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The Nature of Stress and Its Relation to Cardiovascular Disease

Hans Selye

I. Stress and Adaptation

A. Stress: Definition and Description

Much confusion has arisen in the lay and even in the scientific literature because the term "stress" means different things to different people. Stress is part of our daily life, but it is associated with a great variety of essentially

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dissimilar problems, such as surgical trauma, burns, emotional arousal, mental or physical effort, fatigue, pain, fear, the need for concentration, the humiliation of frustration, the loss of blood, intoxication with drugs or environmental pollutants, or even the kind of unexpected success that requires an individual to reformulate his life-style.

Stress is present in the businessman under constant pressure; in the athlete straining to win a race; in the air-traffic controller who bears continuous responsibility for hundreds of lives; in the husband helplessly watching his wife's slow, painful death from cancer; in a race horse, its jockey, and the spectator who bets on them. Medical research has shown that, although all these face quite different problems, they respond with a stereotyped pattern of biochemical, functional, and structural changes essentially involved in coping with any type of increased demand on vital activity, particularly adaptation to new situations. All endogenous or exogenous agents that make such demands are called stressors. Distinguishing between their widely differing specific effects and the nonspecific (common) biologic response that they elicit is the key to a proper understanding of biologic stress.

From the point of view of its stressor activity, it is even immaterial whether the agent or situation being faced is pleasant or unpleasant; all that counts is the intensity of the demand for readjustment or adaptation that it creates. The mother who is told that her only son died in battle suffers a terrible mental shock; if years later it turns out that the news was false and the son unexpectedly walks into her room alive and well, she experiences extreme joy. The specific results of the two events, sorrow and joy, are completely different, in fact they are opposite to each other, yet their stressor effect—the nonspecific demand for readjustment to a new situation—is the same.

It is difficult to see at first how such essentially different things as cold, heat, drugs, hormones, sorrow, and joy could provoke an identical biologic reaction. Nevertheless this is the case; it can now be demonstrated by highly objective, quantitative biochemical and morphological parameters that certain reactions are totally nonspecific and common to all types of agents, whatever their superimposed specific effects may be.

The conceptual distinction between the specific and the nonspecific consequences of any demand made on the body was the most important step in the scientific analysis of stress phenomena.

Contrary to previously widely held opinion, stress is not identical to nervous tension. It occurs in experimental animals even after total surgical deafferentation of the hypothalamus, which eliminates all neurogenic input. It can occur during anesthesia in man as well as in lower animals. It can occur even in plants, which have no nervous system.

If one seeks to understand the field of stress one must first realize that the word "stress" is often used very loosely, not only by the lay public but by professionals as well. I myself have been guilty, in some of my earlier writings, of implying, as was pointed out by the *British Medical Journal,* that stress is its own cause(!).

The best way to conceive of stress is in its most specific sense, that of a *state* which is recognizable by the presence of an organized set or sequence of bodily changes, which I will shortly describe. The experimental data lead to the inescapable conclusion that any demand (i.e., any agent, situation, or environmental change that necessitates adaptation in order to maintain healthy life) will evoke this standard set of responses, which I call the "stress syndrome." Note that, strictly speaking, the syndrome is *not* stress: it is merely the manifestation of it.

Stress is the state manifested by a specific syndrome which consists of all the nonspecifically induced changes within a biologic system. Thus, stress has its own characteristic form and composition, but its cause is a demand as such, not any particular demand.

With regard to nonspecificity, the concept of stress is not without precedent. All machines, whether animate or inanimate, require energy for any of their activities, be these constructive or destructive. In fact, we shall see that biologic stress is closely linked to, though not identical with, energy utilization. This explains its apparently paradoxical yet inseparable combination with the specific effects of the particular agent that creates a need for adaptive work. Any demand made on the body must be for some particular, that is, specific activity and yet is inseparably associated with nonspecific phenomena (i.e., energy utilization), just as in the inanimate world specific demands made on machines to increase or decrease room temperature, to produce light or sound, to accelerate or decrease motion are invariably dependent on energy utilization. Figure 1 illustrates this.

The bodily changes produced, whether a person is exposed to nervous tension, physical injury, infection, cold, heat, X-rays, or anything else, are what we call stress. This is what is left when we abstract from the specific changes that are produced only by one or few among these agents. In my earlier writings I had defined stress, somewhat more simply but less precisely, as *the sum of all nonspecific changes caused by function or damage,* or *the rate of wear and tear in the body.* Its simplest and most generally accepted definition is *the nonspecific response of the body to any demand.*

Therefore stress is not something to be avoided. Indeed, it cannot be avoided, since just staying alive creates some demand for life-maintaining energy. Even while man is asleep, his heart, respiratory apparatus, digestive tract, nervous system, and other organs must continue to function. Complete freedom from stress can be expected only after death. However, in

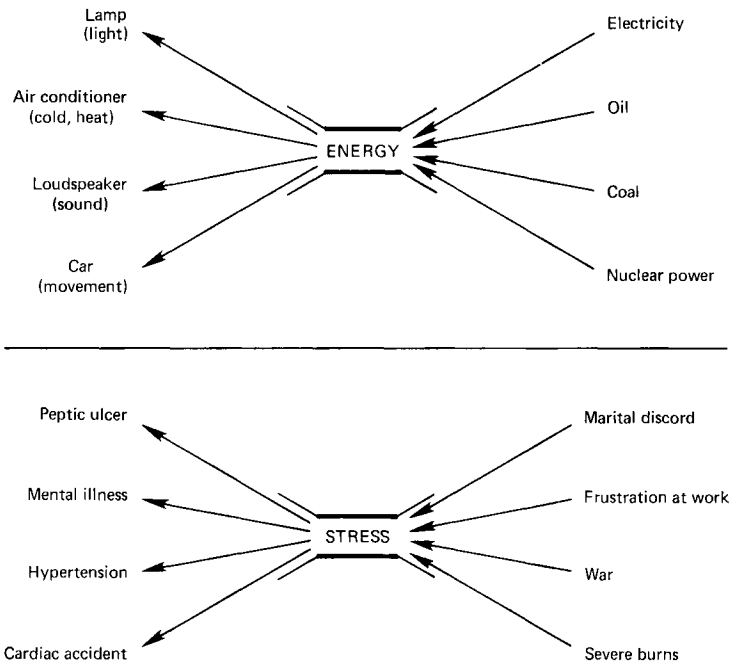


Fig. 1. Each result (*on the left*) is specific, each causative agent (*on the right*) is specific. Yet they are all nonspecific results and agents in that they must go through a common pathway. No direct connection is possible between a result (*on the left*) and a cause (*on the right*).

everyday life we must distinguish between two types of stress effects, namely, *eustress* (from the Greek *eu,* or "good"—as in "euphony," "euphoria," "eulogy") and *distress* (from the Latin *dis,* or "bad"—as in "dissonance," "disease," "dissatisfaction"). Depending on conditions, stress is associated with desirable or undesirable effects.

The presence of stress is evidenced by certain observable and measurable adjustments going on in the body. The workings of stress are extremely complex (see Fig. 2). Apart from specific stimuli, which need not be discussed here, the first effect of any agent or demand made on the body—be it running up a flight of stairs, dealing with a viral infection, or performing a dance—is to produce a nonspecific stimulus (the agent's "stressor effect"). This may be a nervous impulse, a chemical substance, or lack of an indispensable metabolic factor; it is referred to simply as the "first mediator," because we know nothing about its nature. We are not even certain that it has to be an excess or deficiency of any particular substance; it is possible that various derangements of homeostasis can activate the stress mechanism. Undoubtedly, in man, with his highly developed central ner-

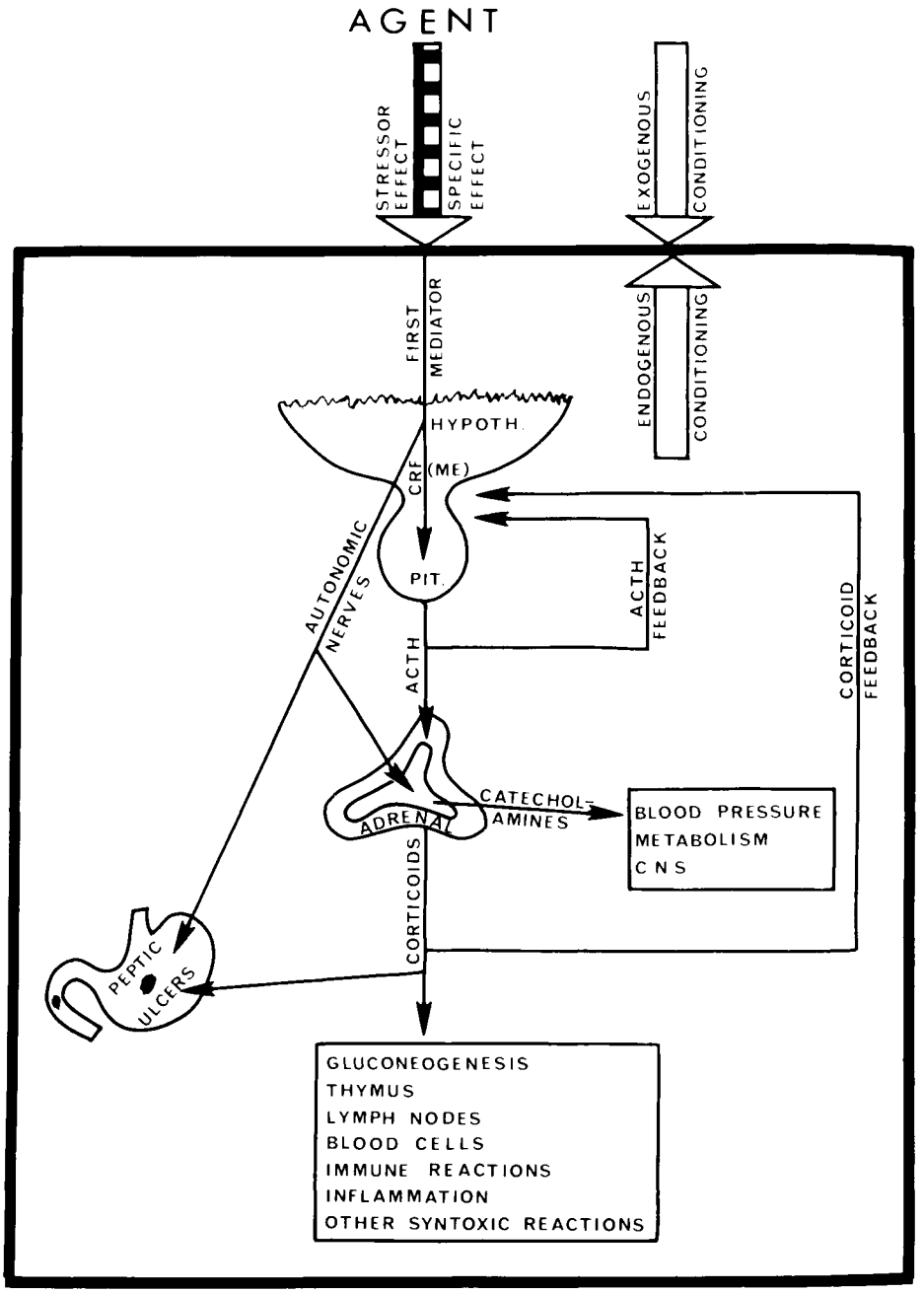
vous system (CNS), emotional arousal is one of the most frequent activators. Yet it cannot be regarded as the only factor, since typical stress reactions can occur in patients exposed to trauma, hemorrhage, and so on, while under deep anesthesia. Indeed, anesthetics themselves are commonly used in experimental medicine to produce stress, and "stress of anesthesia" is a serious problem in clinical surgery.

We have still to identify the first mediator(s), but we do know that eventually stress acts on the hypothalamus and particularly on the median eminence (ME). This action seems largely to be mediated through or modified by nervous stimuli coming from the cerebral cortex, the reticular formation, and the limbic system (especially the hippocampus and amygdala). The incoming nervous stimuli reach certain neuroendocrine cells, most of which are located in the ME. These act as "transducers," transforming nervous signals into a humoral messenger, the corticotropic hormone releasing factor (CRF), which can be demonstrated histochemically in the ME region and can also be extracted from it (see Fig. 2). Oddly enough, the posterior pituitary contains the highest concentration of CRF, and it has been isolated from this source in relatively pure form, thus permitting the approximate determination of its chemical formula as a polypeptide that subsequently was allegedly synthesized. Yet we have no conclusive proof that the CRF-active material extracted from the hypothalamus is identical with that obtained from the posterior lobe, since only the existence of the latter has been definitely ascertained. Although vasopressin (antidiuretic hormone) possesses considerable CRF activity, it is not identical with CRF; this has been shown by the well-documented differences in their chemical structure and physiological activity.

CRF reaches the anterior lobe through the hypothalamo–hypophseal portal system that originates in the ME region within a network of capillaries into which CRF is discharged by the local neuroendocrine cells. It is then carried down through the larger veins of the pituitary stalk to a second capillary plexus in the pituitary. A flow in the opposite direction is supposedly also possible.

The adrenocorticotropic hormone (ACTH) secretion of the anterior lobe is not stimulated by the hypothalamus through nervous pathways descending in the pituitary stalk but rather through blood-borne substances carried by way of the portal veins. That is why transection of the stalk inhibits the ACTH secretion only before vascular connections between the hypothalamus and the gland are reestablished; if regeneration of these vessels is prevented by interposing a plate between the cut ends of the stalk, this pathway is permanently blocked.

In vivo and *in vitro* experiments have both proved that CRF elicits a discharge of ACTH from the adenohypophysis into the general circulation.


AGENT
STRESSOR EFFECT
SPECIFIC EFFECT
EXOGENOUS CONDITIONING
ENDOGENOUS CONDITIONING
FIRST MEDIATOR
HYPOTH.
CRF (ME)
PIT.
AUTONOMIC NERVES
ACTH FEEDBACK
CORTICOID FEEDBACK
ACTH
ADRENAL
CATECHOL-AMINES
BLOOD PRESSURE
METABOLISM
C N S
CORTICOIDS
PEPTIC ULCERS
GLUCONEOGENESIS
THYMUS
LYMPH NODES
BLOOD CELLS
IMMUNE REACTIONS
INFLAMMATION
OTHER SYNTOXIC REACTIONS

On reaching the adrenal cortex, it causes secretion of corticoids, mainly glucocorticoids such as cortisol or corticosterone. These induce glyconeogenesis, thereby supplying a readily available source of energy for the adaptive reactions necessary to meet the demands faced by the body. In addition, they facilitate various other enzymatically regulated adaptive metabolic responses and suppress immune reactions as well as inflammation, assisting the body to coexist with potential pathogens (syntoxic reactions). Furthermore, the glucocorticoids are responsible for the thymicolymphatic involution, eosinopenia, and lymphopenia characteristic of acute stress. Curiously, glucocorticoids are needed for the acquisition of adaptation primarily during the alarm reaction, but not so much to maintain the adjustment during the stage of resistance. ACTH plays a comparatively minor role in the secretion of mineralocorticoids, such as aldosterone, which is regulated mainly by the renin–hypertensin system and the blood electrolytes, whose homeostasis is in turn influenced by them.

This chain of events is cybernetically controlled by several biofeedback mechanisms. Whether an excess of CRF can inhibit its own endogenous secretion is still doubtful because its lifespan in the circulating blood is very short. On the other hand, there is definite proof of an ACTH feedback (short-loop feedback) by a surplus of the hormone, which returns to the hypothalamo–pituitary system and inhibits further ACTH production. We have even more evidence to substantiate the existence of a corticoid feedback mechanism (long-loop feedback) in that a high blood corticoid level similarly inhibits ACTH secretion. It is still not quite clear to what extent these feedbacks act on the neuroendocrine cells of the hypothalamus, the adenohypophysis, or both. (Hence in Fig. 2 the corresponding arrowheads merely point toward the hypothalamo–hypophyseal region in general, without specifying exactly where their target areas are situated.)

Another major pathway involved in the stress mechanism is carried through the catecholamines liberated under the influence of an acetylcholine discharge, at autonomic nerve endings and in the adrenal medulla.

Fig. 2. *Principal pathways mediating the response to a stressor agent and the conditioning factors that modify its effect.* When an agent acts on the body (*thick outer frame of the diagram*), the effect will depend on three factors (*broad vertical arrows pointing to the upper horizontal border of the frame*). All agents possess both nonspecific stressor effects (*solid part of arrow*) and specific properties (*interrupted part of arrow*). The latter are variable and characteristic of each individual agent; they are not discussed here other than to state that they are inseparably attached to the stressor effect and invariably modify it. The other *two heavy vertical arrows pointing toward the upper border of the frame* represent the exogenous and endogenous conditioning factors that largely determine the reactivity of the body. It is clear that since all stressors have some specific effects, they cannot elicit exactly the same response in all organs; furthermore even the same agent will act differently on different individuals, depending on the internal and external conditioning factors that determine their reactivity. (After Selye, 1976.)

The chromaffin cells of the latter secrete mainly epinephrine, which is of considerable value in that it stimulates mechanisms of general utility to meet various demands for adaptation. Thus it provides readily available sources of energy by forming glucose from glycogen depots and free fatty acids from the triglyceride stores of adipose tissue; it also quickens the pulse, raises the blood pressure to improve circulation into the musculature, and stimulates the central nervous system (CNS). In addition, epinephrine accelerates blood coagulation and thereby protects against excessive hemorrhage should wounds be sustained in conflicts. All of this is helpful in meeting the demands, whether they call for fight or flight.

B. The General Adaptation Syndrome (G.A.S.)

This *alarm reaction,* however, is evidently not the entire response. On continued exposure of an organism to any noxious agent capable of eliciting this reaction, a *stage of adaptation or resistance* ensues. In other words, no organism can be maintained continuously in a state of alarm. If the agent is so damaging that continued exposure becomes incompatible with life, the animal dies during the alarm reaction within the first hours or days. If it can survive, this initial reaction is necessarily followed by the stage of resistance. The manifestations of this second phase are quite different from—indeed, often the exact opposite of—those characterizing the alarm reaction. For example, during the alarm reaction, the cells of the adrenal cortex discharge their secretory granules into the bloodstream and thus become depleted of corticoid-containing lipid storage material, but in the stage of resistance the cortex becomes particularly rich in secretory granules. Whereas in the alarm reaction there is hemoconcentration, hypochloremia, and general tissue catabolism, during the stage of resistance there is hemodilution, hyperchloremia, and anabolism, with a return toward normal body weight.

Surprisingly, after still more exposure to the noxious agent, the acquired adaptation is lost and the animal enters a third phase, the *stage of exhaustion,* which follows inexorably if the stressor is severe enough and is applied for a sufficient length of time. Unless interrupted, this stage ends in death.

The development of all three stages is not necessary before we can speak of a G.A.S. Only the most severe stress leads rapidly to the stage of exhaustion and death. Most of the physical or mental exertions, infections, and other stressors that act on us during a limited period produce changes corresponding only to the first and second stages.

The triphasic nature of the G.A.S. gave us the first indication that the body's adaptability, or *adaptation energy,* is finite. Animal experiments have shown quite convincingly that exposure to cold, muscular effort, hemorrhage, and other stressors can be withstood for just so long. After the initial

alarm reaction, the body becomes adapted and begins to resist, the length of the resistance period depending on the body's innate adaptability and the intensity of the stressor. Yet, eventually, exhaustion ensues.

Exactly what is lost, we cannot yet say, except that it is not merely caloric energy. Food intake is normal during the stage of resistance, and so caloric energy is amply available. Apparently, just as any machine gradually wears out, even if it has enough fuel, so does the human body sooner or later become the victim of constant wear and tear.

C. Objections to the Concept

Even though experiments were extremely suggestive, there remained two apparently insurmountable obstacles in the way of formulating the concept of a single, standard response to stress: (1) Different stimuli of equal toxicity (or stressor potency) do not necessarily elicit exactly the same syndrome in different people; (2) the same stimulus may produce different lesions in different individuals.

1. It was eventually shown that though qualitatively distinct stimuli do differ only in their specific actions, their nonspecific stressor effects are essentially the same. (But it must be noted that even the nonspecific effects can be modified by the superimposed specific effects of a particular stimulus.)

2. The occurrence of different lesions in individuals subjected to the same stressors has been traced to "conditioning factors" that can selectively enhance or inhibit one or the other stress effect. The conditioning may be internal (e.g., genetic predisposition, age, or sex) or external (e.g., treatment with certain hormones and drugs, dietary factors, our society, and traditions). Under the influence of such conditioning factors a normally well-tolerated degree of stress can become pathogenic and cause "diseases of adaptation" affecting the predisposed body area.

To sum up: the stressor effects of an agent are nonspecific (i.e., common to diverse stimuli), whereas the specific effects are variable and characteristic of each individual agent. But the response does not depend exclusively on these two actions of the stimulus; the reactivity of the target also plays a role, and this can be modified by numerous internal or external conditioning factors.

Since all stressors have some specific effects, they cannot always elicit exactly the same response, and even the same stimulus will act differently in different individuals, depending on the internal and external conditioning factors.

Although any kind of adaptive activity sets our stress apparatus in motion, it will depend largely on such conditioning factors whether the heart,

stomach, brain, kidney, or liver will break down. They will determine what part of the body is the "weakest link" in a given situation. The concept of conditioning just outlined and the hypothesis that certain diseases are caused by derangements of the G.A.S. mechanism have clarified the relations between the physiology and pathology of stress in many fields.

D. Stress and Disease in General

Of course, every disease causes a certain amount of generalized stress, since it imposes demands for adaptation on the organism. Hence stress plays some role in the development of every disease; its effects—for better or worse—are added to the specific changes characteristic of the disease in question. The effect of stress may be curative (as illustrated by various forms of externally induced stress, such as shock therapy, physical therapy, and occupational therapy) or damaging, depending on whether the biochemical reactions characteristic of stress (e.g., stress hormones or nervous reactions to stress) combat or accentuate the trouble.

Stress is able to combat disease because of the phenomenon of cross-resistance. Thus pretreatment with one stressor may induce resistance by mobilizing the body's nonspecific adaptive system. For example, syntoxic hormones (glucocorticoids) liberated during systemic stress can protect against various excessive and harmful inflammatory or immune reactions. This principle has been applied clinically in the treatment of inflammatory diseases and the suppression of graft rejection. However, there probably exist other forms of cross-resistance.

Even before we knew anything about the mechanism of stress reactions, nonspecific treatments were in use that relied on the exposure of patients to stressors (cold, heat, hydrotherapy, bloodletting, exercise, fever therapy, electroshock, and so on). Some of them had been in use for centuries; it was not known how these agents acted, but there could be no doubt that in many cases they were beneficial. And it is still not clear why some nonspecific therapeutic procedures are more valuable in certain diseases than in others, but probably their specific effects are superimposed on—in some cases, even more important than—their nonspecific effects.

In any case, all these treatments do produce stress and often act through the liberation of stress hormones such as ACTH, corticoids, and catecholamines (adrenaline, noradrenaline). Whenever this is true, it is of course much more acceptable to the patient to receive the hormones from outside (i.e., by prescription) than to count on their production by exposure of the patient to drastic types of nonspecific treatments.

E. The Diseases of Adaptation (Stress Diseases)

Diseases in whose development the nonspecific stressor effects of the eliciting pathogen play a major role are called diseases of adaptation or stress diseases. But just as there is no pure stressor (i.e., an agent that causes only the nonspecific response and has no specific action), so there are no pure diseases of adaptation. Some nonspecific components participate in the pathogenesis of every malady, but no disease is due to stress alone. The justification for placing a malady in this category is directly proportional to the role that maladjustment to stress plays in its development. In some instances (e.g., surgical shock), stress may be by far the most important pathogenic factor. However, in other cases (instantly lethal intoxications, traumatic injuries to the spinal cord, most congenital malformations) it plays little or no role, either because the damage is inflicted so rapidly that there is no time for any adaptive process or because the pathogen is highly specific. In the latter event, whatever develops represents a secondary result and is not the primary component. Typical diseases of adaptation are due to insufficient, excessive, or faulty reactions to stressors, as in inappropriate hormonal or nervous responses.

Some diseases in which stress usually plays a particularly important role are high blood pressure, heart accidents, gastric or duodenal ulcers (the "stress ulcers"), and various types of mental disturbances. Yet there is no disease that can be attributed exclusively to maladaptation, since the cause of nonspecific responses will always be modified by various "conditioning factors" that enhance, diminish, or otherwise alter disease proneness. Most important among these are the specific effects of the primary pathogen and the factors influencing the body's reactivity by endogenous (heredity, previously sustained damage to certain organs) or by exogenous (concurrent exposure to other pathogens and environmental agents, diet) conditioners. Hence the diseases of adaptation cannot be ascribed to any one pathogen but only to "pathogenic constellations"; they belong to what we have called the pluricausal diseases ("multifactorial maladies"), which depend on the simultaneous effect of several potentially pathogenic factors that alone would sometimes not produce disease.

F. Syntoxic and Catatoxic Responses

Biochemical analysis of the stress syndrome showed that homeostasis depends mainly on two types of reactions: syntoxic (from the Greek *syn,* meaning "together") and catatoxic (from the Greek *cata,* meaning "against"). In order to resist different toxic stressors, the body apparently can regu-

late its reactions through chemical messengers and nervous stimuli that either pacify or incite to fight. The syntoxic stimuli act as tissue tranquilizers, creating a state of passive tolerance that permits a kind of symbiosis, or peaceful coexistence with aggressors.

The catatoxic agents cause chemical changes (mainly through the production of hepatic microsomal enzymes) that lead to an active attack on the pathogen, usually by accelerating its metabolic degradation.

Presumably, in the course of evolution the body learned to defend itself against all kinds of aggressors (whether arising in the organism or the environment) through mechanisms that help it tolerate the aggressor (syntoxic) or destroy it (catatoxic). Among the most effective syntoxic hormones are the glucocorticoids. These inhibit inflammation and many other essentially defensive immune reactions and are being effectively used in the treatment of diseases in which inflammation itself is the major cause of trouble (e.g., certain types of inflammation of the joints, eyes, or respiratory passages). Likewise, they have a marked inhibitory effect on the immunologic rejection of grafted foreign tissues (e.g., a heart or kidney transplant).

It is not immediately evident why it should be advantageous to inhibit inflammation or interfere with the rejection of foreign tissues, since both phenomena are essentially useful defense reactions. The main purpose of inflammation is to localize irritants (e.g., microbes) by putting a barricade of inflammatory tissue around them to prevent their spread into the blood, which could lead to sepsis and even death. The suppression of this basic defense reaction is an advantage, however, when a foreign agent is in itself innocuous and causes trouble only by inciting inflammation. In such cases, inflammation itself is what we experience as a disease. Thus in many patients who suffer from hay fever or extreme inflammatory swelling after an insect sting, suppression of defensive inflammation is essentially a cure, because the invading stressor agent is not in itself dangerous or likely to spread and kill. In the case of grafts, it may even be lifesaving.

It is illuminating to distinguish between direct and indirect pathogens. Direct pathogens cause disease regardless of the body's reaction, whereas indirect pathogens cause damage only because they provoke exaggerated defensive responses.

If a man accidentally exposes his hand to a strong acid, alkali, or boiling water, damage will occur regardless of his reactions, because these are all direct pathogens. They would damage even the hand of a dead man, who obviously could not put up any defense reactions. Most common inflammatory irritants, including allergens, are essentially indirect pathogens: They cause disease only through the purposeless defense reactions that they stimulate.

Immunologic reactions, which lead to the destruction of microbes, grafts, and other foreign tissues, undoubtedly developed during evolution as useful defensive mechanisms against potentially dangerous foreign materials. When the attack against the foreign agent is unnecessary or even harmful—as in the case of many allergens, heart transplants, and so on—man can improve on the wisdom of Nature by suppressing this hostility. When the aggressor is dangerous, the defensive reaction should not be suppressed but if possible increased beyond the normal level, which can be achieved, for example, by catatoxic substances that carry the chemical message to the tissues to destroy the invaders even more vigorously than would normally be the case.

Although we know a great deal about the body's capacity to produce its own syntoxic hormones, such as corticoids, we know substantially less about its ability to produce catatoxic substances. Some natural hormones do possess such activities, but they are weak. The most active catatoxic compounds are synthetics, among which the most powerful so far examined is a hormone derivative designated by the chemical name "pregnenolone 16α-carbonitrile," commonly called PCN. This is also the most nonspecific catatoxic substance in that it exhibits the greatest destructive ability against the largest number of poisons.

G. Homeostasis and Heterostasis

Natural homeostatic mechanisms are usually sufficient to maintain a normal state of resistance; however, when the organism is faced with unusually heavy demands, ordinary homeostasis is not enough. The "thermostat of defense" must be raised to a heightened level. For this process I proposed the term "heterostasis" (from the Greek *heteros,* or "other") as the establishment of a new steady state by treatment with agents that stimulate the physiological adaptive mechanisms through the development of normally dormant defensive tissue reactions. Both in homeostasis and in heterostasis the *milieu intérieur* participates actively.

We can stimulate the production of natural protective agents by treatment with chemicals that augment the induction of catatoxic or syntoxic enzymes or by immunization with bacterial products (e.g., vaccination) that increase the body's manufacture of serologic antibodies to combat infections.

In homeostatic defense the potential pathogen (which threatens the fixity of the *milieu intérieur*) automatically activates usually adequate catatoxic or syntoxic mechanisms; when these do not suffice, such natural catatoxic or syntoxic agents can also be administered readymade by the physician.

Heterostasis depends on treatment with artificial remedies that have no direct curative action but that can precipitate the production of unusually high amounts of the body's own natural catatoxic or syntoxic agents so as to achieve fixity of the *milieu intérieur,* despite abnormally high demands that could not be met without outside help.

The most salient difference between homeostasis and heterostasis is that the former maintains a normal steady state by physiologic means whereas the latter "resets the thermostat" of resistance to a heightened defensive capacity by artificial interventions from the outside. By chemical treatment this process induces the body to raise the production of its own natural nonspecific (multipurpose) remedies. However, each type of planned or enforced training of the body through outside interventions also raises resistance from the homeostatic to the heterostatic level.

Heterostasis differs essentially from treatment with drugs (e.g., antibiotics, antacids, antidotes, pain killers) that act directly and specifically rather than by strengthening the body's own natural nonspecific defenses; in treatment with drugs the *milieu intérieur* is passive.

II. Stress and Cardiovascular Disease

A. Generalities

Many of the cardiovascular diseases in the pathogenesis of which stress appears to play an important role usually occur in combination (e.g., hypertension, arteriosclerosis, myocardial infarcts), and so it is difficult to discuss them separately. Furthermore, it is hard to classify the factors involved in the causation of stress-induced cardiovascular disease because of complexities in their interrelations (not to mention the fact that lesions of the cardiovascular system furnish some of the most clear-cut examples of pluricausal diseases). For example, stressors may result in hypertension or cardiac infarction, yet psychogenic stress plays such a preponderant role that it deserves to be discussed in a special section. Also, the conditioning factors that predispose to cardiovascular disease overlap. Undoubtedly, genetic factors are important in determining behavior, the choice of an occupation, the site of residence (urban, rural), or even the type of diet. On the other hand, age, at least the chronologic age of an individual, though a highly important conditioning factor determining predisposition for cardiovascular disease, is largely independent of those just mentioned. Finally, the various indicators of stress and cardiovascular disease (pathologic anatomy, chemical changes, blood coagulability) not only have diagnostic value but also furnish significant data on probably important pathogenetic factors.

B. History

As early as 1812, Corvisart expressed the view that all heart diseases stem "from the action of the organ and from passions of man." He noted that the heart can be injured by crying in infancy, wrestling, fencing, playing wind instruments, laughing, weeping, reading, declamation, anger, madness, fear, jealousy, terror, love, despair, joy, avarice, cupidity, ambition, revenge, and every kind of effort. However, "to conceive man without passions, is to conceive a being without his attributes."

Only in recent times has special attention been given to statistical studies that would prove the relationship between the stressors of daily life (especially extreme muscular effort), traumatic injuries or intense emotional arousal, and cardiac disease.

Animal experiments have shown that, following suitable pretreatment, exposure to virtually any severe stressor can precipitate myocardial necroses or hypertensive vascular disease. For example, Raab *et al.* (1964) have noted that, "Wild rats exposed after periods of isolation to frightening noises (tape recording of hissing cat and squealing rat) displayed myocardial necroses in nearly 70% of the experiments." Sharma and Barar (1966) have observed that in rats, "restraint stress" produces depletion of glycogen from the myocardium with round cell infiltration, edema, focal necrosis, and fragmentation of fibers. Hauss (1973) has found that in rats, the emotional stress produced by restraint elicits typical mesenchymal reactions in the blood vessel walls with increased [^{35} S]sulfate and [^{3} H]thymidine incorporation. Essentially similar changes occur after exposure to other stressors, and these are considered to be the first step in the arteriosclerotic process characteristic of aging. "The deformation of the structure of the arterial wall participates essentially in the development of lipidosis, fibrinosis, and cell necroses. Aggregation of thrombocytes and thrombosis in the arterial wall results from the frequent reduplication of intima cells."

In other words, here again we are dealing with complex pathogenic situations in which both the conditioning or predisposing factors that induce disease proneness and the eliciting stressors play equally important roles.

C. Stressors in General

Evaluation of the literature suggests that various stressors may play a pathogenic role in cardiovascular disease. In predisposed patients myocardial infarcts can follow extracardiac surgical interventions (Vowles and Howard, 1958; Roseman, 1962) and a variety of other physical and mental stressors (White, 1961), though there may be a latency period between the stress and the myocardial infarction. Unaccustomed efforts are particularly

harmful. In the years 1950–1959, 77% of all the claims for cardiac damage made in the state of Washington were for myocardial infarction or acute coronary insufficiency following unusual effort. This is borne out in both clinical practice and laboratory investigation. Yet a review of animal experiments and observations on man suggests that muscular work diminishes the severity and intensity of arteriosclerosis (Schlüssel, 1965).

Stressors in general are also involved in the development of hypertension. Even in workers exposed to continuous industrial noise, the blood pressure shows a great tendency to reach high values and ECG changes have been noted

> in persons exposed to the effect of continuous industrial medium-frequency and high-frequency noise of intensity 85 to 120 db, functional disturbances of the cardiovascular system were frequently observed. Very often the subjects exhibited an instability of the arterial blood pressure. The electrocardiographic data showed bradycardia with a tendency to retardation of the intravesicular conductivity, plus a depression of the T-wave that was most frequently observed after physical stress and at the end of the work-period [Shatalov *et al.*, 1962].

Stress may play a role in the production of endocarditis in that glucocorticoids decrease resistance to infection and both corticoids and catecholamines make increased demands on the cardiac valves by raising the blood pressure (Oka *et al.*, 1960).

D. Psychogenic Stressors

Psychogenic stressors are among the most frequent causes of cardiovascular disease, probably because of man's highly developed CNS. A large number of published observations suggest that tensions and threats arising from interpersonal relations in the family or at work are particularly apt to cause hypertension. For example, one review of the literature combined with personal observations (Wolf *et al.*, 1948) led to the conclusion that "hypertension may represent an atavistic protective reaction of mobilization, invoked inappropriately by these subjects to deal with day-to-day stresses and threats arising out of problems of interpersonal relation. It becomes harmful and leads to illness when this essentially emergency pattern is adopted as a way of life." Another such review (Reiser *et al.*, 1950) demonstrates how often emotionally stressful life situations worsen the course of the onset, associated symptoms, and complications of hypertension and how often relaxing situations improve the condition. Again, Hambling (1970) discussed the role of anxiety and other stressful interpersonal relations in the development of this disorder, and Pflanz (1974) reviewed hypertension as a disease largely dependent on stress, especially stress involved in social maladjustment.

On the other hand, cardiac infarcts are more often the result of acute, intense mental arousal due to life events and changes (Rahe *et al.,* 1974; Theorell, 1974; Lundberg *et al.,* 1975). In predisposed subjects, events causing anxiety and resentment increase the pulse rate, cardiac output, and blood pressure, and impair tolerance to exercise; whereas in the few cases where stress evokes dejection and despair, the cardiovascular response is hypodynamic with bradycardia, decreased blood pressure, and hypotension (Stevenson and Duncan, 1950). In this connection see also von Kerekjarto (1973) for statistical studies on psychosomatic complaints among patients suffering from arterial hypertension, hypotension, or chronic fatigue related to stress.

Arguing violently with superiors or members of the family, witnessing a serious car accident, or lifting a heavy weight may cause ventricular tachycardia, paroxysmal auricular tachycardia, complete heart block, and even sudden death; in fact, both physical and emotional exhaustion can provoke virtually all types of cardiac arrhythmias (and death) in the normal as well as the abnormal heart (Bernreiter, 1956). Presumably, the production by emotional stress in predisposed patients of arrhythmias is due to the release of catecholamines and cortisol (Bellet and Roman, 1970).

One excellent detailed review of the sociologic–demographic literature shows that the causes of sudden death in man may be classified into eight categories: "1) on the impact of the collapse or death of a close person; 2) during acute grief; 3) on threat of loss of a close person; 4) during mourning or on an anniversary; 5) on loss of status or self-esteem; 6) personal danger or threat of injury; 7) after the danger is over; 8) reunion, triumph, or happy ending" (Engel, 1971).

The many statistical studies in this area show that cardiovascular derangements (as well as other diseases of adaptation) depend not so much on the kind of demand made on an individual as on his reaction to it. One review of empirical findings indicates that personality characteristics and individual responses to stressors in life situations are related to coronary heart disease (Caffrey, 1967; experimental work is also considered in this study, especially relating to infarctoid necroses elicited by stress). Mai (1968) discussed the roles of personality and emotional stress in the pathogenesis of coronary disease, and one extensive review supported the hypothesis "of a link between perceived stress in the environment, a personality overreactive to stress and high blood pressure" (Cochrane, 1971).

Much debate has taken place about whether executives or subordinates are more subject to stress-induced cardiovascular disease, but there appears to be no uniformly applicable answer to this problem; the deciding factor is whether a person finds it more stressful to be responsible for giving orders or for having to obey them. Liesse *et al.* (1974), from various psychological

tests, concluded that "patients with ischemic heart disease do not show an exclusive coronary-prone personality pattern. Different patterns can be identified among them. The common psychological coronary-prone component of these different patterns seems to be the incapacity to cope with anxiety or the inadequacy of their defense-mechanisms." Again, a statistical study based on questionnaires led to the inference that what counts in the production of CHD "may not be the amount of situational or intrapsychic stress a person is subjected to but the way he copes with it—his defensive style" (Wardwell and Bahnson, 1973).

In this respect two personality types have been distinguished by Friedman and Rosenman (1959): Type A, characterized by a behavior pattern of intense ambition, competitive drive, constant preoccupation with job deadlines, a sense of time urgency, restless motor mannerisms, and staccato-style verbal respones; and Type B, characterized by a converse behavior pattern. Sometimes a Type C is recognized as having essentially the characteristics of Type B, but with the added element of chronic anxiety. Type A subjects usually have a high cholesterol level, a shortened blood-clotting time, and an increased tendency to develop coronary artery disease, and arcus senilis (see also Rosenman, 1967; Friedman and Rosenman, 1974; Friedman *et al.*, 1975). Allegedly, Type A people succumb to coronary artery disease six times more frequently than Type B people (Friedman *et al.*, 1968).

Other studies have confirmed the findings of Friedman and Rosenman. One extensive review by Morris and Gardner (1969) notes that ischemic heart disease is particularly common among men "showing strong drive, competitiveness, time urgency and preoccupation with deadlines, and the frustrations attendant on these" (Type A). This is true especially in early middle age, and results in particularly fatal disease. The incidence is twice that among Type B patients, who do not exhibit such personality traits. Another review (Johns, 1973) suggests that the "long-term behavior arousal" associated with intense competitiveness interacts with such physical stressors as diet and cigarette smoking to produce coronary heart disease, noting, however, that the physiological mechanisms of this interaction have not been definitely established.

Statistical studies based mainly on questionnaires about subjective criteria and life habits lend credence to the "contention that a coronary-prone behavior pattern predicts the incidence of coronary heart disease in white males" (Wardwell, 1973). The decisive factor (again according to Wardwell) would appear to be that coronary candidates have an unusually strong tendency to manifest psychological and situational states in a variety of physical ways such as "restless activity, ambitious strivings, bodily symptoms of many different sorts, and pathogenic atherosclerotic and thrombo-

tic processes." (For another discussion of the coronary-prone personality, see Zyzanski and Jenkins, 1970.)

It was Friedman and Rosenman who most recently and convincingly called attention to these two types, and they deserve the greatest credit for having clearly delineated them. However, they themselves are the first to point out that, during the nineteenth century, Sir William Osler described a behavior pattern typical of coronary-prone patients. If we accept the tenet that stress, like emotional responsiveness, is equally dependent on life events and on our reactions to them, it is evident that admitting the distinction of Types A and B is essentially equivalent to admitting that stress, especially emotional stress, plays a decisive role in the pathogenesis of cardiovascular disease and is more influential in those who respond to a given event intensely (i.e., with severe stress) than in unresponsive, phlegmatic persons. Of course, this concept is also very compatible with the hormonal theory, in that the tense, excitable Type A person responds more readily with catecholamine and corticoid secretion than does the Type B person.

In a survey of the literature, Carruthers (1969) suggests that among the stressors of modern life, fear, hatred, aggression, and frustration increase catecholamine and particularly norepinephrine secretion as well as the plasma levels of free fatty acids and triglycerides. They also augment platelet adhesiveness and hence can lead to thrombosis. Carruthers adds the comment that "in modern society wrath, reinforced by sloth and gluttony, is the deadliest of the seven sins." Job satisfaction has also been claimed to be inversely related to death from coronary heart disease.

Such activities as driving and public speaking can cause significant biochemical alterations, even in normal persons; according to Somerville (1973) a statistical study shows that experienced drivers who have suffered from coronary heart disease are subject to "angina, sinus tachycardia, ectopic beats and various arrhythmias" when driving. On the other hand, "healthy racing drivers stimulated by the emotions of competition and danger, develop high-grade sinus tachycardia, raised plasma catecholamines and free fatty acids immediately before and after a race." Similar alterations are induced in normal persons by public speaking. Taggart and Gibbons (1971) go so far as to say that angina due to emotional stress, and borderline left ventricular failure, "should be contraindications to holding a driving licence."

For a discussion of the most common emotional stressors and dietary factors involved in coronary accidents, see Russek (1973); and for a review on the stressors of modern life that contribute to cardiovascular disease, see Boulard (1973).

It has been so indubitably established that psychogenic stress is a risk factor in coronary heart disease that the American Academy of Psychosomatic Medicine formulated a resolution in 1973 "that psychosocial stresses must be included among the recognized high-risk factors in myocardial infarction" and suggested "that the psychiatrist and psychosocial team be formally incorporated as an integral part of the Coronary Care Unit for every patient" (Lenzner, 1974). For a discussion of empirical findings on the prevention of coronary heart disease by protection against excessive psychogenic stress, see Turner and Ball (1974).

E. Conditioning

1. Genetics

Undoubtedly, genetic predisposition plays an extremely important role in coronary heart disease. Evidence for this was presented in the previous section, in which the constitutional types of predisposed and comparatively resistant individuals were delineated from the psychologic point of view, but various other risk factors—such as a tendency to excessive eating, smoking, high cholesterol and free fatty acid levels, accelerated blood coagulation and disinclination to exercise—are also largely dependent on inherited constitutional factors. According to a follow-up study of 3,182 men 39–59 years old (Rosenman *et al.*, 1970), CHD appears to run in families, as do hypertension, the smoking habit, high cholesterol, triglyceride and β-lipoprotein levels, and Type A behavior.

See Gertler and White (1954) for an excellent multidisciplinary study conducted at the Massachusetts General Hospital with the cooperation of several experienced cardiologists, reviewing the indices characteristic of the "coronary candidate" and the precipitating agents of CHD, including heredity, athletic activity, endocrine factors, diet, and blood biochemistry. See also Kruse (1960) for an extensive review by a committee on cultural, societal, familial, psychological, and genetic influences on the development of cardiovascular disease, with special reference to stress and the G.A.S.

2. Diet

The dietary factors that predispose to cardiovascular disease in general exert the same conditioning effect on stress-induced hypertension or CHD. The most recognized among these nutritional factors are the foods with high saturated fat content (mainly animal fat) and cholesterol. However, Russek (1967), from a careful survey of the literature and from personal observations, concludes that "the concept of any disease arising from a single cause is obsolete and misleading. Much evidence now suggests that

most of the lethalness of a high fat diet in Western society may actually be dependent on the 'catalytic' influence of stressful living." According to Russek, this is particularly true of CHD.

Excessive sodium intake is also harmful, especially in the presence of renal disease and hypertension, as is gluttony in general, because of the resulting adiposity, which makes increased demands on the circulatory system and at the same time augments the stressor effect of exercise.

For a discussion of the influence of diet on the development of cardiovascular disease, with special emphasis on nutritional factors determining predisposition to stress-induced experimental cardiac necroses, see Bajusz (1965).

Lipman (1960) gave a detailed description of a diet that was thought to alleviate stress-induced hypertension, especially when given in combination with an antihistaminic. Many other measures, such as life habits and exercise, have been recommended for the prevention of cardiovascular disease in man. Raab (1970) examines the interactions between corticoids, catecholamines, and diets, especially on the basis of corresponding animal experiments.

3. Occupation and Social Factors Including Urbanization

Statistical surveys show that the incidence of CHD has greatly increased during the present century, and that the relative immunity of primitive races disappears when they subject themselves to "civilized" life (Stewart, 1950). However, the effect on statistics of constantly improving diagnostic techniques and more accurate reporting of death from CHD must not be neglected (Master, 1960).

One study (Harburg *et al.*, 1973) in high- and low-stress areas of Detroit revealed that social and economic stressors definitely predisposed to increased blood pressure, especially among blacks.

According to Syme *et al.* (1964), geographically and occupationally mobile subjects have a higher CHD incidence than others. This may be ascribed to their need for more frequent readjustment and adaptation to new circumstances.

There is general agreement that urban life is more conducive to hypertension and CHD than rural settings (e.g., see Marks, 1967; Smith, 1967; Gutmann and Benson, 1971), but here again it is difficult to distinguish between the relative role played by crowding, differences in diet, occupations, air pollution, and so on.

In any event, the occupational stressors of industrial society appear to play a dominant role in the high incidence of CHD as well as in establishing a predisposition for it through a rise in plasma lipids, altered hemodynamics, and accelerated blood clotting (Rosenman and Friedman,

1958). Also, according to Russek and Zohman (1958), who studied 100 young coronary patients, "severe emotional strain of occupational origin was observed in 91% of the test subjects as compared with 20% of normal controls. Emotional stress associated with job responsibility appears far more significant in the etiologic picture of coronary disease in young adults than heredity or a prodigiously high-fat diet." The authors add the comment that smoking "would appear to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease." Another study (Russek, 1959) noted that in 91 of 100 patients, prolonged emotional strain related to occupational responsibilities preceded a coronary attack. Smoking was particularly frequent among coronary patients, but again the habit may be a manifestation of inner stress rather than an etiologic factor. Furthermore, much of our envied leisure time is regimented by participation in social, educational, and civic events that "may represent a poor antidote for the emotional stresses of daily business competition."

There is significant statistical evidence against the popular idea that the high responsibility of top management positions entails a greater risk of coronary disease or death. In 1958 Lee and Schneider were surprised to learn that, among more than 1,000 subjects in business, hypertension and cardiovascular disease (arteriosclerosis, CHD, myocardial infarction) were disproportionately low in the executive group. Another statistical study (Mortensen *et al.,* 1959) showed that

> in the Bell Telephone System there is no material difference in coronary mortality between the top management group and the craftsmen and laborers group, but there is a marked difference between top management and middle management which is not explainable from presently available data. The popular notion that high executive positions are associated with high coronary mortality is likely due to the greater publicity connected with such deaths rather than to statistical facts.

Again, in a 6-year study of 1,356 cases (Pell and D'Alonzo, 1963), the age-adjusted incidence of myocardial infarction among male employees was inversely proportional to their annual income.

On the other hand, an extensive study on postal and telegraph workers (Reeder *et al.,* 1973) indicated that "a relatively low job level was related to a relatively high number of EKG abnormalities. These latter findings may be predictive of future coronary artery disease in this group." One possible explanation for these data is suggested by the observation, based on statistical studies, that "job satisfaction is negatively related to a group's rate of death from coronary heart disease" (Sales and House, 1971). Moreover, Pell and D'Alonzo (1963), cited earlier, state that "the demands of a top-management job may be no more stressful than situations commonly encountered by persons in lower job levels, at work and at home," and that

men chosen for advancement may be those whose personal qualities are characteristic of both executive talent and resistance to coronary disease. It is conceivable, for example, that in selecting persons to assume greater responsibilities, supervisors and managers, knowingly or unknowingly, may tend to choose the better adjusted individuals, who by virtue of their personality and psychic state are better able to cope with life's stresses in general.

Lee and Schneider (1958), also cited earlier, note that "the disruption of the harmonious balance between a man and his environment can result from either the demands of the environment or the failure of the man to measure up to them. Success in a career goes hand in hand with good health. The executive, as part of his training, learns to judge the amount of occupational stress he can stand and to appreciate the value of outside avenues of expression."

Nevertheless, it should be kept in mind that other statistical studies give opposite results, which are attributed to the greater drive and willingness to accept stressful responsibilities among those who reach higher echelons. For example, one statistical study, which indicates a high probable correlation between CHD and social, cultural, and even religious factors, suggests that, although further proof is necessary, in the United States "coronary heart disease may be viewed as an alternative to certain personality disorders, particularly for native-born American middle class Protestants, who are culturally not permitted to be weak or to fail to compete successfully" (Wardwell *et al.,* 1964).

In an extensive epidemiologic study on 31,000 men in London (Morris *et al.,* 1953), CHD was found to be more frequent among those holding sedentary jobs. Bus conductors had less CHD than bus drivers, postmen less than telephonists, executives, and clerks. It is implied that these differences are determined by the amount of exercise required by their jobs. Extensive statistical studies among 12,000 members of 14 professional groups in the United States showed that CHD was strikingly related to occupational activity among physicians, lawyers, security analysts, and traders (Russek, 1965). Incidentally, these same studies disclosed that, though smoking was most frequent in stressful occupations, unexpectedly CHD was more common among nonsmokers than among persons who once smoked but gave it up. Possibly, "the ability to stop smoking may imply a resilient personality response to stress and diminished vulnerability to atherogenic influences."

According to Shirom *et al.* (1973), in Israeli kibbutzim, agricultural workers were most likely to experience stress associated with CHD, although the generally accepted predisposing factors among them did not significantly differ from those in managerial, professional, clerical, or factory workers.

In Japan the incidence of arteriosclerotic CHD is extremely low as compared to its incidence among the white North American population, says Matsumoto (1970). "Although the diet factor remains dominant in current thinking, the stress hypothesis merits the most intensive probing as alternate or associated explanations of observed relations and differentiations."

4. Age

Though it is a well-known fact that the incidence of arteriosclerosis and CHD increases with age, youth of itself is of course no guarantee of immunity. Extensive clinical and anatomical studies on coronary arteriosclerosis and cardiac infarcts in 866 patients 18–39 years of age, showed that a fatal coronary attack occurred most frequently during strenuous activity related to combat and other military duties (Yater *et al.,* 1948).

Rats exposed to stressors undergo changes similar or identical to those of the first step in the arteriosclerotic process characteristic of aging. For example, the emotional stress produced by restraint elicits typical mesenchymal reactions in the blood vessel walls with increased [^{35}S]sulfate and [^{3}H]thymidine incorporation (Hauss, 1973).

According to Kappert (1952), in juvenile hypertension, excess production of mineralocorticoids—which activate hepatic hypertensinogen formation and catecholamine secretion—is especially important; however, these findings have not yet been confirmed.

In the literature there is a general impression, not supported by convincing statistical evidence, that fatal CHD occurs more frequently among young people now than some decades ago.

F. Diagnostic Indicators and Other Changes Characteristic of Stress-Induced Cardiovascular Disease

It is virtually impossible in practice to separate diagnostic indicators from other changes characteristic of stress-induced cardiovascular disease that are not particularly helpful in diagnosis. Since all these also help to analyze the pathogenesis of such maladies, they will be discussed here conjointly.

1. Stress Tests

Tests used to evaluate the stress resistance of patients with cardiovascular disease are based mainly on resistance to muscular exercise. Techniques commonly used are the bicycle orgometer, the treadmill, and step tests; isometric exercises are especially useful in the evaluation of left ventricular function (Payne *et al.,* 1973; Helfant *et al.,* 1974).

"Stress interviews" and cold pressor tests also have some diagnostic value (Wolf *et al.,* 1955). Furthermore, in early hypertensive patients, psychogenic stress (e.g., arithmetic under time pressure) causes an unusual rise in pulse rate, blood pressure, blood glucose, oxygen consumption, muscular tone, plasma norepinephrine, free fatty acids, cortisol, and renin activity (Baumann *et al.,* 1973).

The SRE (Schedule of Recent Experience) questionnaire seems to correlate fairly well with coronary heart disease (see Ander *et al.,* 1974; Theorell and Rahe, 1974).

Both emotional and physical stress conditions considerably alter the ECG (Weiss, 1956; Sigler, 1961; Simonov *et al.,* 1975). Several instruments have been devised to determine ECG changes, often in combination with other indices, such as blood pressure variations, by telemetry while patients are exercising on a treadmill (Ellestad, 1967). For the interpretation of various stress-induced ECG changes, the reader is referred to Simonson (1970), So and Oversohl (1974), Amsterdam *et al.* (1974), and Hiss *et al.* (1960), as well as to the preceding references.

ECG responses to isoproterenol have been recommended for the evaluation of myocardial efficiency in preference to arteriography or the treadmill test; however, the claims behind this recommendation require confirmation.

2. Morphology

In patients who died from CHD following severe stress, there was extensive fuchsinophilic degeneration of the myocardium (similar to that seen in experimental animals during the electrolyte steroid cardiopathy with necrosis [ESCN]), indicating a necrosis "of metabolic origin" (Danilova, 1963). A review of the literature also suggested that various nonvascular noxious factors interfering with myocardial metabolism play a decisive role in CHD. This is true especially of the production of microfocal necroses that coincide with or aggravate the pathogenic effects of primarily vascular disturbances (Myasnikov, 1964).

"Stress polycythemia" is manifested by a normal erythrocyte mass, but a high hematocrit reading secondary to contracted plasma volume. This condition can be elicited by a variety of stressors and may be related to certain types of hypertension (Emery *et al.,* 1974).

Sosnierz and Wieczorek (1966) report that in 92 patients who died of various diseases, fuchsinophilic degeneration of the myocardium was constant among old people and absent in neonates; the intensity of fuchsinophilia was particularly high in patients who died under very stressful circumstances.

3. Blood Clotting

It is suggested by histologic evidence that the development of coronary thrombosis is often very gradual, taking several days before pain and occlusion become manifest. Therefore, events immediately preceding the attack are not of etiologic significance. "The pathologic appearances in a series of fatal cases of coronary thrombosis suggest strongly that excessive exercise and emotional stress are intimately concerned in the mechanism of coronary artery thrombosis" (Paterson, 1939).

The frequent lack of correlation between coronary thrombosis and myocardial infarction or "sudden coronary heart death," which was repeatedly emphasized in the earlier literature, has again been demonstrated on the basis of an extensive review. "In more than 50% of the examined acute-recent infarct and sudden coronary heart death cases, an acute-recent occlusion was not detected." In other patients it took place in an already almost completely stenotic vessel so that it could have little effect; hence special attention must be given to the "infarctoid myocardial necroses" such as have been produced in animals by combined treatment with steroids and stressors (Baroldi, 1969).

In conscious patients stressful procedures such as cardiac catheterization caused a rise in the platelet aggregation response to adenosine diphosphate, concurrently with an increase in plasma free fatty acids. It is suggested that catecholamines, released during emotional stress, may be responsible for enhanced platelet aggregation and the development of thrombosis as well as atherosclerosis (Gordon *et al.*, 1973).

In rats immersion in cold water causes platelet aggregation in myocardial vessels, as shown by electron microscopy. "It is concluded that stress, probably via catecholamine secretion that enhances platelet stickiness, can induce intravascular platelet aggregation. It is possible that this mechanism plays a part in the relationship between stress and acute clinical myocardial infarction" (Haft and Fani, 1973; see also Levites and Haft, 1974).

4. Hormones

There is practically no doubt today that hormones participate in the development of stress-induced cardiovascular disease. Evidence in favor of this view has come from observations in man and from animal experiments. Here we shall limit ourselves to clinical findings, since a special section is devoted to experimental cardiovascular diseases.

Since catecholamines liberated from sympathetic nerve endings and the adrenal medulla cause a dramatic rise in blood pressure, their role in hypertension has long been suspected, and the production of what we have called "mineralocorticoid hypertension" in DOC-treated animals has led to many

clinical studies on this and related steroids in patients with various forms of hypertension. [See *Experimental Cardiovascular Diseases* (Selye, 1970).]

The relevant literature has become too voluminous to be discussed here in detail; besides, a large part of it has already been analyzed in our earlier stress monographs (Selye, 1950, 1951; Selye and Horava, 1952, 1953; Selye and Heuser, 1954, 1956). Suffice it to say here that an increase in the plasma and urinary concentration of catecholamines, several mineralocorticoids (DOC, 18-OH-DOC, aldosterone), and renin has repeatedly, though not consistently, been noted in hypertensive patients (Raab, 1968; Palem-Vliers *et al.*, 1974; Esler and Nestel, 1973).

There is good reason to believe that both hypertension and CHD can be elicited during stress through a rise in the secretion of any of these humoral substances, and are often caused by the concurrent overproduction of several among them; one or the other can play the predominant role, depending on conditioning factors.

For a detailed discussion of hormonal participation in the pathogenesis of hypertension and other cardiovascular diseases, the reader must be referred to pertinent reviews and monographs, but it may be useful to summarize at least a few of the more salient facts.

Evidently, catecholamines and corticoids mutually enhance each other's pressor effects, and the hypertensive actions of mineralocorticoids are augmented by a high sodium intake. The latter also predisposes the kidney to damage, especially by mineralocorticoids, including renin-stimulated mineralocorticoid secretion. Thus a vicious circle may develop in which mineralocorticoids elicit renal injury and the resulting rise in renal pressor substances augments mineralocorticoid secretion, which further damages the kidney until fatal malignant hypertension ensues.

In predisposed persons almost any kind of stressor causes a rise in blood pressure as well as in catecholamine and corticoid secretion (Raab, 1966); furthermore, the therapeutic efficiency of both adrenergic blocking agents (e.g., propranolol) and antimineralocorticoids (e.g., spironolactone) supports this hypothesis (Kimura, 1974). It is still difficult, however, to explain the occasional instances of hypertension in which the blood level of renin is subnormal. According to some investigations, this "hyporeninemic hypertension" is probably a pluricausal disease of variable etiology, often dependent on increased production of some mineralocorticoid that decreases renin secretion (Distler, 1974).

A prolonged increase in blood pressure undoubtedly damages the vessel walls and contributes to the development not only of arteriosclerosis but even of the hyalinizing arterial lesions characteristic of malignant hypertension and periarteritis nodosa. All of this presumably can enhance the narrowing of cardiac arteries, and by damaging their endothelium, eventually

results in thrombosis. The latter is further facilitated by the well-known decrease in blood-clotting time produced by catecholamines.

Nevertheless, an increasing body of evidence suggests that many types of myocardial necrosis are not due to coronary thrombosis but to metabolic necroses of the myocardium in which corticoids and sodium play decisive roles, as we shall see in Section G, "Experimental Cardiovascular Diseases." Furthermore, not all cases of sudden death produced by acute stress are due to myocardial necrosis; they may be of purely functional origin (e.g., ventricular fibrillation).

5. Nonhormonal Metabolites

The nonhormonal metabolic changes associated with stress-induced cardiovascular disease are often those characteristic of stress itself, such as a rise in serum FFA and cholesterol (Hammarsten *et al.,* 1957; Jolliffe, 1959; Wolf *et al.,* 1962); these changes are highly subject to the conditioning influence of the diet (Bajusz and Rona, 1972). Allegedly, hypertensive patients also tend to have especially high adrenal cholesterol levels.

In a study of the relationship of cholesterol levels to certain habit patterns under stress, a questionnaire showed marked individual differences in responses among medical students exposed to various psychogenic stressors. The blood cholesterol levels usually increased, but the reverse also occurred occasionally.

> Subjects in the lower cholesterol group more often reported loss of appetite, exhaustion, nausea and anxiety when under stress; in addition, urge to be alone, tremulousness and depression were more frequent than expected, although these items only approached significance. The only item with a significant positive relationship to higher cholesterol levels was urge to eat [Thomas and Ross, 1963].

In another study the highest adrenal cholesterol concentrations were found in patients who committed suicide and in hypertensives, being much above those of persons who died in accidents (Hoch-Ligeti, 1966). Presumably, in both cases the changes are related to stress.

G. Experimental Cardiovascular Diseases

I shall limit myself here to a brief mention of the most salient facts and the citation of a few key references, since work on the role of stress in the production of experimental cardiovascular diseases has been reviewed extensively in the two-volume monograph *Experimental Cardiovascular Diseases* (Selye, 1970). It may be said in essence that, depending on conditioning factors (particularly previous exposure to stress, age, genetic predisposition, the hormonal and nutritional status of the subject), stress may produce

or inhibit the development of cardiovascular diseases, but it almost always influences their course in some respect.

Most of the experimental work in this field has been done to establish the role of stress, or of hormones produced during stress, in *hypertension* with the associated renal and cardiovascular lesions. These include *arteriosclerosis* (of both the atheromatous and the purely calcifying type), and myocardial necroses (caused either by vascular occlusion or by disturbances of cardiac metabolism). It may be said that malignant hypertension with *hyalinizing* cardiovascular and renal disease is most easily reproduced in rats by chronic stress on high sodium diets, especially after sensitization by uninephrectomy. Indeed, in unilaterally nephrectomized rats kept on high-sodium diets, mineralocorticoids (deoxycorticosterone [DOC], aldosterone), somatotropic hormone (STH), or methylandrostenediol (MAD, which probably causes the adrenals to produce mineralocorticoids) easily induce such lesions by themselves, without exposure to stress.

Corticoids undoubtedly play a decisive role here, and a mutual feedback mechanism exists between mineralocorticoids (particularly aldosterone) and the renal pressor system in that renin stimulates aldosterone production whereas aldosterone inhibits renin secretion. This interplay helps to maintain pressor homeostasis under ordinary conditions. However, if the feedback mechanism is defective and intense nephrosclerosis is produced, the blood pressure rises to a level where it further damages the kidney and a vicious circle develops. Possibly, some corticoids can induce nephrosclerosis and hypertension without raising renin production ("hyporeninemic hypertension"); thus the rise in blood pressure is deprived of its self-inhibitory properties and becomes self-perpetuating and independent of renin.

Although this mechanism is far from being adequately proved by experimental evidence, it is obvious that the adrenal cortex plays a decisive role in the production of many types of hypertensive disease. Thus in adrenalectomized rats kept on a fixed dose of glucocorticoids just sufficient to maintain life, neither stress, MAD, nor STH can exert their usual hypertensive, vasotoxic, and nephrosclerotic effects, even if the animals are maximally sensitized by uninephrectomy and a high sodium chloride intake. Yet in adrenalectomized rats, under similar conditions, exogenous mineralocorticoids retain their pressor vasotoxic and nephrotoxic actions. Therefore it is postulated that stress, MAD, and STH do not act on the vascular system directly, but through the intermediary of the adrenals, in which they stimulate the synthesis of mineralocorticoids under certain conditions.

The so-called *adrenal regeneration hypertension* (ARH) has furnished us with another convenient tool for studying mineralocorticoid hypertension and proving that the production of excessive or abnormal adrenal corticoids

may cause hypertensive disease. If one adrenal is removed and the other "demedullated" (an operation that also removes virtually the entire cortex except the glomerulosa), nephrosclerotic hypertension develops with vascular lesions that are indistinguishable from those produced by DOC. Unilateral nephrectomy in rats on a high sodium chloride intake sensitizes for this effect, just as it does for the comparable actions of mineralocorticoids. There is much evidence supporting the view that in rats subjected to this operation, the regenerating adrenal cells of the subcortical layer produce an excessive amount of DOC and related steroids which have a high vasotoxic effect.

The pressor actions of catecholamines are transitory and hardly ever conducive to self-perpetuating nephrosclerotic hypertension. Epinephrine and norepinephrine are effective even in the absence of the adrenals, but appear to potentiate the characteristic vasotoxicity of mineralocorticoids and hence probably play an important part in stress-induced hypertensive disease. Their increased secretion during stress may also raise the coagulability of blood and thereby predispose to stress-induced occlusive vascular thrombosis.

Infarctoid Necrosis

The electrolyte steroid cardiopathies with necrosis (ESCN) are produced in experimental animals, particularly in rats, by the conjoint administration of glucocorticoids and mineralocorticoids, or by steroids (e.g., fluorocortisol) that exert both gluco- and mineralocorticoid actions, but only if this treatment is combined with a high sodium diet or with exposure to sudden stress. A great variety of stressors have proved effective in eliciting this manifestation after conditioning with corticoids and sodium. On the other hand, diets poor in sodium or rich in potassium and/or magnesium, as well as potassium-sparing agents (spironolactone, amiloride) protect against this type of cardiac lesion. Many of these experimental observations have found clinical application in the therapeutic use of low-sodium, high-potassium, or high-magnesium diets, spironolactone and amiloride for cardiovascular disease.

It is also of interest that high-fat diets are particularly effective in causing cardiac necroses in rats pretreated with appropriate corticoids and high-sodium diets. In this respect they may replace stressors.

Finally, it should be mentioned that in rats under identical conditions, acute exposure to stress (forced muscular exercise, restraint, traumatic injuries) *may produce or prevent cardiac necrosis,* depending on circumstances. Gradual pretreatment with stressors, especially forced muscular exercise, can protect the fully conditioned rat (essentially a "coronary candidate")

against the induction of cardiac necrosis by a subsequent extremely severe stress.

These findings further suggest close relationships between the experimental cardiopathies and their clinical equivalents. They may explain the long-puzzling paradox that exercise is considered to be dangerous and also to be of prophylactic value in patients prone to cardiac infarction. Presumably, keeping fit through gradual, comparatively mild exercise induces considerable resistance, whereas sudden extreme muscular effort may precipitate a cardiac accident, especially in persons used to sedentary life and unadapted to muscular effort.

It must be kept in mind, however, that unlike many patients who die from acute coronary accidents, the ESCN of the rat is not primarily due to coronary thrombosis, but to metabolic derangements in the cardiac muscle that predispose it to necrosis at times of increased demands for work. Only secondarily do thromboses tend to develop in necrotic areas of the heart, where the endothelium of the coronary vessels has lost its anticoagulant properties. In this connection, it is of particular interest that several investigators observed an inverse relationship between the incidence of detectable coronary thromboses and the rapidity with which a patient died after clinical manifestations of a heart attack. It has been deduced that probably sudden cardiac death in man is often due primarily to myocardial necrosis and that the occlusive thrombus develops only secondarily in the dead myocardial region. (See *The Chemical Prevention of Cardiac Necroses,* Selye, 1958.) So-called fuchsinophilic degeneration frequently precedes myocardial necrosis in man (as indicated by histologic investigations in patients who died very suddenly after an accident) and in experimental animals during the ESCN.

For the literature on each separate point, the reader is referred to *Experimental Cardiovascular Diseases* (Selye, 1970) and to the references listed and abstracted under separate headings in the encyclopedic treatise *Stress in Health and Disease* (Selye, 1976).

H. Prophylaxis through Coping with Psychogenic Stress

It may be worthwhile here to outline a model for coping with psychogenic stress, since stress-induced cardiovascular disease is evidently such a widespread danger in modern society. We may extend ourselves beyond our field of expertise in so doing, but the gap between the different disciplines that may have an effect on man's well-being needs to be bridged, and the results of basic work on stress should be made available. The following discussion is based on an article that has appeared in Spanish (Taché *et al.,* 1977).

1. Homeostatic Imbalance

Ever since Claude Bernard developed the concept of the *milieu intérieur* and Walter Cannon (1939) coined the term "homeostasis" to refer to the fluid stability of the *milieu intérieur,* scientists have used the notions—knowingly or not—to explain many phenomena that extend well beyond the limits of traditional physiology. We like to express man's daily encounter with the environment in terms of homeostasis. Since harmony within the internal milieu and with the external environment conditions survival, the individual fights to preserve or restore it. An event in the environment becomes a stimulus—or a stressor—whenever an individual's homeostatic equilibrium is disrupted by it.

Homeostasis can be endangered and restored with or without the participation of consciousness. For instance, on the physical level an important loss of blood is countered by vasoconstriction to help maintain adequate arterial tension. On the psychological level, however, stimuli are much more subject to interpretation by the individual. Man's needs being more complex than those of an amoeba, his network of communication with the environment is correspondingly much more elaborate, and the nervous system fulfills this function. Usually the brain is seen as an organ of thought that enables man to philosophize or enter into other highly regarded intellectual activities, but to a biologist the prime function of the nervous system is to allow the individual to deal with his environment, that is, to bring about perception and evaluation of events that may affect his well-being or survival and also to elicit certain types of activity to reestablish harmony when it has been lost.

2. The Adaptive Process

When the body has to adapt to an external event (Fig. 3), perception and interpretation of the stimulus lead to an assessment of the phenomenon and its implications; this may be considered the "input." On the other hand, specific responses are tested, and one or many will be chosen and utilized; this is the "output." If the response is adequate to the challenge, adaptation will follow as the stimulus is dealt with or a new level of homeostasis is reached.

Evaluation of the demand is based partly on an individual's background—genetic make-up, natural capacities, basic education, recent experiences—which he uses as points of reference in assessing the significance of the stimulus. These factors are in a way the cast that will mold certain events to become stimuli or the diffracting crystal that will give special colors to our experiences. The importance of such endogenous and exogenous factors is indicated in Fig. 3.

The behavioral responses may be somatic, intellectual, or emotional.

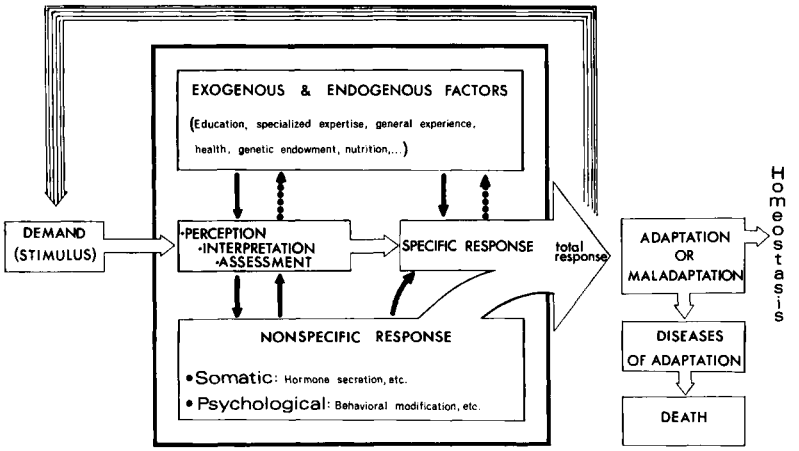


Fig. 3. Dealing with stressors usually entails finding the right specific response to the demand. Since endogenous and exogenous factors preside over the stimulus-to-response process, assessment may be modified by bringing a new outlook, by analyzing the situation from a different viewpoint. The nonspecifically secreted hormones are also meant to play a role in preparing for the specific response phase, but with man's evolved neocortex and with the variety of specific responses now available, these hormones may not help him to cope well with certain aspects of his environment. Dotted arrows indicate possible feedback.

Physiological reactions may arise all along the process, starting with perception; the intellectual response depends on individual predisposition, experience, and expertise, and these can be abetted through learning; the emotional arousal may begin with a growing awareness of the magnitude of the demand and subside once a specific countermeasure has been chosen.

These diagrams are very simple and do not comprise the various phases leading to assessment or specific responses. In reality, many feedback loops exist, through which requests may be made for additional information on the nature of the stimulus and the circumstances surrounding it, and a decision on a specific response may be arrived at after much internal dialogue and testing of possibilities. For the sake of simplicity, these details are not included here, since they are not essential for our discussion.

Stress (the nonspecific response of the body) is initiated at a very early stage: in fact, nonspecific physiological adaptation starts as soon as the body becomes aware of a demand (which could be physiological as well as psychological). The nonspecific response grows with the magnitude of the demand; moreover, if for some reason (such as internal conflict or lack of experience) the specific response is not easy to elicit, the stimulus-to-response process will be slowed down or stopped, and stress will increase

while evaluation of the situation is prolonged, and while tentative, inadequate reactions are probed.

3. The Cost of Stress

The price that one has to pay for such unresolved situations may be quite significant. The psychological distress that usually accompanies internal conflicts is by no means the whole price; secondary physiological modifications may also occur in the body. Stress hormones (e.g., ACTH), of course, are secreted in response to a demand, and, as we have seen, may predispose to cardiovascular derangements; as well, the anterior hypophysis discharges other hormones that control various functions: FSH (follicle-stimulating hormone) and LH (luteinizing hormone), which in women regulate the sexual cycle and in men are responsible for the secretion of the male hormone, testosterone, and the development of spermatozoa; prolactin, which is involved in maintaining pregnancy and stimulating milk secretion after childbirth; and GH, the growth hormone.

In our experiments with rats, it was shown that, during prolonged and intense demands (immobilization), stress hormone concentrations are elevated well above normal values (Fig. 4). (Corticosterone was measured instead of ACTH for practical reasons, but the secretion of these two hormones is known to run parallel during stress.) Other pituitary hormone concentrations fall drastically (GH values drop below 40% of the norm within 24 hr) and, on the whole, stay around the 50% level until the 15th day (Taché *et al.*, 1976).

4. Coping Mechanisms

Stress nowadays is not so much associated with physical survival as with a certain idea of survival. Society has identified new values that have been tagged as "necessary for survival," and in this "game," part of the nonspecific response is needlessly elicited. Sitting for an exam, applying for a job, the climate of competition using money and power as criteria of success—these are some of today's stressors that elicit the old physiological response in preparation for physical activity.

Broadly speaking, coping with stress in our society can be accomplished by (a) removing stressors from our lives; (b) nullifying potential stressors; (c) finding adequate specific responses in dealing with conditions we cannot or do not want to avoid; and (d) relaxing or finding diversion from the demand.

a. Removing Stressors

In some cases at least it would be easier to adjust social conditions to man's needs than to force him to waste his energy trying to adapt to changes

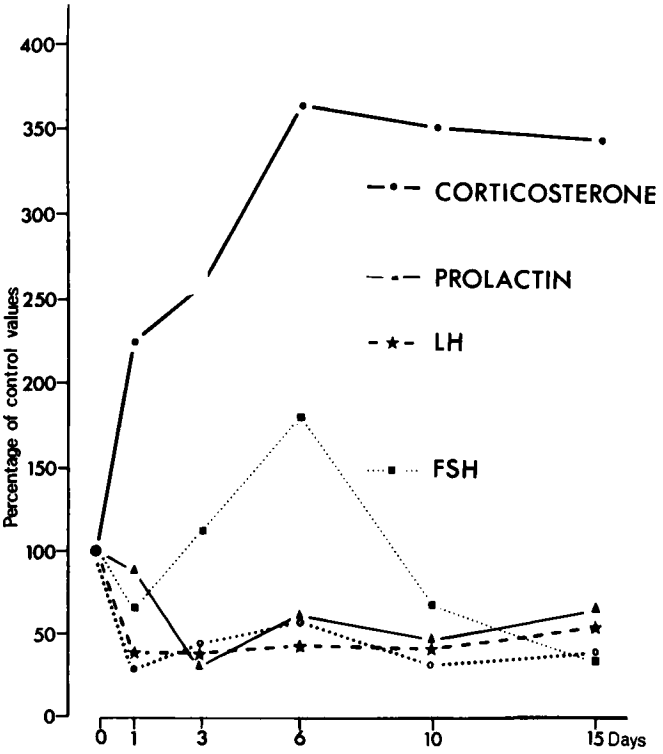


Fig. 4. Effect of chronic immobilization (8 hr daily during 1, 3, 6, 10, or 15 days) on the plasma levels of some sex hormones and the growth hormone in female rats: corticosterone, prolactin, luteinizing hormone (LH), growth hormone (GH same as STH), and follicle-stimulating hormone (FSH). (Tache *et al.*, 1976, by permission.)

in the environment that are of his own making anyway and that he could easily modify. Think of the uselessness of daily traffic jams, overpopulated housing projects, the irrelevance of much of our schooling. When society has a choice in determining certain parameters of the environment, it should not disregard certain needs of man that have been forgotten in recent times: the need to relate, to communicate, to exercise physically, and so on.

b. Nullifying Potential Stressors

Modifying one's perspective of things is an effective individual way of coping with stress. Very often, severe stress is induced unnecessarily, as there is no correspondence between the objective import of an event or circumstance (e.g., the boss's remarks) and the significance attached to it

(the secretary's interpretation). It is not so much *to what* we react as *how* we react that is at the root of the problem.

Allergy is a parallel case in the field of pathology. Although most people will not react to common allergens, certain individuals will mobilize important immunologic defense mechanisms against them. In this case it is not the allergens (what they react to) but the response itself (how they react) that is the cause of disease. The allergen is not injurious to their health per se, but only through provoking unnecessary defense reactions. Taking an exam does not have the same survival significance as living through an epidemic or, as with prehistoric man, facing a pack of wolves. Yet we have not learned to respond in a different way to modern stressors.

Though man will always strive for values, his value system needs constant rethinking. For example, competition is not of the making of our society; it is a law of Nature, a condition of survival. Man has always competed against animals and other men for food, possession of territory, or shelter for his family. But these are basic necessities; without them man's survival is impossible. Today the problem seems to be that nonessentials are now proposed to man as being basic. From the two-family house of some years ago, we have evolved to the two-house family, which in itself would not be bad were it not for the fact that it has now become an "essential," a criterion of success. A new set of values needs to be proposed to man so that the inborn urge to compete will be more usefully gauged to the weight or consequence of the goal.

c. Finding Adequate Specific Responses

In all cases where an event has become a stressor, an adequate specific response elicited as rapidly as possible will relieve stress. Barring quantitative overload, stress levels will decrease as one becomes an expert, develops the tools of the trade, and learns how to use them. In other words, when the capacity to elicit the specific response has been developed, the demand will be assessed differently. A typical case is that of a woman who once told us that she spent three days (and nearly as many nights) writing her first letter as special assistant to a deputy minister, but that now she could write important letters without becoming personally involved.

d. Relaxing or Finding Diversion from the Demand

Relaxation is not as easy to achieve as is commonly believed. After a hard day's work, even highly trained persons will find that tension has accumulated and that they feel tired; although apparently the demand is no longer present, the mind and body keep responding to it.

Yet it is often said that if you can relax your muscles, the psychological cause of your tension will tend to disappear, and we cannot but be im-

pressed by the number of persons who praise the numerous techniques now being publicized that are based on this idea, such as Transcendental Meditation (Bloomfield and Kory, 1976), the Relaxation Response (Benson *et al.*, 1974), Autogenic Training (Luthe, 1969), Transactional Analysis, Yoga, and even some kinds of physical exercise that induce relief from tension. Although such techniques do not seem to work equally well for all, it may still be worth the time and effort to take a close look at them.

5. Priorities for Coping

Reducing stress sometimes entails refusing to be placed under stress and, up to a point, refusing to meet challenges. Regular hours, good eating habits, physical exercise, and physical withdrawal from stressful situations are reported to be associated with fewer stress symptoms than other, more result-oriented techniques such as a change to a different work activity or a new strategy of attack on work (Howard *et al.*, 1975).

We have to realize clearly that work is a biological necessity. Just as our muscles become flabby and degenerate if not used, so our brain slips into chaos and confusion unless we constantly use it for some work that seems worthwhile to us. This in itself, as we have discussed, can cause significant psychogenic stress.

The great Canadian physician William Osler recognized the significance of work in this tribute:

> Though little, the master word looms large in meaning. It is the 'open sesame' to every portal, the great equalizer, the philosopher's stone which transmutes all base metal of humanity into gold. The stupid it will make bright, the bright brilliant, and the brilliant steady. To youth, it brings hope, to the middle-aged confidence, to the aged repose. It is directly responsible for all advances in medicine during the past twenty-five years. Not only has it been the touchstone of progress, but it is the measure of success in everyday life. And the master word is WORK.

We have all heard the sayings, "There is more to life than just work," or, "You should work to live, not live to work." These sound pretty convincing, but are they really? Our principal aim should be not to avoid work but to find the kind of occupation that, for us, is play. The best way to avoid harmful stress is to select an environment (wife, boss, friends) that is in line with our innate preferences—to find an activity we like and respect. Only thus can the need for frustrating constant readaptation that is the major cause of distress be eliminated.

Stress is inseparable from life. In prehistoric times it was the price that man had to pay to survive as an animal; now he pays the same price to accomplish what he considers great things. Those who are convinced that mere physical survival is not enough for them, must realize that there should be a proportion between what they *want* to do and what they *can* do,

between the significance of the challenges they rise to meet and the price they will have to pay as a consequence, and their goals and priorities should be established accordingly.

6. A Code of Behavior

It is my belief that practical recommendations such as the preceding can be expressed as a scientifically based code of ethics. In the light of what my own laboratory and clinical study of somatic diseases has taught me concerning stress, I have tried to arrive at such a code, that is, one based not on the strictures and traditions of society, inspiration, or blind faith in the infallibility of a particular prophet, religious leader, or political doctrine, but on the verifiable laws that govern the body's reactions in maintaining homeostasis and living in satisfying equilibrium with its environment. I would summarize its most important principles briefly as follows:

a. FIND YOUR OWN STRESS LEVEL

The speed at which you can run toward your own goal. Make sure that both the stress level and the goal are really your own, and not imposed on you by society, for only you yourself can know what you want and how fast you can accomplish it. A turtle cannot run like a racehorse, nor can a racehorse be prevented from running faster than a turtle. The same is true of people.

b. BE AN ALTRUISTIC EGOIST

Do not try to suppress the natural instinct of all living beings to look after themselves first. Yet the wish to be of some use, to do some good to others, is also natural. We are social beings, and everybody wants somehow to earn respect and gratitude. You must be useful to others; this gives you the greatest degree of safety, because no one wishes to destroy such a person.

c. EARN THY NEIGHBOR'S LOVE

This is a contemporary modification of the maxim "Love thy neighbor as thyself." It recognizes that not all neighbors are lovable and that it is impossible to love on command.

Perhaps two short lines can encapsulate my philosophy:

Fight for *your* highest *attainable* aim,
But do not put up resistance in vain.

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