Allergy and the General Adaptation Syndrome

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It is with the greatest pleasure that I accepted the invitation of the *International Archives of Allergy and Applied Immunology* to contribute an article concerning those aspects of our work on stress and the adaptation syndrome which may be of interest to its readers. Since I am not an allergist and immunologist myself, it is perhaps desirable to begin by a reference to the many reviews and general articles published by specialists in these fields concerning the general adaptation syndrome (G-A-S) concept in allergy and immunology (1, 2, 4–13, 15–20, 38, 39). In these publications, the readers will find much more adequate discussions of special points than I would be competent to offer.

Evidently, there exist close correlations between the problems confronting allergist and immunologist and the concept of the G-A-S, with it corollary the view that certain maladies are first of all "diseases of adaptation". It is rather significant in this connection that my attention has been focussed upon these correlations by one of the most eminent allergists, Dr. *F. M. Rackemann* of Boston, who pointed them out to me at a time when I had not yet perceived their importance. Furthermore, the concept of the diseases of adaptation was first formulated at the First Annual Meeting of the American Academy of Allergy (New York, December 1944) in a paper which was subsequently published as a monograph in The Journal of Allergy (37).

The most important link between the G-A-S and allergy is probably to be found in the phenomenon of inflammation, which manifests itself in so many ways during both these reaction types that it would be somewhat artificial to single out individual points of detail for the present study. I shall therefore limit myself to a general review of our

work on stress – mainly as it concerns inflammation – leaving it to the readers of this journal to select from it whatever they consider most applicable to the problems of allergists and immunologists.

On the other hand, it would be impossible to survey the unusually extensive literature on the G-A-S and on the "adaptive hormones" in a single article. Besides, we have already done so in a series of monographs (24, 25, 26) which review a total of about twelve thousand papers devoted to pertinent investigations. Furthermore, a greatly simplified digest of this field, with a historic account of how "the stress concept" developed, has recently been the subject of a small booklet, containing seven informal lectures (27).

It is felt therefore that the task assigned to me can be best accomplished by giving a brief synopsis of stress and the adaptation syndrome as it presents itself now, at the close of 1952.

Precursors of the stress concept. Ever since man used the word "disease" he had some, at least subconscious, inkling of the stress concept. The very fact that a single term can be used to denote a great variety of individual maladies, clearly indicates that they have something in common. They possess, as we would now say, some non-specific features which permit to distinguish disease from the condition of health. Yet, precisely because these manifestations are not characteristic of any one disease, they do not help in making a differential diagnosis between them.

These non-specific features of disease have received little attention in comparison with the specific ones, because unlike the latter they did not help to recognize the "eliciting pathogen" or lend themselves to any effective type of specific therapy.

Nevertheless, several early investigators have attempted to elucidate the mechanisms involved in such non-specific reactions. Since our knowledge of the nervous system antidates, by far, the development of modern Endocrinology, it is understandable that, among the two great integrating systems of the body, the nervous and the hormonal system, the former was the first to be examined from this point of view. *Ricker, Speransky, Reilly, Hoff* and many others have gathered important data concerning the rôle of the nervous system in such non-specific reactions as fever, polymorphonuclear leucocytosis, inflammation, etc. In the domain of what may be called "physiologic stress" *W. Cannon*'s studies helped us to understand the part played by the sympathetic nervous system and its humoral affector substances.

Again quite independently, a great deal of progress has been made in the study of pituitary and adreno-cortical hormone by chemists, physiologists and clinicians, too numerous to be mentionned by name.

All the knowledge acquired as a result of these early investigations was absolutely indispensable for the formulation of the stress concept, whose leading motive is one unification. Numerous additional experiments had to be performed to show that the many non-specific respons of individual target organs are closely integrated and actually represent part of a single biologic response, the general adaptation syndrome. Thus it became evident that this pattern of response plays an integral part in the most varied physiologic, pathologic and pharmacologic reactions.

The concept of stress. By a series of experiments on animals, it was demonstrated in 1936 that the organism responds in a *stereotypical* manner to a variety of widely different agents, such as: infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue or X-irradiation. The specific actions of all these agents are quite different. Their only common feature is that they place the body in a state of general (systemic) stress. Hence, we concluded that the stereotypical response, which is superimposed upon all specific effects, represents the somatic manifestations of non-specific "stress" itself.

But what is non-specific "stress"? The term had long been used in physics to denote the interaction between a force and the resistance opposed to it. For instance, pressure and tension cause stress in inanimate matter. The above mentioned non-specific response was thought to represent the biologic equivalent of such physical stress. The term has now been quite generally accepted in this sense not only in English, but – since attempts to translate "stress" led to much confusion – also in most other languages.

The concept of the G-A-S. The most outstanding manifestations of this stress-response were: *adreno-cortical enlargement* with histologic signs of hyperactivity, *thymico-lymphatic involution* with certain concomitant changes in the blood-count (eosinopenia, lymphopenia, polynucleosis) and *gastrointestinal ulcers,* often accompanied by other manifestations of *damage or "shock".*

We were struck by the fact that, while during this reaction all the organs of the body show involutional or degenerative changes, the adrenal cortex actually seems to flourish on stress. We suspected this adrenal response to play a useful part in a non-specific adaptive reac-

tion, which we visualized as a "call to arms" of the body's defence forces and named the "alarm reaction" (32).

Subsequent studies showed that the alarm reaction is but the first stage of a much more prolonged *General Adaptation Syndrome* (G-A-S). The latter comprises three distinct stages, namely:

1. the *alarm reaction* (A-R), in which adaptation has not yet been acquired,
2. the *stage of resistance* (S-R), in which adaptation is optimal,
3. the *stage of exhaustion* (S-E), in which the acquired adaptation is lost again.

The mechanism of the G-A-S. In order to elucidate the kinetics of this syndrome we proceeded as follows:

Rats were *adrenalectomized* and then exposed to stressor agents. This showed us that in the absence of the adrenals, stress can no longer cause thymico-lymphatic involution or characteristic blood-count changes.

When adrenalectomized rats were treated with the impure *cortical extracts* available at that time, it became evident that thymico-lymphatic involution and the typical blood-count changes could be produced by adrenal hormones even in the absence of the adrenals. The latter, therefore, were considered to be indirect results of stress mediated by corticoids.

Conversely, the gastrointestinal ulcers and other manifestations of pure damage or shock were actually more severe in adrenalectomized than in intact animals and could be lessened by treatment with cortical extracts. It was concluded that these lesions are not mediated through the adrenal; they are actually combated by an adequate adreno-cortical response to stress (33).

But what stimulates adreno-cortical function during stress? In 1937, we found that among many surgical interventions tried, only *hypophysectomy* prevents the adrenal response during the alarm reaction. Hence, we concluded that stress stimulates the cortex through an adrenocorticotrophic hormone, now known as ACTH (34).

Then pure cortical steroids became available, thanks first of all to the classical investigation of *Kendall* and *Reichstein*. With these, we could show that administration of *mineralo-corticoids or M-Cs* (such as desoxycorticosterone) produces experimental replicas of the so-called *hypertensive and inflammatory "rheumatic diseases":* notably *nephrosclerosis, hypertension, vascular lesions* (especially peri-

arteritis nodosa and hyalin necrosis of arterioles) (35), as well as arthritic changes resembling, in acute experiments, those of rheumatic fever and, after chronic treatment, those of rheumatoid arthritis (36). Yet, even very high doses of mineralo-corticoids did not induce any noteworthy thymico-lymphatic or blood-count changes.

Significantly, exposure of animals to non-specific stressor agents (e. g., cold) produced marked adreno-cortical enlargement and organ changes very similar to those elicited by the administration of mineralo-corticoids (22).

Gluco-corticoids or G-Cs (such as cortisone) on the other hand, were highly potent in causing *thymico-lymphatic* involution and in eliciting the characteristic *blood-count* changes of the alarm reaction. They also tended to inhibit the hypertensive and rheumatic changes which can be elicited in animals by mineralo-corticoids. Thus, in many respects, the two types of corticoid hormones antagonize each other (23, 24).

The terms "gluco-corticoids" and "mineralo-corticoids" emphasize the saliant metabolic actions of these substances; from a clinical point of view, however, their effects upon inflammation are perhaps of even greater interest. Since the gluco-corticoids inhibit inflammation, while the mineralo-corticoids enhance it, the former may appropriately be called *"antiphlogistic corticoids"* or *"A-Cs"* and the latter *"prophlogistic corticoids"* or *"P-Cs"*, when they are discussed with reference to their effects upon inflammation.

Inflammatory granulomas, especially those produced in the vicinity of joints by the local application of irritants (e. g., formalin, mustard powder), as well as certain allergic reactions, are likewise aggravated by P-Cs and prevented by A-Cs. Apparently, the response of the adrenal cortex is most important not only in defence against systemic stress (affecting the whole organism), but also in the manifold topical defence reactions which occur upon exposure to *local stress* (e. g., bacterial or chemical irritants, responses of a "shock organ" to an allergen (24, 28).

Certain crude anterior-pituitary extracts (23, 29) duplicate the above-mentioned actions of P-Cs upon the cardiovascular system, the blood-pressure, the connective tissue (inflammation) and the kidneys. The hypophyseal preparations which we used, were definitely corticotrophic in that they enlarged the adrenal cortex, but they were particularly rich in the so-called "growth hormone" or *somatotrophic hormone (STH)*. As soon as we were able to obtain purified ACTH,

it became evident that the above-mentioned pathogenic actions of the crude anterior-pituitary preparations could not be due to their ACTH content, since even the highest tolerable doses of the latter hormone failed to duplicate their predominant P-C effects. On the other hand, overdosage with pure STH caused cardiovascular and renal lesions, identical with those previously observed in animals treated with P-Cs. It was concluded that the above-mentioned actions of our crude anterior-pituitary preparations were mainly due to their STH content. It remains to be seen to what extent STH acts indirectly by stimulating the P-C production of the adrenal cortex, or directly by sensitizing the peripheral tissues to M-Cs. Preliminary observations suggest that both these mechanisms may be implicated (30), but this point is not yet settled.

From the internist's point of view, perhaps the most interesting rôle of STH in the Adaptation Syndrome is that it can effectively *combat catabolism and sensitivity of infections.* Animals heavily overdosed with ACTH or A-Cs, tend to lose a great deal of weight. Eventually they die, almost always as a result of generalized septicemia, caused by normally saprophytic micro-organisms. In rats the lung tissue appears to be singularly predisposed to such infections. Under these conditions, adequate doses of STH prevent the loss of body weight as well as the excessive microbial proliferation (31). It remains to be seen to what extent these actions of STH will prove to be of value in the management of infections in man, but experiments on rats have already demonstrated the great influence of these hormones upon resistance to the human type of tuberculosis. Normally the rat is virtually resistant to tuberculosis bacilli; it may be rendered sensitive by ACTH or A-Cs and this sensitivity can in turn be abolished by STH.

Conditioning of hormone actions. As work along these lines progressed it became increasingly more obvious that the activity of the hormones produced during stress depends largely upon a variety of "conditioning factors". Both the production of the "stress hormones" and their effect upon individual target organs proved to be greatly influenced by heredity, previous exposure to stress, the diet, etc. Thus, for instance, the production of corticotrophic hormone by the pituitary is enhanced by a high-protein diet, while the action of M-Cs upon most target organs is augmented by excess sodium.

Stress itself is perhaps the most effective and most common factor capable of conditioning the actions of adaptive hormones. Thus systemic stress augments the lympholytic, catabolic and hyperglycemic

actions of G-Cs, while the salient effect of the adaptive hormones, that of modifying the course of inflammation, naturally cannot manifest itself unless some topical stressor first elicited a phlogistic response.

In the final analysis such factors could actually determine whether exposure to stress would be met by a physiologic G-A-S or cause Diseases of Adaptation. Indeed, in the latter instance, these conditioning factors appear to be responsible for the selective breakdown of one or the other organ. We felt that differences in predisposition through such factors might explain why the same kind of stress can cause diverse types of "Diseases of Adaptation" in different individuals.

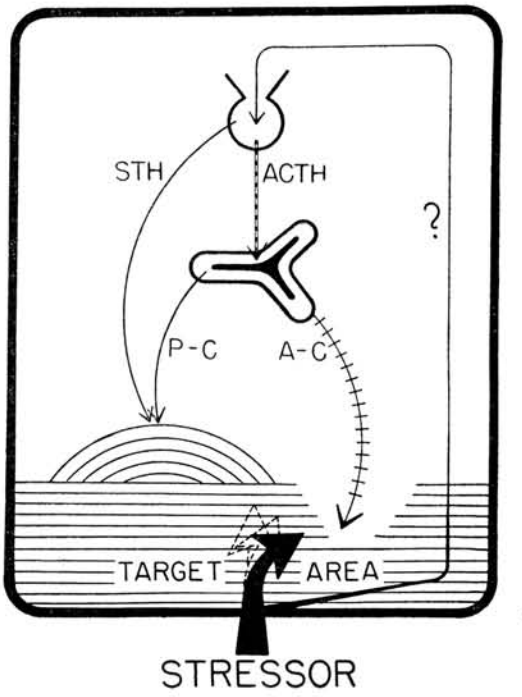

Fig. 1

The concept of the Diseases of Adaptation. From our above-mentioned experiments, we concluded that the pathogenicity of many systemic and local irritants depends largely upon the function of the hypophysis-adrenocortical system. The latter may either enhance or inhibit the body's defence reactions against stressor agents. We think that derailments of this adaptive mechanism are the principal factors in the production of certain maladies which we consider, therefore, to be essentially *Diseases of Adaptation.*

Among the derailments of the G-A-S which may cause disease, the following are particularly important:

1. An *absolute excess or deficiency* in the amount of corticoids and STH *produced* during stress.
2. An absolute excess or deficiency in the amount of corticoids and STH *retained (or "fixed")* by their peripheral target organs during stress.
3. A *disproportion* in the relative secretion (or fixation), during stress, of ACTH and A-Cs, on the one hand, and of STH and P-Cs, on the other.
4. Production by a stress of metabolic derangements, which abnormally alter the *target organ's response* to STH, ACTH or corticoids (through the phenomenon of "conditioning").
5. Finally, we must not forget that, although the hypophysis-adrenal mechanism plays a prominent rôle in the G-A-S, other organs which participate in the latter (e.g., nervous system, liver, kidney) may also respond abnormally and become the cause of disease during adaptation to stress.

Summary. To summarize we might say that all agents which act upon the body or any of its parts exert dual effects:

1. *Specific actions,* with which we are not concerned in this study, except insofar as they modify the non-specific actions of the same agents.
2. *Non-specific or stressor effects,* whose principal pathways (as far as we know them to-day) are illustrated in the adjacent drawing.

The *stressor* acts upon the *target* (the body or some part of it) directly (thick arrow) and indirectly through the pituitary and adrenal.

Through some *unknown pathway* (labelled by a question mark), a stimulus travels from the directly injured target area to the *anterior pituitary.* It notifies the latter that a condition of stress exists and thus induces it to discharge ACTH.

It is quite possible that this "first mediator" of hormonal defence is not always the same. In some instances, it may be an adrenaline discharge, in others a liberation of histamine-like toxic tissue meta-

bolites, a nervous impulse or even a sudden deficiency in some vitally important body constituent (such as glucose or an enzyme).

ACTH stimulates the *adrenal cortex* to discharge corticoids. Some of these, the *prophlogistic corticoids (P-C),* stimulate the proliferative ability and reactivity of connective tissue; they enhance the "inflammatory potential". Thus, they help to put up a strong barricade of connective tissue through which the body is protected against further invasion by the pathogenic stressor agent.

However, under ordinary conditions, ACTH stimulates the adrenal much more effectively to secrete *antiphlogistic corticoids (A-C)*. These inhibit the ability of the body to put up granulomatous barricades in the path of the invador; in fact, they tend to cause involution of connective tissue with a pronounced depression of the inflammatory potential. Thus they open the way to the spreading of infection.

As far as we know, ACTH always stimulates the adrenals to produce the various corticoids in the same proportion and always with a great predominance of A-Cs. However, the *somatotrophic hormone (STH)* of the pituitary also increases the inflammatory potential of connective tissue, somewhat as the P-Cs do; hence, it sensitizes the target area to the actions of the latter.

It is possible that the hypophysis also secretes some special corticotrophin which induces the adrenal to elaborate predominantly P-Cs; indeed, STH itself may possess such effects, but this has not yet been proved. In any event, if ACTH were the only corticotrophin, the actions of the corticoids produced under its influence can be vastly different, depending upon "conditioning factors" (such as STH), which specifically sensitize the target area for one or the other type of corticoid action. Actually, conditioning factors could even alter the response to ACTH of the adrenal cortex itself, so that its cells would produce more A-Cs or P-Cs. Thus, during stress, one or the other type of effect may predominate.

The fundamental reaction-pattern to topical stressors is "inflammation", to systemic stressors the "G-A-S". Various combinations of these two basic responses constitute the essence of most diseases.

Outlook. During the past year, perhaps the most important contribution to our understanding of stress and of the adaptive hormones was the growing realization of the limitations of ACTH and A-C therapy. When ACTH and cortisone were first introduced into clinical

medicine, there was much hope that treatment with these hormones might cure a large number of hitherto incurable diseases; indeed, it was felt that these drugs – and they were considered as merely pharmacologic agents, which means drugs – would have such a wide spectrum of practical application that they would "revolutionize medicine". These hopes did not materialize. The practical value of antiphlogistic hormone treatment, as it is now practised, is limited by its undesirable side-effects and many experienced clinicians recommend that they be not used routinely, even in the treatment of rheumatoid arthritis where they were supposed to be most useful (3, 14, 21). Of course, they will continue to be valuable additions to our therapeutic armamentarium. This is true particularly in the treatment of certain inflammatory diseases of the eye, which do not tend to recur soon after discontinuation of treatment, or can be controlled by the purely local application of A-Cs, without introducing the danger of systemic complications. But, with such drastic limitations, the clinical use of these hormones would be a poor reward for the untiring efforts of all those investigators who studied the mechanism of response to stress with the hope of finding a new avenue to the effective treatment of disease in general.

Although we have not yet learned how to use adaptive hormones efficiently in the treatment of systemic diseases without producing overdosage effects, the healthy body itself knows this secret. To take but one striking example, in the course of exposure to severe stress, the human organism can apparently produce effective amounts of antiphlogistic hormones (e.g., during pregnancy, starvation and other types of stress) without eliciting any serious manifestations of hormone overdosage. It accomplishes this presumably by appropriate compensatory reactions which condition the response to these hormones. We believe therefore that the real future of this field lies not in the merely empiric gathering of data concerning the value of adaptive hormones in this or that disease, unguided by any theory, but in the systematic investigation of the total integrated response to stress.

Pasteur and his contemporaries introduced the concept of specificity into medicine, a concept which proved to be of the greatest heuristic value up to the present time. Each individual well defined disease, they held, has its own specific cause. It has been claimed by many that *Pasteur* failed to recognize the importance of the "terrain" being too preoccupied with the pathogen (micro-organism) itself. This is incorrect. His work on induced immunity shows how clearly

he realized the importance of the "terrain". The theory which directed the most fruitful investigations of *Pasteur* and his followers was that the organism can develop specific adaptive reactions against individual pathogens and that by imitating and complementing these, whenever they are short of optimal, we can treat many of the diseases which are due to specific pathogens.

To our mind, the G-A-S represents, in a sense, the negative counterpart, or mirror image, of this concept: It holds that many diseases have no single cause, no specific pathogen, but are largely due to non-specific stress, and to pathogenic situations which result from inappropriate responses to such non-specific stress.

Hence, if in closing this "outlook" we may venture a prediction, we would like to reiterate our opinion that research on stress will be most fruitful if it is guided by the theory that we must learn to imitate – and if necessary to correct and complement – the body's own auto-pharmacologic efforts to combat the stress factor in disease.

Summary

To summarize we might say that all agents which act upon the body or any of its parts exert dual effects:

1. Specific actions, with which we are not concerned in this study, except insofar as they modify the non-specific actions of the same agents.
2. Non-specific or stressor effects, whose principal pathways (as far as we know them to day) are illustrated in the above drawing (cf. p. 273).

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