The Pathogenesis of Atherosclerosis and Coronary Heart Disease*

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Fifty-five percent of all deaths in the United States are ascribed to cardiovascular disease. The vast majority of these deaths are due directly or indirectly to atherosclerosis and its ischemic complications (table 1, Am. Heart Assoc., 1965; U.S. President's Commission on Heart Disease, Cancer and Stroke, 1964).

Atherosclerosis is defined in Dorland's dictionary (24th edition) as "a lesion of large and medium-sized arteries with deposits in the intima of yellowish plaques containing cholesterol, lipoid material and lipophages." Typical atherosclerotic lesions of the coronary arteries are shown in figure 1. Even a casual inspection of these lesions shows the incompleteness of this conventional definition. It is obvious that thrombosis accounts for the occlusive terminal phase of atherosclerosis and, indeed, is supposed by some to initiate atherosclerosis.

The pathogenesis of the atherosclerotic plaque and of the overlying occluding thrombus remains disputed (Katz and Stamler, 1953; Moses, 1963; Sandler and Bourne, 1963; Thomas et al., 1965). The classical theory of atherogenesis propounded by Anitschkow is probably the most widely accepted. This theory holds that there is a continuous percolation of lipids from the blood stream through the endothelium and media of large and middle-sized arteries. Presumably above some threshold value, the presence of lipids, notably cholesterol, in the inner vascular coats induces the proliferation of primitive smooth muscle cells and disruption of the internal elastic membrane. These new cells appear in the subendothelial space and, along with increasing amounts of amorphous and fibrillar material, raise a fibrous plaque. These lesions are characteristically segmental, occur primarily at points of shearing stress, and are probably universal in all humans. While, unlike the simple antecedent fatty streak, the fibrous plaque is irreversible, it does not impede blood flow and is of no clinical consequence (Thomas et al., 1965). Progression of the proliferative lesion frequently leads to necrosis and the accumulation of more lipid and debris, forming the typical atheroma. Ultimately the atheromatous plaque may rupture, discharge its pultaceous contents into the arterial lumen, and form an atheromatous ulcer. A clot promptly forms over this devitalized and denuded surface, which may be large enough to occlude the already narrowed lumen. This sequence of events seems plausible, but it is curiously rare to find an occluding clot in the coronary arterial system when death has occurred immediately (Weinberg and Helpern, 1959). It is quite possible that fibrinolytic activity persisting after death could account for this phenomenon. If the victim has survived a few hours before death, however, a clot is regularly found. This has led to the paradoxical suggestion that myocardial necrosis may cause the thrombosis (Warren, 1965; Myasnikov, 1964). Occlusion of the arterial inflow to the brain, to a kidney, to a leg, or other organ evokes appropriate signs and symptoms of acute ischemia. These complicated atherosclerotic lesions give rise to no symptoms before occlusion, although they can be visualized by angiogram. The chronic atheroma tends to become cicatricial and calcified.

The major competing theory of atherogenesis is the thrombotic theory originally suggested by Rokitansky and recently revived and extended by Duguid (1949; Katz and

TABLE 1
Deaths and Death Rates for Cardiovascular Diseases by Specific Cause in the United States in 1962*

Cause of Death	Rate per 100,000
Coronary heart disease	284
Stroke	106
Hypertension; hypertensive heart disease	40
Myocardial degeneration	27
General arteriosclerosis	20
Rheumatic fever; rheumatic heart disease	10
All other cardiovascular disease	28
Total	515

*Cardiovascular Diseases in the U.S. Facts and Figures. New York: Am. Heart Assoc., 1965.

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Stamler, 1963; Morgan, 1956; Moses, 1963). Proponents of this theory maintain that the initiating event is the deposition of a clot, perhaps first a platelet clump, but ultimately a fibrin clot. For some reason fibrinolytic mechanisms do not promptly dispose of the clot, which becomes organized, imbibes fat, and finally presents a picture indistinguishable from that of the atheromatous plaque already described. The arterial blood pressure flattens the clot into a lamellar structure; repeated episodes of thrombosis literally silt up the vessel. The thrombotic theory of atherogenesis is especially attractive since it supplies a common explanation for the atheroma and the occluding clot. Although not disproved, neither has it been shown that in patients with clinically manifest atherosclerosis are clotting tendencies enhanced or fibrinolytic activity diminished. Acute alterations in platelet stickiness may be importantly involved in atherogenesis (Slack et al., 1964).

Whatever the ultimate nature of the atherogenic process, it is clear that numerous ancillary factors are involved such as the physical characteristics and composition of the vessel wall; its mobility and the thickness of the tunics; rheological forces; and the amount and the suspension stability of the lipids in the blood. The most frequent and the most lethal manifestation of atherosclerosis is coronary heart disease (CHD), which becomes increasingly common after early middle life when its socioeconomic impact is most devastating. The sequence of events culminating in a heart attack usually evolves over several decades. The diagnosis of CHD prior to this late and often immediately fatal complication is impossible by ordinary clinical methods. Compared with an acute infectious disease, the study of CHD is fraught with many and possibly insuperable problems, as illustrated in table 2. A short time course and specific causation typify acute infectious diseases, while chronicity and multifactorial causation are the rule with degenerative diseases. It is well to remember that *chronic* infectious diseases tend to be protean in their manifestations which may evolve only over many years and are often misdiagnosed despite the ready availability of specific diagnostic tests. Tuberculosis and syphilis need only be cited. Historically, many infectious diseases yielded to empirical modes of control before it was known that they were transmitted by specific biological agents, for example malaria, puerperal fever, and typhoid fever. Such interventions were made possible by accurate observation of host and agent and environment, in short, the epidemiological method. Analogously, it is hoped that the careful longitudinal study of degenerative diseases such as CHD may provide clues to effective, even if empirical, modes of treatment and prevention. Epidemiology is no more than the application of clinical methods to large groups of individuals who can be defined biologically, chemically, culturally, occupationally, and so forth. The interaction of disease and host is observed over time, as modified by endogenous and environmental factors: the ecology of disease. From systematic observation it becomes possible to identify certain etiological factors, that is, characteristics of both host and environment, which appear to be associated with high and low incidence rates of disease. Some of these etiological or risk factors are in theory susceptible to deliberate prophylactic and therapeutic modification. In the case of CHD it is hoped, but far from proved, that such intervention may lessen morbidity and mortality rates. Several of the presently recognized risk factors will now be enumerated and briefly discussed.

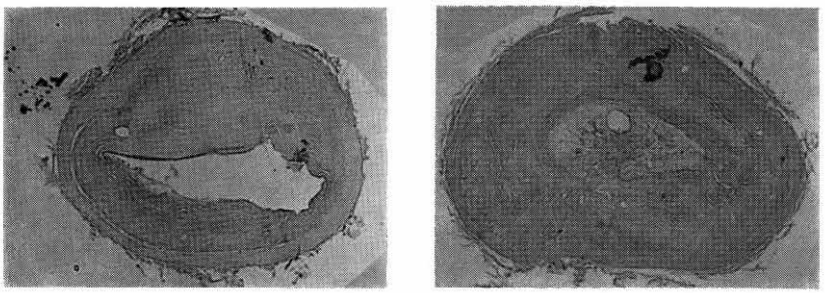

Fig. 1—Atheromatous lesions of human coronary arteries.

TABLE 2
Contrasting Features of Acute Infectious and Chronic Degenerative Diseases

Nosologic Features	Typhoid Fever	Coronary Heart Disease
Pathology	Specific	Atherosclerosis+?
Etiology	*S. typhosa*	Unknown
Pathogenesis	Well defined	Controversial
Susceptibility	Measurable	Not measurable
Clinical Course	Well defined	Silent until onset of myocardial ischemia
Symptoms	Variable	None
Signs	Well defined	None
Treatment	Chloramphenicol	None
Prognosis	Fairly reliable	Unknown
Prophylaxis	Available	Not available

Age. It is by now clear that coronary heart disease is not an inevitable consequence of ageing, for there are populations in which the disease is rare even in old age

(Katz and Stamler, 1953). On the other hand, in susceptible populations, the rate of CHD increases rapidly with age as an expression of the longer operation of pathogenetic mechanisms (fig. 2).

Race. It is doubtful that ethnic origin per se plays a significant role in CHD. All evidence points, rather, to environmental and economic factors as explanations of the observed differences in attack rates between various racial groups (Keys et al., 1958). Undoubtedly heredity also plays an important role, but it is virtually impossible to dissociate nature from nurture.

Local factors characterizing and modifying the wall of the blood vessel have already been briefly mentioned. It should not be forgotten that atherosclerosis may be a non-specific response to any sort of trauma to the vascular lining, specially modified by the presence of large quantities of circulating lipids.

Constitutional factors. The *sex* differential in CHD has long been recognized. The rate of death from CHD in men is far greater than for women until the eighth decade. This disproportion appears to be due to the greater frequency of thrombotic occlusion in men, for the frequency of atherosclerosis at autopsy is about the same for both sexes at all ages (Roberts, Moses, and Wilkins, 1959). Estrogenic activity is the most obvious sex difference, and many studies have purported to show an excess of CHD in women castrated well before the naturally anticipated menopause (Underdahl and Smith, 1947; Robinson, Higano, and Cohen, 1959; Oliver and Boyd, 1959). In these studies, however, angina pectoris has been the primary manifestation of coronary heart disease. In a large and well-controlled study in which either proved myocardial infarction or an abnormal electrocardiographic response to exercise was required as evidence of CHD, no difference between oophorectomized women and hysterectomized but not oophorectomized women was found (Ritterband et al., 1963). *Diabetes mellitus* is notoriously associated with early and severe complicated atherosclerosis. *Myxedema* is traditionally associated with severe atherosclerosis, but statistical verification is wanting. *Obesity* is popularly supposed to increase the risk of a heart attack. As will be shown, there is little evidence that this is true short of gross overweight. The *somatotype* is supposed to be related to coronary proneness. The heavyset, muscular type of man who has run to fat and sloth is considered especially vulnerable. There is, however, no scientific validation of somatotyping (Gertler and White, 1954). *Lipid metabolism,* of all observable and measurable items, seems to show the closest association with atherosclerosis and its ischemic complications. The fat contained in the atheroma and circulating in the plasma are identical in composition and distribution (Page, 1954). The higher the serum cholesterol concentration of groups, not of specific individuals, the higher the incidence rate of CHD (Doyle et al., 1957a; Kannel et al., 1961; Slack et al., 1964). The factors that modify the absorption, transport, clearance, and ultimate disposition of lipids are the objects of intensive research. *Hypertension,* as would be expected, unfavorably influences the course of atherosclerosis. The *emotions* have long been uncritically accepted as playing an important role in disease states, particularly those affecting the heart. It is possible to construct plausible hypotheses implicating emotional stress in atheroma and in thrombus formation, but thus far no scientific evidence has been mustered to support such speculations.

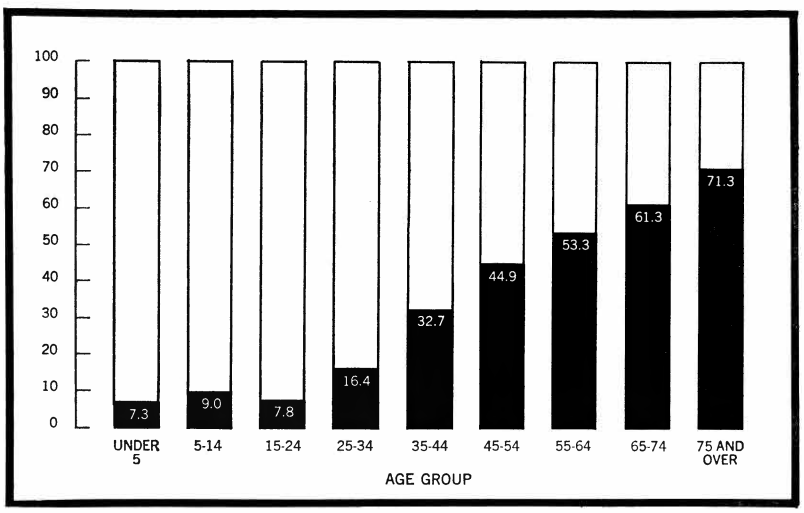

Fig. 2—The increasing death rate from coronary heart disease (CHD) with increasing age as the percentage of all deaths.

Environmental factors. These factors lend themselves well to systematic enumeration and study. This exercise is felt to be worthwhile since so many can potentially be modified with a view to favorably influencing the course of atherosclerotic disease. *Occupation* in some studies has appeared to be associated with an increased incidence of CHD (Moses, 1963). Increased levels of habitual *physical activity* have usually been thought to confer some immunity and sedentary habits to predispose to CHD. The evidence is conflicting, however, and the accurate assessment of physical activity is difficult and unreliable (Moses, 1963). Moreover, with the almost universal application of power assists, few

occupations remain in this country which demand sustained heavy energy expenditure. *Diet* has received great attention. In both world wars, but more accurately documented in the second, there was a striking drop in cardiovascular deaths as well as in thromboembolic disease in those countries in which fat consumption was greatly restricted due to drastic food rationing. The specificity of such an association is, of course, highly questionable (Katz and Stamler, 1953; Moses, 1963). There is, nonetheless, a great intuitive appeal to the proposition that dietary fat intake is closely related to blood lipid levels and to atherosclerosis. The limited observations of Keys, first in southern Italy and subsequently extended to several European countries, have seemed to offer persuasive support to this theory (Keys and Anderson, 1954). The grave difficulties of obtaining reliable information on the amount and type of food actually consumed and differences in physical activity, as well as in other variables, demand extreme caution in the acceptance of this simple triangular hypothesis (Yerushalmy and Hilleboe, 1957). In the United States substantial variations in fat intake in carefully studied populations show no correlation with blood lipid values or with the incidence of new events of CHD (J. H. Browe et al., unpublished data). Recent appreciation of the important influence of carbohydrate intake on blood lipid values further complicates the picture. *Toxins* of all conceivable varieties could in theory play a role in atheroma formation. Trace elements, the mineralization of water, infections and smog have all been suggested. Only tobacco smoking, as will be shown subsequently, has been found unequivocally to be associated with increased rates of CHD.

These, then, are the major factors which are thought to have more or less important associations with CHD. This information originally derived from many sources: clinicians, hospital wards, the autopsy room, death certificates. A major limitation of such information is that it is retrospective. It has been gathered after the event of CHD and hence from a highly selected population. Little if anything is known of the characteristics of the entire population or universe from which the patients come. Numerous selective factors operate which either bring the patient to attention or cause his being overlooked. Observations are unstandardized and, more often than not, incomplete. The alternative to these types of studies is the prospective study, which directs its attention to a defined population from a known universe and employs standardized criteria and observational methods to all participants. Such studies are not particularly glamorous; are laborious in that painstaking, repeated observations must be made for many years; are tremendously expensive; and are, to some extent, inflexible since the experimental design cannot be much altered. Furthermore, unpredictable variations in the characteristics of the population may occur which could influence prognosis: they might, conceivably, all start exercising or stop smoking, or drinking, or overeating. It is scarcely surprising that few such studies have been undertaken. These are, notably, the United States Public Health Service study of a random sample of adult men and women residing in Framingham, Massachusetts, which began in 1949; and the Albany Cardiovascular Health Center study of a large group of middle-aged men working for the State of New York, sponsored by the Health Department, which began in 1953 (Doyle et al., 1957b; Dawber, Moore, and Mann, 1957). Despite various methodological differences, it is gratifying that information on the prevalence and incidence of CHD in these two studies is remarkably similar and is, indeed, very similar to information gathered in other areas of the United States.

Selected findings from the Albany study will now be presented with brief comment on their significance and limitations. The mode of presentation is in the form of a modified life table. This technique permits the amalgamation of observations made for varying lengths of time on individuals of differing age. It must necessarily be assumed that the intensity of the disease process is constant over time and within chronological age (Kinch, Gittelsohn, and Doyle, 1964).

On admission to the study, approximately 3% of the men, then between the ages of 39 and 55 years, had some manifestation of coronary heart disease. Figure 3 shows that the average annual incidence of CHD in the Albany study is about 1%. This basic statistic in the subsequent figures is related to various characteristics

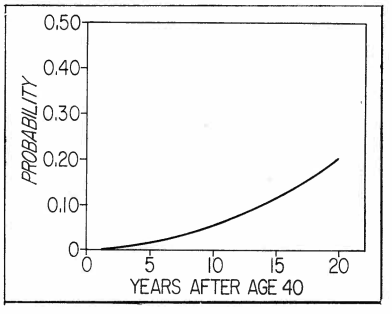

Fig. 3—Annual incidence rate of all manifestations of CHD in men over 40 in the Albany study.

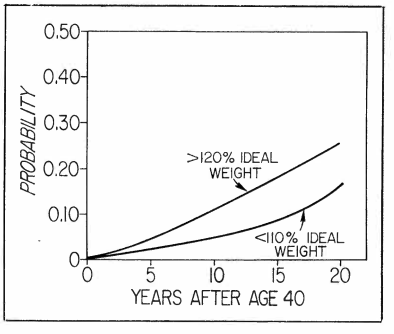

Fig. 4—Annual incidence rate of all manifestations of CHD in relation to total body weight.

thought to influence risk. Incidence rates are related to characteristics measured at the time of entry into the study.

In figure 4 risk of CHD is related to ideal body weight according to the standards of the Metropolitan Life Insurance Company. Little positive or negative association is apparent here, in the Framingham study, or in other studies. It seems likely that the hapless overweight patient has been made a whippingboy on little other than esthetic grounds.

In figure 5 risk of CHD is related to blood pressure standards promulgated some years ago at the Princeton Conference (Doyle, 1960). Once again there is little relationship between blood pressure level and the incidence of CHD. More recently, however, we have reviewed the experience of individuals whose diastolic blood pressure was 100 mm Hg or more on at least half the occasions they were examined. A substantially higher incidence rate of CHD occurs in the consistently and definitely hypertensive population. This observation illustrates particularly well a serious methodological difficulty of the prospective studies, viz. the unavailability of statistical technique to evaluate the influence on prognosis of a risk factor of varying intensity. The arterial blood pressure is notoriously variable. While by arbitrary criteria about 20% of our group are at any one time hypertensive, the composition of this group varies greatly and unpredictably from year to year.

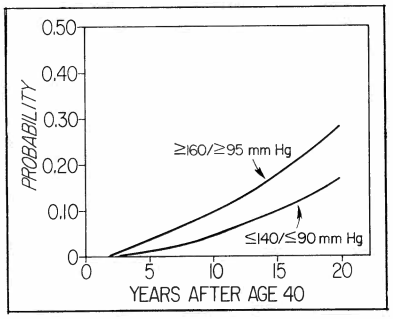

Fig. 5—Annual incidence rate of all manifestations of CHD in relation to arterial blood pressure.

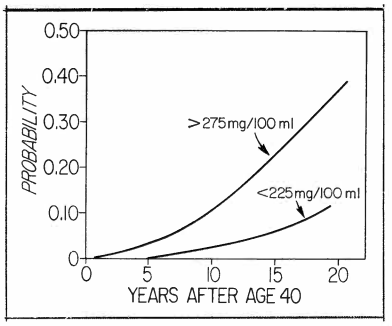

Fig. 6—Annual incidence rate of all manifestations of CHD in relation to serum total cholesterol.

In figure 6 the serum total cholesterol concentration at the time of entry into the study is related to the subsequent experience of CHD. It is clear that those whose cholesterol was below the mean faired better than average while those with only moderate hypercholesterolemia or higher had a rate at least four times higher than the favored group. There is a gradient of risk: the higher the cholesterol level the greater the likelihood of CHD. Unlike the arterial blood pressure, the serum total cholesterol concentration remains remarkably constant so long as it is measured in the same season of the year (Doyle, Kinch, and Brown, 1965). It has been suggested that the serum triglyceride level might be better correlated with susceptibility to CHD than cholesterol. That this is not true is shown in figure 7, in which the population has been divided into thirds according to cholesterol and triglyceride levels (Brown, Kinch, and Doyle, 1965). The geometric relationship of serum total cholesterol and of triglyceride concentrations with the incidence of CHD are different, but neither shows a superior predictive value and both are nearly identical in the higher ranges.

The association between the use of tobacco and the incidence of CHD has been of particular interest since the first major studies of lung cancer. These surveys showed, of course, a twenty-fold greater likelihood of bronchiogenic carcinoma in heavy cigarette smokers than in non-smokers. They also showed a great excess of deaths from CHD (Doll and Hill, 1956; Hammond and Horn, 1958a and b; Dorn, 1959). The early observations made in the Framingham and Albany studies failed to show a significant relationship between tobacco habit and the prevalence and incidence of CHD. Since it appeared likely that this was a statistical artefact due to insufficient numbers, it was decided to pool information on men exposed to risk. This collaborative effort, based on observations made over six to eight years on 4,120 men between the ages of 30 and 62 years, provided convincing evidence that the consumption of 20 or more cigarettes daily is associated with an incidence of sudden death or of myocardial infarction over three times greater than in non-smokers (fig. 8). Ex-smokers and pipe and cigar smokers appeared to be at about the same risk as non-smokers. An anomalous finding was that there is no association between smoking habit and angina pectoris (Doyle et al., 1962; 1964). Similar observations had been made years previously by White and Sharber (1938). This apparent discrepancy may, however, be one of several pieces of collateral evidence that the anatomic and physiologic bases of angina may be different from other manifestations of CHD.

It is only natural to query whether combinations of these risk factors are associated with a risk of CHD equal to or greater than the sum of their individual contributions. Figure 9 is an attempt to answer this question. As might intuitively be assumed, hypertensive, hypercholesterolemic heavy smokers have a risk of CHD five times as great as individuals without these characteristics. Since, however, there are fewer than 8% as

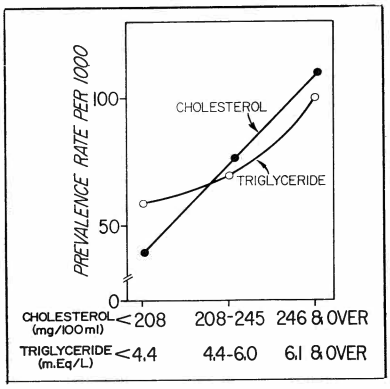

Fig. 7—Annual incidence rate of all manifestations of CHD in relation to serum total cholesterol and serum triglyceride concentrations.

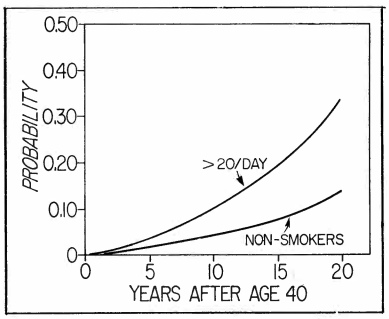

Fig. 8—Annual incidence rate of all manifestations of CHD in relation to cigarette consumption.

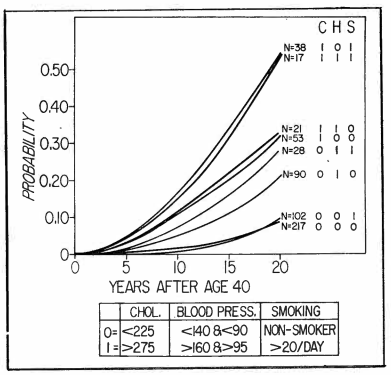

Fig. 9—Probability of developing CHD by cholesterol (*C*), hypertension (*H*), smoking (*S*). Venn diagram, illustrating how few individuals exhibit multiple risk factors.

many individuals in the high risk as in the low risk group, it cannot be asserted with statistical confidence that these differences are real. The solution of the problem of accumulating adequate numbers of reliable observations on the influence of multiple risk factors on susceptibility to CHD is extraordinarily difficult. In the past year we have done cardiovascular screening studies on 6,000 men and women between the ages of 21 and 71 years and have found the combination of risk factors considered in figure 11 in only a very small number of men and women.

Cardiovascular disease, especially CHD, at present accounts for more than half of all deaths in the United States. The anatomic basis of coronary heart disease is narrowing of the coronoray arteries by atherosclerosis. In the majority of instances where death occurs more than a few hours after a heart attack, a fibrin clot is found to have occluded the diseased artery and caused ischemic necrosis of the myocardium nourished by that artery. The pathogenesis of atherosclerosis and of thrombosis is unknown; it is possible that they represent different stages of the same process. Epidemiological studies of the relationship between measurable biological characteristics of defined individuals at risk have permitted identification of what seem to be important etiological factors in CHD. These include the relative immunity of women from the ischemic complications of atherosclerosis; sustained diastolic hypertension; an elevated serum total cholesterol concentration; and consumption of 20 or more cigarettes daily. It is probable but unproved that diet, specifically the ingestion of large amounts of saturated fats, may cause hypercholesterolemia, activate clotting mechanisms, and thus lead to an increased risk of CHD. It is likewise unproved that habitually high levels of physical activity protect against CHD. There is no acceptable evidence that prolonged stress influences the frequency of CHD. Although it is probable that combinations of risk factors increase the risk of CHD, no prospective study has yet been able to provide sufficient numbers of cases to prove this point or to indicate whether risk is simple or compounded.

There is understandably tremendous popular pressure, despite our still inadequate knowledge of the pathogenesis and etiology of CHD, to plunge into widely advertised evangelistic programs for the prevention of CHD. In such an emotionally charged atmosphere it is almost impossible to evaluate such efforts in the required detached and objective fashion. Indeed, it may fairly be questioned whether practical and effective modes of intervention in the course of CHD are yet available. It is to be feared that public disenchantment with such premature interventions may gravely impede scientific investigation into the seats and causes of this major threat to health and longevity.

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