Behavioral Antecedents of Coronary Heart Disease and Atherosclerosis

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The concept of coronary-prone behavior has a long history but a short scientific past. The renowned internist Sir William Osler noted, for instance, that: "It is not the delicate, neurotic person who is prone to angina, but the robust, the vigorous in mind and body, the keen and ambitious man . . . whose engine is always at full speed ahead." Similarly, other clinicians have cited as characteristics of patients with coronary heart disease (CHD), a propensity to dominate others, excessive occupational goals, a profound sense of personal dissatisfaction, poorly modulated hostility, and, frequently preceding the occurrence of clinical symptoms, an accumulation of acutely stressful life events. Yet, only recently have suspected psychosocial antecedents of coronary artery atherosclerosis and its clinical manifestations been the subjects of serious empirical investigation. Despite the novelty of research in this area, the last 10 years have seen publication of a sufficient number of epidemiologic, clinical, and experimental studies to permit tentative conclusions regarding the role of psychosocial variables in CHD and atherogenesis. The purpose of the present review is to summarize and evaluate the current status of this emerging literature.

The first portion of this review examines the relationships of CHD and clinically assessed coronary artery atherosclerosis to three prominent behavioral dimensions in human beings: 1) the Type A behavior pattern; 2) predispositions to anger and hostility; and 3) psychological "stress" and the availability of resources to cope with vicissitudes of the social environment. In this evaluation, we have emphasized the results of prospective epidemiologic investigations rather than the findings of case-control studies contrasting persons with and without a current history of CHD. This is due to the many interpretive difficulties associated with retrospective observations, including systematic diagnostic and selection biases, effects attributable to the condition itself (e.g., physical disability, changes in cardiac performance), and, of particular relevance to behavioral studies, the side effects of many commonly prescribed medications (e.g., the anxiety-reducing effects of beta-adrenergic blocking agents).

Summarized next are the results of studies using animal models to investigate influences of behavioral factors on the development of arterial lesions. This literature subsumes studies on the pathogenic effects of chronic exposure to environmental stressors, as well as relationships between individual behavioral characteristics, such as aggressiveness, and lesion development. Experiments involving the use of nonhuman primates are weighed more heavily than studies of nonprimate species. This relative emphasis follows from two considerations. First, in comparison to other animal models, monkeys — especially those fed cholesterol-containing diets — develop arterial lesions that bear greater resemblance to the coronary artery atherosclerosis observed in humans. Second, primate social organization is more complex and descriptively analogous to the major axes of human social interaction than are behavioral repertoires of other species commonly used in biobehavioral research.

In the third section of this review, we briefly consider potential mechanisms mediating behavioral influences on atherogenesis. This discussion focuses on the possible pathogenic effects of acute hemodynamic disruptions accompanying sympathetic nervous system reactions to stress, as well as of more broadly defined patterns of neuroendocrine response to behavioral stimuli.
Psychosocial Characteristics of Humans at Risk for Coronary Artery Disease

Type A Behavior Pattern

The Review Panel on Coronary-Prone Behavior and Coronary Disease Assembly by the National Heart, Lung, and Blood Institute concluded, in 1978, that "Type A behavior... is associated with an increased risk of clinically apparent CHD in employed, middle-aged U.S. citizens." Recently, results of several new studies have been reported; some provide evidence of a Type A-CHD relationship, others do not. Since there is now a somewhat contradictory literature, it is appropriate at this point to reevaluate the significance of Type A behavior as an antecedent of clinical CHD. In this section, we summarize the findings of relevant prospective epidemiologic investigations, as well as studies examining Type A behavior as a correlate of angiographically documented coronary artery atherosclerosis. Because inconsistent results are often attributed to differences in the methods used to assess Type A behavior, we begin by defining the behavior pattern and describing briefly the more common measurement techniques.

Definition and Measurement of Type A Behavior

As originally described by the cardiologists M. Friedman and R.H. Rosenman, the prototypic Type A individual exhibits an intense, hard-driving competitiveness, a persistent sense of time urgency, and easily evoked hostility. Type A individuals act with haste and impatience, and speak in an accelerated and emphatic manner; they appear extraordinarily alert, with tense facial musculature, and frequently exhibit a variety of characteristic mannerisms (e.g., clenched fist, repetitive foot tapping). Persons who show few of these attributes are said to illustrate a less hurried and more placid Type B behavior pattern.

Type A behavior is ordinarily measured by one of four methods; these are referred to as the Structured Interview for Type A Assessment, the Jenkins Activity Survey, the Framingham Type A Scale, and the Bortner Rating Scale. When assessed by the Structured Interview (SI), individuals are asked a series of questions pertinent to the definition of Type A (e.g., "Do you think you drive harder to accomplish things than most of your associates?"). The interview questions are also presented in a deliberately challenging manner intended to elicit overt expressions of Type A behavior in the susceptible individual. Hence, the SI not only detects aspects of Type A that individuals report as attributes of themselves, but is sensitive also to the various stylistic manifestations (e.g., gestures, body posture) and paralinguistic features (e.g., hostile voice tone and volume) of which individuals may not be aware.

All other instruments for measuring Type A behavior are self-administered questionnaires in which individuals report the extent to which they possess Type A characteristics. These scales tend to measure the competitive, hard-driving, and impatient aspects of Type A, but not its anger and hostility components. Moreover, these instruments rely on the veracity of the subjects' self-reports and, unlike the SI, are insensitive to expressive attributes of the Type A pattern. While all four instruments purport to measure the same behavioral attributes, correlations among the measures are low, and discrepant Type A-Type B classifications occur frequently when two or more of these instruments are administered to the same individuals. For this reason, we identify the specific assessment techniques used in each of the Type A studies described below.

Epidemiologic Studies

Western Collaborative Group Study. The first prospective investigation to examine the coronary risk associated with Type A behavior was the Western Collaborative Group Study (WCGS). Approximately 3200 employed men, all without history of CHD at the start of the study, were followed for 8.5 years. Type A was assessed by the SI at entry into the study and by the Jenkins Activity Survey (JAS) at the midpoint of the investigation. At follow-up, SI-identified Type A men had roughly twice the incidence of CHD (i.e., myocardial infarction, angina, sudden death) as Type B subjects. This association existed even after simultaneous statistical adjustment for the influences of 12 other common risk factors, including hypertension, serum cholesterol concentration, smoking, and age; the adjusted relative risk ratios were 1.9 among men initially 39 to 49 years of age and 2.0 for men 50 to 59 years of age. In contrast to the SI, JAS-Type A scores were not associated prospectively in multivariate analyses with CHD incidence (adjusted risk ratio, 1.3), but did predict recurrent myocardial infarction (MI) among survivors of an initial infarction.11

Framingham Heart Study. Corroboration of the Type A-CHD association derives from the Framingham Heart Study. Here, Type A behavior, as measured by the Framingham Type A scale, was an independent predictor of the 8-year incidence of CHD and MI among men 45 to 64 years old, and of CHD and angina in women of the same age. In men, these effects were observed only among individuals holding white-collar positions, whereas in women, the Type A-CHD association obtained about equally in housewives and women employed over half of their adult lives. Risk ratios for total CHD, MI, and angina (without MI) were 2.9, 7.3, and 1.8, respectively, in white-collar men, and 2.1, 1.3, and 3.6 in women. In addition, the 10-year incidence of cerebrovascular disease was related to Type A behavior in women, but not in men.13

French-Belgium Cooperative Heart Study. Several other prospective investigations may be cited. In the French-Belgian Cooperative Heart Study, Type
A measured by the Bortner Rating Scale was a significant predictor of total CHD, MI, and sudden death among initially healthy men from three European communities who were followed for an average of 5 years. As in the WCGS and Framingham studies, this effect was independent of serum cholesterol concentration, hypertension, smoking, and age.

Belgian Heart Disease Prevention Trial. The preliminary results of the Belgian Heart Disease Prevention Trial<sup>21</sup> appear to support a Type A-CHD association as well. In this study, individuals scoring in the upper one-third of the distribution of JAS-Type A scores had nearly twice the incidence of MI and sudden death at the 5-year follow-up as did persons in the lower one-third of the distribution. However, no tests of statistical significance or multivariate analyses controlling for other CHD risk factors were reported.

Recurrent Coronary Prevention Project. A fifth investigation, the Recurrent Coronary Prevention Project<sup>18</sup>, is a prospective clinical study that examines whether therapeutic alteration of Type A behavior by psychological counseling reduces the risk of recurrent CHD events among post-MI patients. In this study 592 male patients were given a Type A behavioral “intervention” plus cardiology counseling; an additional 270 patients received cardiology counseling only. At the 3-year follow-up, both groups showed a reduction in Type A behaviors, as assessed by questionnaire and by videotaped SIs; yet amelioration of the Type A pattern was more pronounced in the intervention group. Importantly, there was a significantly lower rate of MI recurrence in the intervention condition compared to patients given cardiology counseling alone (7.2% vs 13.2% respectively). This outcome reflected a difference in the rate of nonfatal MIs (4.1% vs 10.6%) and did not extend to fatal events (3.1% vs 2.6%).

Studies Reporting Negative Results. While the foregoing studies support the hypothesis that Type A behavior increases the risk of clinical CHD, other recent investigations yield essentially negative results. In a 1-year follow-up of 189 male coronary patients, Dimsdale et al.<sup>17</sup> reported that Type B behavior pattern, measured by the JAS, was predictive of new morbidity. In the Multiple Risk Factor Intervention Trial (MRFIT), Type A behavior was also examined as a possible antecedent of clinical events.<sup>16</sup> MRFIT subjects (all males) were CHD-free at intake, but were within the top decile of risk for CHD due to cigarette smoking and elevations in blood pressure and serum cholesterol.<sup>19</sup> As part of this study, all subjects (N = 12,772) were asked to complete the JAS and about one-fourth of the sample were given the SI. At the follow-up, an average of 7 years later, neither CHD nor total mortality differed between Type A and Type B subjects identified by either the SI or JAS.

Two additional studies reporting negative findings are the Multicenter Post-Infarction Program<sup>20</sup> and the Aspirin Myocardial Infarction Study (AMIS).<sup>21</sup> The first of these investigations examined behavioral and physiologic predictors of long-term survival after MI; the second was a clinical trial of the effects of aspirin on the recurrence of MI. Both studies contained male and female post-MI patients and assessed Type A behavior by the JAS. In neither investigation was Type A associated with a recurrence of MI or coronary mortality after a follow-up of 3 years.

Finally, the JAS was administered to 2200 men of Japanese descent in the Honolulu Heart Program.<sup>22</sup> Subjects were CHD-free on entry and were followed for 8 years. Type A behavior in this investigation did not predict total CHD, MI, or angina incidence. However, these findings are somewhat difficult to interpret due to several unusual cohort characteristics. For example, CHD incidence in the population studied, Japanese men, is only about one-half that of the U.S. Caucasian population,<sup>23</sup> resulting in relatively few CHD cases to predict at follow-up. The prevalence of Type A behavior in this project (20%) was also appreciably lower than that seen in other investigations (e.g. 50% in WCGS); the psychometric characteristics of the JAS itself also differ between Japanese and Caucasian samples. Still, it must be concluded that when applied to this low-risk population, JAS-defined Type A is not predictive of later CHD.

Summary and Comment

All the studies reviewed here involved prospective investigations of persons who were either free of CHD at intake or had already suffered a CHD event. Among studies of initially healthy individuals, the preponderance of evidence indicates that Type A behavior — as assessed by the SI, the Framingham Type A Scale, and the Bortner Rating Scale — is predictive of CHD incidence at follow-up intervals of 5 to 8.5 years. In addition, where multivariate statistical analyses have been reported, the increased coronary risk conferred by Type A is independent of influences of other common CHD risk factors. The preliminary findings of the Belgian Heart Disease Prevention Trial also suggest a prospective association between JAS-Type A scores and the subsequent occurrence of MI and sudden death; yet this effect is not replicated in the multivariate results of WCGS, MRFIT, or the Honolulu Heart Project.

In contrast to the generally positive findings of prospective investigations involving initially healthy individuals, studies of persons at heightened risk for clinical events due to previous infarction, or, in the case of MRFIT, due to elevations in traditional risk factors, yield largely negative results. Thus, while Type A predicted recurrence of MI in WCGS, it failed to do so in all other studies of post-MI patients, and, in MRFIT, was unrelated to first occurrences of clinical CHD.

Finally, the one study in which Type A behavior was modified therapeutically in post-MI patients demonstrated fewer recurrent nonfatal MIs among treated subjects. Interestingly, evidences of Type A
behavior declined significantly over the 3 years of follow-up in this study, even among subjects who received standard cardiology counseling only (i.e., no psychological counseling). This result suggests that individuals who elect to participate in intervention trials show a reduction of Type A behaviors over the course of their participation, even when modifying Type A is not germane to the interventions they receive. If generalizable to other Type A investigations involving samples drawn from treatment trials, it is possible that intake assessments of Type A (in studies such as MRFIT and AMIS) do not identify the true distributions of Type A and B individuals that prevailed during periods of active risk (i.e., during the follow-up interval). Unfortunately, an absence of repeat testing for Type A behavior in these investigations precludes a direct examination of this issue.

Clinical Angiography Studies

There are now at least 15 published studies examining the relationship of Type A behavior to the extent of coronary artery atherosclerosis, as seen in patients referred for angiographic evaluation. Type A, when assessed by the SI, has been related to the number of vessels occluded 50% to 75% or more in about half of these investigations. In two studies showing a positive association, multivariate analyses revealed the Type A-atherosclerosis relationship to be independent of other risk factors for CHD (serum cholesterol, smoking, hypertension, sex, and age). With few exceptions, though, Type A has not been related to angiographic evidence of atherosclerosis in studies using instruments other than the SI for Type A evaluation.

Comment

These clinical investigations provide little support for a specific association between the Type A behavior pattern and coronary artery disease, and what evidence does exist is based primarily on Type A assessments derived from the SI. This largely negative conclusion is qualified, however, by several methodologic considerations. First, the subject populations described in the majority of studies are exceptionally heterogeneous, often subsuming individuals who differ in age by more than 50 years. Second, there is a very high prevalence of Type A subjects in these studies (60% to 75% when measured by the SI), compared to the more equal distribution of Type A and B individuals in the general population. This suggests the possibility that systematic selection and referral biases may have influenced subject recruitment in some investigations. Third, other sample characteristics, including demographic attributes and prior medical history (especially, history of previous MI or bypass surgery), vary among studies or are not reported. And finally, these difficulties are compounded by the limited numbers of patients included in most investigations; indeed, the median sample size of the 15 studies cited above was only 117 subjects, suggesting that many of the investigations contributing to this literature possess, at best, only marginal statistical power.

Anger and Hostility

Definition and Epidemiologic Studies

Type A subsumes several behavioral attributes (e.g., competitiveness, time urgency, hostility), yet not all of these characteristics may contribute to risk for CHD. In addition, since designation of individuals as Type A requires evidence only of a preponderance of Type A qualities, the specific characteristics responsible for behavioral classification can vary from person to person. If some Type A attributes are unrelated to coronary risk, the inclusion in the study cohorts of Type A subjects identified by risk-irrelevant characteristics will dilute potential Type A-CHD associations. For this reason, recent studies have sought to identify the components of the Type A pattern that are associated most strongly with atherosclerosis and CHD. What have emerged consistently as risk factors or correlates of coronary disease in these investigations are behavioral characteristics relating specifically to individuals' feelings of hostility and to the manner in which they express anger.

In a reanalysis of data from the WCGS, for example, tape-recorded SI responses of 62 incident cases, identified over the first 4 years of the study, were compared with responses of 124 healthy, age-matched controls. Of more than 40 behavioral ratings, eight discriminated cases from controls, and of the discriminant ratings, most measured aspects of anger and hostility. These included overall ratings of "potential for hostility," explosive voice characteristics, and reports of frequent anger and of feelings of irritation when forced to wait in lines.

Potential for hostility has been described as a "stable predisposition to respond to a relatively broad range of frustrating circumstances with varying degrees and combinations of anger, irritation, disgust, arrogance, contempt, resentment, and the like, which may or may not be associated with overt behavior directed against the source of frustration."

Measurement of this dimension can be derived from the SI, as illustrated in the study described above, or achieved through use of standardized questionnaires. One such measure, the Cook Medley Hostility Inventory, has been found predictive of both CHD and total mortality in two recent prospective investigations. In the first of these studies, 255 physicians who had completed the hostility questionnaire in medical school were followed up 25 years later. The second study reported the 10-year incidence of major CHD events (MI, cardiac death) and the crude 20-year mortality statistics on participants of the Western Electric Study; these individuals had also completed the Cook Medley Inventory at the beginning of the study in the late 1950s. The specific relationship of hostility to CHD incidence in the "physi-
ers, these findings suggest that aspects of anger and hostility represent a "toxic" element of Type A, while other components of the behavior pattern, such as competitiveness and time urgency, may be of lesser importance. If so, these results may help account for the inconsistencies in the overall Type A literature. As noted previously, Type A self-report questionnaires do not measure the anger and hostility component of coronary-prone behavior, and, even when individuals are given the SI, classification of a particular person as Type A may be based on attributes other than potential for hostility.

Life Stress and Social Resources

When examined in epidemiologic and clinical investigations, life stress is typically defined as the numerical accumulation of major life events—such as changes in occupational, financial, or marital status and activities—that occur within specified intervals (e.g., 12 months). Occasionally, these events are quantified further by assigning to each a score or value that is thought to reflect the magnitude of its relative impact on the individual. It is often assumed that the deleterious effects of life stresses are offset or moderated by other (protective) socioeconomic variables, termed social resources. Among these resources are social networks and social supports. Networks define the structure and nature of one's social relationships (number of friends, family size, organizational memberships, frequency of social contacts); social support refers to forms of aid (emotional support, financial assistance) that may be drawn upon in times of distress and that are shared among members of a social network.

Prospective Study of Life Stress and CHD

Only one prospective investigation has examined the predictive significance of both life stress and social resources for coronary morbidity or mortality. In the Health Insurance Plan ancillary study of the Beta Blocker Heart Attack Trial, 2320 male survivors of an initial MI were given a questionnaire assessing, among other psychosocial variables, the subjects' experiences of social isolation and recent life events. The 3-year follow-up revealed that patients scoring high on both the social isolation and life stress dimensions were at elevated risk for sudden cardiac death, as well as for death from all causes. This relationship existed even after multivariate adjustment for the influences of other prominent variables known to affect post-MI prognosis.

Studies of Effects of Social Resources

A few other studies have examined the effects related to social resources, without a simultaneous consideration of life stress. In a sample of 10,000 men participating in the Israeli Heart Study, a report of severe psychosocial problems—particularly, family-related difficulties—and anxiety predicted
the 5-year incidence of angina pectoris. Associated with a lower incidence of angina was the "love and support" of one's spouse, as reflected in the subjects' own perceptions of their marital relationships. In the 8-year incidence data of the Framingham Heart Study, 47 analyses of women who had been employed for more than half of their adult years showed clerical workers to have about twice the CHD risk of either white- or blue-collar working women. Importantly, among the clerical workers, lack of support on the job — having a nonsupportive boss — was a significant and independent predictor of CHD. Additionally, in 4653 men of Japanese descent in the Honolulu Heart Project, 48 low scores on an index of intimate social relationships predicted the incidence of nonfatal MI at follow-up of up to 8 years. After adjustment for influences of other risk factors, however, this relationship attained only borderline statistical significance and did not extend to incidence of fatal MI, angina pectoris, or total CHD.

Comment

Taken together, these studies suggest that life stress and inadequate social networks or poor social support are predictive of all-cause mortality, including CHD-related death. A lack of intimate social relationships was predictive of nonfatal MI alone in one study, however, and, in a second investigation, only the 5-year incidence of angina pectoris was reported. Nonetheless, these data all point to the potential importance of life stress and social resources as psychosocial antecedents of coronary disease.

Whether an absence of social resources is predictive of coronary morbidity or mortality only in the presence of extreme life stress, as postulated by some investigators, remains unclear because concomitant life events have not been evaluated in interaction with social resources in most prospective studies. Perhaps more important, the concepts of life stress, social network, and social support are themselves neither conceptually nor operationally distinct. 49 For example, many significant life events entail losses or breaks in social ties (e.g., relocation or death of a family member) and other events, such as divorce, may be outcomes of longstanding, nonsupportive relationships. Additionally, the impact of some life events may result less from the events per se than from the profound disturbances that they introduce into one's social network. These considerations suggest that much additional work is needed, on both methodologic and theoretical levels, to clarify the relationships between stressful life experiences and the ameliorative influence of meaningful and supportive social relationships.

Animal Models of Behavioral Influences on Atherosclerosis

Experimental investigations in a number of animal models have shown that disruption of the social environment and other behavioral manipulations induce significant atherosclerotic changes, generally of the coronary arteries and aorta. A majority of these studies involve use of nonprimate species, such as rabbits, rats, chickens, and mice. Intimal plaques containing intracellular lipid, macrophages, and smooth muscle cells are not a predominant feature of the arterial lesions usually observed in these animals. In rodents, for example, such lesions generally involve an accumulation of connective tissue proteins and, occasionally, mineral between the elastic layers of the arterial media — a process better termed "medial sclerosis." In other animals such as chickens and rabbits, intimal lipid-containing lesions are observed, but they tend to affect the small intramyocardial arteries rather than proximal portions of the main branch coronary arteries as seen in humans. 50 Nevertheless, the studies of nonprimate species summarized below demonstrate the susceptibility of vascular tissue to a variety of behavioral stimuli. (The morphologic, physiologic, and behavioral characteristics of the animal models commonly used in atherosclerosis research are reviewed more extensively by Kaplan et al. 50).

Studies of Nonprimates

Studies of Ratcliffe and associates 51, 52 offer the earliest descriptions of the atherogenic effects of psychosocial phenomena. These investigators reported that during a period of growing population density at the Philadelphia Zoological Garden, the incidence of arteriosclerosis — defined as intimal thickening, with or without lipid accumulation — rose appreciably in both birds and mammals. These effects were attributed to the "social pressures" arising from conditions of crowding, as neither age nor dietary variables could account adequately for the increased arteriosclerosis seen among these animals.

Subsequent experimental studies by the same investigators examined the effects of deliberate manipulation of the social environment on the coronary arteries of chickens and swine. Chickens forced to live in certain heterosexual groupings, for example, showed greater intramural coronary artery stenosis and myocardial necrosis and more frequent myocardial infarcts, when compared to control animals housed in separated cages. The lesions observed among "stressed" chickens began typically as medial thickening, with or without lipid accumulation — rose appreciably in both birds and mammals. These effects were attributed to the "social pressures" arising from conditions of crowding, as neither age nor dietary variables could account adequately for the increased arteriosclerosis seen among these animals.

In a second experiment, 55 cholesterol-fed swine that were raised in groups developed less extensive coronary artery atherosclerosis than animals given the same diet but raised alone or in pairs. The authors suggest that separation of pigs from their parent groups at 6 to 8 weeks of age, at the onset of the experimental manipulation, was especially stressful in these animals, as it served to disrupt already existing social bonds. These results are also noteworthy.
because the anatomic distribution and morphologic characteristics of coronary artery atherosclerosis in pigs closely resemble those found in humans.\(^{50}\)

The results of other relevant studies may be summarized briefly. First, no significant differences in coronary arteriosclerosis were observed between cholesterol-fed chickens identified as either "aggressive" or "passive" animals.\(^{56}\) In studies of CBA/J mice, on the other hand, it has been reported that: 1) animals reared in socially deprived environments developed arteriosclerosis of the intramyocardial arteries and aorta, as well as arterial hypertension, when forced to interact with control animals raised under normal social conditions,\(^{57}\) and 2) dominant males in colonies housing both females and subordinate males developed greater aortic arteriosclerosis than similarly housed subordinate males or control animals living in standard laboratory cages.\(^{58}\) Finally, it has been observed in rabbits that sudanophilic lesions of the aorta are less extensive when these animals receive preferential care (routine coddling) by the experimenter,\(^{59}\) although failure to replicate the "protective" effect of this manipulation has also been reported.\(^{60}\)

**Studies of Nonhuman Primates**

**Similarities to Human CHD and Social Organization**

The pathologic endpoints in the preceding investigations (except for the one study of pigs) involve lesions of either the aorta or secondary and tertiary portions of the coronary arteries, with or without intimal lipid accumulation. It is generally recognized, however, that nonhuman primates — particularly Old World monkeys such as the macaques and baboons — provide a closer model of coronary artery arteriosclerosis in humans.\(^{50,60}\) These species are susceptible to diet-induced hyperlipoproteinemia, and the arteriosclerosis resulting from such diets consists of lipid-containing intimal lesions similar in morphologic characteristics and location to those seen in human beings. Behavioral considerations also favor use of nonhuman primates in studies of psychosocial influences on atherogenesis. The behavioral repertoires of primates are remarkably complex, with relationships among individuals defined by elaborated patterns of agonistic and affiliative interaction. The social organization of most primate groups is characterized by a matrix of relational bonds (e.g., male–female, mother–infant) and by interindividual hierarchies of social dominance.\(^{61}\) Clearly, many of the prominent dimensions of primate behavior — affiliation, social status, competition, aggression — reflect salient aspects of human social behavior as well. Indeed, some of these dimensions, such as competitiveness and aggression, are analogous to behavioral factors cited earlier as potential contributors to coronary disease in humans.

In one early investigation,\(^{62}\) squirrel monkeys fed a cholesterol-containing diet and exposed to shock avoidance or small-cage restraint developed greater arteriosclerosis of the intramyocardial arteries than control animals given the same diet and maintained under normal housing conditions. Unfortunately, squirrel monkeys (and New World species in general) do not mimic humans and the Old World monkeys in the anatomic distribution of their coronary artery lesions.\(^{63}\) All other biobehavioral studies on arteriosclerosis involving the use of monkeys, however, have used either male or female cynomolgus macaques (*Macaca fascicularis*). An advantage of using the cynomolgus monkey is its vulnerability, given a moderate hyperlipoproteinemia, to the development of fatty streaks and the rapid progression of such lesions to fibrous plaques.\(^{64-67}\) In addition, diet-induced atherosclerotic lesions in these animals often have necrosis, mineralization, and the pooling of fat droplets or crystalline lipid.\(^{68,69}\) Cynomolgus monkeys experience MI more frequently than do other nonhuman primates,\(^{70}\) and, as in human beings, coronary artery arteriosclerosis among male cynomolgus monkeys is more extensive than that observed in females.\(^{71,72}\)

**Behavioral Stress**

Previous observations of macaque social behavior indicate that the introduction of unfamiliar monkeys into an already established social grouping is a potent psychosocial stressor. The sudden appearance of strange monkeys is experienced as a threat to existing associations among the animals and provokes an increased frequency of overt aggressive acts (grabbing, hitting) as group members attempt to reestablish hierarchical associations and affiliative coalitions.\(^{73}\) In turn, these observations have provided the basis for an experimental manipulation used in several recent investigations involving cynomolgus monkeys.\(^{74-78}\) In these studies, behaviorally "stressed" animals were placed in periodically reorganized (unstable) social groups for periods of 20 to 30 months. Groups were composed of five monkeys each, and with every social reorganization (scheduled at 1- to 3-month intervals), all animals were newly exposed to either three or four different monkeys. Unstressed controls in these studies consisted of animals assigned to similarly-sized groups having fixed or stable memberships over the course of the investigation.

**Results of Unstable Grouping and Social Dominance**

Among the male monkeys placed in unstable social groups in the first experiment of this series,\(^{74}\) the high ranking or dominant animals developed more extensive coronary artery arteriosclerosis than did their lower-ranked, subordinate counterparts. In the stable social condition, dominant monkeys did not have greater coronary arteriosclerosis than subordinate animals, and, in fact, dominants here were slightly less affected than subordinates. Descriptively, the intimal lesions observed among these animals...
involved numerous foam cells, extracellular lipid, increased amounts of collagen and elastin, and in some instances, mineralization. The atherosclerotic lesions of "unstable" dominant animals in this experiment differed quantitatively, but not qualitatively, from those seen in subordinate monkeys or in dominant animals housed in stable social groups. Finally, relative to other experimental animals, dominant monkeys from the unstable social condition exhibited higher rates of contact aggression and a disruption of ordinary affiliative interactions.

The influences of psychosocial factors on atherogenesis in this study were statistically independent of the animals' total or HDL cholesterol concentrations, systolic or diastolic blood pressure, ponderosity, and fasting glucose concentrations. Yet, all monkeys were hyperlipoproteinemic due to ingestion of a diet high in saturated fat and cholesterol. In a second experiment reported by the same investigators, 75 significantly greater coronary artery atherosclerosis was observed among animals exposed to the same psychosocial stressor (group reorganization), but fed a "prudent" (low cholesterol/low saturated fat) diet. Lesions observed in the latter study, however, were neither extensive nor likely to progress sufficiently to produce clinical manifestations. A comparison of results of these two studies suggests that while behavioral factors can potentiate atherogenesis in the absence of a high cholesterol/high fat diet, psychosocial influences on lesion development are greatly magnified in the presence of diet-induced hyperlipoproteinemia.

Interestingly, in similar studies of female cynomolgus monkeys, subordinate animals developed greater coronary artery atherosclerosis than dominants. 71-76 As in the preceding studies, the behavioral effects could not be attributed to other common risk variables, including serum lipid concentrations and blood pressure. Ovarian function, on the other hand, was disrupted in many subordinate animals, as evidenced by high frequencies of anovulatory menstrual cycles and by luteal phase progesterone deficiencies. 76 Hence, the authors speculate that a behaviorally associated impairment of ovarian function may compromise the female macaque's ordinary "protection" against coronary artery atherosclerosis. Further support for this suggestion is the recent observation that diet-induced coronary atherosclerosis among cynomolgus females exhibiting high rates of endocrinologically abnormal menstrual cycles is equivalent to that of both males and ovariecetomized female controls.77

Comment

With few exceptions, the foregoing studies demonstrate that behavioral variables contribute to the formation of arterial lesions in a variety of animal models. In pigs and cynomolgus monkeys, moreover, such variables promote development of atherosclerotic plaques that are similar in the coronary arteries to lesions seen in humans. Actual behavioral parameters examined in these studies have involved the animals' responses to naturally occurring or experimentally manipulated environmental stressors, as well as individual behavioral characteristics such as social dominance. The findings reported in studies of male cynomolgus macaques are especially interesting, because animals affected most severely by disruption of the social environment — more competitive and highly aggressive, dominant monkeys — exhibit behavioral attributes that are reminiscent of characteristics associated with CHD in humans (viz., Type A behavior, anger, and hostility). The relationship of atherosclerosis to social subordination in female macaques does not have as direct a parallel among human studies, though, as coronary disease in women appears to be related to the same behavioral variables affecting men.

Whatever their descriptive similarities to psychosocial antecedents of atherosclerosis and CHD in human beings, current studies — particularly those based on a primate model — provide good experimental evidence of the impact of behavioral variables on coronary artery atherogenesis. Ultimately, some of these models may also prove useful in examining the relationship of behavioral factors to clinical manifestations of CHD. Cynomolgus monkeys consuming a high fat diet, for instance, have an incidence of MI approximating that of human beings in industrialized countries, 70 and electrocardiographic and pathologic changes indicative of myocardial ischemia may be observed in these animals after development of only moderate arterial stenosis.78

Potential Mechanisms of Behavioral Influences on Atherogenesis

It is noteworthy that epidemiologic and clinical investigations in humans, as well as experimental studies in nonhuman primates, show behavior-coronary disease relationships to be independent of the effects of other physiologic variables associated with atherosclerosis and CHD. The most notable of these other variables are serum lipid concentrations, blood pressure, and, in human beings, cigarette smoking and age. While the mechanism(s) by which psychosocial factors potentiate lesion development are thus unknown, it has been suggested that acute autonomic nervous system and neuroendocrine reactions to stress may contribute to atherogenesis.79-82 Such speculation derives, in part, from the observations that: 1) individuals vary greatly in the magnitude of their physiologic responses to behavioral stimuli; 80 and 2) Type A individuals often exhibit more pronounced cardiovascular and neuroendocrine (e.g., catecholamine) responses than Type B individuals when exposed to frustrating laboratory tasks or other behavioral challenges.84 Also, in several clinical studies it has been reported that CHD patients...
exhibited larger pressor reactions to behavioral stressors than did non-CHD patients or nonpatient controls.85-89 and, in one prospective investigation, large diastolic blood pressure reactions to the "cold pressor test" (immersion of a limb in cold water) were found to predict the 23-year incidence of CHD.90 From such findings, it has been hypothesized that recurrent episodes of acute "psychophysiologic" reactivity may promote atherosclerosis, either through the hemodynamic disturbances related to acute rises in heart rate and blood pressure (e.g., turbulence, sheen stress)79 or as a result of physiologic changes associated with an increased release of certain neuroendocrine hormones (e.g., catecholaminergic influences on platelet aggregation).90-92

Hemodynamic factors clearly play a role in atherogenesis, as in the case of arterial hypertension. Yet among normotensive individuals, it is difficult to isolate hemodynamic influences on lesion development from concomitant effects of the many neurohumoral factors that contribute to cardiovascular regulation. Still, there is some evidence that hemodynamic variables other than hypertension are involved in the pathogenesis of atherosclerosis. Recently, Glagov and colleagues93 suggested that an elevated heart rate alone predisposes one to atherosclerosis at arterial sites subjected to abrupt changes in the direction and strength of pulsatile blood flow, as at the carotid bifurcation or in proximal portions of the coronary arteries. These investigators reported that cholesterol-fed cynomolgus monkeys having either a naturally low heart rate or a heart rate lowered through sinoatrial node ablation developed substantially less coronary artery atherosclerosis than did sham-operated controls having higher heart rates and maintained on the same diet. Significantly, the high and low heart-rate groups did not differ in serum cholesterol or triglyceride concentrations, body weight, or systolic or diastolic blood pressure. Extrapolating from these findings, the authors suggest that protracted elevations in heart rate, when evoked by behavioral factors, may account similarly for associations between psychosocial variables and atherogenesis.

Preliminary evidence of an association between heightened cardiovascular reactions to stress and severity of coronary artery atherosclerosis in an animal model is reported in two other studies of cynomolgus macaques.76,77 Study animals in these investigations were drawn from two of the biobehavioral experiments on cynomolgus monkeys described previously; these were both studies in which all animals were fed a moderately atherogenic diet. It was first observed that, like human beings, both male and female macaques exhibit large individual differences in the magnitude of heart rate elevations they experience during exposure to a standard laboratory stressor (in this case, threat of capture). This variability of heart-rate response permitted the partitioning of animals into clearly differentiated groups of high or low heart-rate reactive monkeys. Necropsy of the animals shortly after the heart-rate assessments were conducted revealed that high heart-rate "reactors" of both sexes had nearly twice the extent of coronary artery atherosclerosis as their low heart-rate reactive counterparts. A similar relationship was also observed at the carotid bifurcation.83 Interestingly, behavioral attributes of the monkeys correlated with individual differences in heart rate response as well. Among males, for instance, heart rates increased most appreciably in response to the experimental stressor in highly aggressive animals, while in females, the largest heart-rate elevations were associated with social subordination and low rates of aggressive behavior.

As noted earlier, it is conceivable that the various patterns of neuroendocrine response to stress also mediate the effects of behavior on atherosclerosis. The cardiovascular adjustments evoked by psychosocial stressors, for instance, are typically accompanied by a more general elevation in sympathetic-adrenal medullary activity. In turn, elevated concentrations of circulating catecholamines have been implicated occasionally in the development of arterial lesions. This may involve effects directly on the artery wall or influences on other pathogenic processes, such as alterations in lipid metabolism and platelet aggregation.90,94,95 In addition, both the pulsatil-adrenal cortical and gonadotropic systems are highly reactive to disruptions of the social environment, and, in many species, are influenced by the animals' social status. The release of corticosteroids is increased when animals are exposed to uncontrollable aversive stimuli and may also be associated with subordinate social status.83 In one clinical investigation, moreover, severity of angiographically assessed coronary atherosclerosis was greatest in men having high plasma cortisol concentrations.96 In a second study, cortisol was found to correlate positively with plasma cholesterol concentrations, but only among Type A individuals.97

With respect to the reproductive hormones, the testosterone concentrations of dominant males are often reported to be greater than those of subordinate animals in both rodents and primates;98 these are two mammalian orders in which social dominance has also been found to predict development of arterial lesions in males, under certain stressful conditions.96,74 In females, as described previously, both a greater severity of coronary artery atherosclerosis and subordinate social status have been associated with chronic ovarian endocrine deficiencies among cynomolgus macaques fed a cholesterol-containing diet.76 These diverse associations are admittedly indirect and, as yet, experimental linkages between the matrix of behavioral and neuroendocrine relationships and atherogenesis do not exist. Nevertheless, sensitivity of the catecholamines, corticosteroids, and reproductive hormones to the same psychosocial factors that are associated with development of arterial lesions in animal models encourages speculation that humoral influences may ac-
count for some portion of the behavioral contribution to risk for atherosclerosis.

Finally, a related question concerns the relative impact of behavioral factors at successive stages in the natural history of atherosclerosis. This question is not easily answered from available studies of non-human primates, as endpoint lesions described in these investigations usually involve well-advanced atherosclerotic plaques, many showing evidence of mineralization, necrosis, and hemorrhage. Yet, it has been suggested that behavior may influence even the earliest stages of lesion development involving injury to arterial endothelium.96 Two recent experiments demonstrate that exposure to behavioral stress does promote endothelial injury in laboratory rats.100, 101 In one study,101 experimental animals were subjected to physical restraint for 5 days and, together with unstressed controls, were infused with tritiated thymidine (a label taken up preferentially by the nuclei of actively replicating cells). Subsequent autoradiographic examination of the aortic intimas of these animals revealed significantly higher rates of endothelial cell replication among restraint-stressed rats, relative to controls. In addition to endothelial damage, the restraint manipulation elicited a significant hemodynamic response, reflected in elevations of heart rate and blood pressure. Administration of propranolol to comparison groups of similarly stressed rats both attenuated the cardiovascular response to physical restraint and “protected” the aorta against stress-induced endothelial injury.

These findings suggest that a sufficiently potent behavioral challenge can cause endothelial cells to turn over in a matter of days and that this effect may be attributable to the cardiovascular adjustments associated with sympathetic nervous system responses to stress. From such injury may follow: 1) infiltration of plasma lipoproteins into the intima, due to increased permeability of the replicating endothelium; and 2) release of mitogenic substances by newly regenerated endothelial cells, promoting intimal smooth muscle cell proliferation and accompanying disruption of the lipid metabolism of these cells.99, 102, 103 If behavioral stimuli can potentiate atherogenesis in this manner, it is reasonable to hypothesize that persons who exhibit a psychophysiologic hyperreactivity under stress will be at greater risk for development of atherosclerosis than less reactive individuals. The studies of stress-induced heart rate reactivity and atherosclerosis in cynomolgus macaques provide initial support for this hypothesis.78, 92 However, much additional investigation is needed to establish adequately, both in animal models and in human beings, a truly prospective association between individual differences in cardiovascular or neuroendocrine reactivity and atherogenesis.

Summary

Over 50 epidemiologic, clinical, and experimental studies of behavioral influences on atherosclerosis and CHD have been reviewed; of these investigations, no more than five were published prior to 1975. Despite some inconsistencies and occasional conceptual and methodologic problems in the studies comprising this relatively young literature, the preponderance of available evidence indicates that psychosocial variables play a significant role in coronary disease. To summarize briefly, the Type A behavior pattern has been found predictive of new CHD in nearly all prospective studies of initially healthy individuals, and therapeutic modification of Type A has been shown to reduce risk of recurrent nonfatal MI. Among most prospective studies of post-MI patients and of persons at heightened risk for CHD due to elevations in traditional risk factors, however, Type A has not been found to predict, respectively, recurrence of MI or initial clinical events. Additionally, Type A individuals have shown more extensive coronary artery atherosclerosis on angiographic examination than Type Bs in a minority of studies, and, generally, only where Type A behavior has been measured by the SI. It is noted that many of these clinical studies may be faulted, though, for their use of small and heterogeneous patient samples and for possible biases in the selection and recruitment of subjects.

In contrast to the globally defined Type A pattern, a high potential for hostility and an inability or unwillingness to express anger (anger-in) have emerged as significant predictors or correlates of coronary disease in all epidemiologic and clinical studies in which these variables have been examined. These consistent results suggest that a predisposition to hostility and anger, and the inhibited expression of such feelings, represent a “toxic” component of the Type A pattern. Several recent prospective investigations indicate also that high levels of life stress and possession of poor or inadequate social resources are predictive of CHD. The concepts of life stress, social network, and social support, as well as relationships among these variables, are not well-understood, however, and much additional work is needed to identify specific pathogenic and protective attributes of the social environment.

In addition to studies of the psychosocial antecedents of CHD in human beings, there now are several published studies of behavioral influences on the development of coronary lesions in animal models. In the majority of these investigations, experimentally manipulated environmental stressors and/or individual behavioral characteristics, such as social dominance, have been found to promote lesion development. In cynomolgus monkeys — which develop intimal lesions of the main branch coronary arteries similar to those seen in humans — chronic disruption of social group memberships has been found to potentiate atherogenesis among males, primarily in the more aggressive, dominant animals. These effects have been reported in studies of both hyper- and normolipoproteinemic monkeys. Among females of the same species, it appears that coro-
nary artery atherosclerosis is associated most strongly with subordinate social status.

Almost without exception, behavior-coronary disease relationships described in the studies of both human beings and animal models have been independent of the influences of other physiologic variables often associated with atherosclerosis and CHD (e.g., serum lipids, blood pressure, smoking, age). Preliminary observations suggest that the hemodynamic disruptions associated with sympathetic-adrenal medullary reactions to stress may potentiate atherogenesis. Cynomolgus monkeys responding to a controlled laboratory stressor with exceptionally large elevations in heart rate, for example, have shown more extensive coronary artery atherosclerosis on necropsy than animals exhibiting a less pronounced cardiac response to stress. It has also been proposed that neuroendocrine reactions to behavioral stimuli, particularly those involving the catecholamines, corticosteroids, and reproductive hormones, may contribute to atherogenesis. Although such relationships are still highly speculative, there is some evidence that chronic ovarian endocrine deficiencies among female cynomolgus macaques are associated with both social subordination and an increased extent of coronary artery atherosclerosis. Finally, exposure to physical restraint, a behavioral stimulus eliciting appreciable increases in heart rate and blood pressure, has been shown to induce endothelial injury in the aortic intimas of laboratory rats. This influence on the earliest stages of atherogenesis appears to be mediated by actions of the sympathetic nervous system, as beta-adrenergic blockade is protective against both the hemodynamic and endothelial effects of this experimental stressor.

References

17. Dimsdale JE, Gilbert J, Hutter AM, Hackett TP, Block PC. Predicting cardiac morbidity based on risk factors and coronary angiographic findings. Am J Cardiol 1981;47:73–76
21. Shekelle RB, Gale ME, Norusis M. For the Aspirin Myocardial Infarction Study Research Group: Type A score (Jenkins Activity Survey) and risk of recurrent coronary heart disease in the Aspirin Myocardial Infarction Study. Am J Cardiol (in press)
26. Frank KA, Heller SS, Kornfeld DS, Sporn AA, Weiss MB. Type A behavior pattern and coronary angiographic findings. JAMA 1978;240:761–763
31. Kranitz DS, Schaeffer MA, Davis JE, Dembroski TM, MacDougal JM, Shaffer RT. Extent of coronary atherosclero-
Type A behavior: Not specifically pathogenic.


94. Haftl JI. Cardiovascular injury induced by sympathetic catecholamines. Prog Cardiovas Dis 1974;17:73–86

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