocrine secretions are necessary only to maintain the target organ in a reactive condition.

Probably many of the actions exerted by corticoids during the general adaptation syn-

drome depend largely on the ability of these hormones to sensitize certain targets for the actions of stress itself.[1,2] The effect of gluco-corticoids on thymus involution is an example. In adrenalectomized rats, neither a stressor such as trauma nor a subthreshold amount of a gluco-corticoid such as cortisol causes thymus involution. However, pronounced thymolysis occurs when trauma is applied after treatment with doses of cortisol that in themselves are ineffective. Here, the stressor could not have acted by increasing gluco-corticoid secretion; the corticoid merely created conditions favorable for induction of thymolysis by the stressor.

Ingle[5,6] has recommended that the term permissive action or supportive action be applied to this type of effect. However, such terms are not readily applicable to cases in which the conditioning is negative, that is, where the hormone prevents rather than permits or supports an action. The antiphlogistic effect of gluco-corticoids is an example of such negative conditioning.

Conditioning and "Pharmacologic" Doses of Hormones

It has been claimed that perhaps conditioning for disease can only occur when "unphysiologic" amounts of hormones are introduced into the body. If this were true, conditioning would be only of pharmacologic significance, and it would not explain the pathogenesis of any disease on the basis of variations in endogenous hormone production. However, a number of observations have shown that sufficient amounts of hormones are produced in the body to modify its susceptibility to disease.

For example, in rats systemic stress inhibits the inflammatory potential, but only in the presence of the adrenal glands. Substitution with near-physiologic amounts of gluco-corticoids in adrenalectomized rats restores their capacity to respond to stress and suppresses the inflammatory reactions. Such experiments do not prove that the anti-inflammatory action of stress is due to an absolute increase in corticoid production. It could still result from a conditioning by corticoids to some nonadrenal-mediated, antiphlogistic stress effect. However, the experiments do prove that the adrenal glands can secrete sufficient amounts of corticoids to diminish inflammatory reactions.

It may be argued that the inhibition of inflammation is not in itself a pathologic phenomenon; however, this would disregard the fact that the spread of some diseases, e.g., tuberculosis or septicemia after a localized infection, depends on the insufficient development of inflammatory barricades that separate the diseased from the healthy tissue.

In addition, experimental medicine has furnished many other examples which show that near-physiologic amounts of hormones can condition for disease. It is known, for instance, that certain aminonitriles can produce a severe bone disease known as osteolathyrism. In hypophysectomized rats, these aminonitriles are virtually ineffective in causing bone lesions; however, the somatotropic hormone (STH), in doses just adequate to maintain normal growth, restores the reactivity of the skeleton to normal levels.

It also has long been argued that the human adrenal gland does not produce any mineralocorticoid that would correspond to the desoxycorticosterone with which we have reproduced various experimental facsimiles of hypertension and of mesenchymal diseases such as periarteritis nodosa, nephrosclerosis and myocarditis. However, it was recently shown that aldosterone, an undoubted natural mineralocorticoid, can be secreted by the adrenal during stress and that the increase in blood pressure and nephrosclerosis, as predicted from animal experiments, does in fact occur in patients with aldosteronism.

What Are Diseases of Adaptation?

Disease is a dynamic process, a fight between the pathogen and the diseased organism. The latter defends itself against the producer of the disease by adaptive phenomena. Hence, adaptation is an integral element of all disease. Of greatest importance are the direct actions of pathogens in some maladies and the failure of adaptive phenomena in others; only in the latter case do we speak of diseases of adaptation.

For example, if a patient who swallows a

large quantity of alkali has perforation of the stomach with subsequent peritonitis, this is not a disease of adaptation. In this case, the morbid phenomena are predominantly direct effects of the pathogen, the alkali. The peritoneal inflammatory phenomena themselves are adaptive reactions, but their participation in the total picture of disease is quite subordinate to the passive, purely chemically induced perforation of the stomach. If similar peritonitis results from perforation of a gastric ulcer which has been induced by constant emotional excitement, then we may speak of a disease of adaptation.

It is especially important to keep in mind that no disease is due exclusively to a "derailment" of adaptive phenomena, nor is there any malady in which adaptive phenomena play no role at all. In order to produce disease, there always must exist some direct, purely aggressive and nonadaptive action of a pathogen. On the other hand, there hardly exists any pathogenic action which does not elicit some adaptive phenomena. Such an overlap between groups does not minimize the practical value of the principle of classification. There hardly exists a disease which could not be properly included in several of the classic categories of pathology. Rheumatic fever is undoubtedly a joint disease, but it is also a cardiac disease, a connective-tissue disease and an infectious disease. Although the subjects of the natural sciences cannot be forced into watertight, nonoverlapping compartments, this does not alter the fact that without classification there is no science. We need the classes, because no generalization is possible without them.

In a narrower sense, we consider as diseases of adaptation those pathologic processes which are predominantly due to stress and are often mediated by a pathogenic hormonal activity. In this sense we can distinguish, at least in principle, the following main groups of diseases of adaptation:

1. Diseases due to an absolute excess or deficiency in the secretion during stress of adaptive hormones, for example, corticoids, ACTH and STH.

2. Diseases due to variations in the absolute blood level of adaptive hormones resulting from a stress-induced derangement of hormone metabolism rather than from increased or decreased secretion.

3. Diseases due to a derangement in the normal balance between antagonistic adaptive hormones, e.g., between ACTH and antiphlogistic corticoids on the one hand and STH and prophlogistic corticoids on the other. Such diseases can result from a disproportion in the secretion or detoxication of these hormones during stress.

4. Diseases due to stress-produced derangements which alter the response of target organs to the adaptive hormones through the phenomenon of conditioning.

5. Finally, we must not forget that, although hormones play a prominent role in the general adaptation syndrome, stress-induced derangements of nonendocrine organs, e.g., the nervous system, liver and kidney, may also cause diseases of adaptation.

Stress-induced Cardiac Necroses

From a purely clinical viewpoint, perhaps the most promising outcome of our investigations on stress is the observation that acute, infarctlike cardiac necroses can be produced by stress in humorally conditioned animals and that this type of sudden cardiac death can be prevented by chemical means. The results of these studies and their possible application to clinical problems already have been discussed at length in a recent monograph.[7] I shall, therefore, present only the high lights.

Combined treatment with certain electrolytes and steroids produces a cardiopathy characterized by necroses (ESCN). In this lesion, the formation of large, infarctlike, necrotic foci is usually preceded by a singular fuchsinophilic degeneration and the death of scattered, individual muscle fibers. This change often stimulates amitotic regeneration of the cardiac muscle in the vicinity of the affected areas (figures 1 to 3).

Of the electrolytes examined, only certain sodium salts could produce an ESCN, following conditioning with steroids. The phosphates, sulfates and the perchlorate of sodium were particularly effective in this respect, while the

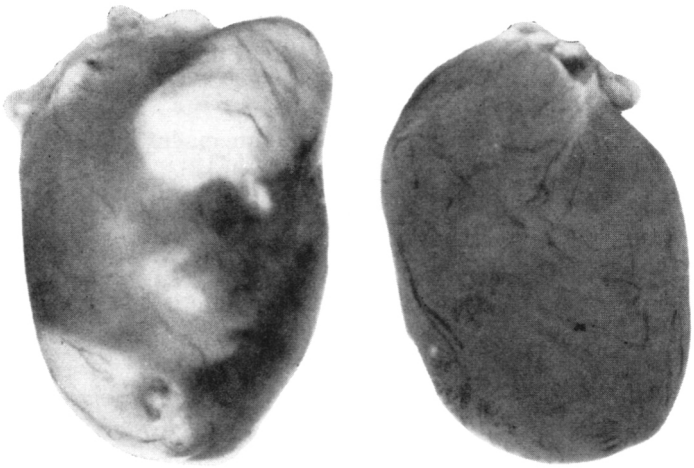

FIGURE 1. Macroscopic aspect of the ESCN. *Left.* Heart of rat treated with Me-Cl-COL plus NaH_2PO_4. The white, necrotic patches in the wall of the right ventricle are clearly visible and are especially marked near the origin of the pulmonary artery. *Right.* Heart of rat given magnesium chloride by stomach tube in addition to treatment with Me-Cl-COL plus NaH_2PO_4. Heart remained perfectly normal.

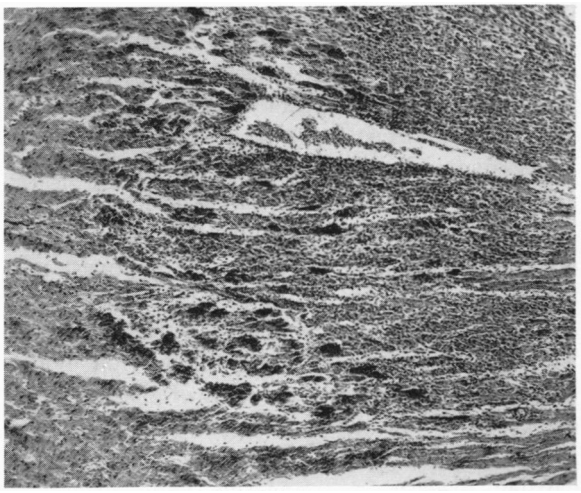

FIGURE 2. Typical aspect of a necrotic patch in heart of rat treated with Me-Cl-COL plus NaH_2PO_4. A dark line of necrotic tissue separates the healthy muscle *(left)* from the center of the lesion where the muscle fibers have already been largely replaced by histiocytes and polymorphonuclear leukocytes. (Hematoxylin-phloxine stain.)

(Figures 1 and 2 reproduced from: Selye, H. and Mishra, R. K.: Prevention of the "phosphate-steroid-cardiopathy" by various electrolytes. Am. Heart J. 55:163-173 [February] 1958.)

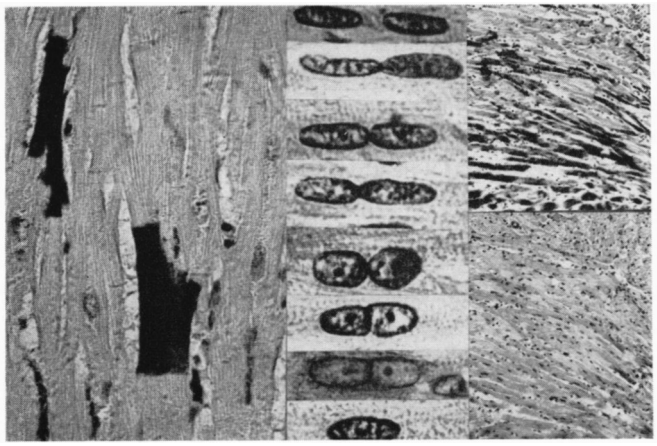

FIGURE 3. Fuchsinophilic degeneration and amitotic division in cardiac muscle in the ESCN. *Left.* Fuchsinophilic degeneration of two cardiac muscle segments between intercalary disks as seen on a longitudinal section taken from the heart of a Rhesus monkey subjected to the stress of forced restraint. Note the sharp limits of the degenerated areas which are bright red in the original section. (Fuchsin stain.) *Center.* Various stages of amitotic division in cardiac muscle fibers. This composite picture is made up of nuclei found in a very small area of one papillary muscle in heart of rat treated with Me-Cl-COL plus Na_2HPO_4. (Hematoxylin-eosin stain.) *Right.* Heart of rat treated with Me-Cl-COL plus Na_2HPO_4. The fuchsinophilic degeneration is almost undetectable using the hematoxylin-eosin stain (*top*), but is very evident on a fuchsin-stained slide (*bottom*) of two closely adjacent sections taken from the same area.

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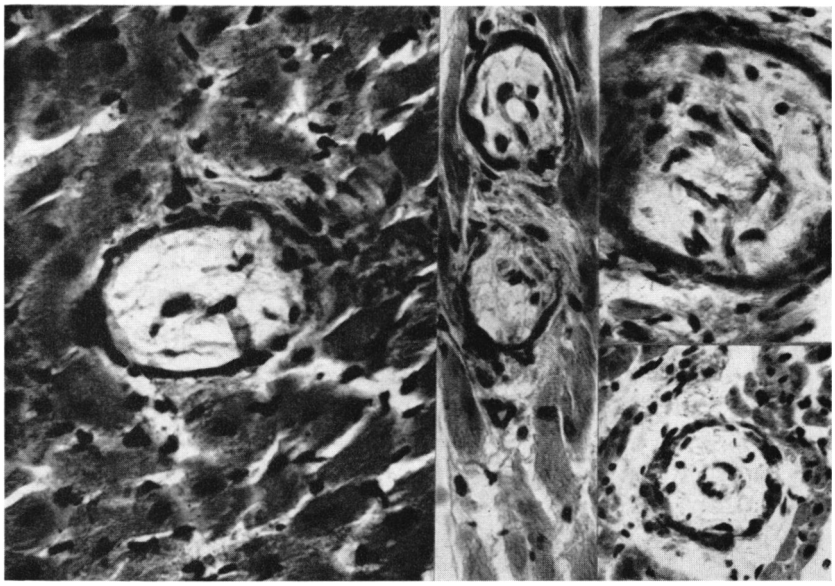

FIGURE 4. Composite picture of several small coronary arteries showing coronary lesions in rat that was first treated with small doses of DHT and then, after 10 days' rest, received Me-Cl-COL plus NaH_2PO_4. This induced an acute, subintimal edema, which constricted or obliterated the lumen of the coronaries. At the dose level used, DHT alone would produce only mild calcification in the walls of some coronary branches. In itself, treatment with Me-Cl-COL plus NaH_2PO_4 exerts no demonstrable effect on the coronary vessels at any dose level. (Hematoxylin-phloxine stain.)

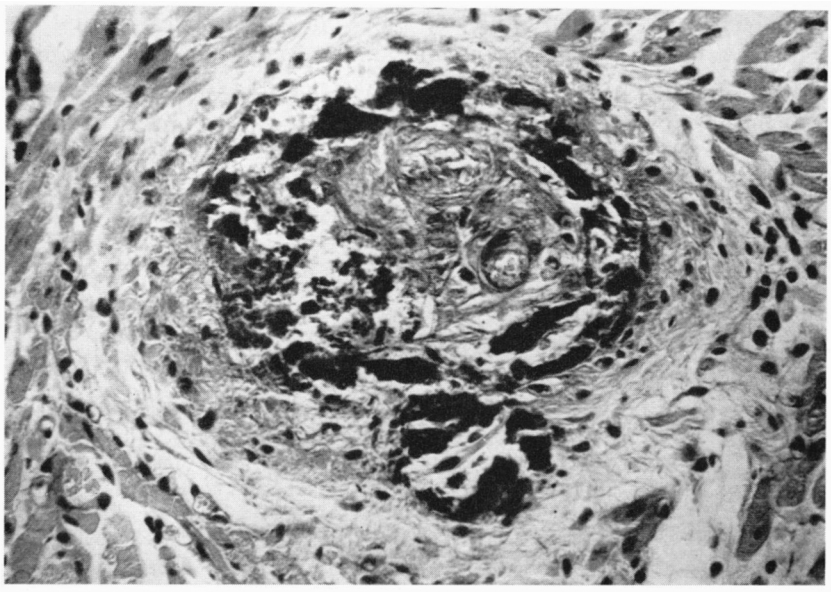

FIGURE 5. Complete obliteration of the lumen of a coronary artery in rat given Me-Cl-COL plus NaH_2PO_4 10 days after treatment with small doses of DHT. Numerous fragmented calcium deposits are visible in the wall, and the lumen is totally obliterated by a fresh thrombus. (Von Kossa's stain.)

(Figures 4 and 5 reproduced from: Selye, H.: The humoral production of cardiac infarcts. Brit. M. J. 1:599 [March 15] 1958.)

chlorides, nitrates and organic sodium salts were inactive. From these observations, we concluded that both the cation (Na) and the anion (PO_4, SO_4 and ClO_4) possess sensitizing properties.

On the other hand, certain electrolytes not only fail to produce an ESCN, but actually prevent its development when they are given concurrently with sensitizing electrolytes to animals suitably conditioned with steroids. Potassium chloride and magnesium chloride proved to be most effective in this respect, although other chlorides also have some desensitizing potency.

Of the steroids tested, only some corticoids proved to condition the heart for the production of the ESCN. Virtually pure gluco-corticoids such as MEDROL® and triamcinolone were ineffective, and pure mineralo-corticoids such as desoxycorticosterone exhibited a comparatively low potency. On the other hand, mixtures of these two types of compounds, as

well as some synthetic halocorticoids which possess the characteristics of mineralo-corticoids and gluco-corticoids in the same molecule, were highly effective. Of the steroids tested so far, 2α-methyl-9α-chlorocortisol (Me-Cl-COL) was the most potent conditioner for the production of the ESCN.

Certain steroids of the vitamin D group, e.g., dihydrotachysterol (DHT), produced a Mönckeberg type of coronary arteriosclerosis, but no coronary thrombosis or myocardial necrosis. However, rats in which a mild coronary sclerosis has previously been produced with DHT become unusually sensitive to the production of cardiac lesions by either stress or the usual electrolyte-steroid treatment. In these animals, the myocardial necroses are extraordinarily severe and induce a sudden aggravation of the coronary sclerosis itself. Normally, the ESCN is not accompanied by coronary lesions; however, when the arteries are previously damaged by DHT, a superimposed necrosis induces a true cardiac infarct with coronary occlusion.

These observations suggested that the electrolyte-steroid treatment, like exposure to stress, may have failed to induce truly infarct-like lesions in the rats' hearts because we always used young, healthy rats whose hearts were not predisposed to vascular occlusion by any pre-existent coronary lesions. When artificial aging was imitated by pretreatment with DHT, thus rendering the coronary arteries especially susceptible to disease, the same humoral means induced close facsimiles of the cardiac infarcts occurring in man (figures 4 and 5). This type of cardiac necrosis with coronary occlusion could also be inhibited by oral administration of potassium chloride or magnesium chloride.

Stress plays a particularly important role in the pathogenesis of these experimental cardiac necroses. As already mentioned, mere conditioning by corticoids, even without administration of sensitizing sodium salts, suffices to predispose the cardiac muscle to the production of necroses by stressors such as cold, heat, trauma, muscular exercise and nervous stimulation. Curiously, sodium chloride, which does not act as a sensitizing salt in the absence of stress, greatly enhances the production of cardiac necroses by stress in the corticoid-conditioned animal. Under such circumstances, potassium chloride or magnesium chloride given orally also exerts a pronounced protective effect.

The prophylactic action of potassium chloride and magnesium chloride is rather nonspecific. We have seen that these compounds can prevent the production of cardiac necroses by (1) sensitizing electrolytes plus corticoids, (2) sensitizing electrolytes plus DHT, and (3) various stressors plus corticoids. This, in itself, indicated that the potassium and magnesium salts had a rather nonspecific effect in protecting the heart. Subsequent investigations showed that magnesium chloride also can protect the heart by preventing the production of necroses by potassium-deficient diets. Indeed, both potassium chloride and magnesium chloride prevented even the induction of those cardiac necroses that normally occur after intravenous injections of proteolytic enzymes such a papain or ficin. It appears, therefore, that the action of these electrolytes is not directed specifically against any one pathogen, but offers some protection to the cardiac muscle against the induction of necroses by various means. Although such a nonspecific prophylactic effect was rather unexpected, actually it is not unprecedented in stress research. The protection afforded by ACTH and gluco-corticoids against various topical stressors that normally cause inflammation likewise represents a rather general preventive effect of this kind. It is a nonspecific antiphlogistic action, a protection against inflammation itself, rather than against the specific actions of one or the other inflammatory irritant.

Comment

I have attempted to discuss some much disputed aspects of stress and the diseases of adaptation, as well as certain novel facets of stress research which we hope will open new avenues in the study of cardiovascular pathology. Actually, the questions raised here have led beyond the limits of what we currently consider typical research on stress. This broader

horizon was barely visible about a decade ago, when I last attempted to survey it.[8] The leitmotiv which prefaced that booklet is perhaps better supported by facts today than it was when I first had the temerity to assert what was then assailed by so many as rank heresy, namely, that:

> Now the great problem in endocrine physiology is no longer "what do the hormones do?" but *what adaptive reactions do they influence?* Now the great problem in endocrine pathology is no longer "which diseases are caused by the excessive function or the destruction of an endocrine gland?" but *in which diseases has the endocrine status a decisive influence?*
>
> Indeed, even apart from endocrinology, the principal endeavor of medicine in general is beginning to change. It is no longer the search for specific pathogens, and for specific remedies with which to eradicate them. We always used to accept as a self-evident fact that each well-characterized individual disease must have its own specific cause. This tenet is self-evident no longer. It becomes increasingly more manifest that an agent does or does not produce disease, depending upon a variety of conditions, some of which have now been definitely identified as being determined by the "adaptive hormones."

There begins to emerge a new and somewhat more complex pathology in which *the main objects of our study are no longer individual "pathogens," but rather "pathogenic situations."*

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