SYMBOLIC stimuli are those that derive their force not from their intrinsic qualities but from their significance to the individual. Cardiovascular symptoms, disability, and death may result from alterations in a wide variety of bodily mechanisms that regulate cardiovascular function. The bodily structures responsible for these alterations include the hypothalamus and other parts of the brain, the pituitary gland and its subsidiaries, the thyroid and adrenal glands, the kidney, and possibly other viscera, such as the liver, the heart, and the blood vessels themselves. There is a growing body of evidence that all these structures are connected with, and capable of, reacting to excitation in the interpretive areas of the brain.

It is likely that a variety of cardiovascular disturbances occur in relation to stressful life experiences from day to day and even many times a day without producing discomfort. Only when pronounced or sustained do such changes become clinically important.

DIRECT EFFECTS OF STRESS

In the category of disorders directly attributable to a stressful situation may be classified "voodoo death" or sudden death in healthy individuals as seen from time to time in our own culture. There has been some difference of opinion among investigators as to whether such effects were attributable to massive sympathetic or to parasympathetic discharges. Cannon\textsuperscript{1} took the former view but more recently the experiments of Richter\textsuperscript{2} indicate that heart slowing as a result of vagal stimuli may be the important factor with the ultimate production of ventricular fibrillation. Richter was able to produce such vagal effects experimentally in rats who were placed in a tank from which they could not escape and in which they were made to swim indefinitely. It is interesting that survival among these rats was greatly reduced when their orienting mustache hairs were cut off, thus putting them into an even more unaccustomed "terrifying" and presumably hopeless situation. Richter further noted that wild rats did not survive this ordeal as well as did the domesticated rats, who had been accustomed over the generations to the arduous buffetings of the experimental laboratory. A comparable observation in a human being was made by Fuqua\textsuperscript{3} who was on duty in a field hospital during the war in Korea. He was examining a marine with symptoms of influenza and, after listening to the breath sounds with his stethoscope, Fuqua said "now stop breathing" as he began to listen to the heart. With that the marine's heart suddenly stopped and he fell to the floor pulseless and remained asystole for approximately 1 minute with no real effective pulsation for at least 2 minutes. Further contributory evidence in human beings was gathered by Furman\textsuperscript{4} in the course of the examining of the hearts of soldiers at the time of induction into the military service. The long line of recruits came for their cardiovascular examination immediately after a blood sampling syringe was withdrawn from their veins. He thus caught many subjects almost in the process of fainting and indeed caught some of them as they were keeling.

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over and falling to the floor. Prompt examination revealed pulse rates in the low 40s and blood pressure that was almost unobtainable. Although many recruits showed tachycardia, those who fainted displayed uniformly a vagal pattern. The basis for such reactions is not clear but certainly anxiety is too simple a psychodynamic explanation for these facts. The soldiers found themselves in many anxiety-producing situations from time to time without fainting. Whether or not there is a special, subtle, and largely unconscious threatening significance in having a pierced skin has never been adequately explained. The experience of snake bite may be somewhat akin to needling in a doctor's office. In any case, herpetologists and those familiar with snakes and snake bites hold that about 85 per cent of sudden deaths that follow snake bite cannot be explained on the basis of the quantity of venom inoculated. Sometimes sudden deaths occur following the bite of nonpoisonous snakes and often a poisonous snake responsible for the bite is not large enough to deliver a lethal dose of venom. Likewise many instances of drowning may be attributable to excessive vagal effects on the heart rather than to asphyxia. According to Kunkel,\textsuperscript{5} water polo players who are prevented from getting to the surface of the water in competition develop a technic of losing consciousness so that they sink to the bottom of the pool whence they are quickly extracted and readily revived to continue on with the game.

The occurrence of various arrhythmias in association with emotional stress is familiar to most clinicians. It is not widely recognized, however, that such disorders as atrial fibrillation and ventricular tachycardia may be induced in apparently normal hearts by circumstances that have a stressful meaning to the individual. Such changes are illustrated in figures 1 and 2 and are reported in detail in a separate publication.\textsuperscript{6}

**Stress as an Aggravating Factor**

The second general category of disturbances attributable to stress are those that contribute to or aggravate disability in patients with already damaged hearts or compromised circulations. Among such mechanisms that are susceptible to alteration by stimuli emanating from the interpretive areas of the brain are, in addition to rate and rhythm, cardiac output, peripheral resistance, and hence the mechanisms that govern the work of the heart. Electrocardiographic changes, especially involving the T waves and similar to those induced by exer-
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It has been shown, however, with appropriate documentation, that hemodynamic changes productive of elevated arterial pressure, reduced renal blood flow, and increased blood viscosity occur as a part of an individual's adaptation to problems and challenges in his daily life.\(^6\)\(^,\)\(^11\) Special attention has been directed to 2 contrasting patterns of hemodynamic adjustment that occur alike in hypertensive and normotensive individuals under stress. One pattern appears to be identical with the "exercise" pattern, which is characterized by an increase in blood pressure attributable to a rise in stroke volume without elevation of peripheral vascular resistance. The other pattern resembles that encountered in injury or hemorrhage. It is characterized by an increase in blood pressure attributable to an elevation in peripheral resistance without a rise in stroke volume. When observed during interviews that deal with pertinent personal conflicts, the "exercise" pattern was manifest when emotional disturbance was relatively overt, while the "high resistance" pattern was more often encountered with a calm exterior and evidence of suppression or repression of emotion.

In essential hypertension there occurs a sustained increase in peripheral resistance without a rise in stroke volume. There was not, however, a significant difference between hypertensive and normotensive subjects in reactions to short-term stressful situations. Neither was there any correlation between an individual's response to interview and his reaction during a cold pressor test or between the type of vascular reaction to stress and the degree of vascular damage as reflected by the eyegrounds, heart size, or kidney function.

Further experimental studies have shown that the renal vasculature shares in the circulatory response to stressful events in the life situation. A decrease in effective renal plasma flow and an increase in filtration fraction occurred in both hypertensive and normotensive subjects during a discussion of pertinent personal conflicts.
It was particularly notable that the mechanisms of the vascular apparatus responsible for raising the blood pressure in response to symbolic stimuli were not impaired by thoracolumbar or even "total" sympathectomy. Either the "exercise" or "high resistance" pattern might still occur, although no longer was there evidence of associated reduction in renal blood flow. It is conceivable that the loss of renal vasoconstrictor activity may protect the kidneys and thereby have a salutary effect on the course of essential hypertension. Perhaps, it may be a factor in the apparent increased survival of sympathectomized patients even without notable reduction of arterial pressure.

The significance of all these findings is not clear but there is nothing incompatible with the view that the life adjustments in individuals with essential hypertension involve initially renal ischemia which may in turn set off a variety of endocrine and other humoral mechanisms with the ultimate development of irreversible tissue damage. In any case it is clear that stressful life experiences are sufficiently prominent among stimuli to elevated arterial pressure to warrant their serious consideration in the clinical management of patients with essential hypertension. The evidence of emotional restraint and the calm exterior often displayed by these patients make it necessary for the physician to exercise special diligence and skill in uncovering meaningful life experiences and the attitudes and reactions associated with them.

A study of personality adjustment among the patients with hypertension did not delineate any characteristic personality "type," but yielded strikingly similar data as regards values, attitudes, and way of life. By and large the hypertensive subjects had grown up feeling the need to excel but at the same time to avoid conflict or too vigorous self-assertion. These strivings, often opposed as they were, led frequently to dilemmas and were manifest, by wary, tentative, and non-committal attitudes with respect to important interpersonal relations and major endeavors in life.

In the author's series 12 per cent of hypertensive patients under psychotherapy lost all evidences of hypertension. These individuals appeared to have developed a more confident and relaxed approach to life, a more optimistic outlook, and an improved capacity for self-assertion.

It is probable that most adaptive functions of the cardiovascular system are responsive to stimuli that owe their force to their special significance to the individual. Thus, like disorders of the gastrointestinal tract, cardiovascular disorders can probably be contributed to or perhaps actually initiated by stressful life situations as well as by antigens, microorganisms, nutritional, climactic, and traumatic stresses. The alterations in renal blood flow that have been induced in human subjects, both normotensive and hypertensive, by introducing stressful topics for discussion are probably germane to the problem of essential hypertension. Such stressful interviews have also been shown to induce an increase in blood viscosity and shortening of the blood clotting time as measured in vitro. Thus the circulatory adaptations that may accompany emotional stress may have far reaching metabolic effects and may compromise circulatory efficiency in those with already existing cardiovascular damage. There has even been speculation concerning the possibility that the stresses and strains of daily life may enter into the mechanism responsible for coronary arteriosclerosis. Currently there is an interesting possibility that the concentration of lipids in the blood may be relevant to the pathogenesis of atherosclerosis and coronary artery disease. The studies of Groover, Friedman and Rosenmann and Hammarsten and his associates have given evidence that the lipid-regulating mechanisms are responsive to situational stresses. The latter studies were undertaken on 12 men ranging in age from 30 to 70. They all had well-documented evidence of myocardial infarction. These individuals were followed at weekly intervals with chemical determination of serum cholesterol, lipid phosphorus, and lipoproteins as estimated by the ultra-
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centrifugal technic. At the same time, each subject kept a written record of everything he ate each day at meals and between meals. The dietary records were later analyzed and roughly quantitated in terms of caloric content and proportion of fat, carbohydrate, and protein in the diet. In addition, the subjects were weighed each week and were carefully interviewed concerning events of the week and their attitudes and reactions to potentially stressful situations. Following the interview the investigator recorded a judgment concerning the presence or absence of significant stress during the week and an estimate of its degree. These data were, of course, gathered and recorded entirely separately from the chemical measurements. Later correlation showed that unusually high cholesterol concentration, more than 15 per cent above the mean, for any individual in the study correlated with a high degree of significance with periods that had been separately judged as especially stressful. Similar correlation was found in the lipoproteins of the Sf 0-12 and Sf 12-20 fractions.

PHYSIOLOGIC RESPONSE "AS IF"

Most individuals who see a cinder in the eye of another begin themselves to lacerate as if there were a cinder in their own eye. A hungry person who sees or even thinks about a delicious meal may salivate and may indeed pour forth increased amounts of acid gastric juice. Another example of the physiologic response "as if" was observed in a study of cardiac output in response to exercise. It soon became evident that it was unnecessary to exercise the subjects in order to induce the characteristic hemodynamic adjustments. They could readily be called forth by the mere discussion of exercise.

Energy requirements for particularly vigorous exertion are presumably supplied by fat mobilization and metabolism. In a large group of untrained adult males ranging in age from 22 to 51 years, Clarke and Balke found that total serum cholesterol rose during exercise and remained high throughout the exercise interval but quickly fell to resting levels after cessation of exercise. Steiger and associates have identified a lipid-mobilizing factor, which is secreted by the pituitary gland in response to starvation, muscular exertion, and to situational stresses. It thus appears that the lipid mobilizing mechanism may be responsive to impulses that emanate from the interpretive areas of the brain and that derive from stimuli which owe their force to their meaning, a physiologic response "as if" great muscular effort were required.

The studies of Hanmarsten and his associates indicated that the patient with coronary artery disease was oriented to life along the line of effort, of doing things "the hard way." The patients placed an especially high value on doing things "on their own," and being solely responsible for their activities and experiences. Like Sisyphus they appeared to be continually carrying a burden and never quite getting it to the top of the hill or the resting place. The occurrence of coronary attacks appeared to correlate with periods when the individuals were carrying an especially heavy emotional load. It may be that in these individuals the mechanisms that govern the concentration of the serum lipid are brought into play in the face of a demand for effort that is figurative as well as literal. Such a theory would tend to explain the favorable results reported by those cardiologists who actually encouraged their coronary patients to engage in vigorous muscular effort.

At the present time the inference is a speculative one that hypercholesteremia in some instances may represent a stress reaction with the individual reacting to a threatening life situation inappropriately, as if great muscular effort were being called for. Notwithstanding such speculation, it is evident that the work of the heart cannot be estimated with any degree of accuracy with reference to the amount of exertion actually undertaken. If the subject is "in training," cardiovascular efficiency will be such that a relatively great load may be carried with a minimum
of work. On the other hand, in training or not, the heart may be called upon to work hard with the subject sitting or lying while contemplating consciously or unconsciously some troublesome personal problem.

Much of the confusion concerning the role of life stress in disease derives from failure to distinguish between cause and mechanism. All mechanisms are perforce organic and at the same time functional, since they involve the functions of units of the body's equipment. Causes, on the other hand, are likely to derive from the outside, often from noxious stimuli in the environment. The causes, which may be multiple, activate the pathogenic mechanisms and produce bodily disorders and disease. The ability of symbolic stresses to participate in the activation of disease mechanisms depends upon the fact that most bodily organs are connected with and responsive to impulses reaching them via autonomic and endocrine pathways from the highest integrative centers of the nervous system, the interpretive areas of the brain.

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