Forty years of stress research: principal remaining problems and misconceptions

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An overview of the main problems and misconceptions in the clinical application and theoretic evaluation of the stress concept reveals that the same 10 problems appear to cause the greatest difficulties in its application, irrespective of the specialty in which it is used: (1) the correct definition of stress, stressors and the general adaptation syndrome; (2) the concept of nonspecificity in biology and medicine; (3) the conditioning of stress responses by diverse endogenous (mainly genetically determined) and exogenous (environmental) factors; (4) the relation between the general and the local adaptation syndromes; (5) the difference between direct and indirect pathogens; (6) the definition of the morbid lesions in whose pathogenesis stress plays a particularly prominent role — the so-called diseases of adaptation; (7) the role of genetics versus that of factors under voluntary self-control in mastering biologic stress; (8) the mode of action of syntoxic and catatoxic hormones, drugs and behavioural attitudes; (9) the so-called first mediator of the stress response, which carries the message that a state of stress exists from the directly affected area to the neurohormonal regulatory centres; and (10) the prophylaxis and treatment of stress-induced damage by pharmacologic and behavioural techniques.

Les principaux problèmes et les conceptions erronées qui entourent la notion de stress ont été relevés. Indépendamment de la discipline dans laquelle le terme est utilisé, il semble que 10 problèmes, toujours les mêmes, soient à l'origine des difficultés rencontrées dans son application: (1) la définition précise de stress, stresseur et syndrome général d'adaptation; (2) le concept de nonspécificité tel qu'utilisé en biologie et en médecine; (3) le conditionnement des réactions de stress par divers facteurs endogènes (de nature génétique principalement) et exogènes (relatifs à l'environnement); (4) la relation entre syndrome général et syndrome local d'adaptation; (5) la différence entre pathogènes directs et indirects; (6) les lésions morbides dans lesquelles le stress joue un rôle spécialement important — les "maladies d'adaptation"; (7) le rôle relatif de certains facteurs (somatiques v. psychologiques) susceptibles de conduire à la maîtrise du stress biologique; (8) le mode d'action des hormones syntoxiques et catatoxiques et des médicaments, ainsi que les leçons qu'on peut en tirer sur le plan du comportement; (9) le "premier médiateur", qui est à ce jour nonidentifié, provenant de la région directement affectée et portant le signal d'alarme aux centres régulateurs neurohormonaux; et (10) la prophylaxie et le traitement des dommages causés par le stress, à l'aide de techniques pharmacologiques et comportementales.

Almost 4 decades ago certain primitive experiments led to the publication of a letter to the editor of *Nature* entitled "A syndrome produced by diverse nocuous agents".[1] Since then more than 110 000 publications have dealt with the different aspects of what is now known as "the stress concept" — publications not only in medicine but also in the behavioural sciences and philosophy. An encyclopedia[2] listing 7518 key references is summarized in the updated edition of "The Stress of Life".[3]

The compilation of these surveys, as well as the many personal contacts I have had with experts during my lecture tours throughout the world, made it seem opportune at this time to present the simplest possible synopsis of the main points likely to cause confusion.

Major points of confusion concerning the stress concept

Irrespective of the specialty in which the stress concept is used, the same 10 problems (some partly overlapping) confuse its application:

1. *The definition of stress, stressors and the general adaptation syndrome*

Stress is the nonspecific response of the body to any demand. A stressor is an agent that produces stress at any time. The general adaptation syndrome (GAS) represents the chronologic development of the response to stressors when their action is prolonged. It consists of three phases: the alarm reaction, the stage of resistance and the stage of exhaustion.

2. *Nonspecificity v. specificity*

These terms may be applied to both the eliciting agent and the response. By nonspecific we mean effects or responses that are characteristic of many stimuli or agents — for example, the manifestations of the alarm reaction, with the secretion of adrenocorticotropic hormone (ACTH), corticoids and catecholamines, thymicolymphatic involution, eosinopenia and peptic ulcera-

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tion. All of these are nonspecific effects in that they can be elicited by innumerable agents that make an intense demand upon the adaptability of the organism. On the other hand, the perception of green light, for example, is a highly specific response since it can be elicited only by light of a given wavelength and only if this stimulus is applied to the retina. However, as we shall see when comparing the GAS with the local adaptation syndrome (LAS), even a highly specific local stimulus, such as intense light or sound, though acting specifically upon the eye or ear, respectively, can also cause a nonspecific systemic (that is, general) stress reaction if it is of sufficient magnitude to mobilize the general adaptive system of the entire body — that is, by causing intense nervous arousal, with consequent stimulation of the hypothalamic-hypophyseal-adrenocortical axis and generalized adrenergic responses.

The stereotyped nonspecific stress responses are highly specific in their manifestations but nonspecific in their cause, whereas generalized tissue catabolism, for example, is a nonspecific (diffuse) manifestation that may be evoked by even highly specific pathogens.

Thus, specificity is always a relative phenomenon. Whatever agent affects us (light, bacteria, hemorrhage, pain) will have its own characteristics but it will also cause stress, which, by definition, is a nonspecific demand for adaptation. Of course, certain agents and responses (e.g., long periods of excessive mental and physical work, with consequent generalized fatigue) are predominantly nonspecific; conversely, the perception of a certain light or sound wave and the production of Koplik's spots by the measles virus are highly specific with respect to the evocative agents and the responses.

In this transition from the ideal, totally nonspecific, pure stress response to greater specificity, the first subdivision is the distinction between "eustress" and "distress" — the former being agreeable or healthy, and the latter, disagreeable or pathogenic. The way a certain stimulus will be received depends upon its intensity and the particular receptiveness of the affected person. From these two main branches can arise a virtually infinite number of ramifications of the agents and the effects that are experienced during eustress and distress. This diversity depends primarily upon conditioning.

3. *Conditioning*

The term conditioning is used in stress research not only in the Pavlovian sense but also to designate any factor that can influence the body's receptivity to a stressor (or stress-induced hormone).

Because all stressors necessarily must have some specific effects of their own, they cannot always elicit exactly the same response. In fact, even the same stimulus will act differently in different individuals, depending upon endogenous (e.g., genetic predisposition, age, sex) or exogenous (e.g., treatment with hormones or drugs, exposure to environmental factors, including air pollution, social influences, etc.) conditioning factors (Fig. 1).

It is a lack of understanding of the role of conditioning that has so often raised questions concerning two types of observations:

A. Qualitatively different stimuli of equal stressor potency (judged by their ability to elicit typical stress manifestations — e.g., ACTH, corticoid or catecholamine production) do not necessarily cause the same stress syndrome in different individuals.

B. Even the same degree of stress induced by the same stimulus may provoke different lesions in different individuals.

4. *GAS v. LAS*

I have coined the term "systemic stress" to emphasize that a GAS is elicited only by stressors that, directly or indirectly, affect the whole body. On the other hand, an LAS is the response to nonspecific demands made upon only one part of the body. Such demands may be made upon a circumscribed, physically or chemically traumatized region of skin or connective tissue and then the manifestations of the LAS will be essentially those of inflammation, necrosis or cell degeneration with regeneration. However, an intense LAS (e.g., in a limited muscle group, sense organ or brain region) may reach such proportions as to affect the body as a whole and produce a GAS through its secondary systemic stressor effects.

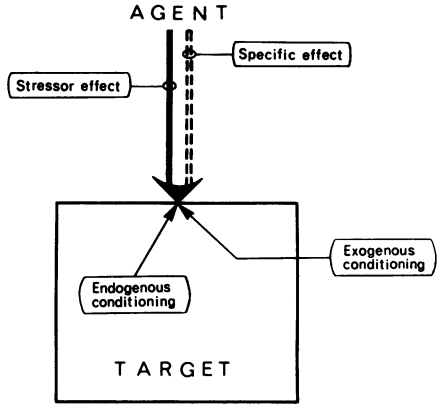

FIG. 1—Factors influencing the response to a stressor.

5. *Direct v. indirect pathogens*

Direct pathogens are those that act as such. Mechanical trauma, intense heat and strong acids or alkalis will cause tissue damage irrespective of the body's response and, more particularly, of the defensive reactions characteristic of stress. That these pathogens are really direct and independent of any vital activity is best demonstrated by the fact that they will affect even a cadaver, in which, obviously, morbid lesions could not develop as a consequence of its own vital reactions.

Other direct pathogens are, for example, endotoxins, spinal cord transection, and x-irradiation. Their effects (fever, paralysis, radiation syndrome) are not evident after death, yet they do act directly. It is true that the body's defensive reactions (particularly the stress response) can be elicited by them in the living organism as a secondary consequence of their direct effects; however, their specific actions are not, or are only slightly, influenced by the stress they produce.

On the other hand, indirect pathogens act only, or predominantly, through the excessive or inappropriate defensive reactions they elicit. For example, emotional, immunologic and inflammatory reactions depend primarily upon such indirect mechanisms.

6. *The definition of the diseases of adaptation or stress-induced maladies*

The diseases of adaptation depend primarily upon an excessive or inappropriate response to indirect pathogens. Included are all "psychosomatic" diseases, allergies and other immunologic responses, as well as excessive inflammatory reactions to, in themselves, harmless agents. The evocative agent itself is often not the cause of the trouble. For example, if emotional responses are prevented by suitable counselling or psychopharmacologic measures, or if immunologic or inflammatory reactions are suppressed by glucocorticoids, it becomes clear that the evocative agent is not inherently pathogenic. Here we are dealing with the curious phenomenon that an essentially useful defensive reaction, developed in the course of evolution for protection (e.g., emotional arousal in preparation for fight, immunologic and inflammatory responses to foreign intruders), can be the major cause of disease if the defence is inappropriate under the circumstances. It is true that, in the course of evolution, most of the inappropriate defence reactions have gradually been eliminated as only the fittest survived;

but evolution is still in progress — we are not yet perfect.

The platitude "Nature knows best" is just as false as "Mother knows best". Nature may know best in terms of millennia of further evolution, but meanwhile this is true only in so far as our brains have learned to correct false, automatic, adaptive defences by physical (e.g., pharmacologic or surgical) or mental (e.g., psychotherapeutic techniques or a code of behaviour) means.

In particular cases many physicians have difficulty grasping the nonspecific aspect of the diseases of adaptation. When faced with the interpretation of a peptic ulcer produced by a burn, they will quite justly emphasize that a peptic ulcer is a specific disease and a skin burn is a specific type of injury affecting a particular region of the body surface. Similarly, if a patient has a cardiac accident after a violent marital dispute, the physician will point out that both the result and the cause were specific. So why speak of a nonspecific stereotyped "stress" element?

Since this problem is so often misunderstood, it may be worth while to illustrate it by examples of well known inanimate machines in which the common factor necessary for their function is the generation of energy that can then satisfy demands at an appropriate receptor. In patients this is comparable to various highly specific morbid lesions produced by equally specific causative agents, but only if the latter generate a stress response (Fig. 2).

Conditioning factors (innate or acquired) determine specifically which pathways and which receptors will be most sensitive to the common stimulus in any one case. Only a few responses are virtually always evident: massive acute liberation of energy produces heat; massive acute stress stimulates the hypothalamic-hypophyseal-adrenocortical axis, as well as the catecholaminergic system, and causes catabolism, and so on.

As Fig. 2 shows, a lamp placed directly in contact with a waterfall will not produce light, and an air conditioner, if only soaked in petroleum, will fail to cool or heat a room. All the effects that can be produced by the inanimate receptors depend upon energy derived from the diverse sources capable of furnishing it. Similarly, the diseases mentioned will not arise in patients exposed to the agents enumerated unless the latter do, in fact, produce stress.

Most of the seeming exceptions to the mediation of the diseases of adaptation by stress are readily explained. Thus, some acute transient stressors (e.g., localized burns) are unlikely to cause hypertension because they do not act long enough; others (e.g., starvation or hemorrhage) will fail to increase the blood pressure because they have a specific hypotensive effect.

7. *Genetics v. self-control*

It would be impossible to answer in quantitative terms the eternal question of the relative importance of genetic predisposition and rational conduct — the ability to respond to the exigencies of life by disciplined, voluntary reactions motivated by the pursuit of a goal that one really can and wishes to attain: in essence, the limits of "free will".

At present, great emphasis is placed upon inherited personality traits in the development of various stress-induced psychosomatic diseases, particularly in the probability of having a coronary heart attack at an early age. We used to describe a person with the behavioural pattern linked with a high probability as a "stress seeker" or a "race-horse type", as opposed to the easygoing "turtle type". In their now-classic studies, Friedman and Rosenman[4] refer to these as "type A" and "type B" persons, respectively, the former being particularly prone, and the latter resistant, to untimely coronary accidents during early middle age.

Although I am a great admirer of the excellent investigations that have led to the characterization of what we now know as the type A personality, which is primarily determined by genetic predisposition, I wish to console those who have been born with this stigma, as I have: the situation is not hopeless. What is important is to live so that one's distress is converted into eustress. In any event, that is what has kept me healthy and happy, and — having reached the age of 68 — even if I should have a coronary accident before this paper appears in print, my death would not be "untimely".

8. *Syntoxic v. catatoxic agents*

Syntoxic refers to agents that carry the message of coexistence with a potential pathogen. The best known examples of such chemical agents are syntoxic hormones, such as glucocorticoids, which suppress many of the usually helpful, defensive, inflammatory or immunologic reactions. Catatoxic refers to impulses for fight and aggression. Some natural steroid hormones (e.g., those of the testes) have catatoxic effects, but more effective are certain synthetic steroid hormone derivatives, such as pregnenolone-16α-carbonitrile (PCN), which induce the synthesis by the liver of aggressive, drug-metabolizing enzymes that can destroy a large number of pathogens (e.g., barbiturates, certain carcinogens and digitalis compounds).

9. *The "first mediator" of the stress response*

We have long been puzzled by the nature of the "first mediator", which carries the message of stress from the directly affected area (e.g., a burned

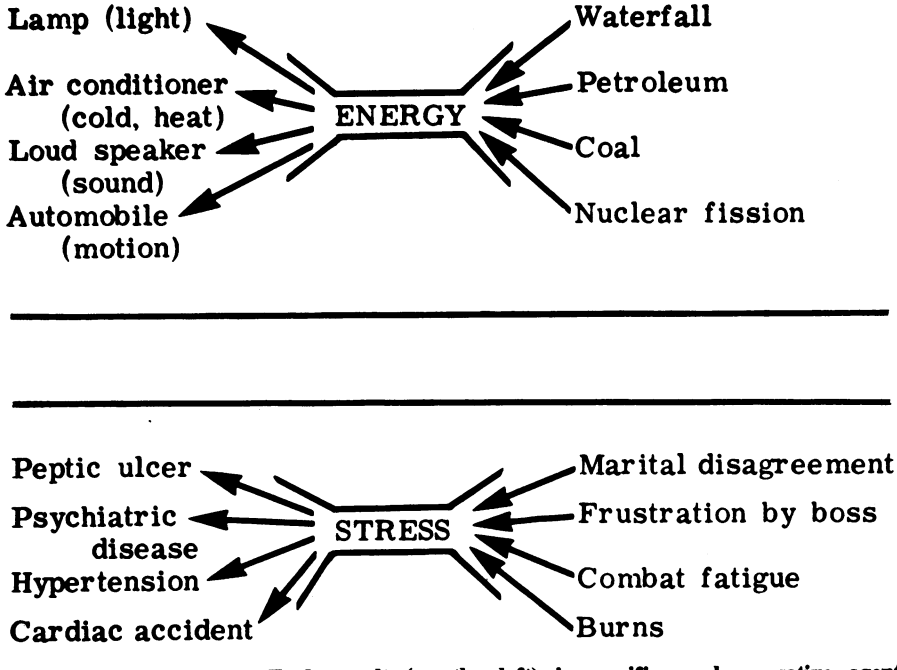

FIG. 2—Nonspecificity. Each result (on the left) is specific, each causative agent (on the right) is specific. Yet they are all nonspecific results in that they must go through a common pathway. No direct connection is possible between a result and a cause.

hand, an excited cerebral cortex or a vascular system depleted of blood) to the centres (e.g., the hypothalamus and adenohypophysis) that regulate homeostatic reactions. We know much about the latter, which regulate the output of the stress centres, but little about the nature of the input.

Undoubtedly nervous impulses and blood-borne chemical mediators carry some of the information that a state of stress exists. In man, with his highly developed central nervous system, psychologic stressors, and particularly emotional arousal, are of primary importance. This is especially true of the most common stressors of daily life (frustration, anger, fear and hate). However, contrary to the opinion of some psychiatrists and psychologists,[5] nervous arousal, especially in the form of a conscious affect or emotion, cannot always be the common pathway. For example, typical activation of the hypothalamic-hypophyseal-adrenocortical axis and the adrenergic system can be accomplished by decortication, surgical intervention under deep anesthesia, or anesthesia itself.

Furthermore, stress occurs in lower animals and plants, which have no central nervous system, and even in isolated cell colonies growing in tissue culture. In addition, the entire hypophysiotropic area can be surgically isolated from the rest of the brain by a tubular knife (generally known as the Halász knife) pushed down from the cortex to the base of the skull. This permits complete "deafferentation" of the hypophysiotropic area, which remains in contact with the hypophysis only through the stalk vessels. This operation causes no reduction in basal secretion of ACTH (which, in fact, is usually above normal) and the adenohypophysis continues to respond to various stressors (e.g., ether, restraint, tourniquet shock or formaldehyde) with an increase in plasma ACTH and corticoid concentrations. In animals with such a completely isolated hypophysiotropic area the compensatory hypertrophy of the remaining adrenal gland is demonstrable after ablation of the contralateral gland. On the other hand, all these stress responses are abolished if the median eminence of the hypophysiotropic area is destroyed.

Hence, it may be taken as well established that blood-borne stimuli can initiate the stress response, even if emotional arousal (or any other cortical stimulus) is prevented from reaching the centres producing corticotropin-releasing factor, the substance that induces the pituitary to produce ACTH.

As yet, nothing is known about the chemical nature of the 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. Identification of the first mediator appears to be one of the most fundamental tasks of future stress research.

10. *Prophylaxis and treatment*

Recommendation of the use of various drugs (tranquillizers, antiadrenergic agents, or even psychedelic agents and vitamins) to "eliminate stress" has caused much confusion. Some certainly diminish the distress of excessive emotional lability but others are totally ineffective or even harmful in any kind of stress situation.

We must not suppress stress in all its forms, but diminish distress and facilitate eustress, the satisfactory feeling that comes from the accomplishment of tasks we consider worth while.

Stress is the salt of life; few people would like to live an existence of no runs, no hits, no errors. Yet it is beneficial for the human machine to rest periodically; hence the development of various religious and psychologic techniques designed to diminish temporarily all forms of biologic stress, close to the minimum compatible with survival. Total elimination of stress — that is, cessation of demands made upon any part of the body, including the cardiovascular, respiratory and nervous systems — would be equivalent to death.

Conversely, for the mobilization of useful adaptive reactions and an increase in general resistance, the use of strong stressors (e.g., physical exercise, hydrotherapy, electroshock, insulin shock, Metrazol [pentylenetetrazol] shock, nonspecific fever therapy) is beneficial in certain situations. We do not know through what mechanism such stressors improve fitness and help the body's efforts to overcome diseases of adaptation, or why one may be more helpful than another, but their efficacy has received ample empirical proof. Presumably the conditioning factors associated with diverse prophylactic and therapeutic procedures, as well as those that accompany the harmful stressors that cause distress, so modify the stereotyped response that a certain degree of specificity becomes evident. For example, the various types of shock therapy are most useful in the treatment of certain psychoses. On the other hand, exercise, saunas, cold showers and the various psychologic relaxation techniques are more efficient in mastering the stress situations of everyday life; they help to turn the distress of fatigue and failure into the eustress of success and fulfilment.

Stress of living: a personal view

To these time-honoured procedures for the mastery of stress I have recently added a code of behaviour described as "altruistic egoism".[6] In essence, it accepts that all living creatures are, and must be, primarily selfish; the big fish has to eat little fish or else it will perish. None of us can expect others to look after us more than after themselves. However, we must avoid meticulously the reckless selfishness of those who think only of themselves. Reckless egoism is even biologically unsound; it creates so many enemies and such feelings of uncertainty that it could never act as a satisfactory permanent guideline through life.

However, we can rid ourselves of guilt feelings and inferiority complexes for our inability to be ideal altruists once we admit that some egoism is indispensable for the maintenance of both the individual and the species.

It is biologically impossible to accept the command "Love thy neighbour as thyself" literally. You cannot love on command. It is up to your neighbour to make himself lovable. Hence the code of behaviour based on altruistic egoism tries to satisfy the natural egoistic tendency to hoard capital for security, just as many animals hoard food or building materials to assure their homeostasis at future times of need. However, in the case of man this capital should be stocked in the form of personal satisfaction, love and goodwill, as he learns to be useful to others.

"Love thy neighbour as thyself" can be translated into a language acceptable to the scientifically oriented thinking of our time. For this we only have to slightly rephrase the motto as *"Earn thy neighbour's love"*.[6]

This attitude will best assure homeostasis and resistance to stressors throughout life and give a satisfactory purpose to one's activities. We have to recognize that man must work and must be selfish and hoard capital to assure his security. None will blame him whose egoistic and capitalistic tendencies express themselves in the insatiable desire to accumulate the goodwill, esteem and love of others by helping them — even if he is motivated by altruistic egoism.

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