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STRESS AND THE GENERAL ADAPTATION SYNDROME*

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With the concept of the general adaptation syndrome we have attempted to integrate a number of seemingly quite unrelated observations into a single unified biologic system. I would draw attention briefly to the work of Claude Bernard, who showed how important it is to maintain the constancy of the "*milieu intérieur*"; Cannon's concept of "homoeostasis"; Frank Hartmann's "general tissue hormone" theory of the corticoids; Dustin's observations on the "caryoclastic poisons," the "post-operative disease," the curative action of fever, foreign proteins, and of other "non-specific therapeutic agents"; the "nephrotoxic sera" of Masugi; and to the "Goldblatt clamp" for the production of experimental renal hypertension.

At first sight it would seem that all these observations have little in common and that there is no reason to attempt their integration into a unified system of physiological and pathological events. Yet most of my research work has been devoted to the construction of bridges between these and many additional facts, since they were thought to be interconnected in nature. Through the comprehension of their unity we hoped to learn how to use them better for the understanding of life and the treatment of disease.

The keynote of this unification was the tenet that all living organisms can respond to stress as such, and that in this respect the basic reaction pattern is always the same, irrespective of the agent used to produce stress. We called this response the general adaptation syndrome, and its derailments the diseases of adaptation.

Anything that causes stress endangers life, unless it is met by adequate adaptive responses; conversely, anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life, and every vital organ and function participates in them. In order to present a well-proportioned outline of the general adaptation syndrome it was necessary, therefore, to peruse every branch of physiology, biochemistry, pathological anatomy, and clinical medicine in search of the "stress factor" in all aspects of normal and abnormal life.

It will take many years, indeed many generations, before the details of the general adaptation syndrome are satisfactorily elucidated. In fact, we shall never truly "understand" this phenomenon, since the complete comprehension of life is beyond the limits of the human mind. But there are many degrees of "elucidation." It seems that the fog has now been just sufficiently dispersed to perceive the general adaptation syndrome through that measure of "twilight" which permits us to discern the grandeur of its outlines but fills us with the insatiable desire to see more.

We realize that many lines in our sketch will have to be hesitant, some even incorrect, if we try to put on paper now what we still see only vaguely. But a preliminary map—albeit largely incomplete and partly inaccurate—is needed *now* by those eager to exploit this field which holds so much promise for all who suffer from stress. I hope that these pioneers in uncharted territories will accept my partial and distorted map in the spirit in which it is offered, to complete and rectify it.

It is in this sense that I should like the reader to consider the following synopsis of what I think I see.

Principal Facts and Theories upon which the General Adaptation Syndrome Concept is Based

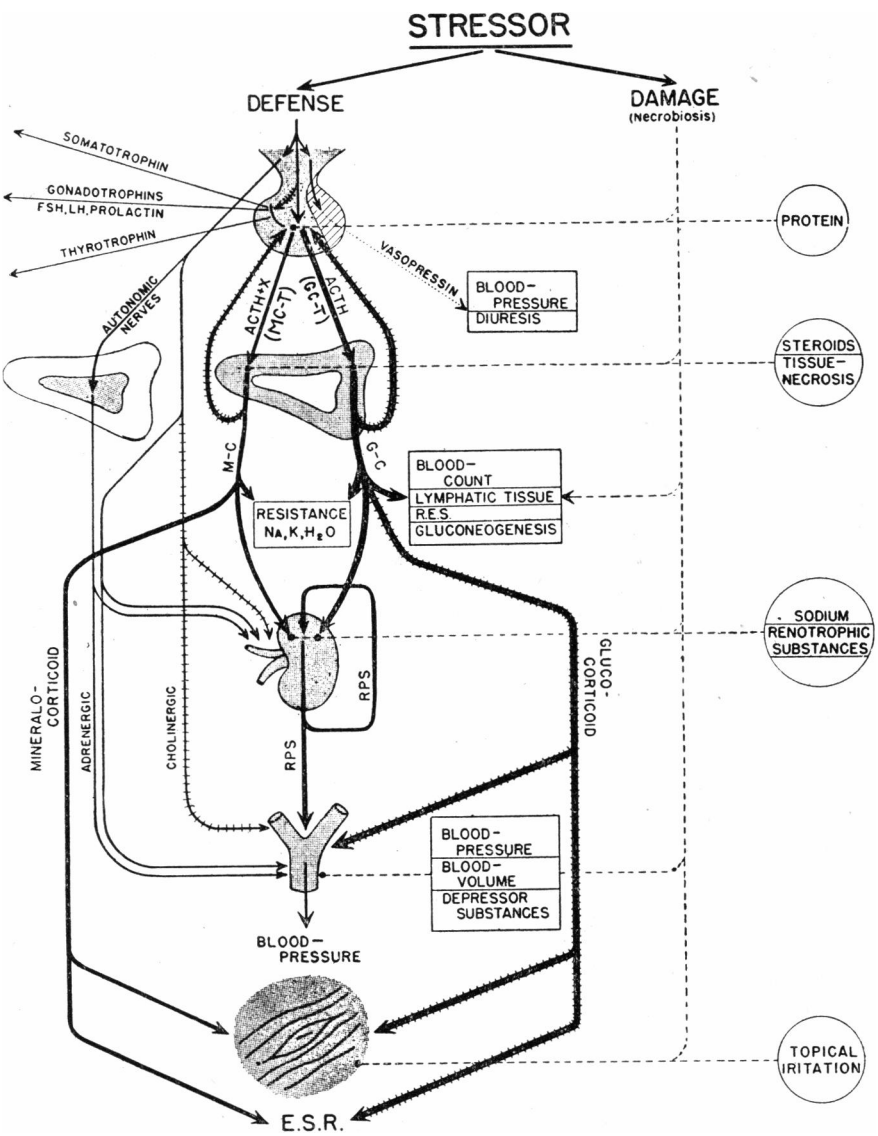
Apart from the many specific defence reactions (e.g., formation of specific antibodies, adaptation to cold, habituation to morphine, hypertrophy of much-used muscle groups) there is an integrated syndrome of closely interrelated adaptive reactions to non-specific stress itself; this has been termed the "General Adaptation Syndrome" (G.A.S.). It develops in three stages: the "Alarm Reaction" (A.R.), the Stage of Resistance, and the Stage of Exhaustion. Most of the characteristic manifestations of the A.R. (tissue catabolism, hypoglycaemia, gastro-intestinal erosions, discharge of secretory granules from the adrenal cortex, haemoconcentration, etc.) disappear or are actually reversed during the stage of resistance, but reappear in the stage of exhaustion. This suggests that the ability of living organisms to adapt themselves to changes in their surroundings, their adaptability or "adaptation energy," is a finite quantity; its magnitude appears to depend largely upon genetic factors.

In the general adaptation syndrome the manifestations of passive non-specific damage are intricately intermixed with those of active defence. This is an inherent characteristic of the stress which elicits the general adaptation

*The first part of the Heberden Oration, given on June 2, 1950. The second part, being principally a commentary on lantern slides, was summarized in the *British Medical Journal* of June 10.

syndrome. In the biological sense stress is the interaction between damage and defence, just as in physics tension or pressure represents the interplay between a force and the resistance offered to it.

In addition to damage and defence, every stressor also produces certain specific actions (e.g., anaesthetics act upon the nervous system, diuretics upon water metabolism, insulin upon the blood sugar) quite apart from their stressor effects. Hence the general adaptation syndrome never occurs in its pure form, but is always complicated by superimposed specific actions of the eliciting stressors. In contemplating any biologic response (e.g., a spontaneous disease, an intoxication, a psychosomatic reaction), it is usually quite difficult to identify individual manifestations as being due respectively to damage, defence, or specific actions of the provocative agent. Only non-specific damage and defence are integral parts of the general adaptation syndrome, but the specific actions of the eliciting stressors modify the course of the resulting general adaptation syndrome (e.g., the glycaemic curve will deviate from the characteristic pattern if insulin is used as the stressor agent; the neurological manifestations will be atypical if the general adaptation syndrome is provoked by ether). In this sense they act as "conditioning factors." Certain circumstances, not directly related to the stress situation, are also prone to alter the course of the general adaptation syndrome. Among these heredity, pre-existent disease of certain organ systems, and the diet are especially important.



The accompanying schematic drawing disregards the specific actions of stressors, since they are not part of the general adaptation syndrome. It attempts to depict only the main pathways through which non-specific stress itself affects the organism and the manner in which such reactions are conditioned.

Defence

The systemic defence measures, against both general and localized (topical) injuries, are co-ordinated through the hypothalamic vegetative centres and the hypophysis. The initial pathways through which stressors act upon these centres are not yet known. Probably either humoral or nervous impulses, coming from the site of direct injury, can induce the hypothalamus–hypophysis system to gear the body for defence. Subsequently both of the two great integrating mechanisms, the nervous and the endocrine system, are alerted.

The Nervous Defence Mechanism.—Nervous impulses descend from the hypothalamic vegetative centres, through the autonomic nerves, to the peripheral organs. The splanchnics induce the adrenal medulla to discharge adrenergic hormones (adrenaline and *nor*-adrenaline) into the blood. Other adrenergic nerves influence their target organs directly through fibres which in the final analysis again act through the liberation of adrenergic compounds, in this case at their endings in the effector organs themselves (blood vessels, glands, etc.). Presumably the discharge of adrenergic hormones into the circulation is most effective when they are needed throughout the body, while the sympathetic nerves are better suited to impart similar impulses selectively to certain circumscribed territories. The most conspicuous results of such neuro-humoral discharges are changes in the contractility of smooth muscle. Owing to an adrenergic vasoconstriction, peripheral resistance increases and the blood pressure rises. This hypertensive response may be further accentuated by an increased cardiac volume and the opening of the "renal shunt," which deviates blood from the cortical glomeruli to the juxtamedullary region of the kidney. This neurogenic activation of the "shunt" is quite comparable to that induced by mechanical interference with the arterial inflow (Goldblatt clamp, "endocrine kidney" operation) into the kidney; hence it augments the production of renal pressor substances (R.P.S.). The latter also cause peripheral vasoconstriction; thus they further augment peripheral resistance in the cardiovascular system and hence the blood pressure rises (cf. below).

There is some evidence of a simultaneous cholinergic discharge during systemic stress. Concurrent activation of both agonists and antagonists occurs in many effector systems during the general adaptation syndrome. Presumably it helps to stabilize the target organs in the face of very powerful stimuli which might otherwise cause excessive deviations from the norm. This concurrent tension of agonists and antagonists is somewhat reminiscent of the simultaneous contraction of flexor and extensor muscles —for instance in a limb—to prepare it against possible displacement by a blow which may come from any direction. However, damage (shock) endangers life particularly through vasodepressor and hypotensive actions ; hence the predominant response during the general adaptation syndrome is a defensive (prophylactic) vasoconstriction and hypertension.

The nervous system also participates in many other defensive reactions during the general adaptation syndrome, e.g., the regulation of water metabolism (through the hypophysial stalk and posterior lobe), the blood sugar (through the hepatic branches of the sympathetic division), and the blood count (through splenic contraction), but for the sake of simplicity these are not specifically indicated in our schematic drawing.

Hormonal Defence Mechanism

The principal endocrine response to stress is characterized by the so-called " shift in anterior-lobe hormone production." This consists in a diminished secretion of somatotrophin, the gonadotrophins (F.S.H., L.H., prolactin) and thyrotrophin—which are not essential for the maintenance of life during conditions of emergency—accompanied by an increase in the secretion of A.C.T.H. Apparently the anterior lobe is unable to produce all its hormones at an optimal rate if it is called upon to discharge extraordinarily large amounts of corticotrophin.

A.C.T.H. is a " gluco-corticotrophic " hormone. It induces the adrenal cortex to produce predominantly gluco-corticoids—e.g., " compound F," cortisone. The latter act upon the blood count (lymphopenia, eosinopenia, polymorphonuclear leucocytosis), the thymico-lymphatic tissue (lympholysis), the reticulo-endothelial system (increased phagocytosis and antibody formation), and gluconeogenesis (transformation of non-sugars into carbohydrates).

The gluco-corticoids presumably influence resistance in many additional ways which have not yet been fully analysed. Through all these actions such steroids help to maintain adrenalectomized animals, even during exposure to stress.

All gluco-corticoids so far examined possess some mineralo-corticoid activity (actions upon Na, Cl, K, and water metabolism) ; thus they resemble the pure mineralo-corticoids, but the latter are much more potent in this respect and possess no gluco-corticoid action. Hence, changes in mineral and water metabolism observed after the injection of A.C.T.H. do not necessarily reflect the production of pure mineralo-corticoids by the adrenal.

The action of gluco-corticoids upon the kidney has not yet been extensively studied. However, preliminary investigations show that they cause marked hyperaemia of the glomeruli and may render the latter permeable to proteins and even blood. Heavy overdosage with gluco-corticoids can produce severe hyalinization and disintegration of glomeruli. This is followed by a rise in blood pressure, presumably mediated through the R.P.S. system. In this respect gluco-corticoids and mineralo-corticoids may mutually synergize each other.

The gluco-corticoids inhibit the production of arteriosclerotic changes (especially periarteritis and hyalinosis). In this respect they antagonize the effects of mineralo-corticoids.

The gluco-corticoids generally inhibit excessive proliferation of fibrous tissue, the formation of intercellular protein deposits (e.g., hyalinosis, collagen disease, allergies) and excessive granulomatous defence reactions against those local irritants which stimulate fibroplastic inflammatory reactions in mesenchymal tissue. They also tend to decrease the erythrocyte sedimentation rate (E.S.R.) through their effect upon the blood proteins. In all these respects they act as antagonists of the mineralo-corticoids.

The mechanism of the marked anti-allergic and anti-histaminergic actions of gluco-corticoids has not yet been elucidated. It may depend upon the breakdown of the proteins which store histamine as a protein–histamine complex.

Many data suggest that under conditions of stress mineralo-corticoid production is likewise increased. Such a rise can also be elicited by certain impure, mineralo-corticotrophic, anterior-pituitary extracts—for instance, lyophilized anterior-pituitary tissue (L.A.P.). Threshold doses of L.A.P. are further activated in this respect by simultaneous administration of A.C.T.H. Apparently the action of the latter can be qualitatively altered by some factor (" X ") present in crude pituitary extracts and L.A.P. This " X factor " appears to be a specific pituitary principle, as it has not been found to occur in similar preparations of other tissues (e.g., liver). The " X factor " is manifestly not A.C.T.H., but it may be identical with one of the other, already known, hypophysial hormones. It could also be a special hypophysial principle, not hitherto identified. Be this as it may, it has now definitely been established that certain pituitary extracts produce a gluco-corticoid type, others a mineralo-corticoid type of reaction. Furthermore, in response to stress the pituitary itself may discharge predominantly gluco-corticotrophic or mineralo-corticotrophic principles.

Mineralo-corticoids

The mineralo-corticoids share with the gluco-corticoids the ability to increase the general resistance of adrenalectomized animals. They also cause severe lesions in the kidney, if large quantities of them are given over a long time. There is distension of the convoluted tubules, proliferation of the spiral segments, hyalinization of the glomeruli, proteinuria, hyaline-cast formation, and, eventually, nephrosclerosis.

It is highly probable that mineralo-corticoids increase the production of renal pressor substances, especially through some direct functional effect upon the convoluted tubules. Even the subsequent morphological changes in this part of the nephron precede the development of glomerular sclerosis. Eventually, however, the gradual constriction of the glomerular capillary bed acts somewhat like the Goldblatt clamp or the " endocrine kidney " operation and, simultaneously with the inhibition of glomerular filtration, increases the endocrine activity of the nephron. At the same time the inactivation of renal pressor substances is impeded and a hormonally induced renal hypertension ensues.

Presumably, both stimulation of R.P.S. formation and inhibition of R.P.S. destruction is thus induced by mineralo-

corticoids. This affects the blood vessels. At first the resulting excess of renal pressor substances causes a functional vasoconstriction with an increase in peripheral resistance and blood pressure. More prolonged overdosage with mineralo-corticoids results in arteriosclerotic changes (especially periarteritis nodosa and hyalinosis), with a consequent permanent increase in peripheral resistance and blood pressure.

In this respect mineralo-corticoids and gluco-corticoids mutually antagonize each other, but since (at least at certain dose levels) their actions upon the kidney are synergistic, it depends upon the "conditioning" circumstances whether the administration of gluco-corticoids to animals overdosed with mineralo-corticoids increases or decreases the blood pressure. (Cf. also conditioning effect of sodium and renotrophic substances, below.)

There is no definite evidence to prove that either type of corticoid has any direct vasopressor effect. Addition of corticoids to perfused vessel preparations does not cause them to contract. Nevertheless, mineralo-corticoids can augment the blood pressure even in the absence of the kidney, presumably by raising the blood volume through their effect on mineral and water metabolism.

Both types of corticoids act back upon the anterior lobe and inhibit its A.C.T.H. production through the so-called phenomenon of "compensatory atrophy." It is not yet known whether corticoids also impede the endogenous production of that "X factor" which renders A.C.T.H. mineralo-corticotrophic. However, this is very probable, since otherwise A.C.T.H. therapy would only aggravate conditions characterized by symptoms of mineralo-corticoid overdosage. If the production of the "X factor" is inhibited in the same manner as that of ordinary A.C.T.H., then the therapeutic action of A.C.T.H. is readily explicable. In both instances the pituitary is exposed to an excess of gluco-corticoids. The latter are even more potent in eliciting the "compensatory atrophy" phenomenon than the mineralo-corticoids. Consequently, endogenous corticotrophic stimuli (including "X factor") are virtually eliminated and the exogenously administered, predominantly gluco-corticotrophic A.C.T.H. acts uninfluenced upon the adrenal cortex.

There is much to suggest that at least certain types of stress (e.g., emotional stimuli) can increase the production of antidiuretic hormone, which is probably identical with vasopressin. This effect is undoubtedly mediated by nerve tracts descending from the hypothalamus to the posterior lobe, since (unlike the discharge of A.C.T.H.) it is abolished by transection of the hypophysial stalk.

Vasopressin exerts important effects upon the blood pressure and diuresis; these may be superimposed upon the typical reaction pattern during the general adaptation syndrome. However, the role of vasopressin secretion during systemic stress has not yet been adequately investigated.

Damage and Other Factors Conditioning Defence

As we have said before, many non-specific actions of stressors merely represent manifestations of damage and are not mediated through either the humoral or the nervous defence systems outlined above. These changes appear to result from necrobiosis of cells not sufficiently protected by the systemic defence mechanism. Thus tissue catabolism occurs under conditions of stress even in the absence of the pituitary, the adrenals, or the sympathetic nervous system. Although gluco-corticoids enhance catabolism, especially of readily dispensable proteins (e.g., that of the thymus, the lymph nodes, and connective tissue), extensive losses of body protein, fat, and carbohydrate can occur even after adrenalectomy.

Catabolites thus produced can condition the defensive chain-reaction of the general adaptation syndrome at various links. We have seen that protein tends to favour the mineralo-corticotrophic type of hypophysial discharge; that sodium increases, while renotrophic steroids decrease, the sensitivity of the kidney to overdoses of mineralo-corticoids, that topical chemical irritation augments the fibroplastic- and hyalinosis-producing action of mineralo-corticoids, and so forth. There is every reason to believe that endogenously liberated protein (or amino-acids), sodium, renotrophic steroids, and irritating metabolites would influence such hormone actions in the same manner as these substances do when they are exogenously introduced into the body. The intensity and the quality of such "endogenous self-conditioning" of the general adaptation syndrome largely depend upon the body's reserve of these metabolites and the intensity with which they are discharged into the blood. Presumably this in turn is influenced by heredity, species differences, previous exposure to stress, the nutritional state of the organism, etc.

We saw that the specific actions of individual stressors may likewise act as conditioning factors. Thus agents causing intense renal damage can sensitize the body to the pressor effects of the general adaptation syndrome, somewhat in the same manner as partial nephrectomy does; pyrogens, histamine, and other stressors capable of causing severe vascular paralysis will selectively "decondition" the arterial tree to the pressor action of endogenous renal pressor substances; microbes, allergens, or local mechanical trauma can stimulate the tissues which come into direct contact with them (somewhat like the formalin or mustard in our "topical irritation arthritis" test) to the formation of a fibroplastic and hyalin-containing granuloma tissue.

Such conditioning factors affect the defence mechanism at different points and may either increase or decrease the efficacy of any one among its individual components. Hence it is evident that the essentially stereotyped defence-pattern of the general adaptation syndrome can manifest itself in widely different ways, depending upon such conditioning factors.

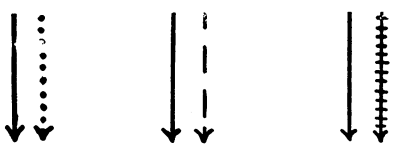
Diseases of Adaptation

This is particularly important for the understanding of the diseases of adaptation. Unless conditioning factors could considerably alter the reaction-pattern to stress, it would be impossible to ascribe rheumatoid arthritis, periarteritis nodosa, allergies, certain types of diabetes, or hypertension to the same causative agent—namely, to systemic stress. The concept that such widely different maladies should result from the same cause has often been considered to be quite contrary to accepted views concerning the causation of disease. Since this tenet is rather fundamental for our interpretation of the diseases of adaptation, it deserves special attention.

Let us point out first that such an assumption is not without precedent in medicine. For example, excessive production of thyroid hormone may be associated with predominantly ophthalmic, metabolic, or cardiac derangements. Before the tubercle bacillus had been isolated it would have been considered most improbable that such dissimilar conditions as Pott's disease, phthisis of the lungs, miliary tuberculosis, and tuberculous lupus of the skin were all caused by the same pathogen; yet this is the case.

We have attempted to demonstrate that the polymorphism of the general adaptation syndrome symptomatology is due to two principal reasons. First, every stressor has specific actions, in addition to its stress-producing ability. The former modify the response caused by stress as such; hence the polymorphism of the general adaptation syndrome manifestations can be due to specific effects of the evocative stressors.

The following schema will illustrate this point. In all three figures the solid arrow represents stress, the other the "contaminating" specific actions. Obviously, the end results of exposure to the three agents represented here could not be the same.



This type of "conditioning" may also be illustrated by an example taken from chemistry. All acids have many properties in common, yet the reactions of each member in this group are essentially different. The characteristics which they share are due to their acidity; the properties which distinguish them are the specific reactions of the carriers of this acid function. In pharmacology the stressor effect is what the drugs have in common; their other properties endow them with "specific pharmacological actions." Both in chemistry and in pharmacology the specific properties condition that non-specific feature (acidity, stress) which the entire group shares. Hence no two acids—and no two stressors—act exactly alike. This may help to illustrate conditioning by specific properties of the stressor.

We have seen, however, that even exposure to the same stressor agent may result in qualitatively different responses. Here polymorphism of the general adaptation syndrome manifestations is due to selective conditioning by factors extraneous to the stressor. This "peripheral conditioning" may occur at the various intermediate stations of the general adaptation syndrome or in the target organs themselves. We have compared this to the manifold effects one can obtain with the same electric current. During an emergency it may be necessary to supply more electricity for a community. This current will always be of the same quality and it will always travel along the same pre-existent main channels. Yet, depending upon the kind of emergency and the special needs of each district, both its quality and its quantity have to be regulated locally in the periphery. Thus the same current can be used to produce mechanical work, sound, light of any colour, heat, or cold, and indeed it may be shut out completely from a locality where it would represent a fire hazard. Of course, the more we approach the periphery of such an electric circuit the more subject it will be to conditioning. First, because the thin terminal wires can more easily be handled than the thick principal cables, and, secondly, because interventions anywhere along the line, above such a peripheral point, would affect the latter.

Essentially the same is true of the general adaptation syndrome. The more we approach the periphery the more often do we note deviations from the standard general adaptation syndrome pattern. All stressors cause an A.C.T.H. discharge, but this may or may not be accompanied by the production of the "X factor," which is necessary for mineralo-corticotrophic actions. Interference at a lower level may cause even more selective deviations from the typical stress response. Thus, transection of the splanchnics may impede adrenaline discharge during the alarm reaction without interfering with any general adaptation syndrome manifestations except those resulting directly from hyperadrenalinaemia. Possibilities for conditioning become ever more selective as we approach the peripheral target organs, each of which can be individually protected or sensitized to the typical actions of the general adaptation syndrome.

It is an inherent characteristic of most ramifying systems that side branches are more readily influenced than main lines. The following schematic drawing will help to illustrate this.

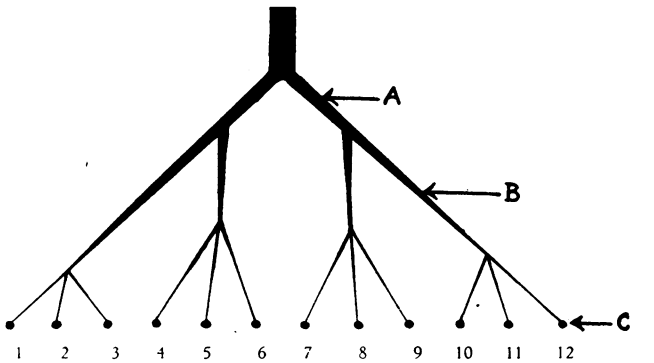


Illustration of selective conditioning in a ramifying system. Here 12 target organs received impulses through branches of a single main line. Conditioning at A would affect targets 7–12 without affecting targets 1–6. Conditioning at B permits targets 10–12 to be singled out specifically. Conditioning at C influences only the one target organ marked 12.

Principal Criticisms of the General Adaptation Syndrome Concept

The general outlines of the general adaptation syndrome concept have not been challenged, but some of its aspects became the subject of much debate and criticism; these deserve special consideration here.

Why are the "Diseases of Adaptation" so Polymorph in their Manifestations if they are all due to Stress?—We mention this question only for the sake of completeness, since it has already been answered in the preceding section. We believe that the principal reasons for this polymorphism are the so-called "conditioning factors"; namely, the specific effects of the evocative stressors and other exogenous or endogenous factors (heredity, pre-existent disease of certain organs, diet, previous exposure to stress, etc.) which can effect, selectively, certain pathways or target organs of the general adaptation syndrome response.

Why does Exposure to the same Stressor produce Disease only in certain Individuals?—It is undoubtedly true that the same drug, microbe, emotional irritant, or physical injury may produce a disease of adaptation in one person and be tolerated with impunity by another. It should be recalled, however, that the general adaptation syndrome is a useful, normal physiological reaction to stress; only its derailments have been interpreted as diseases of adaptation. Hence exposure to a stressor can be expected to produce such diseases only if the defence reaction is inadequate. Thus, for instance, in our experimental efforts to produce the hyalinosis–hypertension syndrome in rats by exposure to cold we found it necessary to perform unilateral nephrectomies and to keep the animals on high-sodium, high-protein diets. All these conditioning circumstances failed to produce disease in the absence of stress, but upon exposure to cold they caused a derailment of the general adaptation syndrome, with consequent cardiovascular lesions, nephrosclerosis, and a rise in blood

pressure. It is very probable that in man also, under the influence of stress, similar diseases would develop only when the general adaptation syndrome is prevented from evolving in a normal manner, as a result of adverse conditioning factors.

Desoxycorticosterone (D.C.A.) may not Occur in the Adrenals.—The fundamental work concerning the diseases of adaptation has been performed in animals treated with excesses of D.C.A. It is this work which led to the concept that diseases could be due to an excessive mineralo-corticoid production. Yet evidence now at hand is insufficient to prove with certainty that desoxycorticosterone is produced, as such, by the adrenal cortex.

It will be recalled that L.A.P. (a mineralo-corticotrophic extract) also causes similar lesions in intact though not in adrenalectomized animals. Even if desoxycorticosterone itself were not secreted by the suprarenal cortex, the above observations would still strongly suggest that some similarly acting principle is produced as a result of hypophysial stimulation. Furthermore, the "amorphous fraction" of Kendall, the "sodium factor" of Hartman, and desoxocortisone have all been shown to possess typical mineralocorticoid actions. All these substances have been prepared from the adrenals by several investigators and in good yields, so that there can be no question about their being natural products of suprarenal activity.

The Doses of D.C.A. used in the Fundamental Experiments on the "Diseases of Adaptation" may exceed the Amounts produced endogenously by the Adrenal itself.—This criticism has been voiced particularly with regard to the earliest experiments, in which D.C.A. was given in the form of injections to non-sensitized animals. Subsequently, with the introduction of the pellet implantation technique, especially in animals sensitized by unilateral nephrectomy and/or high-sodium diets, much smaller amounts of the hormone proved to be disease-producing.

It must be remembered, furthermore, that there is no objective reason to consider the pathogenic amounts of mineralo-corticoids as being beyond the limits of what could be produced in the body during stress. The quantities excreted in the urine of men who had received D.C.A. in doses conducive to hypertension, increased blood volume, oedema, and renal damage do not exceed those eliminated by patients after burns, traumatic injuries, or acute infections. If we can judge by the amounts of gluco-corticoids required to produce remissions in those spontaneous diseases which have been simulated in the animal by D.C.A. overdosage, then this criticism appears to be even more unjustified. About 10 mg. of D.C.A. a day, given over a period of weeks, would certainly be pathogenic in man, while 80–100 mg. of cortisone is usually required to produce a pronounced remission, for instance, in rheumatoid arthritis or lupus erythematosus.

How can one Reconcile the Fact that the "Rheumatic–allergic type" of Disease is produced by Corticoids in Animals and nevertheless responds so favourably to Corticoid Therapy in Man?—This question hardly deserves much comment now, although it was often asked just after the introduction of cortisone into clinical practice. The original animal experiments of necessity had to be performed with D.C.A. (a mineralo-corticoid), since this was the only adrenal steroid available in adequate amounts. Its effects upon many target organs are the reverse of those produced by gluco-corticoids (e.g., cortisone). As we now know, this is due partly to a peripheral antagonism at the level of the target organs themselves and partly, perhaps, also to the inhibition by gluco-corticoids of mineralo-corticoid production, through the "compensatory atrophy" phenomenon.

The Urinary Elimination of Corticoids is not always demonstrably Abnormal in the Diseases of Adaptation.—As we have repeatedly emphasized in this paper, diseases of adaptation do not necessarily result from an absolute deficiency or excess of corticoids; they can also ensue as a consequence of an improper balance between gluco- and mineralo-corticoid secretion, or be caused by a state of "relative hypocorticoidism." Thus in our "topical irritation arthritis" the introduction of an irritant into the joint region produced a violent arthritis in perfectly normal animals, yet it failed to do so after pre-treatment with an excess of A.C.T.H. or cortisone. This clearly shows that the adequacy of corticoid production can be assessed only in proportion to the pathogen which creates a need for such hormones. It is highly probable that pathogenic factors which cause disease in individuals whose corticoid production remains "normal" would fail to do so if the adrenals responded with an increase in hormone discharge commensurate with the increased requirements occasioned by an abnormal situation. Indeed, it is quite possible that many individuals who carry the pathogens (whatever these may be) of rheumatoid arthritis, allergies, lupus erythematosus, and so forth can remain in perfect health throughout life because—through the general adaptation syndrome mechanism—they have rendered these potential pathogens quite innocuous. To use an analogy from an entirely different field, one might compare them with the typhoid or meningococcus carrier who lives in perfect harmony with the deadly germs present in his body.

It should be mentioned, furthermore, that some evidence of an anomaly in steroid metabolism has been noted in patients suffering from the rheumatic–allergic diseases (e.g., increased pregnandiol excretion after the administration of progesterone, anomalies in 17-ketosteroid elimination).

Research along these lines has been handicapped, principally because of the difficulty of assaying blood or urine specifically for mineralo-corticoid activity. However, several recently published improvements in the relevant techniques hold great promise as regards the elucidation of this important problem.

Clinical Applications of the General Adaptation Syndrome Concept

As regards clinical medicine, we feel that the principal value of the general adaptation syndrome concept is that, by helping us to understand the role of the stress factor in disease, it enables us to adjust our therapeutic measures accordingly.

Non-specific Therapy.—It becomes increasingly more evident that many of the time-honoured, though not spectacularly effective, non-specific therapeutic measures—such as fever therapy, shock therapy, parenteral administration of foreign proteins, blood-letting, or mere starvation—are beneficial, largely through the general adaptation syndrome. Often their principal value appears to be that they stimulate A.C.T.H. and gluco-corticoid production. Wherever this is so, it may be preferable in the future to inject A.C.T.H. or cortisone. In certain instances, however, non-specific therapy proved efficacious where A.C.T.H. failed. For instance, in mental patients who did not respond to A.C.T.H. it could be shown by subsequent shock therapy that they are benefited by non-specific stress. Here presumably certain specific changes, incident to the shock, act as conditioning factors of the hypophysis–adrenal

discharge, or separately through other channels of the general adaptation syndrome (e.g., the nervous system or the catabolic response of the alarm reaction).

There is a striking parallelism between the diseases empirically shown to respond to non-specific therapy and those which show dramatic remissions under the influence of A.C.T.H. and cortisone (e.g., rheumatoid arthritis, various inflammatory conditions of the eye, allergies). Through the use of the corticotrophic and corticoid hormones we are on the threshold of developing a modern version of non-specific therapy which is much more effective than the old and lends itself better to a scientific analysis of its mechanism.

Dietary Treatment of Cardiovascular and Renal Diseases.—Diets poor in seasoning (spices, salt) and/or protein have long been recommended in the treatment of hypertension, nephritis, nephrosis, and allied conditions. However, the results were rarely spectacular, and, in the absence of any convincing rationale which could justify their use, they have not been received with sustained enthusiasm. Purely empirical observations on a heterogeneous clinical material failed to show clearly even whether the detrimental effects of highly seasoned food are due to sodium, chloride, or condiments in general. It also remained a subject of debate whether certain vegetable proteins are more readily tolerated than meat, and especially whether—in the face of heavy urinary protein losses in renal disease—it is better to prescribe low-protein diets, to protect the kidney against overwork, or rations rich in protein, to substitute for the constant urinary losses.

A study of the mechanism through which stress causes cardiovascular and renal disease has established certain definite facts concerning the part played by protein and minerals in the pathogenesis of the experimental replicas of such maladies. If these data can be applied to the corresponding clinical diseases—and there is much reason to think that they can—then we shall soon be able to prescribe diets on a much more rational basis.

Corticotrophin and Corticoid Therapy.—Undoubtedly the most important pertinent data are those derived from the clinical use of A.C.T.H. and cortisone. Since only very limited amounts of these hormones have been available up to date, it is not yet possible to assess their scope accurately. However, it is precisely now that some general orientation in this field is most urgently needed. By way of a summary, let us say, therefore, that (apart from their obvious utility in hypocorticoidism and anterior-pituitary deficiency) A.C.T.H. and/or cortisone have been shown to be of value in the following conditions:

- Agranulocytosis
- Alcoholism
- Allergies, various (in addition to those specifically mentioned here)
- Allergic rhinitis
- Asthma
- Atopic dermatitis
- Blepharitis
- Choroideremia
- Choroiditis
- Conjunctivitis vernalis
- Dermatomyositis
- Drug sensitization
- Eczema
- Exfoliative dermatitis
- Erythema multiforme
- Fevers (apparently irrespective of aetiology, though probably normalization of the temperature is not always an advantage)
- Gouty arthritis
- Hay-fever
- Haemolytic ânaemias of various kinds
- Herpes zoster
- Hodgkin's disease
- Idiopathic hypoglycaemia
- Iritis
- Iridocyclitis
- Keratitis
- Leukaemias (various)
- Loeffler's syndrome
- Lupus erythematosus disseminatus
- Lymphosarcoma
- Nasal polyps
- Nephrosis
- Neurodermatitis
- Ophthalmologic conditions (especially those characterized by allergic and inflammatory manifestations)
- Periarteritis nodosa
- Pneumonia (pneumococcus, "primary atypical")
- Psoriasis
- Retinitis (centralis, pigmentosa)
- Retrobulbar neuritis
- Rheumatic fever
- Rheumatoid arthritis and spondylitis
- Serum sickness
- Tuberculosis of the larynx
- Ulcerative colitis
- Urticarias (various)
- Uveitis
- Vasomotor rhinitis

Preliminary data suggest that this type of treatment may also be of value in the following conditions:

- Boeck's sarcoid
- Glaucoma
- Hepatitis
- Hypertension
- Hyperthyroidism (especially in normalizing the B.M.R. and reducing the exophthalmos)
- Keloids
- Liver cirrhosis
- Myasthenia gravis
- Nephritis (especially if due to allergy)
- Pemphigus
- Scleroderma
- Thromboangiitis obliterans (Buerger)

Available data suggest that A.C.T.H. and/or cortisone are of no value in:

- Amyotrophic lateral sclerosis
- Carcinomas of most types
- Congestive heart failure
- Diabetes mellitus
- Multiple myeloma
- Poliomyelitis

A.C.T.H. and/or cortisone may produce harmful effects in:

- Acne vulgaris
- Congestive heart failure
- Cushing's syndrome
- Diabetes mellitus
- Hypertensive disease of certain types
- Nephritis of certain types
- Osteoporosis
- Peritonitis
- Septicaemia
- Wound healing

In this connexion it should also be emphasized that under certain conditions A.C.T.H. and/or cortisone may actually cause:

- Acute pulmonary oedema
- Ascites
- Marked decrease in resistance to infections
- Obscuring of the criteria of disease (e.g., fever and abdominal rigidity in peritonitis, the haematological manifestations of systemic diseases, the acceleration of the pulse in acute infections, etc.)

Problems for Future Research Concerning the General Adaptation Syndrome

At this point it may be stimulating to contemplate some of the most important tasks that lie before us. However, in order to do so effectively we must first consider the direction this type of work has taken during the last few years.

In 1947 I emphasized that: "For the species, the most important role of the hormones is reproduction, but for the individual it is differentiation and adaptation. It becomes increasingly more obvious, furthermore, that the principal medical application of endocrinology is not the treatment of the primary but of the secondary diseases of the endocrines. Tumours and hyperplasias of endocrine glands, with consequent hormone overdosage, or destruction of incretory organs with the resulting hormone deficiency syndromes, are instructive simple experiments of nature which have taught us much about the endocrines. But these are rare diseases in comparison with the hormonal derangements resulting from maladaptation to stress.

"The main fatal syndromes of internal medicine (various cardiovascular, renal rheumatic, and old-age diseases) may belong to this latter group; they are probably by-products of faulty hormonal adaptative reactions to a variety of non-hormonal pathogenic agents. The apparent cause of illness is often an infection, an intoxication, nervous exhaustion, or merely old age, but actually a breakdown of

the hormonal adaptation mechanism appears to be the most common ultimate cause of death in man" (Selye, 1947).

Similar considerations led Albright (1943) to point out that: "The physician who calls himself an endocrinologist and confines his interests to such unfortunate members of society as might appear in the side-show of a circus never realizes that pneumonia, a broken leg, and a bad burn involve important changes in adrenal cortical function (cf. 'alarm reaction' of Selye), that the disturbance in homoeostasis occasioned by chronic renal insufficiency is ameliorated by a secondary hyperparathyroidism, that the somatotrophic action of testosterone propionate may be of use in many conditions other than male hypogonadism, and so on."

Laroche (1948) stressed particularly in connexion with the experimental work on the general adaptation syndrome that: "These experiments throw a new light upon a series of maladies which could not hitherto be related by pathologists to any particular hormonal derangement: certain hypertensions, certain types of chronic nephritis, the rheumatic affections, periarteritis nodosa, etc. Since these conditions can be elicited by a hormonal derangement, one wonders whether it would not be possible to effect their re-equilibration by means of other hormonal actions?"

I pointed out that: "It would be tempting to survey all the diseases of unknown aetiology from this new point of view and to determine whether those among them which apparently can be caused by a variety of agents belong to the category of the diseases of adaptation" (Selye, 1946). This has been accomplished, to the best of my ability, in my book now about to be published. Let us consider now some of those questions the solution of which appears to be particularly rewarding when we survey the general adaptation syndrome concept as it presents itself during the early months of 1950.

Adaptation Energy.—Ever since 1937 I have been intrigued by the fact that an already acquired adaptation to a certain stressor agent is gradually lost in the course of chronic exposure. This means that the "adaptation energy" (or adaptability) of the organism is a finite amount. There is a singular similarity between the manifestations of the exhaustion stage, which ensues when adaptability is lost, and those of physiological senility. No doubt inestimable advantages would accrue to the practice of medicine if we succeeded in identifying "adaptation energy." So far we can report no progress along these lines.

The Physio-pathology of Periodicity.—In addition to the irreversible exhaustion of senility, or of the "exhaustion stage" in the general adaptation syndrome, there is a temporary exhaustion or fatigue which ensues after less prolonged exposure to stress. From this condition recovery occurs most readily as a result of rest.

Stress-reactions—such as the general adaptation syndrome—are optimally effective during short emergencies; perhaps largely because most of the "stress hormones" (adrenergic substances, A.C.T.H., corticoids, R.P.S.) are well tolerated only during short periods and tend to cause severe complications if they act upon the body persistently over a long time. Thus, for example, the amounts of endogenous corticoids which spill over into the urine during a brief emergency (e.g., burns, emotional upsets, trauma, muscular work) are as high as those found in Cushing's disease, yet they do not produce "Cushingoid" manifestations. The same is true of patients who receive large amounts of such hormones for medicinal purposes during a short time. The intermittent secretion of A.C.T.H. during various stress situations (infections, nervous stimuli, etc.) may also explain the comparative rarity of "Cushingoid" changes in chronic disease; though here "deconditioning" metabolic changes probably also play a part. It may be rewarding to examine the mechanism of recovery from brief periods of overdosage with the "stress hormones" in order to learn how to avoid complications when they are therapeutically administered.

But there are many other data to stimulate interest in "periodicity."

A certain degree of cyclicity is nearly as characteristic of life as adaptability itself, and the lack of periodicity, or rigidity, is almost equivalent to death. The female sexual cycle, the pulse, the sleep rhythm with all the concomitant diurnal variations, the interchange between activity and rest, between work and play, the periodic renewal of cells in various organs are all indispensable for the maintenance of normal life. Stressors tend to disrupt this periodicity in many ways. It would be interesting to examine the possible relations between the diseases of adaptation due to stress and what might be called the "diseases of periodicity."

From time to time we feel the urge to reorganize our classifications in medicine, even if nothing really new is added—just as we rearrange the contents of our desk-drawers. It gives us a chance to eliminate the useless objects and to put the most useful ones into accessible positions. It may even call to our attention some long-forgotten item which we banished into obscurity at a time when we failed to realize its now so obvious utility.

We found it of interest to rearrange medicine in the book to which I referred above according to the general adaptation syndrome concept, but it may be equally, or even more, fruitful for some future investigator to rearrange them as "diseases of periodicity."

The Problem of the "First Mediator."—In the course of my work I have repeatedly had occasion to deplore the paucity of information concerning stimuli which, during stress, induce the pituitary to discharge A.C.T.H. Transection of the stalk (with all its nervous and blood-vessel connexions between hypophysis and hypothalamus) does not necessarily impede this response. The nervous pathways between the hypothalamus and the pituitary may be of importance in the event of exposure to purely neurogenic stressors; it remains to be seen, however, what carries the "stress message" to the anterior lobe from a burned skin, a traumatized limb, or tissues damaged by systemic infections and intoxications. I have expressed the opinion that perhaps an A.C.T.H. discharge could be caused by any derangement in the chemical or physical characteristics of the blood, but this is merely a hypothesis. Further work along this line is badly needed.

The possible Therapeutic Value of General Adaptation Syndrome Components, other than Adrenaline, A.C.T.H., and Gluco-corticoids.—Up to now attention was principally focused upon the utility of the adrenaline and gluco-corticoid discharges, the former mediated by the sympathetic, the latter by A.C.T.H. It is highly probable that many other manifestations of the general adaptation syndrome participate in raising resistance. In this connexion one might think of *nor*adrenaline, mineralo-corticoids, anti-diuretic hormone (vasopressin), acetylcholine, histamine, the products of lympholysis, and even endogenous anti-histamines.

How Perfect is the Correlation between Gluco-corticoid and Anti-arthritic Activity?—Up to the present time all our observations suggest that the power of a compound to inhibit rheumatoid arthritis or "topical irritation arthritis," to cause thymico-lymphatic involution, eosinopenia, and glycogen deposition in the liver and to antagonize certain manifestations of the "hyalinosis syndrome" are all correlated activities. In the terms of steroid pharmacology this would mean that these are subordinate actions of the gluco-corticoid potency, just as vaginal cornification, uterine oestrus, and testicular atrophy are subordinate actions of the folliculoid (oestrogenic) potency. It is not certain, however, that this apparent lawfulness will apply to all steroids which may become available in the future. There is some reason to believe that cortisonediene (a compound differing from cortisone by the introduction of a second double-bond at C_{6-7}) possesses certain gluco-corticoid activities without being capable of causing a remission in clinical rheumatoid arthritis. Further elucidation of these aspects of steroid pharmacology would undoubtedly extend the scope of pharmaco-therapy in the diseases of adaptation.

How Perfect is the Correlation between Mineralo-corticoid and Hyalinosis Activity?—In general, preparations with marked mineralo-corticoid actions (NaCl retention, K elimination, diuresis) are also most effective in producing experimental hyalinosis. However, in comparing the actions of L.A.P., desoxocortisone, and desoxycorticosterone this parallelism does not appear to be perfect. Furthermore, at very high dose levels, in certain vascular territories (e.g., kidney) even gluco-corticoids can cause hyalinosis, though in other target organs they inhibit such changes even at the same dose levels. We wish to stress the need for a more profound analysis of the correlation between mineralo-corticoid and hyalinosis activity.

Selective Conditioning in General.—We saw that some factors (diet, drugs, etc.) can selectively increase or decrease the action of stress hormones upon certain organs. In order to accentuate the desirable and to minimize the undesirable effects of A.C.T.H. and cortisone it is imperative to learn more about the activities of such "conditioning factors."

Selective Conditioning of the Adrenal Response in Particular.—The possibility of influencing the adrenal, at will, to produce different kinds of hormones deserves special mention. The adrenal cortex can produce a variety of compounds—namely, mineralo-corticoids, gluco-corticoids, testoids, folliculoids, and perhaps even "lipo-corticoids." We have shown, furthermore, that the morphological response of the adrenal cortex can also be qualitatively altered by conditioning factors. We concluded that the pharmacology of the adrenal cortex is not merely limited—as has hitherto been thought—to a more or less intense stimulation by A.C.T.H. It would be of the greatest interest to learn more about the factors which permit us to induce the adrenal cortex to respond in qualitatively different ways.

In this respect the recently discovered "X factor," which appears to be present in impure A.P.E. and L.A.P., is of special interest. It may be a new hormone or a mixture of already identified anterior-lobe principles. In any case, we shall have to attempt its identification in order to understand how the hypophysis can react to stress by discharging mineralo- and gluco-corticoids in variable proportions.

The recent demonstration that *nor*adrenaline is produced by the adrenal medulla raises the possibility of its participation in emergency reactions. Up to now only adrenaline has been considered in this connexion. Are there factors which can condition the adrenal medulla to produce either adrenaline or *nor*adrenaline predominantly?

Selective Hypocorticoidism.—The problem of selective hypocorticoidism is closely related to that previously discussed. The syndrome produced by excess mineralo-corticoids has often been compared to that of adrenal insufficiency. In both instances there is a tendency to develop hypoglycaemia, a predisposition to arthritis, a decreased resistance to various types of stressors, and, in certain circumstances, thymico-lymphatic hyperplasia. In these respects, manifestations of hypocorticoidism resemble those of a mineralo-corticoid excess. On the other hand, hypertension and hyalinosis are characteristic only of the latter. The relationship between complete hypocorticoidism (as caused by adrenalectomy) and selective hypo-gluco-corticoidism (as induced by mineralo-corticoid overdosage) requires further study.

Why is R.P.S. Maximally Produced When it is Minimally Detoxified?—It has been noted that conditions which cause the kidney to produce an excess of R.P.S. also interfere with its ability to detoxify such pressor substances. Indeed there appears to be a rather close inverse parallelism between R.P.S. production and R.P.S. detoxification. Perhaps such compounds as D.C.A. and such interventions as the "endocrine kidney" operation change the direction of a reversible chemical reaction between R.P.S. and some inactive precursor. If in the body the total amount of R.P.S. plus its precursor was fairly constant, factors which would tend to direct the process towards R.P.S. production would then automatically diminish its inactivation. This is but one of many possible explanations of the observed facts, but in view of the great practical importance of renal hypertension the field certainly deserves a systematic analysis.

Why is A.C.T.H. (or Cortisone) Capable of Producing Remissions both in Granulocytic Anaemias and in Agranulocytosis?—Perhaps here granulocytosis and agranulocytosis are merely secondary manifestations of a response to some evocative agent whose stressor effect is mitigated by gluco-corticoids. The condition is apparently comparable with the rise in body temperature occasioned by cortisone in Addisonian hypothermia, though the same compound depresses fever caused by a variety of pathogens. The mechanism of such dual responses remains to be elucidated.

Is the Similarity in the Pharmacological Effects of Adrenergic and Corticoid Compounds merely Coincidental?—Adrenergic compounds and corticoids share a number of actions, such as the ability to produce hyperglycaemia and hypertension, to increase muscular efficiency, and to antagonize certain types of allergic reactions. It may be significant that such varied effects are shared by hormones of the adrenal cortex and medulla, but the cause and purpose of these similarities—as those of the morphological proximity between adrenal cortex and medulla—remain obscure.

Other Miscellaneous Problems

The inhibition of wound healing and regeneration by gluco-corticoids raises the possibility that mineralo-corticoids may act inversely, but this remains to be shown.

The frequent occurrence of purulent infections (e.g., pulmonary, renal, or hepatic abscesses) in animals and the occasional development of peritonitis in man treated with

large doses of gluco-corticoids suggest that these hormones may be useful tools in the analysis of inflammations in general.

The role of the corticoids in the pathogenesis and treatment of hypertension, eclampsia, peptic ulcer, psychosomatic derangements, various types of tumours, etc., has merely been suggested by the experiments completed up to date. Further work along these lines would be highly desirable.

A.C.T.H. and cortisone substitutes are urgently needed for therapeutic purposes. The possibility of synthesizing A.C.T.H. from its constituent amino-acids is now under investigation, and it is quite possible that certain steroids of cortisone-like structure may help to decrease the high cost and increase the availability of these useful compounds.

It will also be necessary to explore systematically those drugs which could act as gluco-corticoid synergists in certain specific instances. Some such problems have already been discussed under the heading of "conditioning," but many cognate applications come to mind. For instance, it might be useful to depress granuloma formation in tuberculosis and other infectious diseases in order to expose micro-organisms to the destructive effect of antibiotics. It should be explored whether, in the absence of encapsulation and granuloma formation, micro-organisms would be more readily attacked by antimicrobial agents.

The Necessity for Specialists in Adaptation and Problems of Stress.—Finally we should like to emphasize that the science of adaptation is beginning to develop into a separate branch of medicine. Apart from specialists in certain techniques (surgery, *x*-ray, laboratory diagnosis) and target organs (heart, gastro-intestinal tract, skin, eye), we will need the specialist in stress and adaptation.

Just like his colleagues in other disciplines, he will have to borrow from cognate fields. The ophthalmologist has to acquaint himself with certain aspects of surgery, internal medicine, allergy, etc.; the cardiologist must know a good deal about *x*-ray findings, the physics involved in electrocardiography, etc. Similarly the stress specialist will have to devote a good deal of his time to the study of internal medicine, experimental physiology and pathology, allergy, neurology, endocrinology, and so forth. Nevertheless, the immensity of the subject-matter related to stress problems will undoubtedly require the training of specialists who may be consulted in connexion with diseases in which the stress factor plays a predominant part.

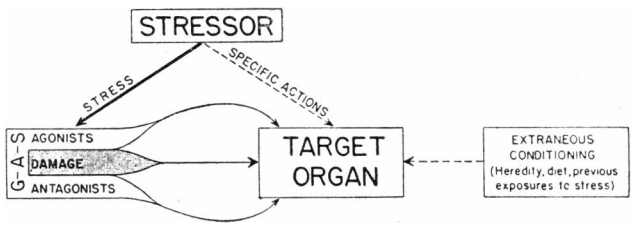
Diagrammatic Synopsis of the General Adaptation Syndrome Concept

And now in these last few paragraphs I should like to summarize concisely what appears to me the most important outcome.

All agents can act as stressors, producing both stress and specific actions. No agent can produce one without the other. The specific actions affect the target organs in a variety of ways. Stress acts only through the general adaptation syndrome. It causes defence and damage.

The defence mobilizes agonists and antagonists, which, through their interaction on the target organ, stabilize the latter and adjust its response to injury. But stress also invariably causes some degree of damage through the general adaptation syndrome. This likewise affects the target organ, though not through the humoral and nervous mediators of non-specific defence.

Factors extraneous to the general adaptation syndrome (e.g., heredity, diet, previous exposure to stress) can condition these responses. Thus in the final analysis the reaction of the target organ will depend upon the specific actions of the stressor, the effects of the resulting general adaptation syndrome (agonists, antagonists, non-specific damage), and extraneous conditioning factors. This explains how the essentially stereotypic general adaptation syndrome response can lead to a variety of polymorph syndromes and why so many apparently unrelated diseases are amenable to therapy by "stress hormones."



Disease consists of two components—damage and defence. Up to now medicine attempted to attack almost only the damaging pathogen (to kill the germs, to excise tumours, to neutralize poisons).

As regards defence, hitherto medicine limited itself to such vague advice as the usefulness of rest, wholesome food, etc. A study of the general adaptation syndrome suggests that henceforth we will be able to rely upon much more effective means of aiding adaptation to non-specific local or systemic injury by supplementing the natural defensive measures of the general adaptation syndrome whenever these are suboptimal.

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The annual "Heberden Round" was conducted by Professor F. Coste, professor of rheumatology in the University of Paris, at the Hôpital Cochin on May 20. Members of Professor Coste's unit and his associates presented cases and short papers. The president and many members of the French branch of the Ligue International contre le Rhumatisme attended, and members of the British branch were also invited. Professor Coste gave a review of his attempts to stimulate the pituitary and the adrenal glands or to produce cortisone-like effects; epinephrine, general anaesthesia, carotid sinus stimulation or infiltration with procaine, *x* rays, and short-wave diathermy directed to the glands had all been tried. He had also used androgens, oestrogens, desoxycorticosterone acetate in large doses, alone and in conjunction with ascorbic acid, and, also without effect, △-4-pregnenolone. Dr. Delbarre then showed a film illustrating the effects of A.C.T.H. in rheumatoid arthritis, and read a paper, in which he reviewed 40 cases of myelomatosis seen during the past three years. Other papers were by Dr. J. P. Amoudruz on the use of tomography of the sacro-iliac joints in early ankylosing spondylitis; Professor Merle D'Aubigne on the treatment of spondylolisthesis; Dr. J. Forestier on a type of ankylosing vertebral hyperostosis; and Dr. Mathieu Pierre-Weil on angina in rheumatoid arthritis. Dr. G. D. Kersley gave an account of an unusual case of gout and Dr. E. G. L. Bywaters described cases of the post-rheumatic arthrosis of Jaccoud. The Society was entertained to lunch by Professor Coste, and paid a visit to Enghien, where they were again entertained. A reception was also given by the British Council.