

STRESS AND CARDIOVASCULAR DISEASE

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HISTORICAL BACKGROUND

■ The appreciation that emotional factors can have a powerful influence on the heart, and the acknowledgment of some intimate, although poorly understood, heart-mind connection, is certainly not new. Aristotle, and later Virgil, actually taught that the heart rather than the brain was the seat of the mind as well as the soul, and a similar belief can be found in ancient Hindu scriptures and other Eastern philosophies. Almost 2000 years ago, Celsus commented on this mind-heart relationship, noting that “fear and anger, and any other state of the mind may often be apt to excite the pulse.” Our earliest uses of the word clearly indicate its conceptualization as the seat of one’s inmost feelings, temperament, or character. Broken hearted, heartache, take to heart, eat your heart out, heart of gold, heart of stone, stouthearted, are words and phrases we still use to vividly symbolize such beliefs.

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 cen-

tury elevated surgery from a mechanical trade to an experimental science, suffered from angina, and being a keen observer complained, “my life is in the hands of any rascal who chooses to annoy and tease me.” He turned out to be somewhat of a prophet, since in fact an argument did precipitate his death from a heart attack. Napoleon’s favorite 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 ambition.

One hundred and fifteen years ago, von Dusch, a German physician, first called attention to the fact that excessive involvement in work and similar types of behavioral patterns appeared to be the hallmark of people who developed coronary heart disease. Toward the end of the last century, Sir William Osler, an astute clinician, succinctly but accurately described the coronary-prone individual as a “keen, and ambitious man, the indicator of whose engines are set at ‘full speed ahead.’” In the 1930s, the Menningers suggested that coronary heart patients tended to have strongly aggressive behavior, and a decade later, Flanders Dunbar, who introduced the term “psychosomatic” into American medicine, characterized

such individuals as being authoritarian with an intense drive to achieve unrealistic goals. Fierce ambition and compulsiveness to achieve power and prestige were emphasized by many subsequent investigators, and over 30 years ago, a rising incidence of coronary heart disease in England was attributed to increased stress.

PATHOPHYSIOLOGY OF STRESS-INDUCED CORONARY HEART DISEASE

Attempts to study the mechanisms whereby emotional states could produce cardiovascular damage and sudden death received tremendous impetus as a result of the investigations of Walter Cannon at Harvard University in the early part of this century.¹ Cannon's studies showed that the response to the stress of acute fear resulted in a marked increase in sympathetic nervous system activity and an outpouring of adrenaline, which prepared or assisted the animal in fight or flight, and had great survival value. His subsequent studies of the mechanism of voodoo death or spells cast by bone pointing also implicated a flooding of the system with adrenaline as the most likely cause of a fatal arrhythmia.

In the late 1940s, Hans Selye's formulation of the stress concept, general adaptation syndrome, and diseases of adaptation provided further insights into stress-induced heart disease in humans.² His original concept of stress as a nonspecific stereotyped response was formulated largely by observing and analyzing the biochemical, endocrine, and pathologic changes that resulted from intense or prolonged pituitary-adrenal cortical stimulation. Selye's subsequent research in the 1950s 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.³ He emphasized the important significance of sodium, potassium, magnesium, and calcium in modulating such effects. These findings were subsequently corroborated in humans and now form the basis of various therapeutic strategies and pharmacologic approaches.

THE STRESS CONCEPT

Selye's concept of the general adaptation syndrome and diseases of adaptation dominated

stress research in the 1950s and 1960s with its emphasis on the ACTH-adrenal cortex axis. However, subsequent refinements in endocrine techniques led to a recognition that the response to stress in humans involved a vast repertoire of hormonal secretion including a variety of other pituitary and target gland hormones, the renin-angiotensin system, prostaglandins, and more recently, powerful brain peptides such as serotonin, dopamine, melatonin, prolactin, and endorphins.⁴ Furthermore, far from being nonspecific, these patterns of neurohumoral responsiveness appeared to vary greatly from individual to individual and even in the same person at different times. The precise role of these various agencies in facilitating or mitigating the effects of stress on the cardiovascular system is still poorly understood and requires extensive investigation. Currently, attention is also being focused on central nervous system structures and mechanisms that initiate and transmit the stress signal, with evidence suggesting that both heart rhythm and force of contraction are regulated by the same centers in the frontal cortex of the brain that stimulate sensory receptors during acute fear. Experimental animals that would normally succumb to ventricular fibrillation due to severe psychological stress are protected if the nerve pathways from the frontal cortex to the brain are severed or temporarily blocked by freezing, and the search is on for some pharmacologic agent that might provide the same benefits.

The terms coronary occlusion and myocardial infarction were previously used synonymously, and they still are by many physicians who continue to view this sequence of events as the pathologic cause of all heart attacks. That concept was taught in medical school as a consequence of Herrick's postmortem observations in 1912, which demonstrated that a heart attack or myocardial infarction was due to occlusion of a coronary artery by a clot or thrombus. We now recognize that myocardial infarction can occur in the absence of significant coronary obstruction. We are increasingly recognizing the important role of coronary vasospasm in the production of anginal symptoms, and conversely, it is not unusual to find severe coronary atherosclerosis in patients who have never had cardiac symptoms.

Stress may also lead to accelerated atherosclerosis and coronary occlusion because of elevated cholesterol, triglycerides, free fatty acids, increased platelet adhesiveness, polycythemia, accelerated blood clotting, increased fibrinogen, haptoglobin, or plasma seromucoids. In my opinion, however, the most significant development in our understanding of stress-related heart attacks 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 that can be recognized under the microscope and appears to be identical in laboratory animals and in humans who have had cardiac deaths as the result of an acutely stressful situation.

Over this entire period of time, the concept, definition, and use of the term stress was constantly changing but not evolving. Cannon initially employed the term in 1914 as a physicist or engineer might, although it was clear that his appreciation included both physical and emotional stimuli.

The chance of gaining insight into the strength and endurance of stabilizing factors of the organism, and thus its ability to resist the operation of disturbing forces, makes it worthwhile to inquire where the limits lie beyond which stresses overwhelm these corrective factors and significantly alter the steady state of internal environment.⁵

The term stress was popularized, however, by Selye, who defined it as a nonspecific response to a variety of noxious stimuli. Others used it to describe the resultant pathology such as a stress ulcer. Moreover, the term that had been primarily used by research scientists studying endocrine and pathologic effects was steadily creeping into the psychological and behavioral literature. Stress was now conceived of as any physical, psychological, or symbolic stimulus that could elicit a physiologic response. The confusion was so great that as early as 1950, one critic using verbatim citations from Selye's writings complained that "stress, in addition to being itself and the result of itself, is also the cause of itself."⁶ In recent

years, stress has become more of a psychological concept embracing environmental and social conditions, as well as anxiety, frustration, and almost any other threat.

Thus, we usually think of stress as being due to something external that threatens us. What appears to be much more important, however, is how we perceive that external stimulus and what adaptive or coping strategies have been developed. Attempts to quantify or rate such external stressors as in the Holmes-Rahe Social Readjustment Rating Scale, generally place death of a spouse at the head of the list. Other stress factors include divorce, jail term, death of a family member or friend, loss of some other close emotional relationship, retirement, changing jobs, or moving. In recent years we have begun to appreciate and acknowledge a host of other more insidious, chronic factors such as job stress, unemployment, crowded living conditions, and other psychosocial influences as playing an equally important role, although they are much more difficult to characterize or quantify. There is abundant and increasing evidence that such factors may play a role in other stress-related disorders including cancer.⁷ Widowed individuals die at rates 3 to 12 times higher than their married counterparts for all leading causes of death including heart disease, cancer, cirrhosis, tuberculosis, accidents, homicides, and suicides.

TYPE A—SYNONYMOUS WITH CORONARY-PRONE BEHAVIOR?

More germane to this discussion is the recognition that stress can also be internal or self-generated. Our current appreciation of this subject stems from the work of Rosenman and Friedman and their elucidation of a profile of coronary-prone behavior.⁸ These investigators were intrigued by the fact that two-thirds of the heart attacks in the United States occurred in men, while in Mexico the incidence was equal between men and women. The same equal split appeared to exist in southern Italy but not in northern Italy, where the ratio was four men to one woman. This disparity was obviously not due to any difference in diet or other environmental factor, and on further analysis appeared to be related more to social, cultural, and behavioral attitudes that might

best come under the heading of "maleness." Such individuals, labeled Type A, exhibited certain characteristic activity patterns including:

(1) Self-imposed standards that are often unrealistically ambitious and pursued in an inflexible fashion. Associated with this is a need to maintain productivity in order to be respected, a sense of guilt while on vacation or relaxing, 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 finish a sentence in conversation, usually in dramatic fashion, by varying the speech, volume, and/or pitch, or by alternating rapid bursts of words with long pauses of hesitation for emphasis, indicating intensive thought. Type A persons 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 individuals are usually self-centered, poor listeners, often have an attitude of bravado about their own superiority, and are much more easily angered, frustrated, or hostile if their wishes are not respected or their goals are not achieved.

(5) Increased muscular activity in the form of gestures, motions, and facial activities such as grimaces, gritting and grinding of the teeth, or tensing jaw muscles. Often there is frequent clenching of the fist or perhaps pounding with a fist to emphasize a point. Fidgeting, tapping the feet, leg shaking, or playing with a pencil in some rhythmic fashion are also seen.

(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 end of a sentence for emphasis.

Type A individuals tend to be very competitive and are usually rushed, and consequently they eat, talk, and do most other activities quickly. They generally try to do too

many things at once, are frequently preoccupied with what they are going to do next, and tend to have few interests outside their work.

Type A characteristics have been described in detail simply to emphasize that it is a complex overt behavioral pattern that can only be identified by personal observation of the individual. 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 individual. 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, or a constant sense of time urgency. The most commonly used instrument, the Jenkins Activity Survey, detects three main behavioral syndromes: (1) hard-driving temperament, (2) job involvement, and (3) speed and impatience.⁹ Although the three scores derived correlate with the total evaluation, they are not necessarily related to one another, and the overall accuracy is only about 70% when compared with a structured personal interview. It should 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 be expected to exhibit all of the above characteristics, and conversely, many Type A traits can be found in Type B or Type C (Type B with anxiety) persons.

As our understanding of this complex subject expands, it is possible that certain components of Type A behavior such as time urgency, latent hostility, aggressiveness, or authoritarianism may be found to have a greater predictive significance for coronary heart disease or correlation with norepinephrine secretion patterns, vascular hyperreactivity, and other phenomena that mediate stress-induced myocardial damage. However, despite these variables and pitfalls, Type A coronary-prone behavior has now been unequivocally established as an independent

risk factor as significant as any other known entity¹⁰ The observation of increased catecholamine excretion in such individuals, and the known deleterious effects of such agents on the myocardium, have prompted many investigators to reevaluate and question current concepts of the pathogenesis of coronary heart disease.

RISK FACTORS AND CORONARY HEART DISEASE

The current concept of risk factors for heart attacks has been derived to a large extent as a result of analysis of the Framingham data. This long-term ongoing study consisted of making periodic observations on residents of this Massachusetts town, including physical examination, social habits, and various biochemical measurements. Analysis of heart attack victims initially indicated that in general they tended to smoke more, had elevated blood pressures, and higher cholesterol levels than controls. Subsequently, triglycerides and high density lipoproteins and HDL cholesterol ratios were suggested as having additional prognostic implications. The validity of such markers was supported by prospective studies in which it was possible to predict a cohort of individuals at greater risk for heart attack simply because they exhibited a higher incidence of these risk factors. Armed with this information, the conclusion seemed obvious—stop cigarette smoking, lower cholesterol and blood pressure with diet and medication, and coronary heart disease will be reduced. But that has turned out not to be the case, simply because association never proves causation.

In fact, most attempts to reduce the incidence of heart attack by removing any or all of these risk factors have been unimpressive. Less than a year ago, the disappointing results of the seven-year, \$115 million MRFIT Study were published in the *Journal of the American Medical Association*.¹¹ MRFIT is an acronym for Multiple Risk Factor Intervention Trial, which was designed to show the beneficial effect of cessation of smoking and lowering of cholesterol and blood pressure. However, those patients in whom the desired results were achieved did not receive any significant protection. In fact, the hypertensive patients treated with diuretics

had a higher incidence of heart attacks than controls (possibly because of a tendency toward hypokalemia, which potentiated adrenergic effects).

In contrast, over this same period two other studies designed to reduce the likelihood of recurrent heart attacks were so successful that they had to be halted before their completion for ethical reasons. One was a trial using techniques to remove damaging Type A behavior,^{12,13} and the other was the National Heart, Lung, and Blood Institute study of almost 4000 patients, where it was found that after only two years, the administration of propranolol had reduced mortality by 26%.¹⁴ Both of these findings again strongly suggest that stress-related sympathetic nervous system drive and catecholamine secretion is the major culprit in coronary heart disease. Behavioral modification is aimed at turning the adrenaline spigot off, and beta blockers appear to interfere with the harmful actions of noradrenalin 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 agent tested for this purpose. As a consequence, some authorities have suggested that beta blockers should be administered to all heart attack patients, provided there are no contraindications.

From an evolutionary or teleologic viewpoint, stimulation of the sympathetic nervous system and a jolt of adrenaline made a lot of sense for primitive man. Flooding the system with such compounds caused the pupils to dilate 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 and 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 not an occasional confrontation with a saber tooth 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 lives. The tragedy is that our bodies still respond in that same old archaic fashion. Unfortunately, that release of adrenaline 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 "Diseases of Civilization".

There is some suggestion that this may become a learned and fixed response. A hypothesis with the formidable title, *An Opponent Process Theory of Acquired Motivation*,¹⁵ basically asserts that man is by nature predisposed or susceptible to various addictions that may provide a sense of pleasure. However, if deprived of something that is craved, an opposite emotional state results. When you're in love, it's an exhilarating feeling, but if you can't be with your loved one, you are apt to be blue. People who are hooked on sky diving or skiing become severely depressed if the weather interferes with their activities for a few days. Similarly, withdrawal from alcohol, narcotics, or tranquilizers produces an emotional state exactly opposite from the sensations those substances induce.

Other studies show that Type A individuals, even while under anesthesia for coronary bypass procedures, exhibit a greater increase in systolic blood pressure than Type B controls. They also have more arrhythmias and other complications, and 50% longer hospital stays. Thus, the repetition of exaggerated sympathetic responses in Type A persons may result in a learned response that tends to perpetuate this type of behavior.

It seems plausible that the Type A individual has perhaps become addicted to his own adrenaline, and unconsciously he seeks ways to get those repeated surges. That could come in the form of constructing little games, like getting to the airport a few minutes before takeoff, or 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 until the last min-

ute—so that there will be some sort of contest or last-minute challenge. Deprived of that adrenaline 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 individual, but deadly for some Type A persons who would be off the wall in a matter of hours. It has been suggested that beta blockers may help to alter Type A behavior by blunting these unconscious self-induced injections of adrenaline and thus diminishing their addictive potential.

EUSTRESS—CAN STRESS EXERT HEALTH-PROMOTING EFFECTS?

One should also consider the alternative hypothesis that certain behavioral patterns or emotional states may be protective for coronary heart disease. Both of the great coordinating and integrating adaptive mechanisms of the body, the central nervous and endocrine systems, appear to operate on a system of checks and balances. Sympathetic activity is opposed by parasympathetic influences in the autonomic nervous system, and the relationship between the pituitary and target glands similarly appears to be governed by a self-regulatory servomechanism. It does not seem unlikely, therefore, that if bad things (distress) can make us sick, positive emotions (eustress) such as faith, love, humor, or creativity can exert opposite effects, or promote wellness. Type A individuals who are productive, creative, derive pride from their accomplishments, or who are doing something they enjoy that also gives pleasure to others—what Selye called altruistic egoism—probably flourish because of such behavioral patterns. It is possible that the effects of such good stress are mediated by release of endorphins and other small brain peptides known to accompany stress responses. Symphony conductors (Fiedler, Münch, Toscanini, Sir Adrian Boult), musicians, and other creative and performing artists (Rubinstein, Horowitz, George Burns, Bob Hope) are good examples. Surely such individuals are under tremendous amounts of stress, but somehow they learn to enjoy or utilize it to their advantage and generally lead long, healthy, productive lives. It seems more likely that it is the Type A individual, constantly frustrated

by an inability to achieve unrealistic self-imposed goals, who is at greatest risk for a heart attack.

ASSOCIATION NEVER PROVES CAUSATION

If we apply the same reasoning responsible for identifying standard risk factors and examine various data with respect to alcohol consumption, we might conclude that it is necessary for a man weighing 176 pounds to consume 7 ounces of hard liquor, or more than a fifth of wine, or more than five cans of beer every day to keep from having a heart attack (Table 1). Thus, it may be that it is not that one's cholesterol or blood pressure are too high, or that one smokes too much, but why these things occur that is important. All of these so-called risk factors can also be manifestations of stress or consequences of coronary-prone behavior, and their significance and association may be due largely to this relationship. Tax accountants under the stress of deadlines, and students taking final examinations have higher cholesterol levels regardless of diet or activity. Correlations have also been found with depression, low self-esteem, and neuroticism, as well as such Type A personality traits as dominance, aggression, hostility, achievement, motivation, and competitiveness.

Type A coronary-prone behavior has now been acknowledged as being as significant a risk factor for heart attacks as any other known

entity. In future years we may also be talking about occupational stress, social isolation, bereavement, retirement, and loss of other emotional relationships as additional important psychosocial risk factors for heart disease and other stress-related disorders.¹⁶ Further insight into how these effects are mediated offers great potential for our understanding of the pathogenesis of coronary heart disease, as well as its prevention and treatment. For the practicing physician, the lesson seems quite clear that many times it is more important to know what kind of patient has the disease than what kind of disease the patient has. ▲

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Table 1 • Amount of Alcohol Needed Daily to Prevent Heart Attacks*

Weight (lbs.)	Spirits (80 proof)	Wine (12%)	Beer (3.6%)
110	4.3 oz.	14 oz.	38 oz.
132	5.1	17	46
154	6.0	20	53
176	6.9	23	61
198	7.7	26	69
220	8.6	29	76

* Author's interpretation from Turner TB, Bennett VL, Hernandez H: The beneficial side of moderate alcohol use. *Johns Hopkins Med J* 1981; 148:53-63.

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