

Stress “Addiction”: Causes, Consequences, and Cures

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EDITOR’S NOTE

The term “stress” is commonly used, but unfortunately is often poorly defined. Hans Selye originated the concept that the organism responds in non-specific ways to any demand for change; the emphasis in his work was on the destructive effects to the body mediated by stimulation of the pituitary-adrenal cortical axis upon exposure to unpleasant stimuli. As new hormones were discovered, such as prolactin and melatonin as well as endorphins, the complexity of the response became more apparent.

The link between the psychobiological response to stress and health is an age-old observation. Centuries ago, physicians noted that intense emotional stress and a variety of behavioral patterns, including excessive involvement in work, characterized people who developed coronary heart disease. More recently, Cannon's studies showed that the reaction to the stress of acute fear involved a marked increase in sympathetic nervous system activity and an outpouring of epinephrine; other studies have shown that myocardial infarction may often be associated with excessive norepinephrine at myocardial nerve endings even in the absence of significant coronary artery occlusion.

The so-called Type A personality, with his/her vulnerability to cardiovascular disease, presents a number of dominant personality characteristics: unrealistically high ambition, persistent vigilance, hyperactive responsiveness, a low level of frustration tolerance, and a constant need to perform. These features are, of course, only a few manifestations of a much more complex behavioral pattern, but one which has been shown to be statistically significant as a risk factor for heart disease.

The question is: Why do such individuals perpetually seek out stress and react to it in the very way that is so detrimental to their overall psychological and physical well-being? The author poses the possibility that there may be pharmacologic dependency to epinephrine and other central nervous system mediators, so that the indi-

vidual is driven to seek, again and again, situations that will increase the amount of such substances in the body. Only then can he or she feel comfortable. When not exposed to stress, serious dissatisfaction or even depression can ensue. Is this a learned pattern of behavior with the establishment of epinephrine habituation, a kind of within-the-body drug dependency state? Could there actually be physiological changes of an addictive nature?

The answers are by no means clear. However, intervention has already proved effective in reducing heart disease risk, including behavioral modification and the use of propranolol to block the effects of catecholamine secretion on heart function.

The Need for Definition

Stress has become the modern metaphor, the buzz word of the 1980s. Despite its ubiquitous popularity, however, it remains very difficult to define – at least to a scientist's satisfaction. Much of the confusion stems from the fact that stress means or represents something different for each one of us.

Customarily, we think of stress as an external noxious event producing undesirable physiological responses that may result in various illness syndromes. The term was coined, so to speak, only a few decades ago by the brilliant Canadian investigator Hans Selye, who viewed it as a “nonspecific” response of the organism to any demand for change.¹ Selye's studies showed that when laboratory animals were subjected to any unpleasant stimulus or challenge, very consistent, almost stereotyped responses were observed. These appeared to be due to stimulation of the pituitary-adrenocortical axis, with resultant increased hormone levels that produced macroscopic and microscopic pathologic changes in the gastric mucosa, lymphoid tissues, and adrenal cortex.

Whether the stressor took the form of extreme heat or cold, severe frustration, loud noises, bright lights, or exhausting muscular exercise, the same acute changes were observed. Continued exposure to stress led to appreciation that there appeared to be three phases to this response. The first was termed the “alarm reaction,” which was viewed as a call to arms of the body's defenses and was characterized by marked stimulation of the sympathetic nervous system and pituitary-adrenocortical responses. If the stress was persistent, a “stage of resistance” appeared to ensue in which the body's adaptive defenses were maintained. Finally, prolonged stress resulted in a “stage of exhaustion” and death. Selye termed this tripartite response the “General Adaptation Syndrome.” Pathologic changes in various tissues and organs observed during various phases of the response to stress appeared identical to morphological and microscopic findings seen in such clinical disorders as hypertension, coronary heart disease, peptic ulcer, and rheuma-

toid arthritis. Selye reasoned that such disorders in humans might similarly be caused by stress; he labeled them "Diseases of Adaptation."

However, the term "stress" quickly attracted all sorts of interest, and moved out of the domain of endocrinology and biology, as it became increasingly adopted by psychiatrists, psychologists, behavioral scientists, sociologists, and eventually the general public. In the vernacular, it appeared to be synonymous with distressing emotional factors. Others used "stress" to denote the pathologic results of distress, such as a peptic ulcer or heart attack. Eventually the term embraced not only the offending stimulus (stressor), as well as the physiological and biochemical responses to that stimulus, but also resultant disease states. The definition of "stress" had become so complex that one commentator complained that "stress, in addition to being itself and the result of itself, is also the cause of itself."²

Selye later discovered that "conditioning" the animal with dietary or hormonal manipulation could produce different types of pathology, leading to the suspicion that the effects of stress were not predictably uniform. As refinements in endocrine techniques became more sophisticated and animal research was extended to clinical experimentations, it became increasingly apparent that, far from being nonspecific, the response to stress in humans was highly variable and personalized. In fact, there appeared to be a whole repertoire of neurohumoral secretions, which varied from individual to individual or even in the same individual at different times. As new hormones, such as prolactin and melatonin, could be measured more accurately, it was found that they, in addition to pituitary trophic hormones other than ACTH, were also significantly affected by stress. This was particularly true in the case of the endorphins, whose secretion during stress paralleled that of ACTH and appeared to be governed by identical adrenocortical feedback mechanisms.

To further complicate matters, it became apparent that stress in humans involved not only the acute life-threatening or irritating stimuli studied in laboratory animals but also a host of chronic repetitive irritating hassles that occur in daily life, as well as less easily quantifiable chronic psychosocial factors, such as bereavement, loneliness, crowding, and chronic depression. In the past few years, these factors have assumed increasing importance and appear to be linked with a higher incidence of malignancy and a host of other disorders characterized by impaired immune-system responses.^{3,4}

Stress, Behavior, and Health: An Ancient Observation

In all of the above discussion, we have dealt with the model of stress as a function of the organism's response to external influences. Over the past three decades, however, attention has been directed to the realization that

stress can also be self-generated as a consequence of certain behavioral characteristics or traits. The prime example of this is seen in the individual with Type A coronary-prone behavior pattern, one component or consequence of which may be inadvertently self-induced epinephrine habituation or addiction.

The close relationship of emotions, personality, and cardiovascular disturbances is certainly not a new observation.⁵ Almost 2000 years ago, Celsus noted that “fear and anger, and any other state of the mind, may often be apt to excite the pulse.” William Harvey commented in 1628: “Every affection of the mind that is attended either with pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.” John Hunter, who during the 18th century elevated surgery from a mechanical trade to an experimental science, suffered from angina. Being a keen observer, he complained: “My life is in the hands of any rascal who chooses to annoy and tease me.” That statement turned out to be somewhat prophetic since, in fact, an argument did precipitate his death from a heart attack. Napoleon's physician, Corvisart, wrote that heart disease was due to the “passions of the mind,” among which he included anger, madness, fear, jealousy, terror, love, despair, joy, avarice, stupidity, and – last but not least – ambition.

One hundred and fifteen years ago, von Dusch, a German physician, first called attention to the fact that excessive involvement in work appeared to be the hallmark of people who developed coronary heart disease. Toward the end of the last century, Sir William Osler succinctly but accurately described the coronary-prone person as a “keen and ambitious man, the indicators of whose engines are set at ‘full speed ahead.’” In the 1930s, the Menningers suggested that coronary heart patients tended to exhibit strongly aggressive behavior, and a decade later, Flanders Dunbar, who introduced the term “psychosomatic” into American medicine,⁶ characterized such persons as being authoritarian with an intense drive to achieve unrealistic goals.

More Recent History: The Cardiovascular Response to Stress

Attempts to study the mechanisms whereby emotional states could produce cardiovascular damage or sudden death received tremendous impetus as a result of the investigations of Walter Cannon at Harvard in the early part of this century. Cannon's studies demonstrated that response to the stress of acute fear resulted in a marked increase in sympathetic nervous system activity and an outpouring of epinephrine, which prepared the animal for lifesaving “fight or flight.”⁷ His later studies of the mechanism of “bone pointing” or “voodoo” health also implicated a flooding of the system with epinephrine as the most likely cause of fatal arrhythmia.⁸

Selye's formulation of the stress concept in the late 1940s provided further insight into the role of pituitary and adrenocortical factors in modulating cardiovascular responses to stress. His subsequent research included the experimental production of "metabolic cardiac necroses," in which direct biochemical injury to heart muscle rather than occlusion of the coronary vessels was the causative factor.⁹

More recently, it has been observed that stress may also lead to accelerated atherosclerosis and coronary occlusion because of elevated cholesterol, triglycerides, and free fatty acids, increased platelet adhesiveness, polycythemia, accelerated blood clotting, increased fibrinogen, haptoglobin, plasma seromuroids, etc. We have also become increasingly aware of the important role of stress-induced coronary vasospasm in the production of clinical symptoms and disease.¹⁰ Even more significant has been the identification of myocardial infarction in the absence of significant coronary occlusion due to the excessive release of norepinephrine at myocardial nerve endings. This has now been demonstrated to produce a specific type of myocardial damage which can be recognized under the microscope and appears to be identical in laboratory animals, as well as in humans who have succumbed to sudden cardiac death as the result of an acutely stressful situation.¹¹

The Type A Personality

Our current appreciation of coronary-prone behavior and its possible relation to epinephrine addiction is due almost entirely to the ground-breaking efforts of Friedman and Rosenman.¹² These investigators noted that conventional risk factors – such as elevated cholesterol, hypertension, and smoking – accounted for less than half the cases of heart attack in their practice. They were intrigued by the fact that two-thirds of the heart attacks in the United States occurred in men, although in Mexico the incidence was 50-50. The same equal split appeared to exist in southern Italy but not in northern Italy, where the ratio was four males to every female. Such a disparity did not appear to be due to any difference in diet or environmental factors and on further analysis appeared to be more related to certain social, cultural, and behavioral attitudes that might best come under the heading of "maleness." Such individuals, labeled Type A, exhibited certain overt characteristic activity patterns, including:

1. Self-imposed standards that are often unrealistically ambitious and are pursued in an inflexible fashion. Associated with this is a need to maintain productivity in order to be respected, a sense of guilt during vacations or relaxation, an unrelenting urge for recognition or power, and a competitive attitude that often creates challenges even when none exist.

2. Certain thought and activity styles, characterized by persistent vigilance and impulsiveness, usually resulting in the pursuit of several lines of thought or action simultaneously.
3. Hyperactive responsiveness, often manifested by a tendency to interrupt or abruptly finish a sentence in conversation, usually in dramatic fashion by varying the speech, volume, or pitch or by alternating rapid bursts of words with long pauses for emphasis, indicating intensive thought. Type A's often nod or mutter agreement or use short bursts of laughter to obliquely indicate to the speaker that the point being made has already been anticipated.
4. A tendency to have unsatisfactory interpersonal relationships, due to the fact that Type A's are usually self-centered, are poor listeners, often have an attitude of bravado about their own superiority, and are easily angered or frustrated if their wishes are not respected or their goals are not achieved.
5. Increased muscular activity in the form of gestures and motions and facial activities, such as grimaces, gritting and grinding of the teeth, or tensing of jaw muscles. Often there is clenching of the fist or perhaps pounding with a fist to emphasize a point. Fidgeting, tapping the feet, leg shaking, and playing with a pencil in some rhythmic fashion are other favorites.
6. Irregular or unusual breathing patterns with frequent sighing, produced by inhaling more air than needed during speaking and then releasing it during the middle or at the end of a sentence of emphasis.

Type A's tend to be very competitive, are usually rushed, and, as a consequence, are rapid when eating or talking and in most other activities. They generally try to do too many things at once, are more concerned with quantity than with quality of effort, are frequently preoccupied with what they are going to do next, and tend to have few interests outside of their work.

I have gone into some detail in describing Type A characteristics simply to emphasize that it is a complex overt behavioral pattern that can be identified only by personal observation. In clinical practice, its evaluation requires a structured personal interview conducted by a trained investigator using standardized challenges designed to elicit the characteristics noted above. It is almost impossible to detect in the very sick, bored, depressed, or detached person. Accurate assessment therefore requires considerable expertise, making large-scale studies relatively time-consuming and costly.

A variety of questionnaires have been devised to detect such aspects of Type A behavior as competitiveness, ambition, impatience, hostility, preoccupation with work, and a constant sense of time or urgency. The most commonly used instrument, the Jenkins Activity Survey, detects three main behavioral syndromes: (1) hard-driving temperament, (2) intense job involvement, and (3) speed and impatience. Although the three scores derived correlate with the total evaluation, they are not necessarily related to one another, and the overall accuracy is limited when compared with a structured personal interview. It should also be emphasized in evaluating any self-administered questionnaire that Type A individuals are often unaware of

many of their behavioral patterns or will deny them. No single Type A individual should necessarily be expected to exhibit all of the above characteristics; conversely, some Type A traits can be found in Type B or Type C (Type B with anxiety) subjects.

Studies of Heart-Disease Risk

As our understanding of this complex subject has expanded, it seems likely that certain components of Type A behavior – such as time urgency, latent hostility, and aggressiveness – may be found to have a greater predictive significance for coronary heart disease, increased norepinephrine secretion patterns, vascular hyperreactivity, or other phenomena that mediate stress-induced myocardial damage. Despite any imprecision in its quantification, however, Type A coronary-prone behavior has been unequivocally established as an independent risk factor for heart attack as significant as any other known entity.¹³ The observation of increased catecholamine excretion in such persons and the known deleterious effects of such agents on the myocardium have prompted many of us to reevaluate and question current concepts of the pathogenesis of coronary heart disease.

Several years ago, the disappointing results of the seven-year, \$115 million MRFIT study were published in the *Journal of the American Medical Association*.¹⁴ MRFIT is an acronym for Multiple Risk Factor Intervention Trial, which was designed to show the beneficial effect of stopping smoking and lowering cholesterol and blood pressure. However, patients in whom the desired behavioral and physiological changes were achieved did not receive any significant protection. In fact, the hypertensives treated with diuretics had a higher incidence of heart attacks than did controls (possibly because of a tendency toward hypokalemia, which potentiated adrenergic effects).

In contrast, over the same period, two other studies designed to reduce the likelihood of recurrent heart attacks were so successful that they were halted before their completion so that controls would not be denied the benefit of intervention. One was a trial using techniques to reduce damaging Type A behavior;^{15, 16} the other was the NHLBI study of almost 4000 patients, in which it was found that after only two years the administration of propranolol had reduced mortality by 26%.¹⁷ Both of these findings again strongly suggest that stress-related sympathetic nervous system drive and catecholamine secretion are the major culprits in coronary heart disease. Behavioral modification is aimed at turning off the epinephrine-norepinephrine spigot, and propranolol and other beta-blockers appear to blunt the damaging effects of such agents on the cardiovascular system. The benefits of behavioral modification have since been confirmed in other

studies, and the protective effects of other beta-blockers in preventing heart attacks have now been demonstrated for almost every such agent tested for this purpose.¹⁸⁻²¹ As a consequence, some authorities have suggested that beta-blockers be administered to all heart-attack patients provided that there are no contraindications.

The Evolutionary Point of View

Now, from an evolutionary or teleologic viewpoint, stimulation of the sympathetic nervous system and a jolt of epinephrine made a lot of sense for primitive man. As a consequence, the pupils dilated so that he could see better and glycogen stores in the body were quickly broken down to elevate the blood sugar and provide additional energy. Blood was directed away from the gut, where it was no longer needed for digestive processes, and shunted to the muscles of the arms and legs so that he could fight better or run faster. The blood pressure rose, and there was an increased flow of blood to the brain to improve cerebral function – in short, a whole host of adaptive changes occurred to prepare our ancestors for life-preserving “fight or flight.”

However, the nature of stress for modern man is quite different. It is not an occasional confrontation with a sabertooth tiger or pack of wolves but, rather, problems at work or at home, financial difficulties, or simply getting stuck in a traffic jam on the way to a vital appointment. Furthermore, such challenges and provocations occur not once a fortnight but many times during our daily life. The tragedy is that our bodies still respond in the same old archaic fashion. Unfortunately, that release of epinephrine is now not only purposeless and inappropriate but actually harmful, with lethal potential for causing a heart attack, sudden death, stroke, hypertension, peptic ulcer, diabetes, and a variety of other disorders that might appropriately be labeled “disease of civilization.”

Stress Habituation

It seems plausible that the Type A coronary-prone person may have become habituated to stress, a learned, fixed response with obviously damaging consequences; there is even a remote chance that physiological changes may establish an actual addiction to epinephrine or other central nervous system substances. Support for this comes from Solomon's “opponent-process theory of motivation,”^{22, 23} which basically asserts that man is by nature suscep-

tible to various habits and addictions that provide a sense of pleasure. However, when man is deprived of the thing that is craved, an opposing emotional state often results. The exhilarating feeling of being in love can change to melancholy if you can no longer be with the object of your affection. People who are hooked on skydiving may become severely depressed if the weather interferes with their activities for a day. Similarly, withdrawal from cigarettes, alcohol, narcotics, tranquilizers, or recreational drugs often produces emotional states that are opposite from the sensations those substances induce.

The Learned Response

Because of his or her psychological condition, the Type A individual may unconsciously seek ways to get those repeated surges or highs. That could come in the form of constructing little contests, like getting to the airport a few minutes before takeoff, turning a car trip into a race by establishing certain times at which check points must be reached, or purposely leaving a desk untidy or delaying an assignment to the last minute – just so there will be some sort of contest or last-minute challenge. Deprived of that epinephrine stimulus, the Type A individual is apt to be irritable and depressed. Thus, recuperating from a heart attack by spending three weeks on a deserted beach might be a perfect prescription for one person but deadly for some Type A's, who could be in a state of agitation in a matter of hours. Beta-blockers may help to alter Type A behavior by blunting the unconscious self-induced production of epinephrine and norepinephrine, diminishing their dependency-producing potential.

That this may become a learned or fixed response is suggested by other studies which show that Type A individuals, even while under anesthesia for coronary bypass procedures, exhibited a greater increase in systolic blood pressures than did Type B controls. They also had more arrhythmias and other complications, and 50% longer hospital stays.²⁴ Thus, repetitive or exaggerated sympathetic responses may result in a state that tends to perpetuate this type of behavior. It remains to be seen whether other stress-related neurohumoral agents, such as serotonin or beta-endorphin, also have a potential for inducing habituation or addiction. Such a possibility is suggested by the finding of elevated met-enkephalin in compulsive persons who habitually mutilate themselves and those who show profound disturbances in appetite manifested by bulimia and anorexia.²⁵ Increasing evidence that clonidine can provide significant benefits in a variety of addictive disorders (cigarette smoking and substance abuse) as well as hypertension, Type A behavior and other norepinephrine mediated problems further supports this hypothesis.^{26,27}

The Role of Addictive Mechanisms

If one can become pathologically dependent on stress or epinephrine, it is possible that research on addiction or habituation to other substances, such as cocaine or marijuana, would provide useful information. Like stress, drug habituation and addiction are difficult to define, but an important characteristic common to both appears to be lack of control. Addictive behavior appears to be mediated by changes in neurotransmitter activity in the brain. The rate at which neurons fire is determined by the concentration of neurotransmitters at the synapse. The higher the concentration, the more rapid the transmission and the more intense is the resultant feeling or sensation. It is possible that addiction occurs because people either repeat some behavioral pattern or ingest various addictive substances that elicit a desired mood.

Under normal circumstances, following their release by excitation over neural pathways, neurotransmitters are pumped back into the presynaptic neuron, where they are stored for further use. Certain drugs appear to interfere with this pumping mechanism. As a consequence, the neurotransmitter remains at the synapse and its presence in higher concentration results in more rapid neurotransmission and enhancement of the resultant sensation desired. Heroin and cocaine may induce their euphoric mood by such a mechanism.

One factor that appears to be common in the addictive personality as well as in Type A coronary-prone behavior is a poor self-image. A method of dealing with such feelings of worthlessness is to seek ways of changing or elevating this unpleasant mood. The Type A individual may accomplish this by submersion or preoccupation in excessive work. For others, the driven dependency compensation may take the form of overeating, fasting, chocolate binges, jogging, skydiving, smoking, drinking, gambling, or the use of various recreational drugs.

Obviously, any form of habituation or addiction represents a two-edged sword. While initially providing gratification, it can ultimately prove harmful or lethal. Prime examples of this are the jogger who persists in running despite any number of orthopedic problems that have resulted, which would normally preclude such activity because of pain. The confirmed alcoholic with cirrhosis, the cigarette smoker with emphysema or Buerger's disease, and the compulsive gambler already in debt are other instances. Some people may be unaware of the harmful aspects of their addictions or, alternatively, persist in attempting to satisfy their cravings despite a knowledge of the dire consequences.

Stress- Transmitting Mechanisms

Those people who seem to seek repeated or perpetual epinephrine hyperactivity appear to fit this mold. A variety of significant strategies and ap-

proaches are being explored to address the problem. Currently, attention is being focused on central nervous system structures and mechanisms that initiate or transmit the stress signal. Preliminary evidence suggests that both heart rhythm and force of contraction are regulated by the same centers in the frontal cortex of the brain that stimulate sensory reception during acute fear. If the nervous system pathways from the frontal cortex to the brain are severed or temporarily blocked by freezing, experimental animals that would normally succumb to ventricular fibrillation during severe psychological stress are protected. The search is on for some pharmacologic agent that might provide the same benefits. As mentioned previously, behavioral modification by stress inoculation techniques has proved dramatically effective in preventing recurrent heart attacks in Type A coronary-prone patients. Similarly, propranolol and almost every other beta-blocker studied have proved effective in reducing recurrent heart attacks, as well as sudden death in patients with myocardial infarction.

Finally, we have previously suggested that Type A and coronary-prone behavior may not be synonymous and that certain components – such as aggression, competitiveness, latent hostility, and time urgency – may be more predictive for coronary events.⁵

It has been recently proposed that hostility or “cynicism” is the Type A component most associated with future heart attacks.^{28, 29} However, such studies utilized the Cook and Medley 50 item “Ho” subscale of the MMPI,³⁰ and more critical analysis suggests that this does not measure hostility *per se*, but rather a variety of traits including authoritarianism, rigidity and competitiveness.³¹ In addition, there is no correlation with the hostility component of Type A³² or the more relevant characteristic association with blood pressure hyperreactivity.³³ High Ho ratings seem more predictive of overall causes of mortality, including cancer, rather than CHD specifically.³⁴ Association never proves causation. What appears to be emerging is that anger and its expression are the most important aspects of behavior that predict or contribute to coronary heart disease. The ancient Greek dictum “To measure is to know” seems particularly applicable. Fortunately, Spielberg has developed assessment techniques that have reliability and construct validity which will enable us to prove the correctness of this premise.^{35, 36}

Many persons with apparently flagrant Type A behavior appear to thrive on stress and lead long, healthy, productive lives. Certain symphony conductors, performing artists, and entertainers represent good examples. Analysis of such stress-resistant personalities suggests that in general such persons are in control of their activities, have a strong commitment to what they are doing, and enjoy or respond to challenges rather than being overwhelmed by them. Recent research has challenged the conventional concept that autonomic responses to positive and negative emotions are the same. A recent study reported not only that autonomic activity could be differenti-

ated between such states but also that even negative emotions (such as sadness, fear, and disgust) could be further differentiated by simply contracting facial muscles into the expressive forms associated with these affective states.³⁷

Similarly, persons who are productive, who have pride of accomplishment, and who derive pleasure from doing something they enjoy that benefits others appear to have health patterns different from those of Type A counterparts who are constantly frustrated by self-imposed unrealistic standards and goals. Such behavior, which Selye termed altruistic egoism, makes sense from an evolutionary or teleologic viewpoint. When primitive man was faced with a natural disaster, such as a flood or attack by a pack of wolves, banding together with others to combat such life-threatening situations had survival value. Consequently, nature tended to perpetuate the survival of a species so motivated. From another viewpoint, the craving for an epinephrine-induced high may no longer be required for persons whose self-esteem has been significantly raised by activities that are productive and fulfilling.

While stress is a complex phenomenon, it is apparent that many of its disastrous consequences are mediated by the release of neurohumoral chemicals related to epinephrine as well as various small brain peptides, either as a response to external stimuli or as unappreciated consequences of self-induced secretion. Such agencies have now been demonstrated to have a profound effect on the cardiovascular system, as well as on immune competency, and play a significant role in the development of hypertension, coronary heart disease, cancer, and a variety of infectious disorders. Further insight into behavioral and pharmacologic methods of interrupting this vicious cycle of stress dependency offers great promise for the treatment and cure of many common "Diseases of Civilization."

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