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CONFUSION AND CONTROVERSY IN THE STRESS FIELD

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An attempt is made to further clarify present areas of controversy in the stress field, in response to a two-part article by Dr. John W. Mason which concludes in this issue of the Journal of Human Stress. *The author tries to elucidate each source of confusion enumerated by Dr. Mason. The continued use of the word "stress" for the nonspecific response to any demand is deemed most desirable. The once vague term can now be applied in a well-defined sense and is accepted in all foreign languages as well, including those in which no such word existed previously in any sense. Subdivision of the stress concept has become necessary as more recent work has led to such notions as "eustress," "distress," "systemic stress" and "local stress." Confusion between stress as both an agent and a result can be avoided only by the distinction between "stress" and "stressor." It is explained that the stress syndrome is — by definition — nonspecific in its causation. However, depending upon conditioning factors, which can selectively influence the reactivity of certain organs, the same stressor can elicit different manifestations in different individuals.*

The first article in this journal was "A Historical View of the Stress Field" by John W. Mason,[1] appropriately described on the cover as being concerned with "confusion and controversy in the stress field." I am very grateful to the publisher for having invited me to give my opinion on these matters for the readers of the *Journal of Human Stress.* I have accepted gladly, because Dr. Mason has correctly called attention to those particular problems which cause most of the confusion in stress research. It is for this reason that I have used as my title for the present article the wording selected by the Journal to describe the essence of the preceding one.

Although, in many respects, Dr. Mason disagrees with my explanation of what I have called the "stress syndrome" or "General Adaptation Syndrome" (G.A.S.), he has succeeded in presenting his views in a very fair, objective manner. He has managed to accomplish this largely by using direct quotations, and I will try to emulate his style in this paper.

I went through his two-part essay,[1] conscientiously collecting the 11 most common sources of confusion or misunderstanding that have been pointed out by its author, and adding one of my own, and I shall attempt to answer each of them as best I can.

Source of confusion No. 1: *Use of the terms "stress" and "biologic stress."*

In my first paper, entitled "A Syndrome Produced by Diverse Nocuous Agents,"[2] I recommended the term "G.A.S." for the three distinct phases:

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(1) the alarm reaction; (2) the stage of resistance; and (3) the stage of exhaustion. Its manifestations, the now classic "triad," were particularly obvious in the first stage and consisted of adrenocortical enlargement, thymicolymphatic atrophy, and peptic ulcers. In this particular publication, I did not mention the word "stress" because of adverse public opinion against my previous use of it, although apparently this was the first paper on the stress syndrome as presently envisaged.

Actually, I had first used the term "stress" for a nonspecific biologic reaction the year before, in connection with the gonadal atrophy that also characterizes severe and chronic forms of it.[3] The role of the pituitary as an indispensable intermediate link in eliciting the typical adrenocortical enlargement of the alarm reaction was described even earlier, in 1933, when I was testing the first comparatively pure ACTH preparations, extracted from cattle hypophyses by my former chief, Professor J.B. Collip. Whereas all kinds of crude extracts stimulated the adrenal cortex of intact animals, only those containing ACTH had such an effect after removal of the pituitary by a technique that I had developed for this purpose.[4] It was in the reception of these papers and of my many public lectures on stress that I found that the word (used in conversational English mostly for mental tension) was not readily acceptable in my sense, since I wanted to emphasize that we were dealing with a syndrome accompanied by objectively measurable somatic manifestations, and elicited by a variety of emotional and physical agents.

Subsequently, however, I found it easier to employ the term "stress" for the manifestations of this syndrome at any one time, reserving the expression "G.A.S." for its triphasic evolution in time. The entire history of this early period has been the subject of several articles.[5-7] There, I have also explained why I introduced the term "stress," in my sense of the word, into all foreign languages where no equivalent word had existed before, either for the vague conversational or for the objective scientific concept. To the best of my knowledge, this expression is now employed in the medical literature of all nations in the sense in which I use it.

" . . . I found it easier to employ the term 'stress' for the manifestations of this syndrome at any one time, reserving the expression 'G.A.S.' for its triphasic evolution in time."

In any event, Dr. Mason[1] is quite right in saying that the word "stress" had been used in the English language for mental arousal since time immemorial. Indeed, I have pointed out that, in a vague manner, the concept must have been known even to the caveman when he returned hungry and cold from a day of strenuous hunting.[6,7]

I certainly did not discover stress, but only the stress syndrome; by my first observations on the triad, I demonstrated that there is such a thing as a totally nonspecific stereotyped reaction pattern. Let me reemphasize here that my initial contribution was to show that there exists an integrated nonspecific syndrome produced by diverse agents, and that the pituitary-adrenocortical axis plays an important role in it.

Source of confusion No. 2: *The impact of Walter Cannon's concept of the "flight-or-fight reaction" in the maintenance of homeostasis during acute emergencies is not sufficiently recognized.*

My first extensive review article on "The General Adaptation Syndrome and the Diseases of Adaptation"[8] was specially dedicated (in a prominently placed "box" just under the title) to the memory of Cannon, whose work "has been the author's greatest inspiration." In addition, I have always taken great pains to point out that the emergency discharge of the adrenal medulla, as produced by an acute psychogenic stressor, was the first major contribution providing the stress concept, as subsequently formulated, with an objective somatic basis.[9-16]

In fact, I had many stimulating conversations with Cannon, although I failed to convince him that the pituitary and the adrenal cortex play a role in the stress response, or that this reaction is triphasic and nonspecific. He — like Mason[1] — considered the stereotyped discharge of epinephrine as primarily resulting from arousal or "nervous stress and strain," thereby clearly and correctly separating it from the specific homeostatic mechanisms necessary for the maintenance of body temperature, blood pressure, blood calcium, blood sugar, etc.

As we shall see later, stress in my sense is a common feature of all these homeostatic mechanisms, although they all differ in the kind of specific regulatory responses that must be superimposed upon stress.

Source of confusion No. 3: *"There are still some workers who accept Selye's views of stress, some who use modifications of them, some who regard them yet as unproven working hypotheses, and some who simply reject or ignore them."*[1]

Among the more than 100,000 publications which constitute our stress library, I could find none doubting the existence of a single stereotyped "syndrome produced by diverse nocuous agents," in which activation of the pituitary-adrenal axis plays a decisive role. However, with more recent, sophisticated methods it is possible to show that essentially the same syndrome is also elicited by demands for adaptation, experienced as agreeable or beneficial; these are designated as "eustress," in opposition to "distress." Yet, the essential features of stress (e.g., the discharge of stress hormones, such as ACTH, corticoids, and catecholamines) are common to both.

Source of confusion No. 4: *The definition of biologic stress has constantly changed over the years.*

It is true that in 1936 we could show the classic triad of adrenocortical enlargement, thymicolymphatic atrophy, and peptic ulcers only in experimental animals exposed to noxious agents. As just mentioned, since that time we have found that "stress is the nonspecific response of the body to any demand," not only to noxious stimuli.

The term "systemic stress" was not a new definition, but had to be introduced when we discovered that there is also a "local stress" and a "Local Adaptation Syndrome" (L.A.S.) to nonspecific demands, made only upon one part of the body. Like the distinction between eustress and distress, these are not changes in the original definition of stress, but are further clarifications or subdivisions within the concept.

Source of confusion No. 5: *Stress is both the evocative agent and the result.*

At first, we employed such designations as cold stress, heat stress, traumatic stress, etc., both for the provocative cold, heat, or trauma and for the resulting nonspecific stereotyped

response. Unfortunately, many authors still use this loose terminology. I must admit that I also find it difficult to avoid this, without employing such complicated circumlocutions as "stress produced by cold." However, as long as we distinguish clearly between "stress" (the nonspecific syndrome) and "stressor" (that which causes it), the correct meaning is readily apparent. Similarly, we speak of typhoid fever, scarlet fever, or rheumatic fever, fully realizing that a temperature of 102° is always the same, whether it is the result of one or another of the specific causative agents. Furthermore, "sunburns," "X-ray burns" and "steam burns" are, respectively, the results of sun rays, X-rays, or steam.

In this connection, it also might be pointed out that I was never "inclined towards defining 'stress' variously in terms of either *stimulus, response, or interaction between stimulus and response,*"[1] but I have tried to emphasize that the nonspecific syndrome of stress is the result of such an interaction. It was to make this distinction perfectly clear that I had to introduce the term "stressor" as the cause of "stress."

Source of confusion No. 6: *Since the publication of the first edition of* The Stress of Life[6] *". . . at the present time, 20 years later, remarkably little has changed in this state of affairs"*[1] *as therein described.*

This is true in a way, as will be seen from the updated second edition due to appear this year. The basic concept of nonspecificity, of the important role played by the hypothalamo-pituitary-adrenocortical axis, and of the stereotyped, nonspecific syndrome remains unaltered. Yet, a great deal has been added in the way of methodology to clarify such new concepts as "eustress," and to explain the puzzling fact that, through selective conditioning agents, the actual manifestations of a single stereotyped response to the stressor may assume very different aspects.[16,17]

Source of confusion No. 7: *How can the same agent (the stressor) produce diverse manifestations or even different diseases?*

This has been one of the fundamental problems ever since the beginning of modern stress research. Instead of attempting to resolve it by theoretic analysis, I have spent many years in the laboratory trying to devise experiments which might help to answer the question that has been raised because of two types of observations:

- Qualitatively different stimuli of equal stressor potency (as judged by their ability to elicit the triad or ACTH and corticoid production) do not necessarily cause the same syndrome in different individuals.
- Even the same degree of stress induced by the same stimulus may provoke different lesions in different individuals.

These findings have been discussed recently at some length in *Stress Without Distress.*[17]

The fact that different stressors, or even the same stressor, can cause different lesions in different individuals has been traced to what I have called "conditioning factors" that can selectively enhance or inhibit one or the other stress effect. Thus, conditioning may be internal (for example, genetic predisposition, age, or sex) or external (treatment with certain hormones, drugs, environmental elements, or dietary constituents). Under the influence of such conditioning factors (which determine sensitivity or disease-proneness), a normally well-tolerated degree of stress can

become pathogenic and cause diseases of adaptation, selectively affecting predisposed body areas. Indeed, even without producing morbid lesions, it can accentuate or diminish the response of one or another nonspecific stress parameter. Although stress itself is defined as the "nonspecific response of the body to any demand," the weakest link in a chain will be the one that selectively breaks under tension. Similarly, the weakest part of any animate or even inanimate machine will be the one that fails when a nonspecific, general demand is made upon the performance of the whole.

As illustrated in Figure 1, every agent possesses both stressor and specific effects; the former are nonspecific by definition, and common to diverse stimuli, whereas the latter are variable and characteristic of each individual agent. These specific actions will also modify the stereotyped stressor effect of the agent. Since all stressors necessarily do have some specific effects, they cannot always elicit exactly the same response, and even the same stimulus will act differently in different individuals, depending upon the above-mentioned internal and external conditioning factors that determine reactivity.

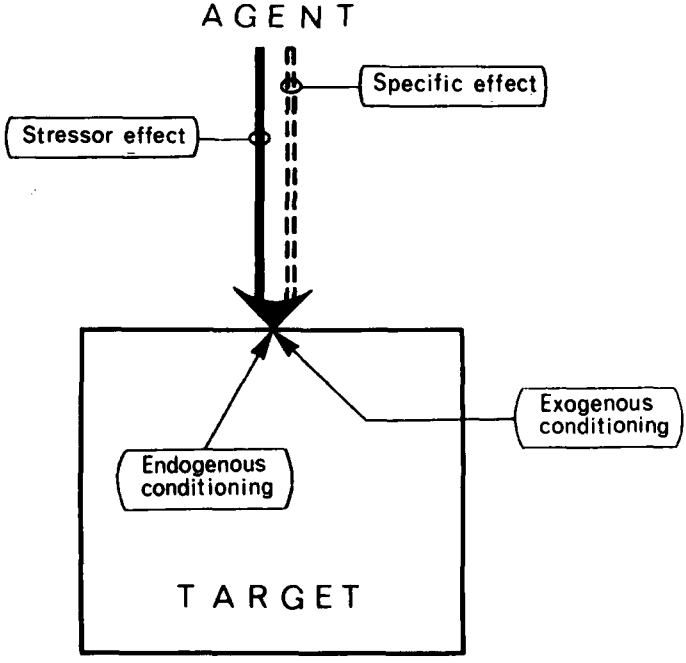

Fig. 1. Factors influencing the response to stressors.

Source of confusion No. 8: *Why assume the existence of a "first mediator(s)"?*

No matter which part of the body is directly affected by the stressor (a burn to the hand, decortication, deep anesthesia) the message of a "demand" for homeostatic reactivity eventually is relayed to the hypothalamo-pituitary-adrenocortical axis. This can be accomplished only by some messenger(s) carrying the information that a state of stress exists. In this connection, Mason[1] quotes my remark verbatim: "As yet, nothing is known about the chemical nature of this first mediator; so far as we know, it may be a chemical by-product of activity or the lack of some important blood constituent that cells use up whenever they function. The identification of this first mediator appears to be one of the most fundamental tasks of future stress research."

Unfortunately, I cannot put it more clearly today, except perhaps by reemphasizing that to carry the same information, the messenger need not always be the same. For example, no matter what type of work creates depletion of fuel in a cybernetically-controlled machine, the message is always the demand for more energy.

Source of confusion No. 9: *Why not accept emotional arousal as the common cause of stress responses, since it is one of the "most ubiquitous or relatively 'nonspecific' reactions common to a great diversity of situations"?*[1]

I foresaw the possibility of this question when I said in *Stress Without Distress*[17(p.30,31)]: ". . . quite recently, Dr. John W. Mason, a former president of the American Psychosomatic Society and one of the most distinguished investigators of the psychologic and psychiatric aspects of biological stress, devoted an excellent essay to an analysis of my stress theory. He suggested that the common denominator of stressors may simply be activation of 'the physiological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole.' In man, with his highly developed nervous system, emotional stimuli are in fact the most common stressors — and, of course, these would be encountered most frequently in psychiatric patients.

"It must not be forgotten, however, that stress reactions do occur in lower animals that have no nervous system, and even in plants. Furthermore, the so-called stress of anesthesia is a well-recognized phenomenon in surgery, and numerous investigators have tried to eliminate this undesirable complication of the loss of consciousness."

Recognition of the fact that stress is not necessarily due to nervous arousal has induced many experts in this field to speak more precisely of "neurogenic stress" or "psychogenic stress" when this particular form is meant.

Prior to its publication, I submitted the manuscript of my book[17] to Dr. Mason, so that he might comment on these remarks. Upon receiving his reply, I then added: "However, in a letter (which he has allowed me to quote) Mason clarifies the preceding sentence by saying that 'when psychological influences are minimized, such stressors as heat and fasting do not provoke certain hormonal responses characteristic of stress, although other stressors such as cold and hypoxia continue to evoke these hormonal responses'."[17 (p.158)]

I agree with him but, in my opinion, all this is explained by the effects of different conditioning factors and by the well-documented fact that not all stressors reach the headquarters of the "hypo-

physiotropic area" in the hypothalamus through the same pathways.

This has been demonstrated particularly by the important finding that the entire hypophysiotrophic area can be surgically isolated from the rest of the brain by a special knife (generally known as the Halász knife) pushed from the cortex down to the base of the skull. Using this instrument, it is possible to accomplish a complete deafferentation of the hypophysiotrophic area, which remains in contact only with the pituitary through the stalk. After this intervention, there is no reduction in basal ACTH secretion; in fact, this is usually above normal, and the anterior lobe can still respond to various stressors such as ether, restraint, tourniquet shock, formalin, etc. by a rise in plasma ACTH, resulting in increased plasma corticoid levels. Even removal of one adrenal still causes hypertrophy of the contralateral gland. These reactions do not occur if the median eminence, in the hypophysiotrophic area, is destroyed.

There remains no doubt that humoral stimuli can initiate the stress response, even when emotional arousal or any other cortical stimuli are no longer able to reach centers producing the corticotrophin-releasing factor (CRF).

Source of confusion No. 10: "*. . . most, if not all hormones, characteristically respond to multiple stimuli.*"[1]

As I emphasized nearly 20 years ago in the first edition of *The Stress of Life*,[6] specificity and nonspecificity are always relative, in the sense that few (if any) agents produce only one change, and the number of "side effects" varies. However, alterations produced by only one or a few agents are conveniently referred to as "specific," in opposition to those that affect many organ systems indiscriminately. Stress is by definition nonspecific in its causation; that is, it is "the response of the body to any demand," just as is energy utilization, though its phenotypes may be vastly different, depending upon the previously mentioned conditioning factors.

Of course, administration of CRF, ACTH, or corticoids may elicit certain manifestations generally ascribed to stress, in a highly specific manner. The same may be said about some drugs (e.g., amphenone) which specifically interfere with the stress mechanism itself. However, this hardly could justify abandoning the concept of nonspecificity, any more than the fact of an albino Negro or a deeply pigmented Caucasian Addisonian would justify the distinction between black and white races in anthropology.

Source of confusion No. 11: *The shift in anterior pituitary activity.*

Ever since my earliest observations in 1935 and 1936 I have expressed the view that during stress there is "a shift in anterior pituitary activity." Although Mason[1] did not mention this problem, I would like to add it to my own list of "confusions" in the stress field, because, in this respect, I am afraid I have misinterpreted my pertinent observations, unfortunately causing considerable debate in the world literature. The basic observations were correct. When the organism is under considerable stress it has to secrete an increased amount of ACTH and corticoids to maintain life, even at the cost of a decrease in growth, gonadal development or, during lactation, milk production. I felt that the anterior pituitary cannot maximally produce ACTH, STH (somatotrophic or growth hormone), FSH, LH, and LTH at the same time.

However, this interpretation has never been proven by actual hormone determinations. I fully agree with Mason that in this, as well as in many other respects, the exact mechanism of the hormonal reactions to stressors will have to be clarified, but this will not be too difficult with the new radio-immunologic methods of hormone determinations.

Even now we certainly can say, however, that a shift in anterior pituitary activity occurs during stress, although this may not be wholly due to an inability of the pituitary to produce other hormones while engaged in maximal ACTH secretion.

Source of confusion No 12: *"It is tempting to suggest that we might be better off without the term 'stress' at all, given our present crude level of insight, but perhaps the notion of a generic term which somehow ties together the threatening or taxing demands of the environment on living organisms strikes some deep, responsive chord within us which keeps alive the use of 'stress' terminology in spite of all the confusion it creates."*[1]

I believe that the *Journal of Human Stress* will have a long and fruitful existence, despite the suggestion in its lead article that the very term "stress" be banned. I trust that this Journal will survive, because it has shown its desire to act as an open forum for frank but non-aggressive discussions of confusing points by inviting Dr. Mason and myself to review vastly opposing points of view. It has given us a chance to expose them to the judgement of all investigators in what I consider a very promising field of research.

Perhaps the most potent stimulus to progress in research is the frank but fair and unemotional discussion of our doubts.

INDEX TERMS

stress, stressor, distress, eustress, General Adaptation Syndrome, Local Adaptation Syndrome, homeostasis.

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