GROWTH AND DEVELOPMENT OF THE STRESS CONCEPT AND ITS SIGNIFICANCE IN CLINICAL MEDICINE

By
PAUL J. ROSCH
A.B., M.A., M.D.

Reprinted from
MODERN TRENDS IN ENDOCRINOLOGY

Published by
BUTTERWORH & C0. (PUBLISHERS) LTD.
LONDON

CHAPTER 21

THE GROWTH AND DEVELOPMENT OF THE STRESS CONCEPT AND ITS SIGNIFICANCE IN CLINICAL MEDICINE

PAUL J. ROSCH

IT IS NOT the purpose of this chapter to analyse in detail the tremendous wealth of material that has accumulated on this subject over the past 20 years. This important service has been and is being rendered in comprehensive fashion elsewhere (Selye, 1950, 1951; Selye and Horava, 1952, 1953; Selye and Heuser, 1954, 1955-1956). Our main effort will be to trace the salient features of the development of Professor Selye's theory, and to offer an appreciation of its present value to clinical and laboratory investigators.

INTRODUCTION

The desire to create order out of chaos, and to make rational the obscure, is a fundamental prerequisite for the scientific investigator, whether his field of interest be cosmology, nuclear physics, or the practice of medicine. Attempts to systematize and correlate the diversified phenomena comprising the subject of disease began with the Hippocratic concept of " pónos ", but were limited for the most part to the last century, the work of Virchow, Pasteur and Koch being pre-eminent in this regard. Apart from such purely nosologic efforts, theories of medicine have also centered about the response of the individual to disease, and in this area the prescient investigations of Claude Bernard provided a firm foundation for all further studies, particularly those of Walter Cannon.

In the past two decades yet another impressive basis for a unified theory of medicine has evolved, in the form of Professor Hans Selye's concept of non-specific stress, and adaptational syndromes. As is the case with any significant departure from established modes of thinking, these new theories were greeted with a range of sentiment varying from complete rejection to unqualified endorsement. In many instances there was considerable misunderstanding concerning the relationship of these concepts to the discovery and utilization of adrenocorticotrophin (ACTH) and cortisone, and still further confusion regarding their direct application to clinical medicine. Thus, an editorial in the "British Medical Journal" for June 17, 1950, described the value of a theory as being " its capacity to weld together isolated facts into a whole greater than the sum of those facts, and in its capacity to stimulate research ". It further stated " No theory in living memory has possessed these virtues to a greater extent than that of the General Adaptation Syndrome " (Anonymous, 1950). Three weeks later, in the same journal (Meiklejohn, 1950), we find the publication of Stress as perhaps " serving very well the same purpose that Galen's book did in the former Middle Ages ", the writer cautioning that " we would do well to remember that, through deductive speculation, civilized

society was once plunged into the Dark Ages ". The confusion is best exemplified by still another analysis (Roberts, 1950) from the same publication, also within the same three-week period, in which the author came to the conclusion that "Stress, in addition to being itself and the result of itself, is also the cause of itself".

Most of the misunderstanding arose from the widespread practice of specious over-generalization without thorough knowledge of the fundamentals of stress research. On the other hand, experiments by competent investigators, carefully designed to test the validity of specific aspects of this theory, were responsible for bringing about certain modifications and extensions of the initial concept as well as defining the areas where further gaps remained.

THE GENERAL ADAPTATION SYNDROME

The concept that the organism reacts to distressing situations in terms of highly integrated metabolic activities is not new. It was Cannon (1914) who first published his investigations on the adrenal medulla, in which he showed that emotional stimuli were capable of releasing a substance which would prepare the animal for flight or for defence. We are all familiar with such adrenergic responses which cause tachycardia, increased cardiac output, hyperglycaemia, possibly contraction of the spleen, and numerous other sympathomimetic activities such as widening of the pupils, horripilation, and other phenomena which might teleologically be interpreted as being purposeful reactions.

It was somewhat against this background that Professor Selye first reported (Selye, 1936) a series of experiments which indicated that laboratory animals, exposed to a variety of widely different and even opposite noxious stimuli, all responded in the same stereotyped manner. This pattern of response, to non-specific stress, was characterized by enlargement of the adrenal cortex, involution of the thymus and lymphatic organs, and the development of gastro-intestinal ulcers. Since its nature suggested a " call to arms " of the body's defences, it was termed the " Alarm Reaction ". Further investigations revealed that if exposure to the specific stressor was continued, a stage of resistance would occur, during which increased resistance resulted in adaptation to the specific stressor, and finally, after prolonged exposure, a stage of exhaustion would ensue, during which the acquired adaptation or resistance was lost. To this tripartite response was given the name, the " General Adaptation Syndrome ". Its three phases were, the " Alarm Reaction ", when adaptation had not yet been acquired, the " Stage of Resistance ", when adaptation to the specific stressor was maximum, and the " Stage of Exhaustion ", in which the acquired adaptation was useless or lost. Failure of the organism to adapt successfully might occur as a result of lack of adaptational responses, excessive adaptational activities, or abnormal adaptational reactions. Such disorders arising from failure of the organism to adapt successfully were termed " Diseases of Adaptation ", although more properly they should be considered as disorders of maladaptation.

Alarm reaction

On further study, the alarm reaction appeared to comprise two sets of phenomena, those which were passive, and represented signs of damage or shock,

and others which appeared purposeful manifestations of active defence against damage. In those examples of stress from which the organism eventually recovered, the signs of injury tended to appear before the manifestations of defence phenomena, and the alarm reaction could be conveniently subdivided into two separate phases, a " phase of shock ", and a " phase of countershock ". Thus, gastro-intestinal ulcers appeared in the initial phase, and adrenal cortical enlargement with signs of increased activity and reparative, defensive actions comprised the second, or countershock phase. This second phase of the alarm reaction apparently merged imperceptibly into the stage of resistance in cases of exposure to chronic stress, but its individual identity was established by showing that exposure to transient, sub-lethal, systemic stress did not result in a state of resistance, although certain phenomena of the shock phase could be reversed.

Stage of resistance

The stage of resistance was characterized by increased resistance to the specific stressor to which the body had been exposed, but a decreased resistance to other stimuli presented at the same time. This gave rise to the concept of " crossed resistance ", or " non-specific resistance ". Many of the morphological and bio-chemical changes of the alarm reaction disappeared during the stage of resistance, and, indeed, some of the effects were even reversed (deposition of lipid into the adrenal cortex).

Stage of exhaustion

The stage of exhaustion represented the composite picture of all non-specific systemic reactions which inevitably developed following protracted over-exposure to stressors. In these instances, adaptation which had initially developed could no longer be maintained. It was found that even a perfectly adapted organism could not indefinitely maintain a state of complete resistance, and this gave rise to the concept of " adaptation energy ". Once adaptation was lost, hallmarks of the alarm reaction reappeared, such as thymicolymphatic involution, gastro-intestinal ulcerations, and loss of adrenal lipid.

The general adaptation syndrome, then, represented the sum of all non-specific systemic reactions of the body which result from long, continued exposure to chronic stress. It apparently evolved in three phases, characterized by the alarm reaction, the stage of resistance, and stage of exhaustion. Fundamental to this concept was the realization that the manifold histological, morphological, biochemical and functional alterations produced by a variety of systemic stressors were essentially identical, irrespective of the nature of the specific stressor. Superimposed on these non-specific responses could be seen the effects of specific damage elicited by the noxious stimulus, but this was incidental to rather than a part of the organism's defence pattern. The reaction could be elicited only by systemic stress; it was a general reaction. The response helped to acquire resistance; it was adaptive: its individual aspects were integrated and mutually dependent; it was a syndrome. These features were to be distinguished from specific adaptive responses such as immunization against yellow fever, since this latter type of reaction was not evoked by systemic stress, and the type of resistance produced was sharply limited to the specific stressor.

EXPERIMENTAL BACKGROUND

The first experiments that were performed attempted to study the effect of the stressor (cold, muscular exercise, and so forth) in adrenalectomized laboratory animals, and this showed that in the absence of the adrenals, stress could no longer produce thymicolymphatic involution as well as certain other characteristic changes. On the other hand, gastro-intestinal ulcers were actually more severe in adrenalectomized than in intact animals, and could be lessened by treatment with certain cortical extracts. It was concluded that these latter lesions were not mediated through the adrenal, but were actually combated by an adequate adrenal cortical response to stress. On the other hand, when adrenalectomized rats were treated with the impure cortical extracts available at the time, it became evident that the characteristic thymicolymphatic involution as well as other stigmas of the alarm reaction could be reproduced by these crude agents even in the absence of the adrenal. It was further concluded that these changes were indirect results of stress, and were mediated by certain corticoids.

In 1937, an attempt was made to ascertain what stimulated the adrenal cortex during stress. It was found, after many surgical interventions, that only hypophysectomy prevented the adrenal response during the alarm reaction. Subsequent experiments demonstrated that stressors were able to stimulate the adrenal cortex via a pituitary adrenocorticotrophic substance, later identified as ACTH.

Later, due to the efforts of Kendall and Reichstein, more purified steroids became available. Using desoxycorticosterone acetate (DOCA) it was possible, under certain experimental conditions, to reproduce in rats the characteristic evidences of damage seen in the general adaptation syndrome. These included, among others, nephrosclerosis, arthritis, myocarditis, hypertension, and polyarteritis nodosa. Yet, even high doses of these compounds could not cause thymicolymphatic involution or certain blood changes characteristic of adrenal activity during stress. When cortisone and other glucocorticoids became available, it was evident that these were the agents responsible for the effects noted on lymphoid tissue and, more important, that these agents could inhibit and protect against certain manifestations of damage produced in animals by DOCA. This was the first demonstration of a possible concept of adrenal checks and balances, of corticoid antagonism. For a more completely documented description of the development of these concepts, reference should be made to a monograph of Selye (1952).

THE LOCAL ADAPTATION SYNDROME

It had been realized for some time that many local responses to topical injury were non-specific, and not limited to a specific agent. The characteristic phenomena of inflammation might result from trauma, infection, chemical irritation or burns. Investigation of the action of topical stressors revealed that certain similarities existed between systemic and local non-specific responses. Thus, protracted topical stress induced a " Local Adaptation Syndrome ", characterized by the familiar tripartite response. The local alarm reaction reveals degeneration and necrosis in its shock phase, acute inflammation and hyperplasia in its countershock phase. This is followed by a local stage of resistance characterized by chronic

inflammation, hypertrophy, and hyperplasia, and eventually a local stage of exhaustion, manifested by degeneration, necrosis, and atrophy, ensues. It was even possible to demonstrate the phenomenon of crossed resistance. The possibility of interrelations between the general and local adaptational syndromes appeared likely with the realization that both were non-specific defence reactions and that both evolved in three similar stages. Furthermore, it could be shown that both these syndromes were unusually modified by certain adrenal and pituitary hormones, and that if the two responses developed simultaneously in the same organism, they greatly influenced one another. This was particularly true in the case of altered tissue reactivity to topical stressors in the presence of systemic stress. Thus, the fundamental reaction pattern to topical stressors was a local adaptation syndrome, with inflammation, to systemic stressors, the general adaptation syndrome. It was postulated that various modifications of these two basic responses might constitute the essence of certain diseases.

TERMINOLOGY

The terminology which had to be adopted to describe the activity of adaptive hormones is now considered. The isolation of aldosterone from the adrenal has more or less ended the unitarian conception of adrenal cortical secretion. However, of the various 30 or more steroids identified in the venous effluent of the adrenal to date, possibly only three give evidence at present of being true hormones, and they are aldosterone, cortisol or hydrocortisone, and corticosterone. Whether the others are metabolites or precursors remains to be seen. In any event, from a functional viewpoint, adrenal cortical secretion is most conveniently understood from a trinitarian approach. This concept holds that the adrenal exerts its physiological influences in three main spheres, carbohydrate metabolism, electrolyte metabolism, and the vague realm of sex steroids.

Carbohydrate metabolism

Carbohydrate metabolism is influenced predominantly by the glucocorticoids, also called glycogenic steroids or " sugar hormones ". Examples of this group are cortisol and cortisone. In addition to its effects on carbohydrates, which are mediated by gluconeogenic actions and inhibition of the hexokinase reaction, the glucocorticoids in general are also protein catabolic (or anti-anabolic) and, in addition, generally possess lympholytic and eosinopenic properties. More important for the purposes of this discussion is the pronounced effect that this class of compounds has on the inflammatory process and on wound healing.

Electrolyte metabolism

The electrolyte controlling steroids, mineralocorticoids or " salt hormones ", were initially represented by 11-desoxycorticosterone but are now best exemplified by the naturally occurring aldosterone or electrocortin. In addition to promoting the reabsorption of sodium and the excretion of potassium, these compounds appear also to antagonize certain non-carbohydrate activities of the glucocorticoids.

The sex steroids

The sex steroids, or testoids, also known as " N " or " protein hormones ", are

presumably much like those of gonadal origin, having similar effects on secondary sex characteristics and favouring protein anabolism. Whether the adrenal cortex normally secretes an androgen, and what the stimulus for its production is, remains uncertain and raises the problem of more than one ACTH. A weak androgen is elaborated during the normal process of steroidogenesis, but it is then hydroxylated to cortisol. Although not concerned here with this group of compounds, it should be anticipated that increasing interest will centre about the possible role of this element of adrenal activity in the pathogenesis of certain degenerative disorders, particularly senile osteoporosis and coronary artery disease (Starr, 1956).

The generalizations made above are deceptively broad. It must always be kept in mind that because of the close structural similarity of these compounds, no clear-cut separation of function is expected. Thus, glucocorticoids have slight effects on electrolyte activity, some mineralocorticoids produce repercussions in carbohydrate metabolism, and other compounds have intermediate activities. With the synthesis of 9-*alpha* halogenated compounds and, more recently, the 2-methylated analogues of these, it is possible artificially to produce agents with extremely potent actions in both spheres, or, as in the case of the compounds with a double bond in the 1, 2, position, to produce actions almost only in one area. This does not detract, however, from the usefulness of making the artificial separation.

Lyophilized anterior pituitary extract

It has been noted that certain effects of stress appeared to be mediated via adrenal cortical activity and others appeared to be combated by adequate production of certain hormones. Reference has also been made to the apparent primary role of the pituitary in the mediation of the stress response. Further experiments designed to elucidate the role of the pituitary in this chain of reactions were undertaken, the principal agent utilized at this time being crude lyophilized anterior pituitary extract. Such hypophyseal preparations appeared to be definitely corticotrophic, in that they caused enlargement of the adrenal cortex. Of considerably greater interest was the demonstration that these extracts tended to simulate the damaging effects of mineralocorticoids, especially as regards the production of nephrosclerosis. When subsequent advances led to the isolation and purification of pituitary hormones it could definitely be shown that ACTH was not the agent responsible for this activity of lyophilized anterior pituitary extract. On the other hand, somatotrophin (STH), or growth hormone, did under certain conditions reproduce nephrosclerotic changes similar to those observed with DOCA and the crude pituitary preparations.

More studies indicated that STH was able to reverse or antagonize certain catabolic effects of ACTH. It tended to prevent the weight loss and susceptibility to infection seen in animals heavily over-dosed with ACTH or glucocorticoids. For example, the rat's normal resistance to tuberculosis could be overcome by pretreatment with ACTH. Concomitant administration of STH would abolish this sensitivity. Thus, there appeared to be a similar set of checks and balances at a hypophyseal level, such that STH was to ACTH as mineralocorticoids were to glucocorticoids $\left[\frac{\text{STH}}{\text{ACTH}} = \frac{\text{mineralocorticoids}}{\text{glucocorticoids}}\right]$.

PROPHLOGISTIC AND ANTIPHLOGISTIC EFFECTS

The convenient subdivision into glucocorticoid and mineralocorticoid activity proved valuable also in serving to delineate other spheres of adrenal activity. Thus, the bulk of initial experimental evidence led to the hypothesis that anti-rheumatic, thymolytic, eosinopenic and infection facilitating properties were linked for the most part to glucocorticoid activity. On the other hand, mineralocorticoids not only did not possess these effects, but in some instances antagonized such activities. This was particularly true in the case of inflammatory reactions, where it could be demonstrated that glucocorticoids had strong anti-inflammatory or antiphlogistic properties, whereas mineralocorticoids were apparently prophlogistic, in that they appeared to stimulate the proliferative reactivity or inflammatory potential of connective tissue. The analogy extended further to embrace the actions of pituitary hormones in this respect, and it could be shown that ACTH did indeed exert antiphlogistic effects, presumably (but not necessarily) through the predominant liberation of glucocorticoids, whereas STH had prophlogistic activities. Thus, STH was to the mineralocorticoids, as ACTH was to the glucocorticoids $\left[\frac{\text{STH}}{\text{mineralocorticoids}} = \frac{\text{ACTH}}{\text{glucocorticoids}}\right]$.

THE PROBLEM OF ALDOSTERONE

There are many gaps in the above thesis. One important objection is that aldosterone has been disappointing in its prophlogistic activities as measured by its ability to counteract the anti-inflammatory effects of cortisol (Selye and Heuser, 1954). These studies were performed with the dosage of aldosterone calculated in terms of its equivalence to desoxycorticosterone with respect to sodium activity. When compared weight for weight desoxycorticosterone and aldosterone are equally prophlogistic (Selye, 1955). Using the cotton pellet implantation technique (Desaulles *et al*., 1955) it was found that aldosterone had comparatively little prophlogistic activity, although, curiously enough, in small doses it did have minimal activity in this regard. This is not too surprising in view of other properties of this compound, such as its effect on carbohydrate metabolism, eosinopenic properties, and protection afforded adrenalectomized animals against water intoxication (Gaunt *et al*., 1955). In these areas it has glucocorticoid rather than mineralocorticoid effects. Although it resembles DOCA more than cortisol in areas other than mineral metabolism, as witnessed by its inability to restore protective influences of antihistamines against anaphylactic shock, it falls short of being the prototype of the concept of an ideal mineralocorticoid because of its lack of parallel prophlogistic properties. It is important to note, however, that it does have some effects in this direction.

Significance of desoxycorticosterone

It is quite possible that aldosterone is not the final answer in the problem of endogenous mineralocorticoid excretion. It has not been established unequivocally that all the sodium-retaining activity of adrenal extracts is due to aldosterone or to other known steroids, and the problems of isolation and extraction still offer significant obstacles. There is evidence to suggest that desoxycorticosterone may

yet play a significant role in normal metabolism. Small quantities have been recovered in perfusates of the gland *in vitro* (Hechter *et al*., 1951), and in the dog its concentration in the adrenal vein has been found to be elevated after administration of ACTH, and reduced after hypophysectomy (Farrel *et al*., 1954). Of considerable interest is the first recorded report of the spontaneous occurrence of significant amounts of desoxycorticosterone in human urine (Bongiovanni, 1955). This study suggested the possibility that desoxycorticosterone is normally produced as an intermediate compound in the synthesis of cortisol, the conversion being facilitated by the enzyme 11-ß hydroxylase. If a deficiency of this enzyme exists, or if it is inactivated, the conversion cannot proceed. This situation apparently obtains in some cases of congenital adrenal hyperplasia, and it is thought that the accumulation of desoxycorticosterone is responsible for the hypertension that is seen in these cases. Desoxycorticosterone may thus be a natural precursor for both cortisol and aldosterone (Wettstein *et al*., 1955), a concept that has interesting implications in view of the previous experiments mentioned.

The possibility of still other mineralocorticoids is raised by the isolation of 17α, 19-dihydroxy-11-desoxycorticosterone from bovine adrenal perfusates (Levy and Kushinsky, 1954). This compound is of particular interest in that it is more potent than DOCA in the sodium-retaining test, but apparently has less eosinopenic (and presumably glucocorticoid) effects than aldosterone.

THE VALUE AND USE OF A THEORY

While it is not necessary for our concept to ascribe mineralocorticoid potentialities to STH itself, it is of interest to note that such properties have been described and demonstrated to be operative even in the absence of the adrenal (Stein *et al*., 1952). Conversely, there may be found clinical (Scott and Kalz, 1956) and laboratory (Menkin, 1953) evidence suggesting that ACTH has local anti-inflammatory properties *not mediated via the adrenal*, thus completely rounding out the concept of duality and antagonism in the hypophyseal sphere.

All the above observations are consonant with the general theory previously outlined but they are by no means necessary for its existence, nor would their absence represent a source of serious detraction. On the other hand, if this theory were unable satisfactorily to embrace all the known existing facts, it would obviously no longer be useful or tenable as such. The reader must appreciate that we are, after all, dealing with a theory, rather than a law, and more particularly, we are concerned with very broad generalities within the rather flexible framework of that theory. With this in mind, there are a number of complex variables which must be mentioned if only in summary fashion.

Predominance of antiphlogistic or prophlogistic corticoid activity

At any peripheral target site, the over-all effect will depend on the predominance of antiphlogistic corticoid (AC) or prophlogistic corticoid (PC) activity. This relationship is somewhat unusual, in that with a fixed ratio of the two types of steroids, the cortisol action predominates at high doses, while the DOCA effect is most easily perceived at low levels. This perhaps explains why in adrenalectomized animals, desoxycorticosterone stimulates inflammatory responses, while in

the presence of the adrenal, these effects are much more difficult to demonstrate. It may also explain the results noted in the cotton pellet implantation experiment referred to above (Desaulles *et al*., 1955).

In terms of this net result at the target site, it is easily conceivable that in some instances the inflammatory response is beneficial and desirable, while in others it may be deleterious. Whether or not this plays a role in the determination of ultimate predominance of AC or PC activity is of teleological interest, but highly conjectural. It is quite likely that such factors as the nature, quantity, and chronicity of the stressor, as well as the nature and location of the target will modify the response. Perhaps the most important single factor is the phenomenon of conditioning, and this will be discussed later.

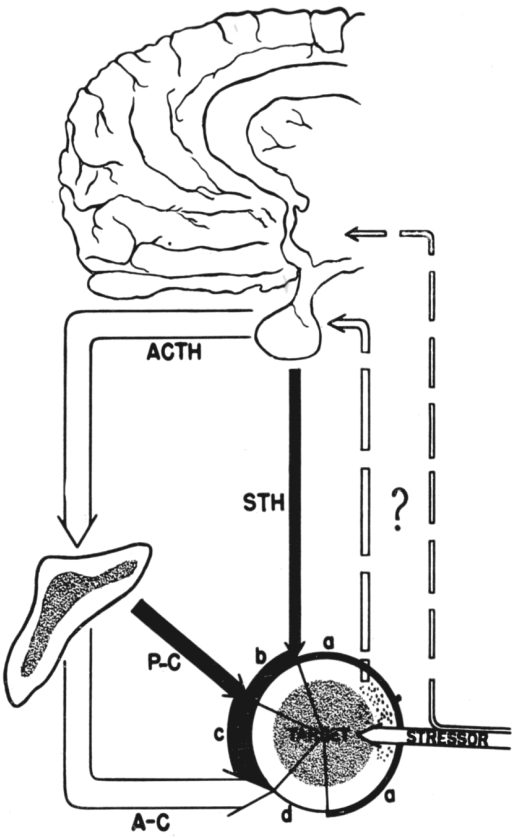
Finally, nothing has yet been said about the vague but obviously significant participating and co-ordinating influences exerted by the central nervous system and the autonomic nervous system. Equally important, and equally unknown, are the complex interactions of other endocrine glands which play less clearly defined roles in the over-all response to stress. However, as previously noted, the value of a theory is its ability integratively to absorb new information, and it is hoped that the stress concept will be reinforced rather than compromised when such important ancillary information is obtained. Fig. 15 summarizes the available information concerning the potential interrelations between systemic and local reactions to a topical stressor.

THE EXCEPTIONAL ROLE OF THE KIDNEY

The kidney possesses rather unusual properties that distinguish it from other targets of corticoid activity. It has been noted previously that nephrosclerosis may be produced by desoxycorticosterone under certain conditions. If cortisol is given simultaneously, this phenomenon is aggravated rather than prevented or ameliorated. Hence, in this instance, there is no glucocorticoid-mineralocorticoid antagonism, but rather a synergism. A similar synergism exists in the therapy of adrenal insufficiency. Of further interest is the observation that the nephrotoxic effects of STH (and methylandrostenediol) are prevented by adrenalectomy, although other properties (for example, prophlogistic activities) are not.

FIG. 15—The stressor penetrates the normal defences (a) to reach the target. Damage to the target produces local inflammation, and if sufficiently severe, degeneration and necrosis. This appears to stimulate a variety of local factors, which tend to repair the damage. Through some unknown pathway (represented by ?), a stimulus travels from the injured target directly to the anterior pituitary. The nature of this " first mediator " of hormonal defence is poorly understood. It conceivably may differ according to the nature of the target, or the characteristics of the stressor. In some instances, it may be represented by a discharge of adrenaline, in others it may be a neural or neurohumoral stimulus. Such possibilities include the release of histamine-like substances or tissue metabolites at the site of injury. On the other hand, the chain reaction may be set off by a local transitory deficiency of some vital component of cellular metabolism (enzyme, catalyst, vitamin, glucose). Indeed, any combination of factors mentioned may be operative. As indicated in the diagram, the stressor may, in addition, act directly via hypothalamic-hypophyseal pathways. In any event, stimulation of the anterior pituitary leads to an increased output of ACTH and the resultant liberation of glucocorticoid or antiphhlogistic corticoid (AC) hormones, such as cortisol and cortisone. These agents inhibit the ability of the target to put up granulomatous barriers, and in certain situations cause involution of

connective tissue elements as well as suppressing the normal inflammatory response. Under less clearly defined conditions, mineralocorticoids or prophlogistic corticoids (PC) are released, such agents favouring normal connective tissue defences. The mechanism of participation of mineralocorticoid or prophlogistic hormones in this phase of the response to stress requires much more investigation. It appears evident that under certain circumstances, such as the stress of surgery, increased amounts of aldosterone are also liberated (Llaurado, 1955). The mechanisms regulating the release of STH are still less clear. We have seen that the effect of this compound is to augment the natural tissue defence mechanisms, but whether it accomplishes this by sensitization of the affected areas to the prophlogistic action of (PC) hormones, or whether it may actually be responsible for the stimulation of production of these steroids in the adrenal cortex (Beck, 1955) is not known. We have adopted the former concept as the one best supported by the available evidence although both possibilities do exist.



In this diagrammatic sketch, the width of the circumference of the outer circle represents the existing state of local defence activities at any one moment, in terms of connective tissue activity. Those agents tending to augment this granulomatous potential are depicted as solid black arrows, those tending to inhibit it are represented by the white arrows. The normal defence potential is indicated by the width of segment (a). The effect of STH is slightly to augment this potential (b) but this occurs mainly by providing a substrate or sensitizing the affected tissue to the more profound prophlogistic effects of PC hormones, which result in the maximum width at (c). However, AC hormones may not only completely negate these effects, but also may be sufficiently anti-inflammatory to diminish even the normal tissue response, as indicated by the thinness of the segment at (d). (*See* text for discussion of other factors that modify these activities.)

CLINICAL CORRELATIONS

The crucial test of the general adaptation syndrome theory is the ability to find clinical corollaries to support the experimental evidence which has been presented. There are a number of problems that complicate the satisfaction of this requirement, and they will be discussed below. It is instructive to note, however, that the administration of DOCA to a patient with Addison's disease apparently resulted in focal areas of necrosis in heart muscle and skeletal muscle, with evidence of

polyarteritis nodosa (Thompson, 1950). In another patient with this disease, vascular changes in the kidney resembling nephrosclerosis were attributed to DOCA administration (Deamer and Silver, 1950). Intensification of arthritis in patients with Addison's disease who were receiving DOCA has recently been reviewed (Kirkeby, 1954), and the rapid development of incapacitating arthritis following the administration of DOCA was also noted. The tendency to develop hypertension on otherwise minimal or moderate doses of DOCA is a not uncommon problem in the experience of any clinician who has handled a number of cases of Addison's disease. There are other examples which might be cited and, conversely, there is a considerable lack of evidence, but on the whole, clinical findings to date, though meagre, tend to be explicable on the basis of certain broad principles of the theory.

CONDITIONING

Subjection to stress

Reference has already been made to the phenomenon of conditioning, and its critical role in the interpretation of the stress concept has been mentioned. Conditioning, as viewed here, may be taken to comprise any factor which modifies the target organ's response to corticoid action, or which alters the corticoid response to stress. This obviously covers a wide field and includes such diverse factors as age, nutrition, and heredity, as well as previous treatment with corticoids. Probably the most important conditioning factor is previous subjection to stress, which conceivably might affect both the reactivity of a target organ and the release of adaptive hormones. The definition given above is perhaps not a true representation of its usual meaning in stress research, since the term as employed by Professor Selye has the connotation of sensitization or desensitization, and implies that the conditioning activity modifies the response in terms of quantity only. As will be developed later, it is conceivable that the ability to cause altered or qualitatively different responses should also be anticipated and reserved for this activity.*

Cardiovascular and renal damage

The most familiar example of conditioning action is the enhancement of the development of cardiovascular and renal damage by unilateral nephrectomy and salt loading in the rat prior to treatment with DOCA. Under these conditions hypertension readily ensues, although without such measures chronic or prolonged treatment with DOCA is necessary to get the desired effect. A more complicated extension of this conditioning phenomenon is afforded by considering the additional effect of thyroidectomy in the unilaterally nephrectomized, salt-loaded, DOCA-treated rat (Salgado, 1954). When this procedure is performed, there is complete protection against hypertension as well as against the myocardial and renal lesions caused by DOCA, but, oddly enough, the incidence of mesenteric polyarteritis is exaggerated. It is supposed that this represents a dissociative conditioning of the conditioning agent. Thiouracil has similar effects but does not cause increased

* In fairness to Professor Selye, it must be admitted that when his concept is viewed in terms of the reaction theory, it becomes apparent that in any mosaic of actions, selective conditioning will bring about phenomena which impress us as being qualitatively different from the unconditioned response (for example, increasing the yellow component in a blue dye may result in a green colour).

polyarteritis, so that it merely blocks or conditions the conditioning agent. The reader will surely appreciate the complexity and futility of extending this type of observation further.

Individual stressor reaction

The problem of conditioning offers one of the greatest obstacles and challenges to the attempt at applying the precepts of stress research to clinical medicine. Here, the phenomena of conditioning may prove to be more important than any other factor in determining the quality (type) as well as quantity (degree) of the response. The problem is conveniently illustrated in the following Table.

TABLE
INDIVIDUAL STRESSOR REACTION

ECTOMORPH	*Tends to react to situations by cerebration* Serious Intellectual Enjoys reading Tends to be introverted	Cerebrotonic
ENDOMORPH	*Tends to react to situations in terms of the gastro-intestinal tract* Jovial Good natured Enjoys sensual pleasures Tends to be extroverted	Viscerotonic
MESOMORPH	*Tends to react to situations in terms of physical activities* Competitive Aggressive Enjoys athletics Tends to be ambiverted	Musculoskeletotonic

Let us assume that we have three individuals of the same age and sex, and apparently similar in all respects except their body type. One is an ectomorph, one an endomorph, and the other a mesomorph. Psychiatrists and students of somatology tell us that body type has considerable influence on, or correlates well with, general affect, and reactions to situations. Thus, ectomorphs tend to be introverts; they are usually tall, slender individuals, and tend to be serious, to enjoy reading, and to be cerebrotonic. The endomorph, a round individual, is usually jovial, good natured, extroverted, and enjoys sensual rather than intellectual pleasures: he is said to be viscerotonic. The mesomorph is the well-developed athletic type, very muscular and strong, delighting in physical prowess, and allegedly musculoskeletotonic.

Theoretically if each of these men were approached by a bandit and ordered to forfeit his money or his life, the ectomorph, being cerebrotonic, would try to talk his way out of the situation, perhaps by reasoning with the bandit and persuading him that he was taking a great risk and would not get much money anyway. The endomorph, being viscerotonic, would tend to express himself via his gastro-intestinal system, and possibly respond to the situation with nausea, vomiting, abdominal pain, or, more commonly, diarrhoea. The mesomorph, expressing

himself via his musculoskeletal system, would theoretically punch the fellow in the jaw, or run as fast as he could.

In this admittedly made to order illustration, we would have three individuals, similar in all respects save in their body build (conditioning factor), exposed to the same qualitative and quantitative stressor, reacting in three entirely different ways. Obviously, few persons fall wholly into one of these categories, and being combinations of each, the responses would be much more complex and difficult to anticipate, that is, if the relationship between reaction pattern and body type is valid. It is equally clear that many other factors would control the response, and the difficulty in ascribing priority to any one conditioning factor is readily seen.

It may be argued that the example cited has no endocrinological implications and that it describes purely behavioural reactions to a specific stressor. Nevertheless, it may be wondered if, in these three individuals, the eosinophils all dropped the same amount, whether the blood sugar response was identical, and whether one individual might not have a rise in blood pressure, when another was unaffected or going into shock. The point is raised merely to indicate the tremendously important role, yet undefined, of nervous mechanisms in integrating and modifying the response to stress, and to illustrate the complex variables that are covered by the term conditioning.

CONDITIONING VERSUS PERMISSIVE ACTION OF HORMONES

Stress or corticoids as conditioning agents

The problem of conditioning reaches its *ultima Thule* when one is forced to consider stress or corticoids as conditioning agents. It is necessary to have a clear understanding of terms, since this subject has aroused much controversy and misunderstanding. As has been noted, derangements are thought to occur during the general adaptation syndrome as a result of quantitative disturbances of adrenal response, or by alterations in the balance of glucocorticoid versus mineralocorticold. If the situation is examined further, it is readily apparent that the determination of whether excess hormone of either type is present at the target site is a function not only of the amount of hormone produced, but of less tangible factors, such as the need of the peripheral target for the steroid in question, the rate of utilization, the rate of detoxication, and our ubiquitous companion, conditioning.

It seems quite likely that, in addition to its ability to increase corticoid production, stress also affects certain peripheral targets by increasing their sensitivity to corticoids, a conditioning effect which was first recognized clinically by Thorn *et al.* (1955). These investigators found that only apparently in severe stress could an actual excess of cortisol-like activity be demonstrated, but that even mild stressors could elicit characteristic manifestations of glucocorticoid response without demonstrable evidence of increased hormone secretion. Thus, it might be argued that stress apparently sensitized or conditioned the peripheral target to the action of glucocorticoids, producing relative hypercorticoidism.

Role of the adrenal

An alternate and equally tenable hypothesis is the suggestion that the role of the adrenal in the development of alterations following stress is a more or less passive one. In other words, certain metabolic consequences of the response to

stress require the presence of corticoids, but are not dependent upon increased adrenal cortical secretion for their existence. In this sense, the adrenal does not cause the effect, but merely permits it to occur by maintaining normal or increased tissue reactivity. Restated in another way, adrenal hormones condition the reaction of the target to the stressor. Such an explanation would equally well explain the results noted in Thorn's experiment. A further extension of this proposition holds that the increased adrenal secretion during stress serves to maintain homeostasis rather than cause hypercorticoidism. The increase in corticoids is occasioned by the increased need of the tissues for the corticoids. At this level, therefore, a state of eucorticoidism or hypocorticoidism may exist, due to the balance existing between availability and utilization.

Steroid diabetes

The leading proponent of the concept of the " permissive " action of hormones is Ingle, and he has recently reviewed his position on this subject (Ingle, 1956). A particularly important experiment concerns the phenomenon of steroid diabetes due to 11-oxygenated steroids. The point is made that it is difficult to exacerbate experimental diabetes by non-specific stress. Many stressors caused a decrease in the severity of experimental pancreatoprivic diabetes as determined by reduction in glycosuria, and " when the diabetic adrenalectomized rat treated with maintenance doses of cortical extract is exposed to severe stress, the glycosuria decreases, as though the animal has now become adrenally insufficient " (Ingle and Nezamis, 1950; Ingle, 1951). The demonstration by Engel (1952) that the catabolic response to stress occurs before the response to corticotrophin or to glucocorticoids, and the notation by Venning (1955) that, in general, increased aldosterone elimination begins only several days after trauma, whereas electrolyte alterations suggestive of mineralocorticoid activity occur almost immediately (Moore, 1954), also suggests that certain adrenal responses to stress require, but are not caused by, adrenal activity.

There are certain arguments that might be offered to these examples. Although it is common practice one wonders if, in this instance, it is justifiable to make the assumption that adrenal cortical activity can be effectively estimated by such easily influenced and metabolically remote criteria as the level of the blood sugar, much less glycosuria. Another assumption which is made is that the two forms of diabetes are additive, so that having a state of regulated pancreatoprivic diabetes, the addition of steroids (stress) would invariably cause an exacerbation. The mechanism of steroid diabetes is apparently different in certain important respects from that of diabetes mellitus, particularly with respect to alterations in pyruvate metabolism (Frawley, 1955a, 1955b). If partial pancreatectomy interfered with the mechanism of steroid diabetes in some way, this experiment would have to be re-examined, although evidence to support this is quite remote (Knick, 1954). Certainly, alloxan and phloridzin diabetes are not equatable. If one wished to extend the argument further, it might be postulated that evidence exists that stress may cause hyperglycaemia in part via increased glucagon excretion (Fedeli and Jelmoni, 1955). In this eventuality, pancreatectomy would inhibit such glucocorticoid manifestations of stress and the increased need of the tissues for energy in the form of carbohydrate would decrease the glycosuria. Obviously, the specific effects of the stressor used might also play a determining role in the amount of

glycosuria due either to direct extra-adrenal action on the blood sugar or renal threshold. Unwarranted assumptions and criticisms such as those offered, do not detract from the important and significant implications of Ingle's observations, but they do emphasize the need for more refined criteria of the response to stress.

Wound healing

There is other evidence against a purely permissive role for the adrenal during stress. It is known that non-specific stress elicited by traumatic surgery tends to inhibit wound healing. In adrenalectomized rats maintained on small amounts of adrenal cortical extract, the stress of traumatic surgery does not result in a delay in wound healing (Chassin *et al*., 1954). In this instance, at least, increased adrenal activity does not serve to maintain homeostasis, but rather to cause hypercorticoidism. A similar argument which may be offered is that the criteria used to denote the effects of stress are those characteristic of corticoid activity. If the adrenal merely played a supporting role, it might be suspected that the effects noted would be those of the stressor, rather than the adrenal cortex.

7-hydroxycorticoid concentrations

Recent studies of free plasma 17-hydroxycorticoid concentrations in adrenalectomized dogs maintained on cortisol suggest alternative possibilities (Steenburg and Ganong, 1955). In these experiments the test animals were exposed to immobilization, anaesthesia, and surgery. All were adrenalectomized and all were given identical infusions of cortisol. The plasma level of corticoids was significantly higher in the anaesthetized and operated animals than in the conscious immobilized ones. The logical conclusion would appear to be that surgical trauma can activate a mechanism which delays the disappearance of free 17-hydroxycorticoids from the circulation.

Hepatic damage

There is definite morphological evidence of hepatic damage during the alarm reaction (Selye, 1950), and in rats exposed to a variety of stressors (formalin, cold. spinal cord transection) there is marked reduction in hepatic function as measured by the bromsulphthalein test (Mann and Lemonde, 1951). In patients with liver disease, the rate of disappearance of intravenous cortisol is inversely proportional to the degree of hepatic damage measured by the bromsulphthalein test (Brown *et al*., 1954) although tetrahydrocortisone disappears at an independent rate. These and other studies support the suggestion that impaired hepatic detoxication of corticoids may participate in the hypercorticoidaemia caused by trauma (Tyler *et al*., 1954).

Eosinopenia

Eosinophil counts during the experiment noted by Steenburg and Ganong (1955) demonstrated an interesting paradox. The most profound eosinopenia occurred when the animals were immobilized, and when blood corticoid peaks were lowest. A further drop was demonstrated in three adrenalectomized animals, which were operated upon without replacement hormone, and without a demonstrable rise in the circulating corticoid level. This indicates that the eosinophil is sensitive to substances other than those of adrenal origin (at least in the absence of

the adrenal) and further suggests that certain manifestations of the stress response require no corticoid permissibility or adrenal participation.

Thus, many theoretical possibilities can be conceived of interaction between stress and the adrenal: (1) non-specific effect due to over-production of corticoids; (2) non-specific effect due to decreased elimination of corticoids; (3) non-specific effect due to conditioning of the target by corticoid activity causing increased sensitivity; (4) non-specific effect due to the stressor but requiring the presence of corticoids to maintain tissue reactivity; (5) specific effects due to the stressor itself and not influenced by adrenal factors; (6) specific effects due to the stressor itself requiring adrenal activity; and (7) any combination of the above.

In the author's opinion, there is no irreconcilable conflict between the concepts of conditioning and permissive action. However, while it is interesting and valuable to speculate about the possible modes of hormonal participation, it is more important to keep sight of basic principles and to avoid not seeing the forest for the trees. We must not be preoccupied with deciding whether to view these activities of the adrenal cortex as conditioning (Selye), permissive (Ingle), homeokinetogenic (Conn) or providing grease for the metabolic axle wheel (Engel). The important contribution is the observation that the adrenal has anything to do at all with non-endocrine disease.

PRIORITY VERSUS AUTHORITY

Inevitably, in discussions of this sort, the spectre of priority looms up and confuses the issue by injecting personalities, and by associating temporal priority with authority. To set the record straight, the relation between hypophysectomy and adrenal cortical activity was noted in amphibia 40 years ago (Allen, 1917; Smith 1916), and the ability to correct this defect with pituitary extract was described shortly afterwards (Smith and Smith, 1923). Comparative results in mammals were reported over 30 years ago (Smith, 1927). Partial separation of ACTH from other anterior pituitary hormones was accomplished by Collip *et al*. (1933). Experiments demonstrating that adrenal cortical hyperplasia followed stress and could be suppressed by administration of adrenal cortical extract were performed by Ingle over 20 years ago, and reported shortly afterwards (Ingle, 1938). The sedulous investigator will even find the term " stress " used in describing " the essentially adrenal character of shell-shock and war neuroses " 40 years ago (Harrower, 1916, 1929). Such observations often lead to polemics which prove nothing. They tend to confuse the issue by raising the question of *who* is right, rather than *what* is right. The basic materials were certainly present in 1936 before the initial concept of the general adaptation syndrome was stated. Again, the important contribution has been the attempt to integrate existing factual matter, and the demonstration that the adrenal could be involved in some way with non-endocrine disorders and adaptive processes.

An unfortunate criticism of the stress concept is that it has attempted to claim credit for the discovery and use of ACTH and cortisone (Meiklejohn, 1950; Rosenberg *et al*., 1952). Nothing could be further from the truth. The author can state from personal experience that Professor Selye has disavowed any responsibility for, or influence on, the development of these agents. Moreover, he has stated (Selye, 1951), " Actually the reverse is true. It is I who throughout the years

have been stimulated and aided by the investigations of those who have prepared corticoids and ACTH ", and again, " From all this, I hope that it will be perfectly clear now, that it was not the work of Hench that was inspired by the observations of the Montreal group, but it is our work that receives its greatest inspiration from theirs ". One could hardly misconstrue this as a claim for priority.

PITFALLS

One must always anticipate the danger of generalizations extending far beyond the support of actual data which they intend to generalize. There is a natural tendency for any theorist to attempt to fit more into his conceptual framework than it can possibly contain. The application of the concept of cybernetics to the complicated intricacies of the human brain is an example of this. From an epistemological point of view, it may well be impossible to solve the problems which have been posed.

One pitfall in the use of the general adaptation syndrome is the attempt to use it as a rigid law, rather than as a theory. It is not possible, in the present state of knowledge, to account for the aetiology of all disease processes and, even among those we think we understand in terms of this concept, the endocrine response to stress may be only one of several modifying factors. Thus, while adrenalectomy and hypophysectomy modify the stress response, they do not totally prevent it. Similarly, the stage of resistance can be produced in adrenalectomized rats if they are exposed to stressors gradually. It has already been noted that, under certain circumstances, eosinopenia following stress may not be mediated through the adrenal.

In many instances the problem of over-generalization arises from the over-extension of an analogy. To illustrate, we note that cortisol inhibits the inflammatory response or is antiphlogistic. As supporting evidence accumulates, we generalize and say that probably glucocorticoids in general are antiphlogistic. We note that DOCA and some mineralocorticoids are prophlogistic, and that they antagonize the actions of cortisol in this respect. Hence, perhaps all, or most, other mineralocorticoids are also prophlogistic. These suppositions have proved to be useful and are in accord with existing facts. They serve as a scaffold on which to form other deductions, but if conflicting material is discovered, the scaffolding has to be torn down and remodelled, for it no longer has firm foundations.

May we, on the basis of the facts noted above, assume that glucocorticoids and mineralocorticoids will always be antagonistic? The answer is obviously in the negative, since we know that the activities of DOCA may be complementary and synergistic in the treatment of Addison's disease, as well as in the experimental production of nephrosclerosis. In this instance we would have been guilty of pushing the analogy too far. Instead of using it as a sort of metaphor to describe one phenomenon in terms of another quite distinct phenomenon, we have made the dangerous assumption that the phenomena really are the same sort of thing, and that we can find in one an equivalent with all the features of the other. This is the defect of all analogies; we may come to think that they will help us to interpret and even explain phenomena when, in fact, they only help imperfectly, and often unrealistically. This is not to say that analogies are not helpful and useful, but they should only extend so far as they are supported by existing facts.

Another pitfall is the temptation to employ a sort of *post hoe ergo propter hoc* type of argument. Thus, the demonstration that corticoids benefit rheumatoid arthritis is not sufficient evidence in itself to conclude that rheumatoid arthritis is due to a local deficiency of corticoid, any more than it could be due to a local deficiency of aspirin or phenylbutazone. Accompanied by other pertinent evidence, it is a valuable observation, and might support such a hypothesis. This type of reasoning may often be used efficaciously, as in the diagnosis and treatment of mild hypothyroidism by therapeutic trial. It is important to remember, however, that a potential fallacy in the basic hypothesis exists. Serious students of stress will avoid these pitfalls.

ANTELOPES AND ADAPTATION

Mindful of the pitfalls of analogy, one still notes that teleological concepts are always the most appealing, and that the basic supposition of the general adaptation syndrome finds many supporting analogies in Nature. Let us consider, for example, the adaptational problems posed by evolution, as in the case of the antelope.

We comprehend that an essential feature of the adaptation of antelopes is the development of horns. It is their principal means of offence in struggles within their group and of defence against attack from other animals. All the 23 varieties of antelope in the Belgian Congo possess horns, yet they are otherwise quite dissimilar (Schouteden, 1947). There must be one type of horn which is basically the most efficient, and with minor variations in proportion or shape depending on the size and habits of the animal. Yet, it is clear that none of these antelopes possess this " best horn ". Some horns are too small to be effective (duiker), others are prohibitively unwieldy (kudu). The horns of the impala, with their double curve, achieve the same placement and direction as those of the reedbuck which has a single curve, but they are much weaker mechanically and without affording any conceivable advantage.

If evolution were operating under a fixed plan, such radical discrepancies would not occur. On the other hand, there is a definite orientating factor since all the animals appear to have horns which serve them adequately, if imperfectly. It appears that different mutations have occurred in different lines, and that as long as they have served the adaptive end, that is, the development of a functional horn, they have been retained with ancillary disadvantages. This illustrates the principle of " opportunism " in evolution (Simpson, 1949) which is the ability to meet a need with what is available, even if it is not the best available, and even if it is harmful in other ways. One cannot subscribe to the finalist or vitalistic theory that the changes which arise are the best ones needed for adaptation, but conversely, if there were no orientating factor at all, and the horns developed purely by chance, then we should have bizarre results, and ineffectiveness. We have seen that however imperfect, the horns are useful.

Perhaps adaptation to stress resembles adaptation in evolution. The adaptational requirement imposed by stress is the restoration of homeostasis, in this case the development of effective horns. The requirement is satisfied by using the best means at hand, though often these are not the most efficient means; bad side-effects or diseases of adaptation may result, for example, unwieldy and burdensome horns. One could not assume that the over-all result was the best

possible, but conversely, one could not conceive that the end-results happened by chance, since they are reproducible; and if there were no adaptation to stress, the antelopes would succumb immediately, since there would be no homeostasis, in the guise of effective horns. The analogy cannot be pushed too far, but numerous other examples could be cited to illustrate that Nature frequently hyperreacts to a stimulus by an exaggerated or inappropriate response which is potentially harmful, that is, hyperplasia followed by malignancy, scar tissue, and keloids.

CONCLUSIONS

What then can we say of the present value and limitations of the concept of stress and adaptive disorders? Certain important principles have to be kept in mind. One of the most important and least respected is the realization that the response to stressors is, by definition, a non-specific reaction. It is not a disease state, but in its ideal form, a physiological response to injury which has, as its main purpose, the preservation of vitality and the maintenance of the constancy of the *milieu intérieur*. This interpretation must be differentiated from that in more widespread usage and denoting damage or injury. The concept of Pasteur and Koch postulated that disease was caused by specific pathogens, and that the organism responded by specific adaptive reactions. The therapeutic implications were obvious and based on the principle of complementing and imitating such reactions when they were deficient.

The general adaptation syndrome is, in one sense, the antithesis of this. It holds that many diseases have no single cause and no single pathogen, that certain disorders are largely due to non-specific stress and exaggerated or inappropriate responses, which are by-products of otherwise physiological adaptive processes. It implies also that antistress therapy ideally should attempt to complement the individual's own purposeful adaptive pharmacological efforts, and so emulate the *vis medicatrix naturae*. Further, by the understanding of the *modus operandi* of disorders of adaptive failure, it might conceivably be helpful to utilize those agents, which would oppose the specific hormones which played a role in their pathogenesis, even if Nature did not use such a mechanism.

It is too early to be able to offer an adequate appreciation of the concept of stress and the general adaptation syndrome. Its implications are staggering, and in the words of a notable authority, " If it is true, it will represent the greatest advance in the understanding of diseases since the introduction of the germ theory " (Ingle, 1951). As emphasized previously, interpretation of human disease in terms of animal experimentation is likely to be fraught with danger; this is particularly so in the field of stress.

It is difficult to understand something, unless you can measure it. The tests used to evaluate adrenal function are still rather crude, and those employed to measure stress are certainly less than adequate. Thoreau, in paraphrasing Confucius, once wrote, " To know that we know what we know, and that we do not know what we do not know, that is true knowledge. " The second half of this aphorism is most applicable to our thesis.

The concept as it stands certainly offers more than a series of ingenious pharmacological exercises. It provides a firm framework for educated speculation based on the premise that hypophyseal-adrenal pathways are involved in the

responses to stress, and that certain disorders may result from inappropriate by-products of these responses. Moreover, it is responsible for the demonstration that the adrenal may be involved in the production or maintenance of certain non-endocrine disorders, and it attempts to define those areas in which stress therapy is likely to be most effective.

In the author's opinion, its greatest contribution cannot be assessed at this stage. " to strive, to seek, to find, and not to yield. "

No theory could ask for more.

ACKNOWLEDGEMENTS

The author wishes to express his appreciation to Professor Hans Selye and Professor Dwight Ingle for reviewing this manuscript prior to publication.

REFERENCES

Allen, B. M. (1917). *Biol. Bull.*, **32,** 117.

Anonymous (1950). *Brit. med. J.*, **1,** 1410.

Beck, J. C. (1955). In *The Hypophyseal Growth Hormone, Nature and Actions, an International Symposium*. New York; McGraw-Hill.

Bongiovanni, A. M. (1955). *J. clin. Endocrin.*, **15,** 1524.

Brown, H., Willardson, D. G., Samuels, L. T., and Tyler, F. H. (1954). *J. clin. Invest.*, **33,**1924.

Cannon, W. B. (1914). *Amer. J. Physiol.*, **33,** 356.

Chassin, J. L., McDougall, H. A., Mackay, M. I., and Localio, S. A. (1954). *Proc. Soc. exp. Biol.*, N. Y., **86,** 446.

Collip, J. B., Anderson, E. M., and Thomson, D. L. (1933). *Lancet*, **2**, 347.

Conn, J. W., Fajans, S. S., Louis, L. H., Seltzer, H. S., and Kaine, H. D. (1954). *Recent Prog. Hormone Res.*, **10,** 471.

Deamer, W. L., and Silver, H. K. (1950). *J. Pediat.*, **37,** 490.

Desaulles, P., Schuler, W., and Meier, R. (1955). *Experientia*, **11,** 68.

Engel, F. L. (1952). *Endocrinology*, **50,** 462.

— (1953). *J. clin. Endocrin.*, **13,** 155.

Farrel, G. L., Rauschkolb, E. W., Royce, P. C., and Hirschmann, H. (1954). *Proc. Soc. exp. Biol., N. Y.*, **87,** 14 1.

Fedeli, S., and Jelmoni, G. (1955). *Folia endocrin., Pisa*, **8,** 231.

Frawley, T. F. (1955a). *Amer. Soc. Clin. Investigation*. 47th Meeting, p. 29.

— (1955b). *Ann. N. Y. Acad. Sci.*, **61,** 464.

Gaunt, R., Renzi, A. A., and Chart, J. J. (1955). *J. clin. Endocrin.*, **15,** 621.

Harrower, H. R. (1916). *Prescriber*, **10,** 203.

— (1929). *Endocrine Diagnostic Charts* . p. 29. Glendale; The Harrower Laboratory.

Hechter, O., Zaffaroni, A., Jacobsen, R. P., Levy, H., Jeanloz, R. W., Schenker, V., and Pincus, G. (1951). *Recent Prog. Hormone Res.*, **6,** 215.

Ingle, D. J. (1938). *Amer. J. Physiol.*, **124,** 627.

— (1951). *Ann. intern. Med.*, **35,** 652.

— (1956). In *Fifth Annual Report on Stress* (Selye, H., and Heuser G., 1955-56), p. 161 New York; MD Publications.

— and Nezamis, J. E. (1950). *Amer. J. Physiol.*, **162,** 1.

Kirkeby, K. (1954). *Acta med. scand.*, **149,** 43.

Knick, B. (1954). *Acta neuroveg.*, **9,** 316.
Levy, H., and Kushinsky, S. (1954). *Recent Prog. Hormone Res.*, **9,** 357.
Llaurado, J. G. (1955). *Lancet*, **1,** 1259.
Mann, H. B., and Lemonde, P. (1951). *Rev. canad. Biol.*, **10,** 167.
Meiklejohn, A. R. (1950). *Brit. med. J.*, **2,** 164.
Menkin, V. (1953). *Brit. J. exp. Path.*, **34,** 420.
Moore, F. D. (1954). In *Fourth Annual Report on Stress* (Selye, H., and Heuser, G., 1954), p. 172. Montreal; Acta Inc.
Roberts, F. (1950). *Brit. med. J.*, **2,** 104.
Rosenberg, C. A., Woodbury, D. M., and Sayers, G. (1952). *J. clin. Endocrin.*, 12, 666.
Salgado, E. (1954). *Endocrinology*, **55,** 377.
Schouteden, H. (1947). *Ann. Mus. Congo belg.*, C, ser. 2, 3 fasc.
Scott, A., and Kalz, F. (1956). *J. invest. Derm.*, **26,** 361.
Selye, H. (1936). *Nature*, **138,** 32.
— (1950). *The Physiology and Pathology of Exposure to Stress* . Montreal; Acta Inc
— (1951). *First Annual Report on Stress*. Montreal; Acta Inc.
— (1952). *The Story of the Adaptation Syndrome*. Montreal; Acta Inc.
— (1955). *Science*, **121,** 368.
— (1956). *The Stress of Life*. New York; McGraw-Hill.
— and Heuser, G. (1954). Fourth Annual Report on Stress. Montreal; Acta Inc.
— — (1955-56). *Fifth Annual Report on Stress*. New York; MD Publications.
— and Horava, A. (1952). *Second Annual Report on Stress* . Montreal ; Acta Inc.
— — (1953). *Third Annual Report on Stress*. Montreal; Acta Inc.
Simpson, G. G. (1949). *The Meaning of Evolution*. New Haven; Yale University Press.
Smith, P. E. (1916). *Anat. Rec.*, **11,** 57.
— (1927). *J. Amer. med. Ass.*, **88,** 158.
— and Smith, I. P. (1923). *Endocrinology*, **7,** 579.
Starr, P. (1956). *J. Chron, Dis.*, **4,** 321.
Steenburg, R. W., and Ganong, W. F. (1955). *Surgery*, **38,** 92.
Stein, J. D. Jr., Bennet, L. L., Batts, A. A., and Li, C. H. (1952). *J. Physiol.*, **171,** 587.
Thompson, W. O. (1950). *Year Book of Endocrinology*. p. 224. Chicago; The Year Book Publishers.
Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., and Reddy, W. (1955). *Trans. Ass. Amer. Phycn.*, **66,** 48.
Tyler, F. H., Schmidt, C. D., Eil-Nes, K., Brown, H., and Samuels, L. T. (1954). *J. clin. Invest.*, **33,** 1517.
Venning, E. H. (1955). Quoted in *Fifth Annual Report on Stress* (Selye, H., and Heuser, G., 1955-56), p. 67. New York; MD Publications.
Wettstein, A., Kanut, F. W., and Neher. (1955). *Ciba Fdn. Colloq. Endocrin.*, **8,** 170.