7 October 1955, Volume 122, Number 3171 SCIENCE

Stress and Disease

Hans Selye

Almost two decades have passed now since the publication of a short note on "A syndrome produced by diverse nocuous agents" (*1*). Since that time, the relationships between this "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 certain aspects of the stress problem will find a key to the world literature in the monographs (*2–10*) and yearbooks (*11–14*) that are especially devoted to this topic. Hence there is no need to burden this text with numerous references. It may be opportune, however, to take stock now in the form of a brief synopsis surveying the most fundamental facts that we have learned about the relationships between stress and disease. This will give us an opportunity also to outline what we would consider to be the principal scope and the limitations of this new approach to problems of medicine (*15*).

Ever since man first used the word *disease*, he has had some inkling of the stress concept. The very fact that this single term has been used to denote a great variety of manifestly distinct maladies clearly indicates that they have been recognized as having something in common. They possess, as we would now say, some "nonspecific disease features" (the feeling of being ill, loss of appetite and vigor, aches and pains, loss of weight, and so forth), that permit human beings to distinguish illness 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 to the physician, for, unlike the specific symptoms and signs, they did not help him to recognize the "eliciting pathogen" or to prescribe an appropriate specific cure. Whenever it was impossible to determine precisely what the cause of the trouble was, therapy had to be limited to such general measures as the recommendation of rest, an easily digestible and yet nutritious diet, protection against great variations in the surrounding temperature, or the use of salicylates to stop pain.

Experience had likewise shown long ago that what we now call nonspecific stress can also have certain remarkable curative properties under certain conditions. Nonspecific therapy was consciously or unconsciously based on this principle. In the Middle Ages, flogging of the insane was practiced "to drive the evil spirit out of them." This procedure was subsequently replaced by the more humane fever therapy, Metrazol shock, insulin shock, electroshock, and numerous other measures, but all of these have in common the property of producing a state of systemic, nonspecific stress. Such practices as bloodletting, fasting, or the parenteral administration of milk, blood, and colloidal metals may serve as additional examples of nonspecific procedures, which undoubtedly can produce beneficial results in patients afflicted by a variety of diseases. These measures were, and some of them still are, widely used for lack of more effective and less traumatic means of therapy. However, the mechanism of their action remained obscure, and therefore scientifically minded physicians were always reluctant to use them, for they recognized that these treatments were actually stabs in the dark whose consequences could never be accurately foretold.

Perhaps the most fundamental difference between medieval and modern medicine is that the former was primarily based on pure empiricism and directed by mysticism and intuition, whereas the latter attempts to understand the mechanisms of disease—through an objective scientific analysis—and to treat it by influencing well-defined points along the pathways of its development. Up to the present time, the greatest progress that has been made along these lines has resulted in specific therapeutic procedures that are designed to eliminate in each case the particular primary cause—the eliciting pathogen of a disease—for instance, by chemotherapeutic measures or with the surgeon's knife.

By contrast, throughout the centuries, we have learned virtually nothing about rational, scientifically well-founded procedures that would help the body in its own natural efforts to maintain health quite apart from the attacks on the pathogen. Yet, often, the causative agent cannot be recognized or is not amenable to any therapeutic procedures directed specifically against it. Besides, elimination of the causative agent frequently does not cure, because the effects of the disease producer may greatly outlast its actual presence in the body. Let us remember that it is not the microbe, the poison, or the allergen but our reactions to these agents that we experience as disease. A man may die from a single exposure to ionizing rays, a rheumatic heart, or an infectious nephritis long after the original cause of his illness is no longer present in his body.

Whenever the available procedures of specific therapy are imperfect, the physician is forced to say that he has done what he could and "nature will do the rest." The fact is that very often nature actually does the rest, but unfortunately not always. Indeed, we may say that the leitmotiv of our work on stress was the question: "How does nature do 'the rest' and, when nature fails in this, could we not help if we learned more about natural methods?"

When we were first confronted with the "alarm reaction," the idea that presented itself most vividly was that the very tangible and accurately measurable

Dr. Selye is director of the Institute of Experimental Medicine and Surgery at the University of Montreal, Canada.

morphologic characteristics of this first stage of the stress response might give us a key to the objective scientific analysis of systemic, nonspecific reactions. The enlargement of the adrenal cortex and the atrophy of the thymus and lymph nodes, for example, were changes that could be expressed in strictly quantitative terms, and they were certainly not specific, since any agent that caused systemic damage or stress elicited them.

A multitude of questions presented themselves immediately. Which among the manifestations of this alarm reaction are useful for the maintenance of health and which are merely signs of damage? How does an injury to a limited area of the body reach the various internal organs that are eventually affected during the alarm reaction? For instance, how does a trauma to one limb eventually influence such distant structures as the adrenal cortex or the thymus? Which organ change is the cause and which the consequence of another structural alteration? For instance, does the disintegrating thymus tissue liberate substances that stimulate the adrenals or does the enlarged adrenal cortex secrete hormones that affect the thymus?

It was quite evident, of course, that to answer these questions would take much time and probably long series of often monotonous stereotypic experiments, using various stressors on various species of animals. Nevertheless, a general blueprint for the dissection and clinical utilization of the stress syndrome presented itself immediately. In particular, we asked ourselves five questions, which we thought would now be amenable to experimental analysis: (i) What are the changes characteristic of stress as such? (ii) How does the stress response evolve in time? (iii) What are the pathways through which stress reaches various organs? (iv) Are there "diseases of adaptation," that is, maladies principally the result of errors in the adaptation syndrome? (v) To what extent are the animal experiments on stress applicable to clinical medicine?

None of these questions has been fully answered, and, indeed, the complete clarification of biologic problems is hardly an attainable aim. However, partial answers have been obtained to all of these basic questions, and—most important of all—it appears that they have been so formulated that further progress is now largely a matter of time.

We have learned, for instance, that acute involution of the lymphatic organs, diminution of the blood eosinophiles, enlargement and increased secretory activity of the adrenal cortex, and a variety of changes in the chemical constitution of the blood and tissues are truly nonspecific and characteristic of stress as such. It has also become evident that they represent a syndrome, in that they are closely correlated with one another, both in time and in intensity. Whenever dissociations among them tend to occur, it can usually be shown that these are attributable to one of the following two reasons: (i) either the specific actions of the evocative agent are superimposed upon the stress syndrome and thus obscure some of the nonspecific manifestations (for example, if insulin is used as a stressor, the glycemic response is masked by the hypoglycemic effect of the hormone); or (ii) one of the pathways through which stress acts in the organism is deranged (for example, stress causes no thymus involution after adrenalectomy).

No agent produces only stress. Hence, in actual experimentation, the stress response is invariably complicated by certain superimposed specific changes, and in every species—indeed, in every individual—one or the other pathway is more or less functional than the rest. These factors tend to mask or deform the typical stress response, and failure to recognize them was undoubtedly the principal handicap to clear characterization of the stress response in the past. Let us now return to our five basic problems and enumerate at least the most important facts about them that have come to light during these 20 years of research on stress.

Changes Characteristic of Stress

In attempting to answer the question, "What are the changes characteristic of stress as such?" the first problem was, of course, to define *stress,* at least as accurately as definitions can be formulated in biology. The word, especially when it is used with its mate *strain,* has long been in everyday usage, but its significance in biology had never been defined. The layman speaks, for instance, of *eyestrain* or *mental stress* in referring to rather specific complaints. Cannon, the great student of homeostasis, also used the terms *stresses* and *strains* in connection with specific reactions. He emphasized, for instance, that the stresses and strains of oxygen lack, hemorrhage, and starvation elicit totally different and specific homeostatic reactions. Conversely, it is a characteristic of the stress syndrome, as we understand it, that it is always the same, no matter what happens to elicit it. For over-all responses, which include specific and nonspecific features—and this is even more true of purely specific responses—the term now used would be *reaction* (not *stress*) and the eliciting agent would be called a *stimulus* (not a *stressor* or *alarming stimulus*). Such specific reactions are precisely the part of the over-all response that we must subtract to arrive at our stress syndrome.

To make this distinction clear, we always used the term *nonspecific stress* in our early publications. Later, unfortunately, it became customary to omit the adjective, for brevity's sake. To avoid confusion, we then pointed out that in the sense in which we use the term, stress may be defined as a nonspecific deviation from the normal resting state; it is caused by function or damage and it stimulates repair.

Here, the nonspecific causation of the change has been selected as its most characteristic feature. However, even the term *specific* had been used somewhat loosely in medicine; we therefore defined a nonspecific change as one that can be produced by many or all agents, as opposed to a specific change, which is elicited only by one or few agents. Correspondingly, a nonspecific agent acts on many targets, a specific one acts on few targets, and a stressor is an agent that causes stress.

Of course, we realized from the outset that these, like all biologic definitions, are imperfect, but trying to formulate them helped us to impart precision to our own concepts of *stimulus, stressor, stress, specific,* and *nonspecific.* Among other things, these considerations brought out with particular clarity the fact that stress is not necessarily the result of damage but can be caused by physiologic function and that it is not merely the result of a nonspecific action but also comprises the defense against it. These are cardinal facts, as we shall see later when we consider the relationship between stress and disease.

In our efforts to identify the characteristics of stress, our main problem was to eliminate all specific manifestations that are typical either of the agent or of the reacting organism. Hence, a large number of animal species had to be studied, following exposure to a great variety of essentially different stimuli, to compare the resulting structural, chemical, and functional changes. This made it possible to determine which are the responses common to all types of exposure, and only these could be considered to be truly nonspecific—that is, the result of stress as such. The residue that remained after subtraction of all the specific changes is the general-adaptation syndrome.

In this response, every part of the body is involved, but the two great integrators of activity, the hormonal and the nervous systems, are especially important. The facts known today may lead us to believe that the anterior pituitary and the adrenal cortex play the cardinal roles in coordinating the defense of the organism during stress. This view is probably distorted by the fact that the syndrome has been

studied primarily by endocrinologists, and investigations concerning the participation of the nervous system are handicapped by the greater complexity of the required techniques. It is considerably easier to remove an endocrine gland and to substitute for its hormones by the injection of extracts than it is to destroy minute individual nervous centers selectively and then restore their function to determine the role they may play during stress.

Stress Response in Time

To establish the evolution of the stress response in time, animals had to be repeatedly exposed to stressors (cold, forced muscular exercise, bloodletting, and drugs) of a constant intensity over long periods of time. It was found that, after a while, the same agent does not continue to produce the same nonspecific response. For instance, treatment with a drug that initially causes discharge of adrenocortical lipid granules will later actually promote accumulation of lipids in the adrenal cortex, after the animals have become more resistant to the damaging effects of the agent. Upon still more continued exposure, sooner or later, this acquired adaptation is invariably lost; then the animals again show signs of damage, and their adrenal cortices again discharge their lipid granules.

These adrenal changes are taken as only one example among the many characteristics of the general-adaptation syndrome that show such a triphasic pattern (for example, glycemia, chloremia, and body weight). In fact the whole syndrome is essentially triphasic; thus its manifestations depend as much on the stressor effect of the eliciting agent as on the time elapsed since the organism was first exposed to it.

The three stages of the stress syndrome are (i) the alarm reaction, in which adaptation has not yet been acquired; (ii) the stage of resistance, in which adaptation is optimum; and (iii) the stage of exhaustion, in which the acquired adaptation is lost again.

The physicochemical basis of the curious terminal loss of acquired adaptation is still quite obscure. Exhaustion cannot be fully compensated, either by changes in the caloric intake or by any known hormonal substitution therapy. The term *adaptation energy* has been suggested to designate the adaptability that is gradually consumed during exposure, but despite much research we have learned nothing about the nature of this "energy."

Many of the changes characteristic of the stage of exhaustion are strikingly similar to those of senility. It is tempting to view the general-adaptation syndrome as a kind of accelerated aging. It appears as though, because of the greater intensity of stress, the three major periods of life —infancy (in which adaptation has not yet been acquired), adulthood (in which adaptation has been acquired to the usual stresses of life), and senility (in which the acquired adaptation is lost again)— are here telescoped into a short space of time.

However, these will remain sterile speculations until some ingenious mind can devise new experimental procedures with which to analyze them in quantitative terms. It is only to stimulate thought along these lines that I venture even to mention these problems here. I hope that some talented young mind, still sufficiently uninhibited by textbook knowledge to see a new approach, will follow this trail. To me it seems more promising of truly great progress in the understanding of life and adaptability than any other aspect of stress research.

Pathways of Stress

To clarify the pathways through which stress reaches various organs, it was merely necessary to use the classic procedures of experimental medicine— namely, the destruction of suspected relay stations and, wherever possible, their restoration (for example, removal of an endocrine gland and substitution therapy with extracts containing its hormones.) Figure 1 helps to summarize the principal data that have come to light in this respect.

All agents that act on the body or any of its parts exert dual effects: (i) specific actions, with which we are not concerned in this review, except insofar as they modify the nonspecific actions of the same agents and (ii) nonspecific or stressor effects, whose principal pathways (as far as we know them today) are illustrated in Fig. 1. The stressor acts on the target (the body or some part of it) directly (thick arrow) and indirectly by way of the pituitary and the adrenal. Through some unknown pathway (labeled 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 adrenocorticotrophic hormone (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 histaminelike toxic tissue metabolites, a nervous impulse, or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme). During stress it is rarely the lack of adrenal corticoids that stimulates ACTH secretion, through a self-regulating "feed-back" mechanism.

ACTH, alone or in cooperation with other hormones, stimulates the adrenal cortex to discharge corticoids. Some of the cortical hormones, the mineralocorticoids, also known as prophlogistic corticoids (P-Cs), 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 (examples are desoxycorticosterone and aldosterone).

However, under ordinary conditions, ACTH stimulates the adrenal much more effectively to secrete glucocorticoids, also known as antiphlogistic corticoids (A-Cs). 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 can suppress inflammation, but, by this same token, they open the way to the spreading of infection (examples are cortisol and cortisone).

Certain recent experiments suggest that, depending on the conditions, ACTH may cause a predominant secretion of one or the other type of corticoid. However, be this as it may, the "growth hormone," or somatotrophic hormone (STH), of the pituitary increases the inflammatory potential of connective tissue very much as the prophlogistic corticoids do; hence, it can sensitize the target area to the actions of the prophlogistic corticoids.

It is possible that the hypophysis also

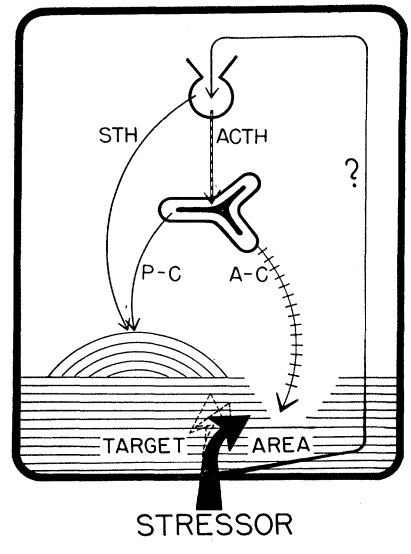

Fig. 1. Diagram illustrating the principal pathways of the stress response. [After Selye (*3*)]

secretes some special corticotrophin that induces the adrenal to elaborate predominantly prophlogistic corticoids; indeed, STH itself may possess such effects, but this has not yet been proved. Probably the electrolyte content of the blood can also regulate mineralocorticoid production. In any event, even if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence can be vastly different, depending on "conditioning factors" (such as STH) that 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 antiphlogistic or prophlogistic corticoids. Thus, during stress, one or the other type of effect can predominate.

As work along these lines progressed, it became increasingly more evident that the actions of all the "adaptive hormones" (corticoids, ACTH, STH) are so largely dependent on conditioning factors that the latter must be considered to be equally as important, in determining the final outcome of a reaction to stress, as the hormones themselves. It will be rewarding, therefore, to discuss this topic thoroughly.

Conditioning of hormone actions. Heredity, age, previous exposure to stress, nervous stimuli, the nutritional state, and many other factors can affect both the production of the adaptive hormones and their effect on individual target organs. The action of mineralocorticoids on most of their target tissues is augmented, and that of glucocorticoids is diminished, by an excess of dietary sodium. However, stress during the secretion of adaptive hormones is perhaps the most effective and most common factor capable of conditioning their actions. Thus systemic stress augments the antiphlogistic, lympholytic, catabolic, and hyperglycemic actions of antiphlogistic corticoids. Furthermore, one of the salient effects of the adaptive hormones, that of modifying the course of inflammation, naturally cannot manifest itself unless some "topical stressor" (for example, a nonspecific irritant acting on a circumscribed tissue region) first elicits an inflammatory response.

A few words about the recently introduced concept of the "permissive actions" of corticoids may be in order here. This hypothesis assumes that the corticoids do not themselves affect the targets of stress but merely permit stressors to act on them. Thus the presence or absence of corticoids could only allow or disallow a stress reaction but could not 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 or 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 overproduction of corticoids during stress—would result not from any actual increase in corticoid secretion but from the extra-adrenal actions of the stressors themselves. The presence of corticoids would be necessary only in a "supporting capacity" to maintain the vitality and reactivity of tissues (*16*).

Actually, it is precisely in the specific and not in the nonspecific (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. However, these are specific reactions; they are not characteristic either of stress or of the corticoids and could not be duplicated in the absence of the specific stimulus (STH and sexual stimulation), even with the highest doses of corticoids.

The characteristics of antiphlogistic corticoid overproduction that we see in the alarm reaction (for example, atrophy of the lymphatic organs, catabolism, and inhibition of inflammation) are also impeded by adrenalectomy; they are also restored even by mere maintenance doses of antiphlogistic corticoids in the presence of stress, because the latter sensitizes, or conditions, the tissues to them. The fundamental difference is, however, that —unlike specific actions—these nonspecific effects can be duplicated, even in the absence of any stressor, if large doses of antiphlogistic corticoids are given.

The importance of such conditioning influences is particularly striking in the regulation of stress reactions, because, in the final analysis, they are the factors that 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, caused by such factors, might explain why the same kind of stressor can cause diverse types of diseases of adaptation in different individuals.

"Buffering action" of the adrenals. It has long been noted that it is much more difficult to obtain overdosage with either glucocorticoids or mineralocorticoids in the presence than in the absence of the adrenals. Thus, for instance, cortisol exerts its typical actions (for example, on inflammation, body weight, and the thymicolymphatic organs) at much lower dose levels in intact rats than it does in adrenalectomized rats. This is largely, if not entirely, the result of the absence of mineralocorticoids, for it proved possible to restore the glucocorticoid resistance of the adrenalectomized rat to normal by treatment with small doses of mineralocorticoids (desoxycorticosterone and aldosterone). Even a mere excess of dietary sodium can, at least partially, substitute for the adrenal in such experiments; hence it is reasonable to assume that here the mineralocorticoids antagonize the glucocorticoids, as a direct result of their effect upon mineral metabolism.

These experiments definitely disproved the so-called "unitarian theory" of adrenocortical function, which was still held by some of the most distinguished adrenal physiologists a short while ago. It is clear not only that the cortex produces more than one kind of corticoid but that the mineralocorticoids and the glucocorticoids are mutually antagonistic in many respects, as postulated by the "corticoid balance theory."

However, several observations still did not seem to be consonant with our concept of corticoid antagonism. For instance, in the presence of the adrenals, both in experimental animals and in man, it proved extremely difficult to stimulate inflammatory reactions much above normal, even with very large doses of mineralocorticoids. On the other hand, glucocorticoids always succeed in overcoming the buffering action of an intact adrenal, as long as the dosage is sufficiently high.

It is only quite recently that the cause of this apparent exception to the concept of adrenal hormone antagonism has been clarified by the demonstration that the corticoids act in accordance with the "law of intersecting dose-effect curves."

Law of intersecting dose-effect curves. When a solution containing fixed proportions of cortisol acetate and desoxycorticosterone acetate (DCA) is administered to adrenalectomized rats, the cortisol action (catabolism, thymolysis, and inhibition of inflammation) predominates at low, and the opposite, desoxycorticosterone type of activity, predominates at high dose levels. This was ascribed to the fact that the DCA activity rises rapidly to its optimum level, but then a "ceiling" is reached, and raising the dose further will not increase the effect. The cortisol type of activity, on the other hand, rises more slowly but does not flatten out until it far exceeds the ceiling of its antagonist (Fig. 2).

The relationship between the two types of corticoids explains why it is readily possible to overcome the adrenal buffer with appropriate doses of cortisol-like hormones, whereas even the highest doses

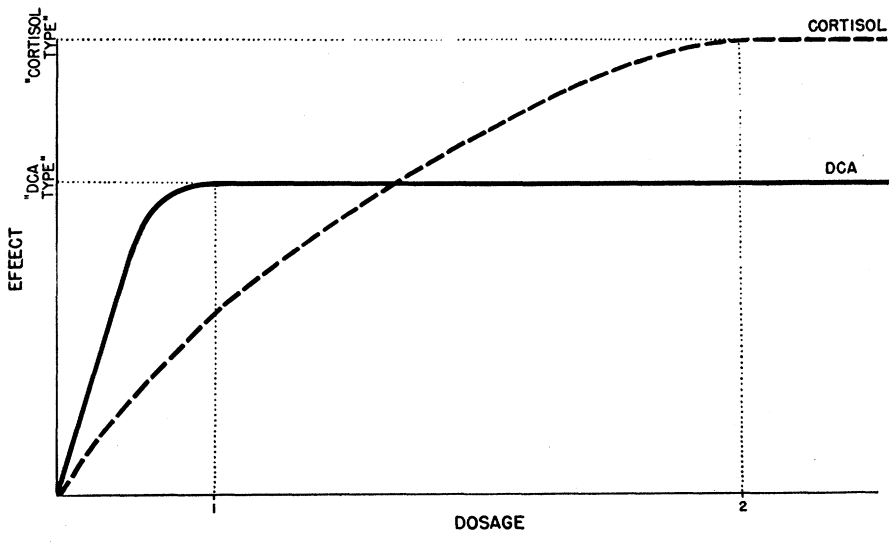

Fig. 2. Effect of varying the dose while the cortisol/desoxycorticosterone quotient is kept constant. Difference in the slopes results in intersecting dose-effect curves. [After Selye and Bois (*18*)]

of DCA cannot inhibit this effect. In the presence of the adrenals the normal level of mineralocorticoid production is usually already at its optimum of efficacy. This may also explain the frequently made observation that in adrenalectomized animals and man—where the starting point is below the mineralocorticoid ceiling—desoxycorticosterone stimulates inflammatory phenomena (for example, arthritis), and this can be antagonized by concurrent treatment with cortisol.

However, in certain respects, the desoxycorticosterone action does not appear to have a definite ceiling. Thus, in the rat, the production of renal damage by desoxycorticosterone is quite proportional to the amount given, within a very wide dose range.

Exceptional position of the kidney among the targets of corticoid activity. Numerous observations show that there exists a rather special relationship between the corticoids and the kidney, a relationship that clearly distinguishes renal tissue from other targets of corticoid activity.

Thus, the renal damage (nephrosclerosis) produced with high doses of desoxycorticosterone, in the rat, is not antagonized but is actually aggravated by concurrent treatment with cortisol. In other words, here there is no mineralocorticoid-glucocorticoid antagonism.

Furthermore, the kidney-damaging effect of various agents (for example, cold, foreign proteins, large doses of STH-preparations, and methylandrostenediol) can be prevented by adrenalectomy, while their extrarenal effects (including, for instance, the influence of STH and methylandrostenediol upon inflammation) are not markedly affected.

The cause of this exceptional reactivity of renal tissue to corticoids is not yet known. However, two factors undoubtedly play an important role here: (i) glucocorticoids and mineralocorticoids are not strictly antagonistic (and may even be synergistic) in their actions on the kidney; (ii) the inability of mineralocorticoids to produce more than a limited effect on extra-adrenal tissues (no matter how much the dose is raised) does not apply to the kidney.

In the preceding discussion we have just barely mentioned the "topical stressors," but now we shall have to consider these a little more carefully before we turn our attention to the diseases of adaptation.

Concept of the local-adaptation syndrome. In Fig. 1 we have indicated that nonspecific damage to a limited tissue area can influence the pituitary-adrenal system and consequently initiate systemic reactions to stress. It has long been known, furthermore, that many local responses to injury are nonspecific; it has been observed, for instance, that a variety of topical stressors (burns, microbes, drugs) share the power of producing local nonspecific 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 general-adaptation syndrome, which is characterized by manifold morphologic and functional changes throughout the organism, topical stress elicits a local adaptation syndrome, the principal repercussions of which are confined to the immediate vicinity of the eliciting injury. They consist, on the one hand, of degeneration, atrophy, and necrosis and, on the other hand, of inflammation, hypertrophy, hyperplasia, and, under certain conditions, even of neoplasia.

At first sight, there appears to be no striking similarity between the systemic and the local reaction types. A patient in traumatic shock furnishes a characteristic example of the general-adaptation syndrome and, in particular, of its earliest stage, the shock phase of the general alarm reaction. On the other hand, an abscess formed around a splinter of wood represents a typical example of the local-adaptation syndrome and, in particular, of its stage of resistance, during which the defensive inflammatory phenomena predominate. On the surface, these two instances of disease reveal no striking similarities; yet more careful study shows them to be closely related: (i) both are nonspecific reactions, comprising damage and defense; (ii) both are triphasic (with systemic or local alarm, resistance, and exhaustion); (iii) both are singularly sensitive to the adaptive hormones (ACTH, STH, and corticoids); (iv) if the two reactions develop simultaneously in the same individual, they greatly influence each other—that is, systemic stress markedly alters tissue reactivity to local stress and vice versa.

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

Are There Diseases of Adaptation?

By diseases of adaptation, we mean maladies that are caused principally by errors in the adaptation syndrome. Thus we arrived at the conclusion that the pathogenicity of many systemic and local stressors depends largely on the function of the hypophysis-adrenocortical system. The latter may either enhance or mitigate 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 (*17*).

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 has been discontinued. Here, we speak of "metacorticoid" lesions. The possibility that a temporary excess of endogenous mineralocorticoids could in-

duce similar delayed maladies deserves serious consideration.

Among the derailments of the general-adaptation syndrome that may cause disease, the following are particularly important: (i) an absolute excess or deficiency in the amount of adaptive hormones (for example, corticoids, ACTH, and STH) produced during stress; (ii) an absolute excess or deficiency in the amount of adaptive hormones retained (or "fixed") by their peripheral target organs during stress; (iii) a disproportion in the relative secretion (or fixation) during stress of various antagonistic adaptive hormones (for example, ACTH and antiphlogistic corticoids, on the one hand, and STH and prophlogistic corticoids, on the other hand); (iv) the production by stress of metabolic derangements, which abnormally alter the target organ's response to adaptive hormones (through the phenomenon of "conditioning"); and (v) finally, we must not forget that, although the hypophysis-adrenal mechanism plays a prominent role in the general-adaptation syndrome, other organs that participate in the latter (for example, nervous system, liver, and kidney) may also respond abnormally and become the cause of disease during adaptation to stress.

With this in mind it may be convenient for investigative purposes to classify as "diseases of adaptation" those maladies in which an inadequacy of the adaptation syndrome plays a particularly important role. This means that the term should be used only when the maladaptation factor appears to be more important than the eliciting pathogen itself. No disease is purely a disease of adaptation, anymore than it could be purely a disease of the heart or an infectious disease, without overlap with other nosologic groups. Conversely, there is no disease in which adaptive phenomena play no part.

It is undoubtedly useful to realize, however, that some agents are virtually "unconditional pathogens," in that their influence on the tissues is so great that they cause damage almost irrespective of any sensitizing or adaptive factors (for example, immediate effect of x-rays or of severe thermal and mechanical injuries, and the actions of certain microorganisms to which everybody is susceptible.)

Most disease-producing agents, however, are to a greater or lesser extent "conditionally acting pathogens"; that is, their ability to produce illness is largely dependent on our adaptive reactions to them. Here, correct adaptation may prevent disease, (for instance, a focus of tuberculosis perfectly held in check by an appropriate inflammatory barricade), but insufficient or excessive adaptive reactions may themselves be what we experience as illness (excessive and unnecessary inflammation around an otherwise harmless allergen).

Application of Animal Experiments to Clinical Medicine

Since most of the fundamental work on stress had been performed on laboratory animals, it was reasonable to question its applicability to problems of clinical medicine. It may now be said, however, that although there are certain differences in the stress response of every species, the general pattern of reaction is essentially the same in the various kinds of experimental animals and in man. Furthermore, a good deal of evidence has accumulated in support of the view that the experimental similes of spontaneous diseases produced in animals by exposure to stress, or by overdosage with certain adaptive hormones, are closely related to the corresponding maladies of man.

Let us merely mention a few of the most striking similarities in the responses to stress and to adaptive hormones of animals and man.

Morphologic and functional adrenocortical changes during stress. There can be no doubt that, during intense stress (for example, severe mechanical or thermal injuries and massive infections), the adrenal cortex of man, just as that of laboratory animals, shows morphologic changes characteristic of hyperactivity. At the same time, there is a demonstrable increase in the blood concentration and urinary excretion of corticoids and their metabolites. The other manifestations (morphologic, functional, and chemical) of the stress syndrome also failed to exhibit any fundamental dissimilarity in the reaction patterns of animals and man.

Corticoid requirements during stress. During stress, the corticoid requirements of all mammals are far above normal. After destruction of the adrenals by disease (as after their surgical removal), the daily dose of corticoids, necessary for the maintenance of well-being at rest, is comparatively small, but it rises sharply during stress (for example, cold, intercurrent infections, and hemorrhage), both in experimental animals and in man.

Anti-inflammatory effects of corticoids. The same antiphlogistic corticoids (cortisone and cortisol) that were shown to inhibit various types of experimental inflammations in laboratory animals exert similar effects in a human being afflicted by inflammatory diseases (for example, rheumatoid arthritis, rheumatic fever, and allergic inflammations).

Sensitivity to infection after treatment with antiphlogistic corticoids. In experimental animals, the suppression of inflammation by antiphlogistic hormones is frequently accompanied by an increased sensitivity to infection, presumably because the encapsulation of microbial foci is less effective and perhaps partly also because serologic defense is diminished. Thus, even a species naturally resistant to the human type of tuberculosis, such as the rat, can contract this disease during overdosage with ACTH or cortisone. Similarly, in patients undergoing intense treatment with antiphlogistic hormones (for example, for rheumatoid arthritis), a previously latent tuberculous focus may suddenly spread. It is a well-known fact that in patients suffering from tuberculosis the disease is especially readily aggravated by exposure to any kind of stress situation. Rest cures have long been practiced in view of this. It is perhaps not too farfetched to consider the possibility that an increased ACTH and cortisol secretion during stress may play an important part in the development of clinical tuberculosis.

Sensitization to mineralocorticoids by sodium and the buffering effect of the adrenals. In experimental animals, mineralocorticoids tend to raise the blood pressure and to cause vascular and renal damage (nephrosis and nephrosclerosis) often with edema. This effect is aggravated by simultaneous treatment with sodium chloride and becomes particularly severe after adrenalectomy. Similarly, in man on a high sodium intake, and especially after adrenalectomy, otherwise nontoxic doses of desoxycorticosterone will produce hypertension and edema. Apparently, in man as in the laboratory animal, sodium acts as a conditioning factor for mineralocorticoids, while the adrenal exerts a buffering effect.

This may also explain why, in many cases of clinical hypertension, bilateral adrenalectomy exerts a beneficial effect, as long as only cortisone or cortisol is used for substitution therapy, while treatment with desoxycorticosterone restores or further aggravates the hypertensive disease. Apparently, the adrenals of these patients produce some desoxycorticosteronelike factor that plays at least an adjuvant role in the pathogenesis of hypertension.

In patients suffering from rheumatoid arthritis, adrenalectomy has also been reported to exert a beneficial influence if only glucocorticoids are used for maintenance. Furthermore desoxycorticosterone tends to elicit arthritic changes only in the adrenal-deficient but not in the intact patient. This effect of desoxycorticosterone is, in turn, corrected by simultaneous cortisone treatment.

Finally, let us point out that, both in man and in animals, the various charac-

teristic effects of cortisone are also obtained at especially low dose levels after adrenalectomy.

Psychological and psychiatric effects of corticoid overdosage. Considerable attention has been given of late to the possible mental effects of stress and of the adaptive hormones. It would be beyond the scope of this article (and certainly outside my competence) to discuss these in detail, but a few remarks based on our experimental observations may be in order.

It has long been noted 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 great excitation followed by deep anesthesia. It has more recently been shown that such steroid anesthesia can also be produced in man, and, of course, the marked emotional changes (sometimes bordering on psychosis) that may occur in predisposed individuals during treatment with ACTH, cortisone, and cortisol are well known. Several laboratories reported furthermore that the electroshock threshold of experimental animals and their sensitivity to anesthetics can be affected by corticoids.

Thus, it appears very probable that corticoids secreted during stress also have an important influence on nervous and emotional reactions. Conversely, it is now definitely established that nervous stressors (pain and emotions) are particularly conducive to the development of the somatic manifestations of the stress syndrome; thus stress can both cause and be caused by mental reactions.

In conclusion, let us reemphasize that no illness is exclusively a disease of adaptation, but considerable evidence has accumulated in favor of the view that stress, and particularly the adaptive hormones produced during stress, exert an important regulating influence on the development of numerous maladies.

It is virtually certain that our concepts concerning the role of pituitary and corticoid hormones in the pathogenesis of certain diseases of adaptation will have to undergo modifications as more facts become known. However this is true with every theory. The same was true, for instance, of the original theory that related diabetes to a simple hypoinsulinism, when the role of the anterior pituitary was discovered. Yet, the realization of some pathogenic relationship between insulin and diabetes was an almost indispensable step in the subsequent development of this field.

The best theory is that which necessitates the minimum number of assumptions to unite the maximum number of facts, since such a theory is most likely to possess the power of assimilating new facts from the unknown without damage to its own structure. Our facts must be correct; our theories need not be if they help us to discover new facts, even if these discoveries necessitate some changes in the structure of the theory.

Meanwhile, the stress theory, as outlined in this article, permits us to correlate the known facts and furnishes a concrete plan for the systematic development of this field through planned investigation rather than through the mere empirical collection of chance observations.

Outlook

Pasteur, Koch, and their contemporaries introduced the concept of specificity into medicine, a concept that has 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," because he was too preoccupied with the pathogen (microorganism) itself. His work on induced immunity shows that this is incorrect. Indeed, at the end of his life he allegedly said, "Le microbe n'est rien, le terrain est tout."

The theory that 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 that are caused by specific pathogens.

To my mind, the general-adaptation syndrome 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 nonspecific stress and to pathogenic situations that result from inappropriate responses to such nonspecific 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-honored, but hitherto rather vague, concepts as the role of "reactivity," "constitution and resistance," or "nonspecific therapy," in the genesis and treatment of disease.

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

References and Notes

1. H. Selye, *Nature* 138, 32 (1936).
2. ———, *Stress. The Physiology and Pathology of Exposure to Stress* (Acta, Montreal, 1950).
3. ———, *The Story of the Adaptation Syndrome* (Acta, Montreal, 1952).
4. H. G. Wolff, *Stress and Disease* (Thomas, Springfield, Ill., 1953).
5. H. G. Wolff, S. G. Wolf, C. C. Hare, Eds., "Life Stress and Bodily Disease," *Research Publs. Assoc. Research Nervous Mental Disease* 29 (1950).
6. United States Army Medical Service Graduate School and Division of Medical Sciences, National Research Council (Sponsors), Symposium on Stress, Walter Reed Army Medical Center, Washington, D.C., March 16th–18th (1953).
7. H. Ogilvie and W. A. R. Thomson, Eds., "Stress," *The Practitioner* 172, No. 1027 (1954).
8. R. Q. Pasqualini, *Stress.* Enfermedades de Adaptacion. ACTH y Cortisona (Libreria El Ateneo, Buenos Aires, 1952).
9. I. Galdston, Ed., *Beyond the Germ Theory* (N.Y. Acad. Med. Health Education Council, New York, 1954).
10. J. Jensen, *Modern Concepts in Medicine* (Mosby, St. Louis, Mo., 1953).
11. H. Selye, *First Annual Report on Stress* (Acta, Montreal, 1951).
12. H. Selye and A. Horava, *Second Annual Report on Stress* (Acta, Montreal, 1952).
13. ———, *Third Annual Report on Stress* (Acta, Montreal, 1953).
14. H. Selye and G. Heuser, *Fourth Annual Report on Stress* (Acta, Montreal, 1954).
15. The major part of the investigations upon which this article is based was subsidized in part by a consolidated grant from the National Research Council of Canada and in part by the Medical Research Board, Office of the Surgeon General, Department of the Army, contract DA-49-007-MD-186.
16. D. J. Ingle, in *Recent Progress in Hormone Research* (Academic Press, New York, 1951), vol. 6, p. 159.
17. H. Selye, *J. Clin. Endocrinol.* 6, 117 (1946).
18. H. Selye and P. Bois, in *Fourth Annual Report on Stress,* H. Selye and G. Heuser, Eds. (Acta, Montreal, 1954), pp. 533–552.

No university is worthy of the name, that does not do everything in its power to promote original research in its laboratories. It is the duty of the university to see that its professors and teachers are not overburdened with routine teaching, but are given time for investigation and provided with research laboratory facilities and the necessary funds for this purpose.—E. RUTHERFORD.