THE RENAISSANCE IN ENDOCRINOLOGY*

By Hans Selye, M.D., Ph.D., D.Sc., F.R.S. (C.) and Paul Rosch, M.D.

WHEN I was chosen by this Academy to speak to you about the "renaissance in endocrinology," I must admit that I was both honored and dismayed. No doubt it was flattering to learn that your program committee should think if me in this connection, but I seriously doubt that I shall be able to do justice to this imposing title.

Yet the term renaissance or "rebirth" does appear to be eminently applicable to the recent advances which characterize contemporary endocrinology and, indeed, medicine as a whole. Within the comparatively short period of fifty years, the physician's arsenal against disease has been almost completely renovated. In the first decade of this century, a list of ten drugs, thought to be the most important and useful, prominently featured mercury, iron, iodine, and alcohol (Castiglioni, 1947). Since then, and especially in the past ten years, the advent of hormones, antibiotics, radioactive compounds, etc., has necessitated a new ap-

* This address was presented by H. Selye, on the basis of lecture notes from which P. Rosch prepared the text reproduced here in print.

proach to the art of Hippocrates, and has stimulated widespread interest in the study of the nature and cause of disease in general.

It seems to me that advances in medicine may be considered as being of two main types—technical, and philosophic. The technical advances include the application of newer scientific methods and tools to the problems of research. They are responsible for such advances as improved surgical techniques, increasing yields in the extraction or synthesis of drugs, and for many of the useful newer devices such as the mechanical respirator used in poliomyelitis or the artificial kidney employed in the treatment of uremia. This type of progress may be viewed as the result of a *search for knowledge.*

On the other hand, are advances rooted in the sincere desire for a better understanding of nature and a fundamental evaluation of our discoveries. Such philosophic advances are aspects of the *search for wisdom*.

In the long run, the latter is more practical, for, as Tennyson said,

> "Knowledge comes, but wisdom lingers."

Or, as Cowper has distinguished,

> "Knowledge and wisdom, far from being one,
> Have oft-time no connexion. Knowledge dwells
> In heads replete with thoughts of other men;
> Wisdom in minds attentive to their own.
> Knowledge, a rude unprofitable mass,
> The mere materials with which wisdom builds,
> Till smooth'd and squar'd and fitted to its place,
> Does but encumber whom it seems t'enrich.
> Knowledge is proud that he has learned so much;
> Wisdom. is humble that he knows no more."

Actually, both the search for knowledge and the search for wisdom are but two aspects of the study of life, and there are many ways of approaching this study.

There is the tabulation of simple facts, such as the registration of structural detail or of biochemical changes produced by an experimental intervention. This work is safe; it is the *book-keeping of Nature*.

There is the descriptive characterization of complex facts, such as clinical syndromes, or intricate tissue reactions. This work is inspired; it is the *landscaping of Nature*.

Finally, there is the correlation of facts into a unified system, a Science. For the explorer of Nature this yields a practically useful (though not necessarily complete or even correct) map of navigation. It helps him to remember the points he has seen and to discover new ones along the roads of abstractions which connect them. This work is creative; it may lead far astray, but apart from procreation, this is the closest man can come to the *making of Nature*.

It is in this last approach to the study of life that our own modest efforts have been directed, and perhaps we may take this opportunity to review briefly our attempt at a correlation of what seemed to be widely diversified observations, and to explain how this concept relates to some of the newer advances.

The "renaissance in endocrinology" may be thought of as being heralded by the new "era of ACTH and cortisone." It is somewhat embarrassing to have been asked to speak to you on this subject, inasmuch as I did not discover these substances, nor was I the first to use them. My only connection with this field was the formulation of the concept of the "adaptation syndrome," in which ACTH and cortisone and other "corticoids" play a vital role. This syndrome is a natural but complex defense reaction of the body, and helps to protect us against many diseases.

Our further investigations into the study of this natural reactive pattern of body defenses led to the discovery that certain disorders can be brought about when there is an insufficiency, imbalance, or similar derangement of ACTH or corticoid actions during the "adaptation syndrome." Accordingly, we called these "diseases of adaptation."

Among these illnesses produced by failure to adapt correctly are the rheumatic diseases, of which some forms of arthritis are excellent examples. Inasmuch as the adrenal cortex governs corticoid production, and derangements in this process can produce "diseases of adaptation," such as arthritis, it seemed logical to us that this endocrine gland should have an important part in determining whether such conditions will or will not develop, under given circumstances.

Experimental studies designed to test the validity of this assumption proved rewarding; through them, a clearer insight into the true nature of these disorders began to evolve early in the 1940's. They also helped to substantiate many heretofore vague hypotheses, and paved the way for the application, to the problems of clinical medicine, of the stress concept in general, and of the "adaptive hormones" in particular.

THE GENERAL ADAPTATION SYNDROME

With this background in mind, it might be profitable for us now to review, very briefly, some of the principal tenets of this "general adaptation syndrome," in order to facilitate an understanding of its relationship to the concept of disorders of adaptation, and especially the rheumatic allergic diseases.

A series of animal experiments, performed in the course of 1935-1936, showed us that the organism responds in a stereotyped manner to a variety of widely different agents such as infections, intoxications, trauma, nervous strain, temperature extremes, muscular fatigue or X-irradiation. Each of these agents, to be sure, had its own specific effects, in many cases, diametrically opposed (e.g., heat causes dilatation of small blood vessels, while cold brings about vasoconstriction), but common to all was the fact that they placed the body in a state of stress, and that the organism responded in the same stereotyped manner to this stress, regardless of the nature of the agent provoking it. Thus, the resultant effect was the summation and superimposition of the specific actions of the "stressor" upon the general reactive pattern elicited by what I called "nonspecific stress."

Hence, exposure to noxious stimuli induces a state of stress, and the nonspecific adaptive reaction which characterizes the body's response is in the nature of a "call to arms" of the organism's defenses. It was named the "alarm reaction." Further results indicated that this was merely the first development of a much more prolonged "general adaptation syndrome," which comprises three phases: the "alarm reaction," in which adaptation has not yet been acquired; the "stage of resistance," in which adaptation is optimal; and finally, the "stage of exhaustion," in which the acquired adaptation is lost again.

Adaptability is probably the most distinctive characteristic of life. In maintaining the independence and individuality of natural units, none of the great forces of inanimate matter are as successful as that alertness and adaptability to change which we designate as life—and the loss of which is death. Indeed there is perhaps even a certain parallelism between the degree of aliveness and the extent of adaptability in every animal—in every man [Selye, 1950].

It should be emphasized that I said "degree of aliveness" and "extent of adaptability," since inanimate systems can also adapt to certain changes in their surroundings, but even the most perfect man-made automaton cannot approximate the adaptability of the simplest living organism. It seems to me that it is precisely that extraordinary quality of certain aggregates of matter, which endows all parts of their structure with the power of self-maintenance in the face of so many qualitatively different aggressors, that we empirically came to consider Life. What machine could assess whether it should attack or run away from its enemy, could forage for its fuel, develop an ethical order permitting It to exist in a co-operative society with its congeners in order to fight common dangers, or heal a scratch on its surface. No doubt complex mechanical devices have been made to imitate some of these properties of Life and these could be further perfected, but my imagination bogs at the thought that even the adaptability of the simplest ameba could ever be reproduced by man using inanimate ingredients.

Thus everything in life, even its seemingly fundamental dissimilarity from the Inanimate, is a matter of degree—that is why no other generalization about life can be wholly true [Selye, 1951].

Yet, as I said in the introduction, the progress of medical research is largely dependent upon theories and generalizations, even if they are correct only to a certain degree. Let us, therefore, proceed now with our attempt to develop a unified theory of disease in general, on the basis of what we called the "stress concept."

The manner by which stress initiates the biologic "chain reaction" of adaptation is unknown, but a dual course may be assumed. One response leads to *damage* or "shock," possibly through nervous stimuli, deficiencies, or toxic metabolites. The other, its inseparable companion, is concerned with *defense*; it depends largely upon the activities of the pituitary and adrenal glands. We will deal mainly with the latter, since we believe that much information of practical value for the sick can be learned by emulating (if possible with improvements) the body's own techniques of defense.

In conditions of stress, the pituitary is stimulated to secrete what are known as corticotrophic hormones. These influence the adrenal to produce two main types of adreno-cortical hormones or "corticoids."

The somatotrophic or "growth" hormone of the pituitary (STH) acts mainly by sensitizing tissues to "mineralo-corticoids" such as desoxycorticosterone. The adreno-corticotrophic hormone (ACTH) causes primarily a secretion of "gluco-corticoids," of which cortisone is one example. These two types of hormones are secreted by the adrenal cortex in large amounts under stress.

The mineralo-corticoids (desoxycorticosterone-like) and the gluco-corticoids (cortisone-like) have many opposing effects. The former may be viewed as preparing the body for fight, the latter, for surrender. The mineralo-corticoids act so as to put up a barricade of connective tissue against the stressor agent, the gluco-corticoids, to continue the analogy, remove all obstacles from his path. Deficiencies or imbalances in corticoid output caused by stress lead to "diseases of adaptation," which, as you can see now, are really due to maladaptation. In a sense, one might say that they are the results of errors in assessing the relative expediency of defense, or tactical withdrawal, before the foe.

Soon after we observed that arthritic and other rheumatic disorders could be produced by DCA overdosage in animals, it was noted that these same diseases could be treated by DCA-inhibiting corticoids, of which cortisone is the best known example. Interestingly, this latter observation, undoubtedly the most important one along these lines up to date, was made by another group (Hench et al., 1949), working along entirely separate lines. Yet, the results significantly strengthened and supported the legitimacy of this type of thinking and demonstrated its applicability to clinical problems.

To sum up, as you can see in the figure presented below, a stressor agent acts directly (thick black line) and indirectly on the body. The direct effects of each stressor are different, but the general nonspecific reaction induced by stressors is always the same and influences the body via the production of STH, which causes mineralo-corticoid secretion, and ACTH, which is responsible for the stimulation of antagonistically acting gluco-corticoids (shown by cross hatched lines). Derangements in production of either of these four substances result in "diseases of adaptation" as we have explained above.

This concept, which aims at a unification of ideas, is an attempt at something rather new in the study of disease. Heretofore, we used to think and plan along two main lines. One dealt with causal therapy and suggested the use of antibiotics, surgery, etc., either to kill the pathogen or to cut it out. The other therapeutic approach to sickness was symptomatic, such as utilization of aspirin to deaden the pain of a headache regardless of its cause. These are both practical, useful, methods of combating illness. We have

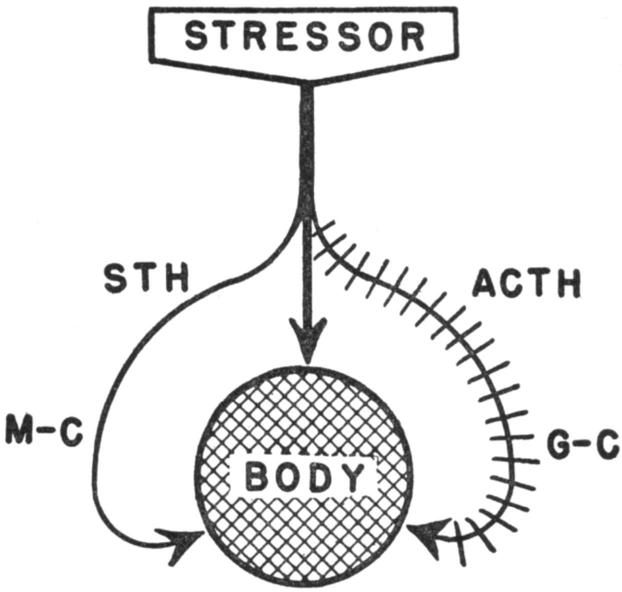

FIGURE 1

FIG. 1. —*Schematic drawing illustrating principal mechanisms effective during exposure to stress.* Body = the whole organism, or any part of it, which is directly affected by a stressor agent; STH = somatotrophic hormone; ACTH = adrenocorticotrophic hormone; M-C = mineralo-corticoid hormones; G-C = gluco-corticoid hormones; simple arrow = stimulates; cross-hatched arrow = inhibits. For explanation see text. (Slightly modified after Selye, *Annual Report on Stress—1951*. Acta Inc. Medical Publishers, Montreal.)

added the general adaptive theory in the hope of integrating and correlating previous work and offering a new approach to the treatment and understanding of disease, through the search for a "stress factor" or "mal-adaptation factor," which would be common to many seemingly different types of disorders. We hope by this to gain insight into the nature of certain illnesses and perhaps develop a cure or prophylaxis for them.

There is need for some unified concept in medicine today. We have had almost no great theorists in this field for many years now; at least none that could be compared to the great creators of new schools of thought, who worked in Europe during the nineteenth and the first part of the twentieth century, such as:

Pasteur	(1822-1895)—	who founded bacteriology and serology
Claude Bernard	(1813-1878)—	responsible for the development of experimental medicine and the concept of the "milieu intérieur," which was developed in our time by Cannon as the theory of "homeostasis"
Virchow	(1821-1902)—	who inspired the study of pathological anatomy and histology
Ehrlich	(1854-1915)—	the pioneer in chemotherapy
Pavlov	(1849-1936)—	who developed the importance of the conditioned reflex and the relationship between mind and body
Freud	(1856-1939)—	who brought to fruition the importance of psychosomatic medicine and psychoanalysis.

However, this golden era of thinkers soon began to degenerate, perhaps because scientists were dazed by the extraordinary efficiency of theories as guides to knowledge. It was forgotten that in the natural sciences, the mere contemplation of potential new pathways into the unknown is of little value in itself. It must be followed by the painstaking experimental exploration of their viability. Disregard of this fundamental truth eventually left Europe with a great excess of "armchair philosophers" given to vague speculation, pompous dialectic theorizing and, eventually, futile priority squabbles.

It is, unfortunately, just at this time that large numbers of young American students and scientists began to visit Europe, attracted by the glorious past of its great universities. Too many of them fell into the hands of masters who attempted in vain to give a semblance of authority to their dialectic teachings, by exaggerating the importance of their rank through academic pomp and circumstance. These young men returned to the United States with a definite aversion to any aspect of science except the search for facts whose value was immediately assessable.

Thus the pendulum began to swing toward the other extreme, the abhorrence of theory. "Pure objectivity" became the fashionable slogan in medical research and this was coupled with an unreasonable fear that any thought expressed in print might subsequently be proven to be wrong. Even today many a scientist concludes an extensive paper, replete with tables and statistical calculations, by stating—often with an air of self-righteousness—that: "the facts reported are certainly correct, but no attempt is made to draw any conclusions from them." This is undoubtedly very honest and no one can question the moral virtue of such investigators, but one may doubt their wisdom. What is the purpose of establishing something with the greatest degree of probability if one ignores its significance? Are not many of those who consistently reject the expression of opinions in science too much concerned with the importance of their own personal prestige? Is it worthwhile to sacrifice the pleasure of trying really to understand Nature for the superficial glory of creating a semblance of personal infallibility?

Undoubtedly, purely objective and descriptive research and the dispassionate registration of facts may lead to the acquisition of important knowledge. Indeed—with adequate financial support—even the mere screening of all possibilities can force Nature to reveal some of her secrets. I must admit (although this is very distasteful to me) that many technical advances have been made in this fashion. However, those who use this kind of approach do not try to conquer Nature by love and understanding, but merely wish to rape her by force. They may possess her substance, but not her spirit.

Our modest attempt to explore the "adaptation syndrome" has not brought forth very much, as yet, that is immediately applicable to the treatment of sickness, but we like to think that it has contributed its share to the "rebirth" of medicine, through its attempt to stimulate thought and again demonstrate the value of approaching research problems with a definite theoretic formulation.

THE VALUE OF A THEORY

It is well to realize that "our facts must be correct; our theories need not be if they help us to discover important new facts" (Selye, 1950). Indeed, once a theory says "nothing but the truth and all the truth" about a certain subject, it has lost its heuristic value and then it is no longer a theory, but merely the enunciation of a fact.

The best theory is that which necessitates the minimum amount of assumptions to unite the maximum number of facts, since it is most likely to possess the power of assimilating new facts from the unknown without damage to its own structure.

It is perhaps insufficiently realized by many that even a faulty theory may be of great value. Pierre Marie's concept of the relationship between the pituitary and acromegaly was directly opposite to what we now know to be true. He found that acromegalic giants had pituitary tumors and concluded that they became tall because their pituitary was destroyed by disease. Actually we now know that such tumorous glands produce a great excess of somatotrophic or "growth" hormone and that this is responsible for the disproportionate increase in the growth of these patients. Surely, no theory could have united the facts observed by Pierre Marie more incorrectly than that which he enunciated. Nevertheless, the very fact that he called attention to some relationship between gigantism and the pituitary was of immense value and stimulated much research, eventually culminating in the discovery of the somatotrophic or "growth" hormone.

The key that opens the door usually also serves to lock it, the most important thing is to find the key that fits the lock of the door we wish to use.

We tried to outline the concept of the "general adaptation syndrome" and the manner in which derangements in the adaptive mechanism to stress may cause disease. As it stands, our map of these uncharted parts of medicine is certainly both incorrect and incomplete, but let us hope that it possesses that critical degree of truthfulness which stimulates to rectify the misdrawn boundary lines and to fill out the spaces where hitherto unexplored territories are shown to lie. This hope is our only justification and apology for having accepted the great honor of participating in this lecture series.

REFERENCES

Castiglioni, Arturo (1947), *A History of Medicine*. New York: Alfred A. Knopf, p. 1055.

Cowper, William (1934), The Task. *Cowper's Poetical Works*, Book VI, lines 88-99. London: Oxford University Press.

Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F. (1949), *Proceedings of the Staff Meeting of the Mayo Clinic, 24*:181.

Selye, Hans (1950), *Stress*. Montreal: Acta Inc. Medical Publishers.

—— (1951), *Annual Report on Stress*. Montreal: Acta Inc. Medical Publishers.

Tennyson, Alfred (1898), Locksley Hall. *The Poetic and Dramatic Works of Alfred Lord Tennyson*. Cambridge Edition. Cambridge: The Riverside Press, line 141.