Reprinted from Progress in Cardiology—10, edited
by Paul N. Yu and John F. Goodwin.

Chapter 2

FUTURE TRENDS IN THE PREVENTION OF CORONARY HEART DISEASE

Part III. Prevention of Coronary Heart Disease: A Cardiologist's View

Frits L. Meijler, M.D.

It is much easier to write upon a disease than upon a remedy.

William Withering, 1778

Why have the editors of this book asked a clinical cardiologist to write a chapter on the prevention of coronary heart disease (CHD)? There must be a reason. Perhaps it is that the tenth anniversary issue of *Progress in Cardiology* is dedicated to one of the most prominent cardiologists of this century. Indeed, Sir John McMichael may be said to be skeptical about the prevention of CHD in general and the role of diets (unsaturated fatty acids) in particular.[31–33] In fact, it must be acknowledged that there is

a fair amount of skepticism among clinical cardiologists concerning the prevention of CHD,[9] although few have been so outspoken as Sir John.

This skepticism may be due to the fact that epidemiology (and its offspring, prevention) of CHD has become a speciality on its own.[3,21] One can either be an expert on clinical cardiology or be versed in epidemiology, but it seems a hard task to master both disciplines in depth. It is either/or. If this were not the case, the present day polemics would probably not exist. The epidemiologists perhaps do not see clearly enough that some of their theories and opinions are not relevant to future CHD patients. Cardiologists, on the other hand, may need more than a superficial knowledge of epidemiology. Without doubt, the editors of *Progress in Cardiology* are well aware of the existing gap between clinical cardiology and epidemiology.

My personal skepticism about the value of epidemiology in the prevention of CHD does not make me an authority on the prevention of CHD.[39–42] Little substantial and relevant knowledge in the field of primary prevention of CHD has been gained since the early 1970's. Therefore, the need for another chapter on this subject may be questioned. And who could ever better the excellent chapter written in 1974 by Henry Blackburn[5] in the third issue of this successful series?

From a clinician's point of view, the effective knowledge of prevention of coronary heart disease, that is, the preventive measures he may take to benefit his patients, seems inversely related to the vast amount of literature on this subject. The Utrecht University Library delivered with ease 1,088 references of papers written on this subject over the last five years. And what have we gained from it all?

There still is no individual who can prevent his coronary heart disease. One may give up smoking, one may change one's diet, one may lose weight and/or lower one's blood pressure, but still there is no guarantee that one will not be disabled by or die from coronary heart disease before the age of 60. It may be that, if whole populations turn away from their epidemiologic sins (risk factors), the incidence of coronary heart disease (CHD) will diminish, but the individual will never know. Statistics do not count for the individual. The cardiologist knows too well that he cannot predictably prevent CHD in his patients. We now know much more about atherosclerosis,[52] thrombocyte aggregation,[51] and coronary perfusion, but whether, when, or how an individual will be struck by CHD, we do not know.

THE PROBLEM

CHD, stroke, and peripheral vascular disease account for about half of all deaths in the United States. For Blackburn, the problem of CHD is its epidemic character: the vast number of its victims. He demonstrated and stressed that "despite the great strides of modern medicine, the estimated life expectancy of men who reach and surpass the age of 40 is actually unimproved in 1970 compared to that in 1900."[5]

Indeed, the epidemic character of CHD is a problem, but it is not *the problem.* The problem is that the cause(s) of CHD is (are) virtually unknown, and the future victim of CHD cannot be identified. In the United States, the age-adjusted mortality rate from cardiovascular disease has declined 30% since 1960.[58] Despite this decline, we must confess that nobody really knows why this has happened;[55] we do not know the cause of CHD, and we do not even know whether it is just one disease.

From recent observations, we have learned that CHD may manifest itself without any demonstrable atherosclerotic narrowing in one of the coronary arteries.[11,15] We have also learned in recent years that there are different types of atherosclerotic lesions of the coronary arteries. Therefore, even atherosclerotic coronary artery disease could consist of more than one disease. For instance, a single obstruction in one artery

may be the beginning of a continuing process, ultimately leading to a generalized atherosclerotic narrowing of the three main branches, or it may remain one lesion in one artery.

CHD looked at through cardiologists' eyes is a mystery. We do not know its cause(s). We do not know its natural history in any specific case, and we are unable to identify its future victims. So, in any given individual, we do not know when or how the disease will strike. The problem is not CHD's epidemiologic occurrence; the problem is our ignorance. One may call this the nihilistic view of CHD prevention, but I am afraid that at present it is the only realistic one. It is not a nihilism of "laissez-faire" or of "gotta die some way, some day,"[5] but it is the nihilism of the sober reality that the cardiologist faces in his daily work. This realism, one hopes, is the beginning of a changing approach that may lead to new understanding, since the approaches we have used until now have yielded little. This changing attitude may lead us back to one of the iron laws of medicine, namely, to study diseases by studying patients. The development of new diagnostic techniques in cardiology has provided considerable insight into the pathogenesis of CHD as a clinical entity and may lead to the discovery of the cause or causes of this plague of mankind.

DEFINITIONS

The use of terms without proper definitions may lead to misinterpretation and confusion. The following definitions have evolved during many years of clinical practice.

Coronary Heart Disease

The title of this chapter is "Prevention of CHD," but so far we have not given any definition of CHD. The unbiased reader in this vast field may wonder what a particular author is writing about when the term CHD is used. We prefer the term CHD over ischemic heart disease because the latter may also be due to extracoronary causes, such as valvular aortic stenosis. For pragmatic reasons, we define CHD as *any clinical symptom due to myocardial ischemia caused by functional or morphologic coronary artery disease* (see the section in this chapter on coronary artery disease).

The term CHD, as used in this chapter, has a purely clinical meaning and encompasses the following syndromes: angina pectoris and its variant forms, impending myocardial infarction, and myocardial infarction and sudden death. These syndromes include major cardiac abnormalities such as arrhythmias, heart failure, cardiogenic shock, and Adams-Stokes attacks, because CHD does not always present itself as a clearly outlined syndrome. There are gradations and overlaps among its different clinical forms. CHD may present itself as a gradually unfolding process, starting with angina pectoris on severe physical exercise, leading to angina pectoris on mild exercise or at rest, and, by impending myocardial infarction and myocardial infarction, to sudden death.

CHD may also start with a myocardial infarction as sudden as a bolt out of a blue sky or with a severe arrhythmia leading to an unexpected death within minutes or hours. One of the most impressive characteristics of CHD is its complete unpredictability, its constant surprises for the patient and his doctors.

Coronary Insufficiency

Myocardial ischemia in this context is caused by *coronary insufficiency* due to an imbalance between myocardial oxygen supply and oxygen demand (Fig. III-1). This imbalance may lead to various clinical symptoms of CHD, depending on location, extent, and/or certain physicochemical aspects of the ischemic myocardium. During manifest coronary insufficiency, there is no such thing as a well-delineated border; an ongoing battle rages back and forth between "normal" and ischemic myocardium.[10,25]

When coronary insufficiency is of sufficient

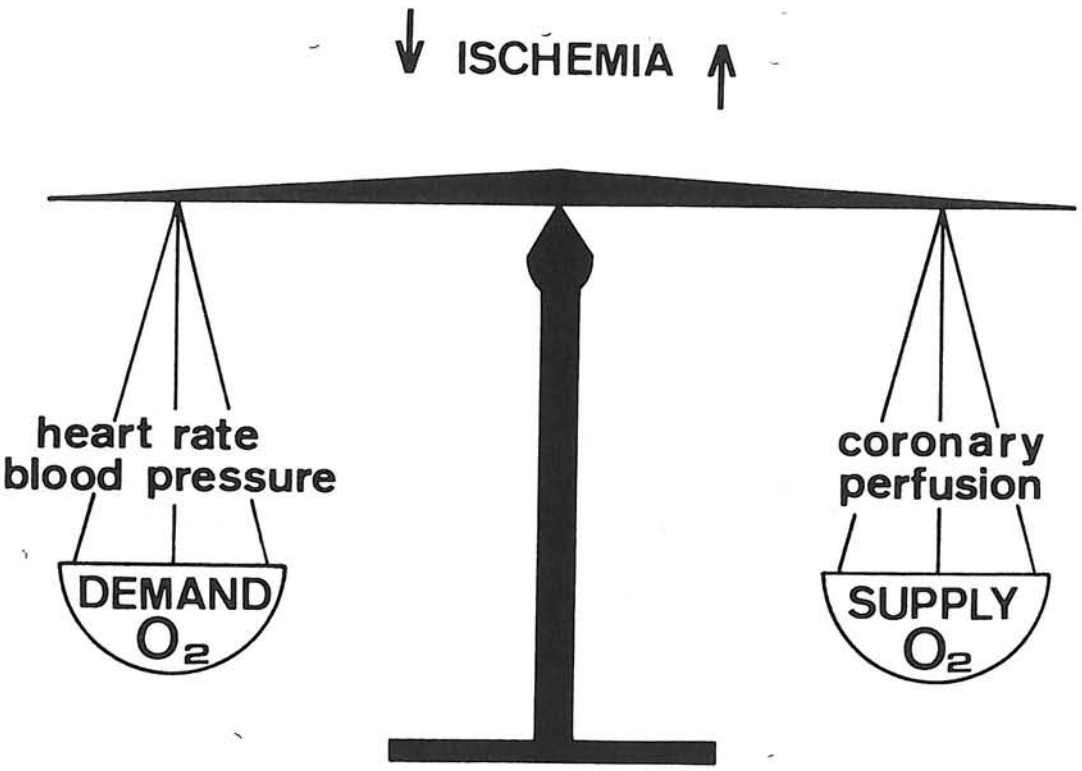

Fig. III-1. Schematic presentation of the normally present balance between oxygen demand and supply of the myocardium. Any increase of O_2 demand that the heart needs has to be provided for by an increase in coronary perfusion. Myocardial ischemia may occur because of a diminished supply, an increased demand, or a combination of these two factors.

duration and degree to cause myocardial infarction (death of tissue), it gives rise to a patchy pattern, with islands of living myocardium in between scar tissue and strands of scar tissue penetrating viable myocardium.[13,14]

Coronary Artery Disease

This disease is usually caused by atherosclerosis of the coronary arteries. However, there are other forms of coronary artery disease or malfunction that cannot be ascribed to atherosclerosis. From a clinical point of view, it is an oversimplification to tar all forms of coronary artery disease with the same atherosclerotic brush.

Coronary Sclerosis

Defined as atherosclerosis of the coronary arteries, coronary sclerosis is the major cause of coronary artery disease and thus of coronary heart disease.

In summary, then, we propose four different terms, namely, coronary heart disease, the clinical syndrome; coronary insufficiency, the underlying pathophysiologic mechanism; coronary artery disease, the structural and/or the functional substrate; and coronary sclerosis, atherosclerosis of the coronary arteries. These four terms or concepts should be well distinguished from one another. Coronary sclerosis or other forms of coronary artery disease may be present and demonstrable without any clinical signs of CHD (Fig. III-2). The opposite may also be true, that is, sudden cardiac death or a myocardial infarction may occur without any sign of coronary artery disease.[15,24]

The prevention of CHD can be divided into the categories primary and secondary, as defined in the following sections.

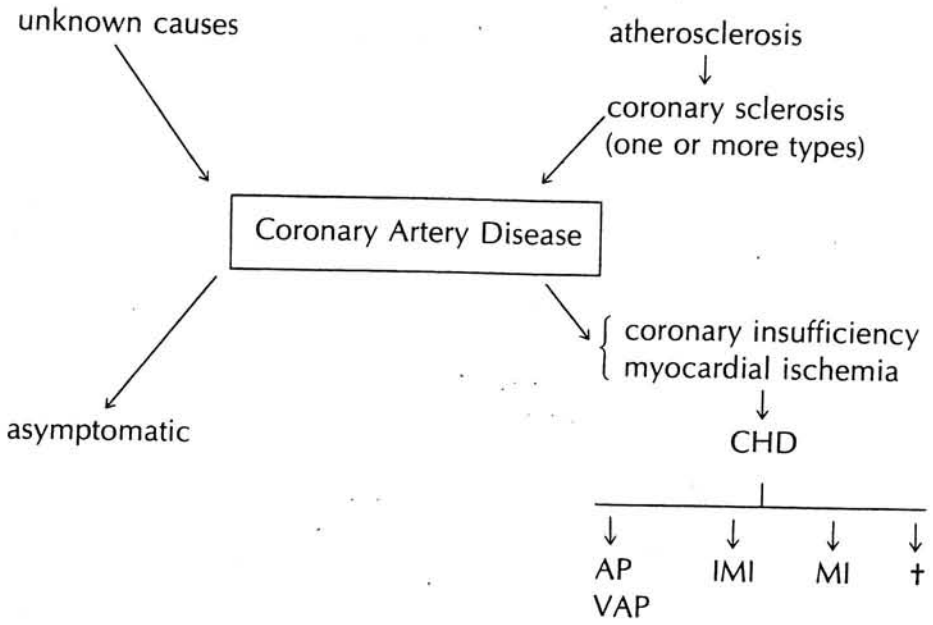

Fig. III-2. Schema of coronary heart disease. *Schema 1:* CHD = coronary heart disease; AP = angina pectoris; VAP = variant forms of AP; IMI = impending myocardial infarction; MI = myocardial infarction; † = (sudden) death.

Primary Prevention

One can define *primary prevention* as any form of action taken to forestall the occurrence of coronary artery disease, such as, for instance, coronary sclerosis. If atherosclerosis can be prevented, coronary sclerosis can be prevented.

Secondary Prevention

One can define *secondary prevention* as any form of action or set of measures taken to prevent coronary heart disease in the presence of coronary artery disease.

There is a clear and fundamental difference between these two forms of prevention. Losing weight in the presence of coronary artery disease may prevent coronary heart disease or may eliminate its symptoms, but weight reduction as such has no primary preventive effect.

Risk Factors

For the term *risk factors,* one may find almost as many meanings as papers wherein the term has been used. In the recent report of the Food and Nutrition Board of the National Academy of Sciences in the United States,[58] risk factors are defined as "those factors found to be statistically associated with an increased incidence of the disease." In the glossary of the new *Heartbook* of the American Heart Association, a guide to the prevention and treatment of cardiovascular disease, risk factors are "characteristics which are associated with an increased risk of developing coronary heart disease."[2] Ideally, a factor should be called a risk factor if, upon elimination of that factor, the incidence of the disease would diminish. Only cigarette smoking seems to satisfy this criterion.

CORONARY HEART DISEASE (CHD)

Epidemiologic and Nutritional Considerations

Until now we have been skeptical about the concepts applied to the prevention of CHD. It is usually easier to criticize former attempts to solve a problem than to contribute new suggestions for its solution. It seems clear, however, that we should change our course. Not only cardiologists, but also epidemiologists and nutritional experts seem

to realize that the present approach has led us into a blind alley. In a recent paper in Scientific American, Stallones demonstrates that the "four major variables known to be associated with the risk of ischemic heart disease in individuals"—hypertension, physical activity, serum cholesterol levels, and cigarette smoking—do not fit the curve of the rise and fall of "ischemic" heart disease in the United States.[55] Hypertension does not fit the trend of the mortality rate from "ischemic" heart disease at all; physical activity fits only the rising curve, serum cholesterol fits only the falling curve, and only cigarette smoking fits both.

In 1979, Ahrens, in a survey in the Lancet, declared the relation of dietary fats to coronary heart disease to be unfinished business.[1] He feels that "it is irresponsible to make the dietary recommendations that are being so widely proposed to the general public at this time."

Pathophysiologic Considerations

The range of symptoms of CHD are all caused by ischemia and necrosis of or scar tissue in the myocardium. The clinical symptoms depend upon the site and extent of the ischemic damage. Myocardial ischemia caused by coronary insufficiency may result from either an increased oxygen demand or a decreased oxygen supply or both (Fig. III-1).

Coronary insufficiency is mainly caused by permanent or temporary narrowing or occlusion of one or more of the major branches of the coronary artery system. The development and worldwide application of coronary arteriography, combined with new, sophisticated techniques for monitoring of patients, dynamic electrocardiography, and nuclear cardiology, have shown a variety of causes of obstruction of coronary artery blood flow.

Because of its unique metabolic characteristics, the myocardium, unlike skeletal muscle, cannot build an oxygen debt, as it uses nearly all oxygen available in the coronary blood. This implies that every change, whether increase or decrease, in oxygen demand must be balanced by a proportional change in coronary blood flow. Therefore, even short interruptions of blood supply to the myocardium impair myocardial cell function and may lead to fatal electrical abnormalities of the heart.[12] Maseri and coworkers,[36] and later other researchers, have shown that a brief interruption of the coronary blood supply to the myocardium caused by coronary artery spasm, even in apparently normal coronary arteries, may result in potentially lethal arrhythmias (Figs. III-3, III-4, and III-5). From coronary angiographic studies, we now know that there is a fundamental clinical difference between a gradual narrowing of a coronary artery by atherosclerotic deposits over the years and an abrupt occlusion of a widely open or partially narrowed artery by spasm.

The biochemical, morphologic, and electrical conditions of the myocardium set the stage for the clinical symptoms of myocardial ischemia due to coronary insufficiency. However, there seem to be numerous ways for the coronary blood supply to become insufficient. Preventive measures of CHD that do not take into account these pathophysiologic facts cannot meaningfully contribute to the solution of the high morbidity and mortality rates for CHD.

CHD versus CAG (Coronary Angiogram)

One would expect to find a relation between clinical symptoms, such as the sort of complaints and/or the type of ECG changes, on the one hand and the underlying coronary artery pathologic changes on the other. One may approach this possible relation between clinical symptoms of CHD and coronary artery morphology, as seen on a coronary angiogram (CAG), from at least two different angles.

The clinical symptoms of CHD may be divided into a number of subgroups (Table III-1), and one may try to relate those groups to the CAG found in each category. The other approach is to use a classification

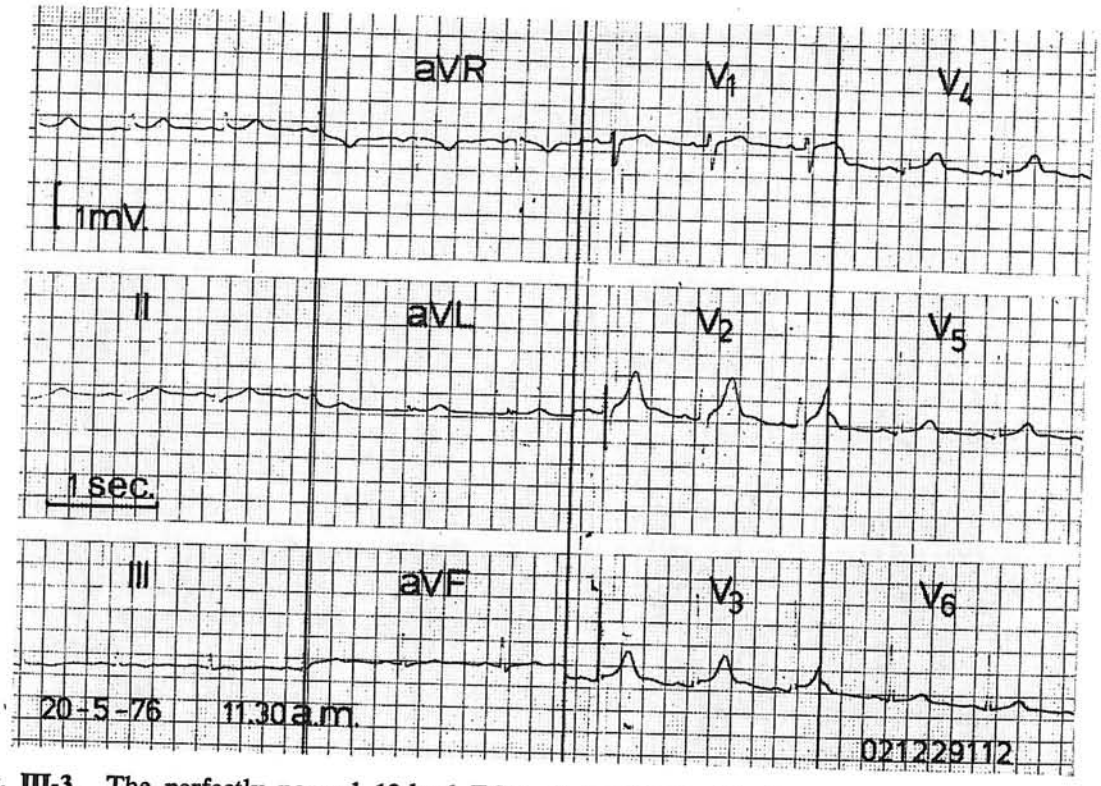

Fig. III-3. The perfectly normal 12-lead ECG of a patient with demonstrated (potentially lethal; see Fig. III-5) coronary spasm. (From Ekelen, W. A. A. J. van, and Robles de Medina, E. O.: Variant forms in angina pectoris. Eur. J. Cardiol., *8*:305, 1978.)

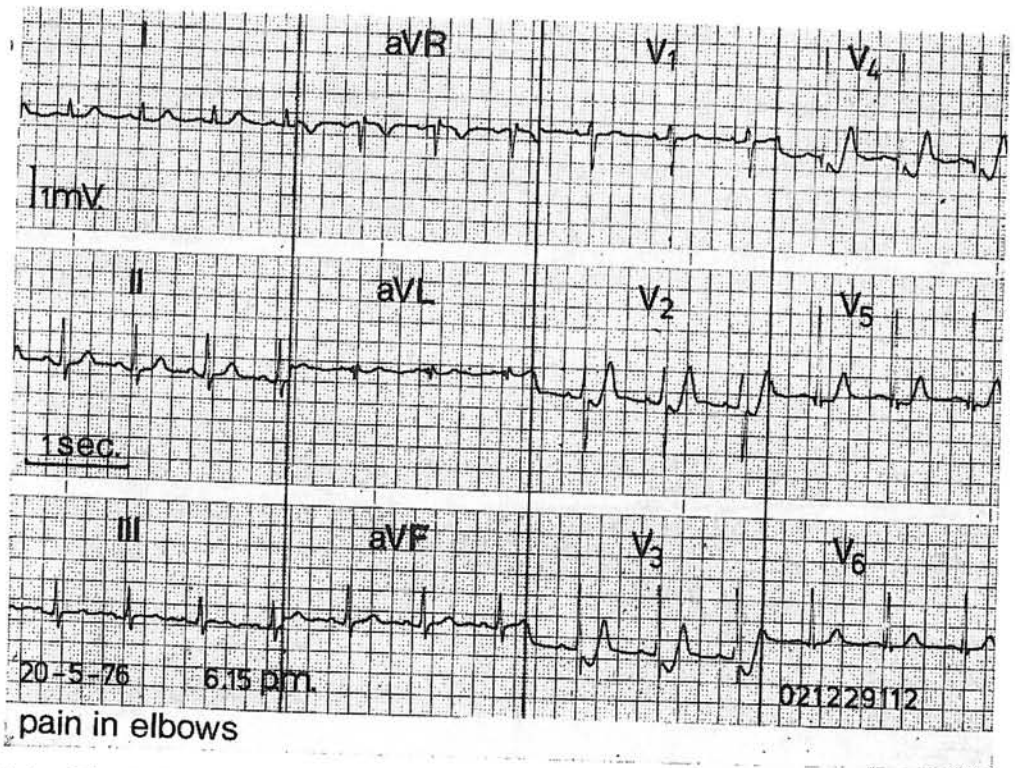

Fig. III-4. The 12-lead ECG of the patient whose ECG is shown in Figure III-3, at the beginning of an anginal attack. There is a marked and specific ST depression in leads V_2, V_3, V_4, and V_5. (From Ekelen, W. A. A. J. van, and Robles de Medina, E. O.: Variant forms in angina pectoris. Eur. J. Cardiol., *8*:305, 1978.)

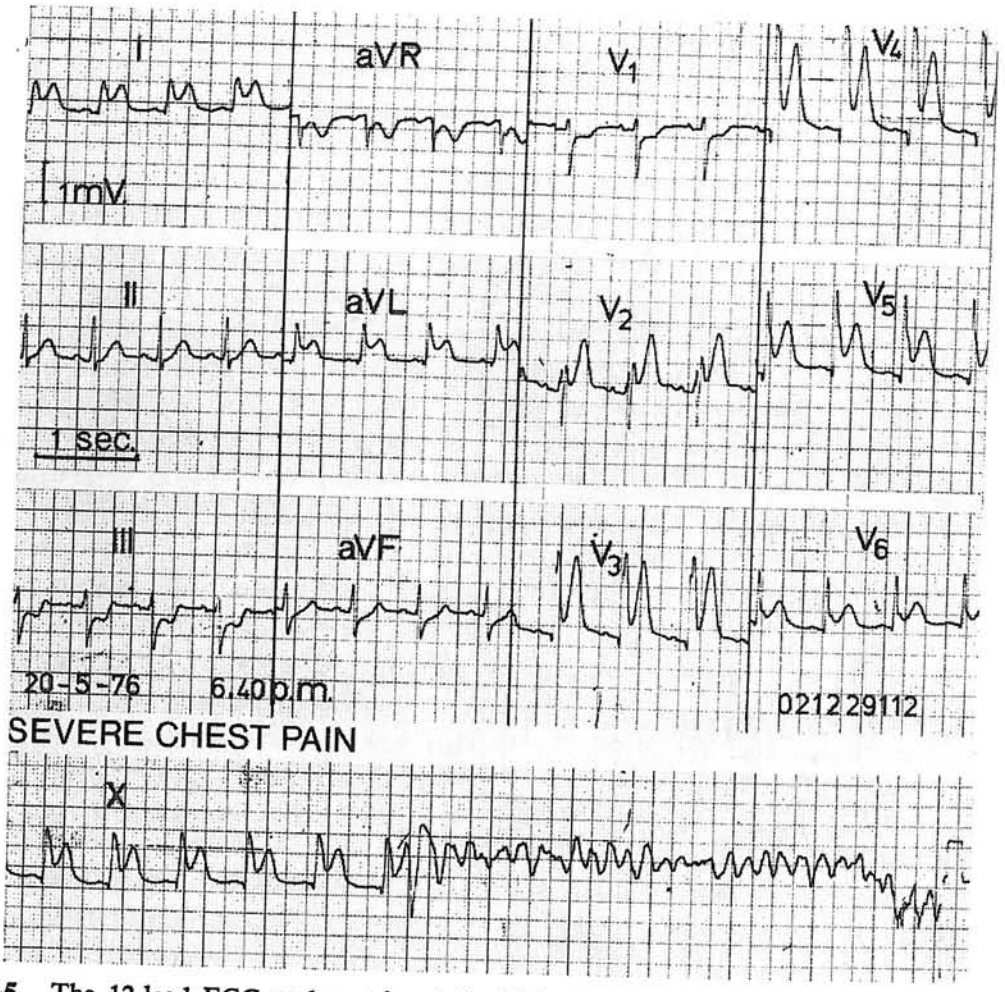

Fig. III-5. The 12-lead ECG and a strip of the X lead of the patient whose ECG's are shown in Figures III-3 and III-4, taken a few moments later than the recording of the ECG in Figure III-4. One may notice a strong ST elevation in leads I, AVL, V_2, V_3, V_4, V_5 and V_6. Ventricular fibrillation occurred during recording of lead X. This is the electrocardiographic substrate of sudden death. One may justifiably assume that this dramatic event is due to the spasm of the left anterior descending artery, as shown in Figure III-11. (From Ekelen, W. A. A. J. van, and Robles de Medina, E. O.: Variant forms in angina pectoris. Eur. J. Cardiol., *8*:305, 1978).

Table III-1. Subgroups of CHD

1. No complaints	
2. Stable effort angina pectoris (AP)	
3. Stable effort AP with AP at rest	
4. Progressive effort AP without AP at rest	IMI (impending myocardial infarction)
5. Progressive effort AP with AP at rest	IMI (impending myocardial infarction)
6. Recent onset of effort AP	IMI (impending myocardial infarction)
7. AP (only) at rest	IMI (impending myocardial infarction)
8. Acute myocardial infarction	
9. Sudden death	

Table III-2. CAG findings in CHD

1. Normal
2. Circumscript solitary obstruction in one coronary artery
3. Circumscript obstructions in more than one coronary artery
4. Diffusely narrowed arteries with or without local obstruction(s)
5. "Rosary"
6. Spasm
7. Slow flow of dye
8. Aneurysmal dilatation(s) of one or more coronary arteries
9. Abnormal origin

of coronary angiograms (Table III-2) and to see whether they relate to clinical symptoms. The results of relating the two categories are schematically demonstrated in Figure III-6.

Subgroups of CHD

If one looks closely at Table III-1, one will notice that we have divided CHD into nine subgroups, more or less arbitrarily. We have chosen a purely pragmatic division. It is well known that in each category (except No. 9), almost any type of electrocardiographic abnormality may be found. For instance, in a patient who has no complaints and who is not aware of suffering from any disease, let alone CHD, one may find severe arrhythmias and/or an infarction pattern on the ECG. In such a patient, one may also find the most malignant abnormalities on the CAG. From Maseri's work[37] we know that ischemic myocardial spells with concomitant ECG changes may occur without pain or discomfort. Therefore, persons who are free of complaints and who are fully able to perform their normal daily physical exercise may have no other signs of CHD. As we shall see later, these complaint-free patients may fall into any category of CAG.

In the last decade, we have learned that, besides classic angina pectoris (AP) as first described by Heberden[19] (Category 2, Table

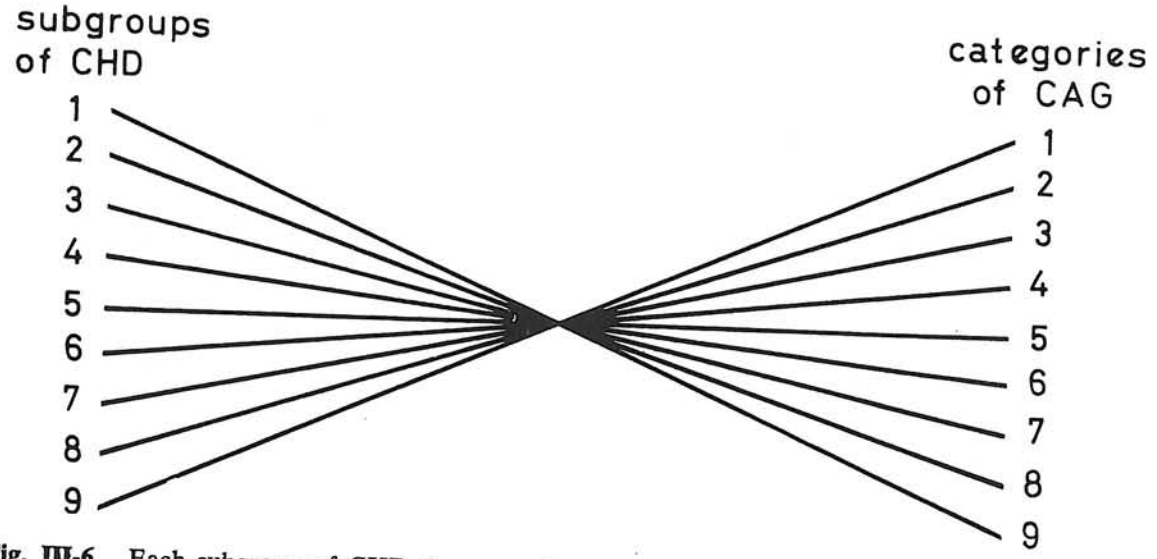

Fig. III-6. Each subgroup of CHD (coronary heart disease) may present itself at any type of coronary artery disease, as shown during coronary angiography (CAG).

III-1), there are other forms of chest pain induced by ischemia that do not conform to the usual pattern of coronary insufficiency due to a fixed stenosis in one or more of the coronary arteries. These other manifestations of AP are best described as being forms of variant angina of which the Prinzmetal type (chest pain at rest with ST elevation on the ECG) is only one.[15]

Some of these variant forms of AP can be considered as impending myocardial infarction (IMI), because they are frequently followed by a myocardial infarction. Recognition of an IMI is important because proper medical and/or surgical interventions may prevent the occurrence of a myocardial infarction.[17,46,60] It is well known that a myocardial infarction is not necessarily preceded by clearly defined signs and symptoms; as said before, a myocardial infarction may strike totally unexpectedly without premonitory symptoms at any time during one's life, at any moment of the day or night.

A myocardial infarction is a clinical syndrome. The first more or less complete description of this dramatic event was written by the famous American cardiologist James B. Herrick.[20] His paper is entitled: "Clinical features of sudden obstruction of the coronary arteries." I emphasize the point that Herrick spoke of "sudden obstruction" without speculating about its cause.

Especially in younger persons, this "sudden obstruction" is not necessarily accompanied by permanent obstructive lesions in the coronary arteries.[26,47] This fact is of great importance for epidemiology and primary prevention of CHD because if myocardial infarction can occur without permanent obstructive lesions in the coronary arteries, it follows that a myocardial infarction in the presence of a permanent narrowing in a coronary artery is not necessarily caused by that narrowing.

A myocardial infarction may occur with any type of coronary artery disease or malfunction of a coronary artery. The clinical symptoms, and in particular their lethal outcome, are due to a variety of pathophysiologic mechanisms resulting from a permanent or semipermanent occlusion of a coronary artery. This is not the place to go into details about the multiple factors that may play a role in the clinical symptoms and in the prognosis of a myocardial infarction. It suffices to stress that many factors differing from person to person set the stage for a clinical syndrome that still has many unsolved secrets for the cardiologist even though it has been almost 70 years since its first complete description.

It follows that the use of the term "myocardial infarction" in epidemiologic studies, without at least some further details, such as infarct size, location, electrical events, pump failure, or septal or right ventricular involvement, is an oversimplification that has clouded the true impact of this aspect of CHD on the individual and on the population at large.

The same story holds true, although with less variation, for sudden death. James has reported that sudden cardiac death may and does occur in persons with normal coronary arteries.[24] This finding implies that sudden cardiac death in persons with abnormal coronary arteries is not necessarily caused by those coronary arteries. Sudden cardiac death may not be due to a coronary event, but statistics in medicine do not take this fact into account. Again, if sudden death can strike without demonstrable coronary artery disease, our mortality statistics should be taken with a grain of salt.

So, CHD may present itself in an almost infinite variety of clinical symptoms, shifting from one syndrome or set of symptoms to another, sometimes in persons with normal coronary arteries, but more often in those with diseased coronary arteries. The only predictable, albeit paradoxical, aspect of CHD is its total unpredictability. Of course, there are some facts. Death, and often sudden death, is considered to be a fixed end

point in CHD. We also know that persons with symptoms of CHD and normal coronary arteries usually have a good prognosis. Over the years, we have learned which early findings are indicative of a good or a bad outcome of the disease, but the dominating characteristic of the disease is, and remains, its erratic and unpredictable course that seems only to be matched by our ignorance.

CAG Findings in CHD

In Table III-2, a spectrum of CAG findings in patients with CHD is listed. Any symptom or set of symptoms of CHD can be associated with any of the CAG findings. Of course, some schematization of clinical symptoms versus CAG findings is possible. We know roughly when to expect a right coronary artery obstruction or a left descending artery lesion, but no cardiologist in his right senses would dare to set high stakes on the CAG outcome with any given set of clinical symptoms.

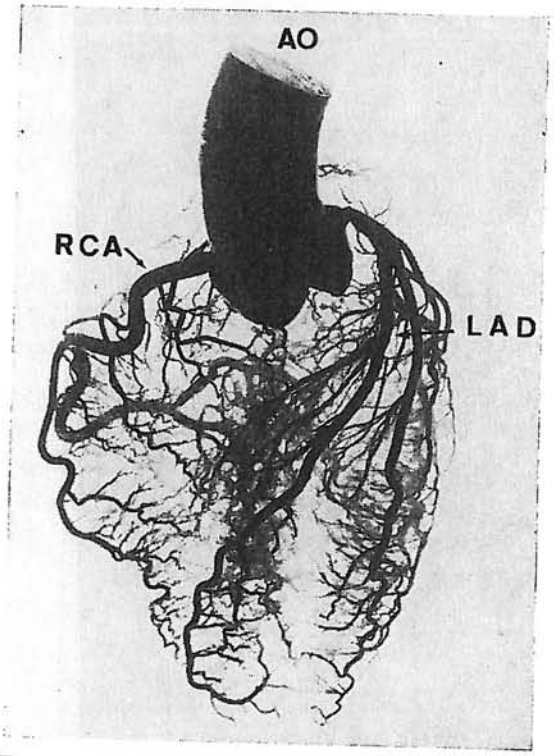

Fig. III-7. The human coronary artery system. The arterial tree of the human heart can be compared to a string bag containing the heart proper. AO = aorta, RCA = right coronary artery; LAD = left anterior descending artery.

The heart is embedded in a string bag of coronary arteries (Fig. III-7). It is clear from looking at Figure III-7 that an almost endless variety of malfunctions in the case of coronary artery disease can be expected. At the same time, the variability of the morphology of coronary artery disease suggests that at least not all of the categories of CHD are caused by atherosclerosis. In Figures III-8 to III-11, we give a few examples.

In Figure III-8 one solitary, circumscript obstruction in the LAD is shown, the other arteries being normal. This finding demonstrates that coronary sclerosis may present itself as an isolated lesion in a single artery.

Figure III-9 shows one circumscript obstruction in each of the three main branches of the coronary tree, another form of coronary sclerosis.

Another example of coronary artery disease is what could be called a "rosary" (Fig. III-10).

An important variety of coronary artery disease is the group of so-called coronary spasm, which may occur in the presence or absence of atherosclerotic lesions (Fig. III-11).[7] The CAG in this figure is of the patient whose ECG's are shown in Figures III-3, III-4, and III-5. These figures demonstrate that a brief total obstruction of a major arterial branch may result in a lethal arrhythmia. It is interesting to note that this patient was able to perform strenuous exercise without any complaints and without specific ECG abnormalities. He accomplished a work load of 222 watts without any complaint and with a normal X-ECG (Fig. III-3).

From these examples, it should be clear that there is no such thing as a simple pattern of coronary artery disease. Hard clinical data show an almost endless variety of symptoms associated with at least nine forms of coronary artery disease. Apparently, CHD is not a single entity and might just as well be the "final common pathway" of different

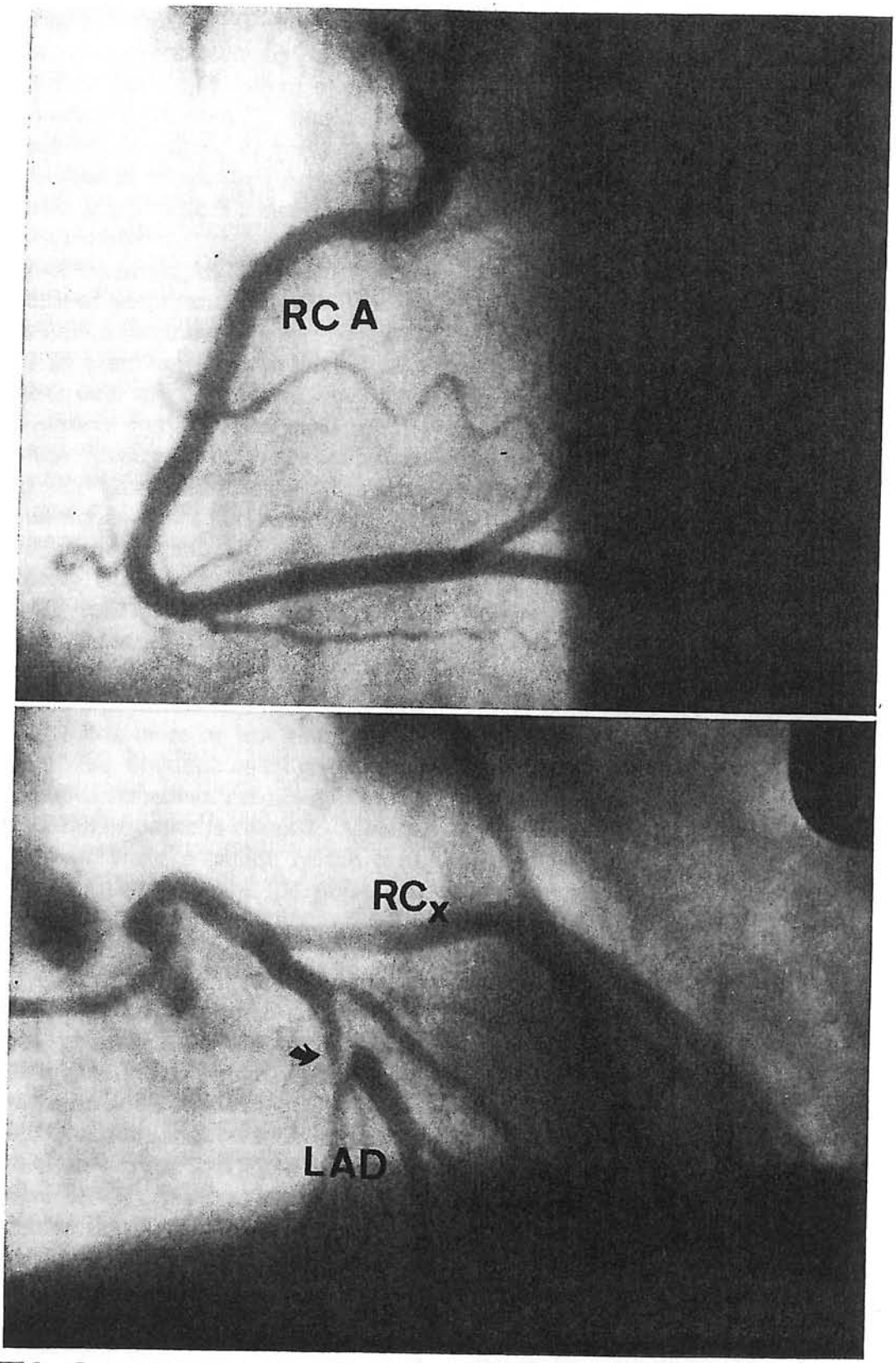

Fig. III-8. Coronary angiogram of a 43-year-old man with class II angina pectoris on effort, showing a single severe obstruction (arrow) in the LAD. RCA = right coronary artery; LAD = left anterior descending artery; RC_x = circumflex artery.

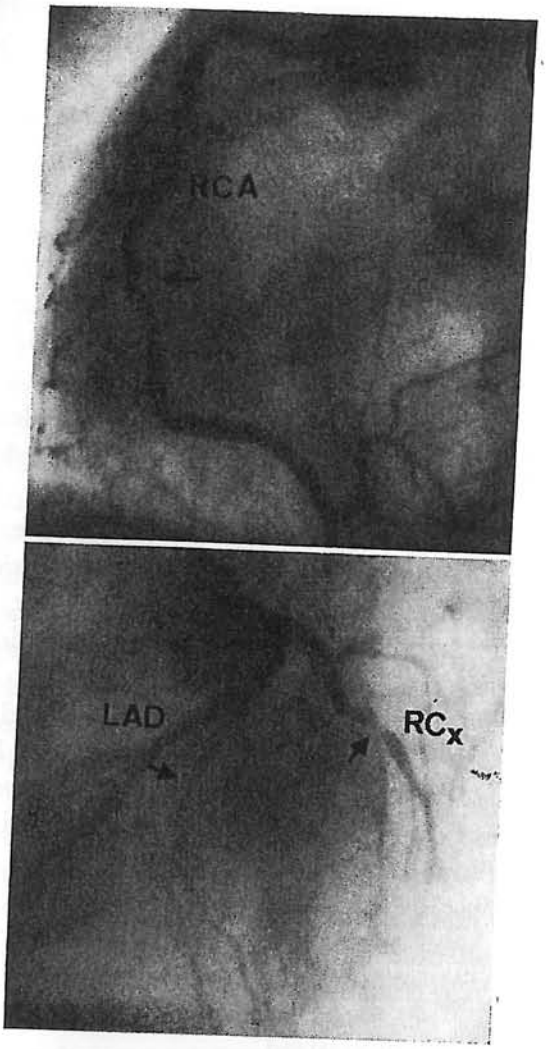

Fig. III-9. Coronary angiogram of a 38-year-old woman with class I angina pectoris, showing multiple, localized obstructive lesions (arrows). RCA = right coronary artery; LAD = left anterior descending artery; RC_x = circumflex artery.

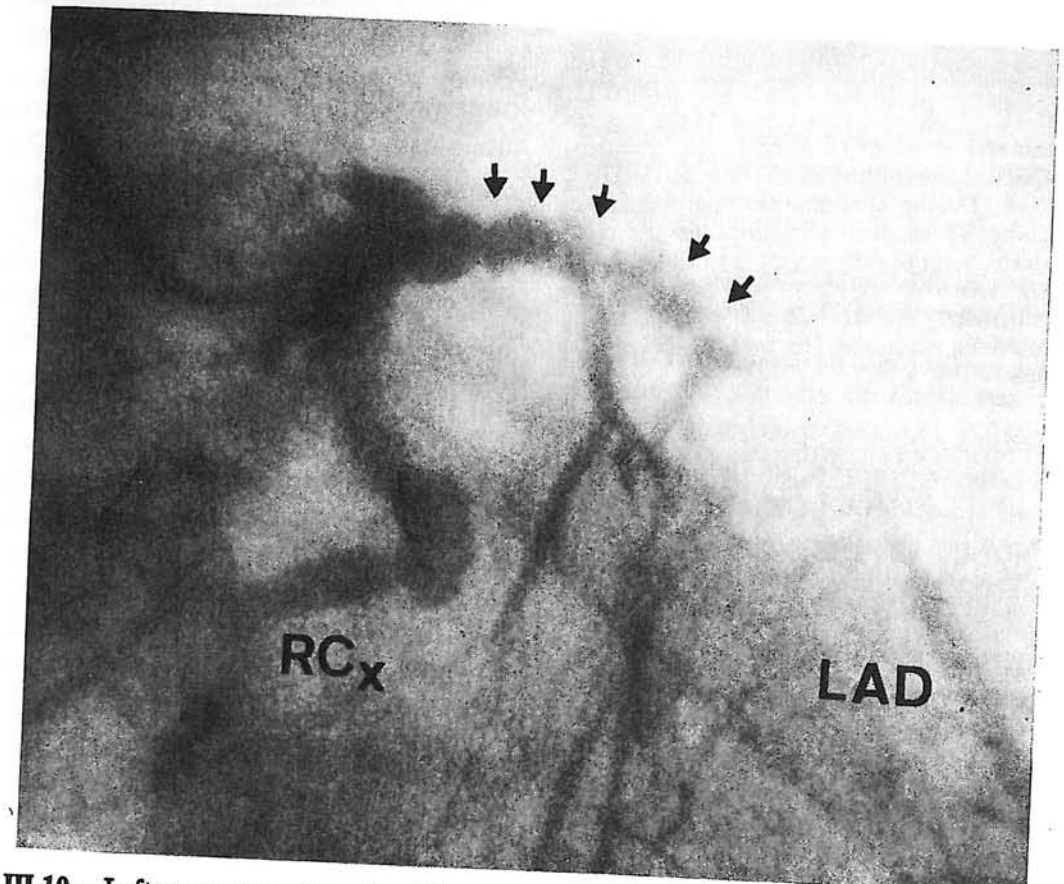

Fig. III-10. Left coronary artery of a 56-year-old man with class III angina pectoris, showing multiple narrowings and dilatations ("rosary") in the proximal part of the LAD as well as the RC_x. LAD = left anterior descending artery; RC_x = circumflex artery.

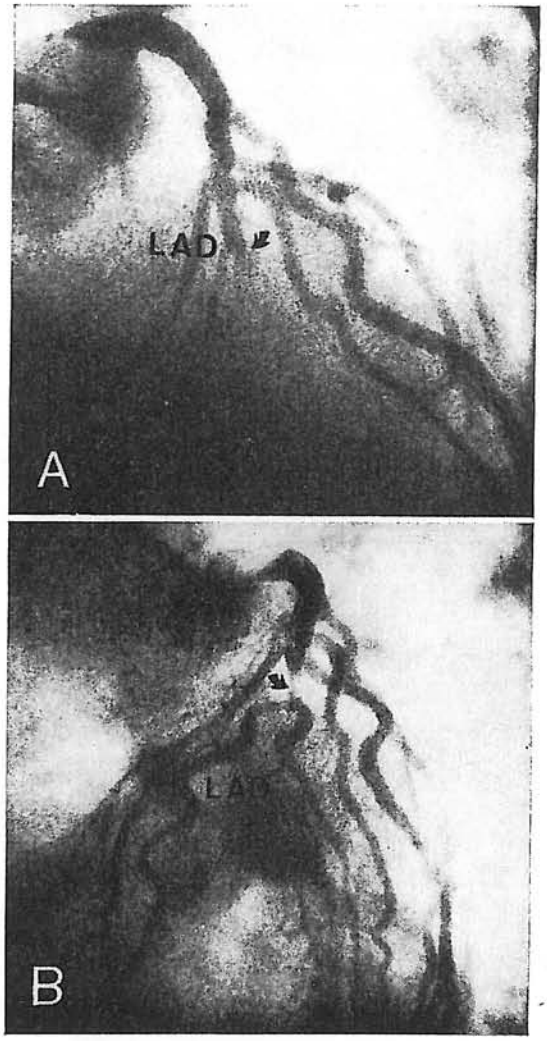

Fig. III-11. Left coronary artery of the patient with Prinzmetal's variant form of angina pectoris, whose ECG's are described in Figures III-3, III-4, and III-5. *A*, During spontaneous complaints accompanied by ST segment elevations on the electrocardiogram, total occlusion was seen in the LAD (arrow). *B*, When nitroglycerin was administered, an approximately 90% stenosis was present at the level of previous occlusion (arrow). LAD = left anterior descending artery.

kinds of coronary artery disease and/or dysfunction of the coronary arteries.

CONCEPT OF RISK FACTORS: A HISTORICAL MISTAKE?

The question whether the introduction and use of risk factors in the approach to prevention and cure of CHD has been of any help is legitimate. When we look at the official definition of the term "risk factor," we see that its interpretation can be so liberally applied that almost any factor in the daily life of our Western culture may be considered as a risk factor.[64]

The most important risk factor of all is being a man. Indeed, at the American Heart Association meeting in 1963 in Los Angeles, one of the striking slogans was: "Being a man is a disease!" One's parents are also a major risk factor, as was recently demonstrated once more by Nora et al.[45] Much lower on their risk scale are other well-known factors such as serum cholesterol levels, smoking habits, and hypertension.[45] Blackburn[5] also mentioned soft water, sedentary habits, personality, and behavior as well as diet, overweight, and obesity. Not only is the term "risk factor" ill-defined, but also the terms CHD, IHD (ischemic heart disease), and even CVD (cardiovascular disease) are explanations for many clinical symptoms and syndromes. If, for the time being, the concept of risk factors is to keep its value, the two most important factors, the male sex and one's family history, which cannot be manipulated one way or another, must be emphasized.

The North Karelia project, a program to reduce coronary risk factors did indeed lower three important risk factors (smoking, cholesterol, and blood pressure). The concomitant decrease in the mortality rate from CVD and in the incidence of acute myocardial infarction (AMI) in North Karelia were compared with those in a matched control area: the difference between the two areas, however, was not statistically significant.[49,53] The falling curve of the incidence of CHD in many parts of the Western hemisphere is one of the major challenges to present-day epidemiologists and cardiologists

When we use the term risk factors in a more rigid way, such as proposed previously, only smoking seems to reduce the incidence of CHD at all ages.[4] Nutrition, in relation to atherosclerosis, is also a risk factor, but as yet it has been difficult to demonstrate a beneficial effect of a change in eating habits on the incidence of CHD.

In countries where more saturated fat is consumed than in others, there is a higher incidence of CHD. But even Blackburn[5] doubts whether middle-aged men "experience any significant reduction in risk from change of diet alone."

It is not the purpose of this chapter to forsake entirely the concept of risk factors in our attempts to reduce the incidence of CHD. Rather, a critical approach should be seen as an honest attempt to break from the way in which risk factors seem to be automatically substituted for the cause(s) of coronary heart disease. The otherwise critical paper by Nora et al. starts with this opening sentence: "The concept that ischemic heart disease (IHD) is the product of genetic and environmental factors is generally accepted. . . . ."[45] Even if that concept is generally accepted, it does not necessarily mean that it represents the truth. CHD need not be a product of genetic and environmental factors; it is sufficient to accept an influence by those factors to find close statistical relationships. Other diseases are linked with genetic and environmental factors, such as diabetes, nephrolithiasis, or bronchial asthma, but yet are not products of these factors.

The overexposure of risk factors in our understandable enthusiasm to fight the disease has possibly, at least in retrospect, done more harm than good. In the Netherlands and probably in other countries as well, we went so far as to prescribe diets with abundant amounts of unsaturated fats in homes for the aged. Persons over the age of 80 were (and are) not allowed to eat an egg on Sunday. Although it may be worthwhile to reduce the intake of saturated fats in our children, there is not enough evidence to do so in adults over 50 years of age or to justify the misleading advertising of diet oils and margarines. If primary prevention by means of changing eating habits is to be effective at all, it should start in early life, but dietary measures to reduce serum cholesterol[38] levels in old-age pensioners weaken the credibility of more sensible approaches to the problem, such as the reduction of cigarette smoking or efforts to study the fundamental aspects of coronary artery disease and/or malfunction. The public should be told the truth about risk factors. The public should know that the occurrence of CHD cannot be predicted and that CHD cannot predictably be prevented.[42]

This is a plea for a realistic approach that, first of all, should concentrate our forces on basic research into atherosclerosis and other forms of coronary artery disease. It also is a plea for continuing research into the pathophysiologic mechanisms involved in the sudden cardiac death of persons in the prime of life. Better understanding and more knowledge of the biochemical, mechanical, and electrical properties of the heart may help to reduce unexpected cardiac calamities.

Despite increasing criticism of curative medicine by politicians, the lay press, and the public, the only effective and measurable means to fight CHD for the time being seems to be to improve the care of patients and to identify the disease at an early stage.[30] Until now, the concept of risk factors has not fulfilled basic scientific requirements, nor has it brought the CHD problem nearer to a solution. As such, the concept might turn out to be one of the major medical mistakes of this century.

ATHEROSCLEROSIS: A DEFICIENCY STATE?

Our knowledge of the clinical and pathophysiologic aspects of CHD has increased over the last 10 or 20 years. Atherosclerosis plays the leading role in the disease, but its cause(s) remain(s) obscure.

In a recent paper on life styles, major risk factors, proof, and public policy, Stamler has emphasized a statistically significant association in population studies between several dietary constituents and mortality rates from coronary heart disease (CHD).[56] Several nutrients, including saturated fat and cholesterol are positively and significantly correlated with CHD mortality rates.

Despite the forceful position taken by the protagonists of the "diet-heart" theory[8,43,54,59] the validity of a correlation between fat consumption and atherosclerosis is equally strongly contested by others.[6,9,32,35,44,48] Nevertheless, it seems well established that atherosclerosis and CHD are rare in countries where little or no saturated fat is consumed.[28] Epidemiologic studies in the United States have yielded negative or low-order correlations when the relation between dietary lipid and serum cholesterol of individuals is tested.[28,62] Abundant clinical experience attests that individuals with a high fat intake and high serum cholesterol levels may show no signs of atherosclerosis or CHD; coronary arteriograms can be normal in middle-aged men eating as much or more saturated fat than others who do have extensive coronary sclerosis.

The evidence available at present supports the notion that saturated fat intake is a prerequisite for the development of atherosclerosis. However, it cannot be considered to be more than a prerequisite because many persons who eat abundant amounts of saturated fat show no clinical and/or morphologic signs of coronary atherosclerosis.

Thus far, we have looked only for reasons certain individuals do develop atherosclerosis, never the reasons others do not. Might it not help, or at least put us on a different track, to invert the question and to ask why in countries where large amounts of saturated fat are eaten so many persons are evidently protected from atherosclerosis? Or, in more general terms, what protects persons, including, for instance, premenopausal women, against atherosclerosis in populations with a high fat intake?

Despite the evidence presented by Gordon et al.,[18] every cardiologist knows of patients with low blood levels of high-density lipoproteins (HDL) in whom atherosclerosis in general and/or coronary sclerosis in particular cannot be demonstrated.

In countries where saturated fat intake is low, the incidence of CHD is low, despite that smoking habits are often even worse than in Western societies. Severe hypertension can be found in Africans without any evidence of CHD.[23] This finding implies that cigarette smoking and hypertension without a sufficient saturated fat intake can hardly be called risk factors for CHD. Without a sufficient amount of saturated fat consumption, in the presence of cigarette smoking and hypertension, CHD does not seem to occur, but CHD does occur without smoking and hypertension, if fat consumption is high enough. This reasoning does not apply to individuals, it is based on epidemiologic studies. It remains to be shown that lowering saturated fat intake will necessarily lead to a decreased incidence of CHD.

If we accept the theory that cigarette smoking and hypertension contribute to damage of the arterial endothelium,[52] then, in addition to cholesterol and all known cholesterol derivatives and blood lipids, there must be the presence or absence of (a) factor(s) that cause(s) or prevent(s) atherosclerosis.

Attention has been focused on the presence of atherosclerosis in young United States soldiers killed in action in Korea and Vietnam,[16,34] but should we not really ask why the majority of the soldiers killed showed no evidence of atherosclerosis, even though they had eaten the same food, had smoked the same number of cigarettes, and had reached adolescence in the same society? And why did the soldiers who died in Vietnam have coronary arteries in better condition than their comrades killed in Korea?

If it is not HDL cholesterol, what then is the factor that protects many middle-aged men and most premenopausal women from acquiring atherosclerosis? Is there a substance, an enzyme, or a hormone produced in sufficient quantity to protect persons against atherosclerosis? Does the production of this substance decrease with advancing age or with declining sexual function? Can the inherited tendency and/or familial prevalence[45] be explained by a genetically linked

deficiency of this substance or substances? If the answer to this last question is yes, atherosclerosis may turn out to be the result of a deficiency state that occurs in the presence of a sufficient intake of saturated fat and that is preceded by sufficient damage of the arterial endothelium caused by cigarette smoking, hypertension, or, as in the case of coronary sclerosis, the hemodynamics of the coronary circulation. This concept may lead to a new and, one hopes, more fruitful direction of research into the causes of atherosclerosis.

GALILEO PHENOMENON IN THE PREVENTION OF CHD

In the last issue of the New England Journal of Medicine for 1980, there appeared a vintage paper by the late Dr. Ingelfinger entitled "Arrogance."[22] The paper suits the current positions taken on prevention of CHD almost too well, and I quote:

> Arrogance enters when those reaching various decisions in the absence of adequate data fail to recognize or to admit how empty their cupboard of information is. Superior scientists or doctors, I should like to believe, are always aware of how little they know. Doubt tempers arrogance and for this reason perhaps some bioscientists might be credited with sophrosyne rather than condemned for its opposite, hubris.

In the previous lines, I have attempted to survey and to put in perspective the present standpoints and certainties of our knowledge of CHD in all its clinical and epidemiologic aspects. We must seek new approaches and exploit new ideas, if we are to progress further. In a way, it is striking how little we have learned from medical history. The most severe verbal battles have been fought over symptoms and diseases that were not understood and/or could not be explained. Learned opinions have become dogmas, and over the ages, doctors have ignored and have ridiculed those colleagues who dared to voice a dissident opinion.

"As had happened with Semmelweis, Lister's reports were received with either indifference or open hostility."[29] This Galileo phenomenon in medicine has stood in the way of, and in fact has made almost impossible, a businesslike discussion on whether and how CHD can be prevented. Only recently, Dr. Ancel Keys,[27] in reaction to a paper by Professor Werkö on diet, lipids, and heart attacks,[63] finished his article with the following sentence: "A biased selection of facts filled out with misinformation and distortion is a disservice to both medicine and the general public." Of course, this is true, but should Dr. Keys suggest that Professor Werkö is guilty of such an act?

The recent report of the Food and Nutrition Board of the American Academy of Sciences[58] has also been met by hostility. The authors have been accused of commercial interest and biased opinions.[50,51] As in the past on other issues, discussions on the prevention of CHD have turned into debates, and debates have become mutual heresies, because facts on the subject are insufficient to convince one another.

CHD is a complicated disease that until now has defied any analytic approach. The best way to make progress is to refrain from accusing others of bad faith and stupidity while reserving good faith and brilliance for oneself. In science in general, and in medical science in particular, there is no such thing as the "truth."

The editors have asked me to concentrate on the future and to base my predictions on the lessons of the past and the present. In the previous paragraphs of this chapter, I have tried to focus on the unresolved clinical problems of CHD, and I have presented a hypothesis that may be worthy of further consideration.

The main lesson of the past and the present is that workers in the field with opposing opinions and different backgrounds should join hands and should start to fight CHD instead of each other. The field has become so complex and so vast that a single person cannot read, let alone grasp, the everincreasing flow of facts and knowledge.

My prediction is that the CHD riddle can only be solved when we have learned more about the disease or set of diseases that now falls under that denominator. Without joint efforts by epidemiologists, lipid biochemists, and clinical cardiologists, CHD will go on defying our intellectual skills. Before the discovery of the microscope, microorganisms "did not exist." Now we are also in need of more knowledge and better techniques to give us new dimensions for solving the problem. The cause of CHD remains obscure because we fail to see it. We do not see it because, like Galileo Galilei (1564 to 1642) in his time, we need the right "telescope."

CONCLUSIONS

The problem with CHD is not only that it is a major cause of morbidity and mortality in the Western hemisphere, but also that the medical profession is ignorant of the underlying pathogenetic mechanisms of the disease.

A rational approach to the prevention of CHD seems futile as long as the cause(s) of the disease is (are) unknown. At this time, it does not appear certain that CHD is just one disease. CHD is a collection of clinical symptoms and syndromes and is not predictably related to functional and/or morphologic coronary artery disease.

Many terms and concepts applied in relation to the prevention of CHD are so liberally defined that their use has caused more confusion than insight in the matter. The concept of risk factors in particular has not fulfilled basic scientific requirements and therefore may turn out to be a major medical mistake.

The present notion that atherosclerosis is promoted by saturated fat intake may lead to the hypothesis that atherosclerosis could be caused by a metabolic deficiency on the basis of, for instance, a genetically linked enzyme deficiency that becomes apparent with increasing age.

For the future of prevention of CHD, it is necessary that basic scientists and clinical cardiologists join their efforts to find the cause(s) of the disease. It is an iron law of medicine that diseases cannot be studied and cured without taking the patient into consideration.

ACKNOWLEDGMENTS

The trend of thought and philosophy in this chapter could never have materialized without continuous support of, and criticism by, members of our staff.

I especially want to mention Drs. W. A. A. J. van Ekelen, E. O. Robles de Medina, P. W. Westerhof, and T. van der Werf. The responsibility for the contents is mine. Dr. Donald Sinclair is gradually becoming our English language conscience. We appreciate his help.

Sir John McMichael to whom not only this book, but also this chapter is dedicated, and Professor J. P. Shillingford have supported me over the years. Dr. Dennis Krikler stimulated and helped me to write the section, "Atherosclerosis: a deficiency state?"

REFERENCES

1. Ahrens, E. H.: Dietary fats and coronary heart disease: unfinished business. Lancet, *2*:1345, 1979.
2. American Heart Association: A guide to prevention and treatment of cardiovascular diseases. In *Heartbook*. New York, E. P. Dutton, 1980.
3. Bailar, J. C., III: What do we know about hypertriglyceridemia? In: cause and effect in epidemiology. N. Engl. J. Med., *302*: 1417, 1980.
4. Ball, K., and Turner, R.: Smoking and the heart. The basis for action. Lancet, *2*:822, 1974.
5. Blackburn, H.: Progress in the epidemiology and prevention of coronary heart disease. In *Progress in Cardiology*. Vol. 3 (Yu, P. N., and Goodwin, J. F., Eds.). Philadelphia, Lea & Febiger, 1974.
6. Borhani, N. O.: Primary prevention of coronary heart disease: a critique. Am. J. Cardiol., *40*:251, 1977.
7. Braunwald, E.: Coronary spasm and acute myocardial infarction—new possibility for treatment and prevention. N. Engl. J. Med., *299*:1301, 1978.
8. Connor, W. E.: Dietary cholesterol and the pathogenesis of atherosclerosis. Geriatrics, *16*:407, 1961.
9. Corday, E., and Corday, S. R.: Prevention of heart disease by control of risk factors: the time has come to face the facts. Am. J. Cardiol., *35*:330, 1975.
10. Cranefield, P. F.: The Conduction of the Cardiac Impulse. New York, Futura, 1975.

11. David, G. K.: *Myocardial Infarctions in Young Adults.* Amsterdam, Thesis, 1979.
12. Durrer, D., Janse, M. J., Lie, K. I., and van Capelle, F. J. L.: Human cardiac electrophysiology. In *Developments in Cardiovascular Medicine* (Dickinson, C. J., and Marks, J., Eds.). London, MTP Press, 1978.
13. Durrer, D., van Lier, A. A. W., and Büller, J.: Epicardial and intramural excitation in chronic myocardial infarction. Am. Heart J., *68*:765, 1964.
14. Durrer, D., et al.: The electrocardiogram in normal and some abnormal condition. Am. Heart J., *61*:303, 1961.
15. Ekelen, W. A. A. J. van, and Robles de Medina, E. O.: Variant forms in angina pectoris. Eur. J. Cardiol., *8*:305, 1978.
16. Enos, W. F., Holmes, R. H., and Beyer, J.: Coronary disease among United States soldiers killed in action in Korea. J.A.M.A., *152*:1090, 1953.
17. Feyter, P. J. de, Majid, P. A., Wardek, R., and Roos, J. P.: Observations on unstable angina pectoris with particular respect to management. Am. Heart J., *98*:431, 1979.
18. Gordon, T., et al.: High density lipoprotein as a protective factor against coronary heart disease. Am. J. Cardiol., *62*:707, 1977.
19. Heberden, W.: Commentaries on the history and cure of diseases. In *Classics of Cardiology* (Willius, F. A., and Keys, T. E., Eds.). New York, Dover, 1961.
20. Herrick, J. B.: Clinical features of sudden obstructions of the coronary arteries. J.A.M.A., *59*:2015, 1912.
21. Hulley, S. B., Rosenman, R. H., Bawol, R. D., and Brand, R. J.: Epidemiology as a guide to clinical decisions: the association between triglyceride and coronary heart disease. N. Engl. J. Med., *302*:1383, 1980.
22. Ingelfinger, F. J.: Arrogance. N. Engl. J. Med., *303*:1507, 1980.
23. Isaacson, C.: The changing pattern of heart disease in South African blacks. S. Afr. Med. J., *52*:793, 1977.
24. James, T. N.: Neural pathology of the heart in sudden death. In *Sudden Death* (Kulbertus, H. E., and Wellens, H. J. J., Eds.). The Hague, Martinus Nijhoff, 1979.
25. Janse, M. J., et al.: Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute myocardial ischemia in isolated porcine and canine heart. Circ. Res., *47*:151, 1980.
26. Kahn, A. H., and Haywood, L. J.: Myocardial infarction in nine patients with radiologically patent coronary arteries. N. Engl. J. Med., *291*:427, 1974.
27. Keys, A.: Coronary heart disease. Serum cholesterol and the diet. Acta Med. Scand., *207*:153, 1980.
28. Keys, A. (Ed.): Coronary heart disease in seven countries. Circulation, *41*(Suppl. II), 1970.
29. Lyons, A. S., and Petrucelli, R. J., II: *Medicine, an Illustrated History.* New York, Harry N. Abrams, 1978.
30. McDonald, L.: Very early recognition of coronary heart disease. In *Progress in Cardiology*. Vol. 8 (Yu, N. P., and Goodwin, J. F., Eds.). Philadelphia, Lea & Febiger, 1979.
31. McMichael, J.: Fats and arterial disease. Am. Heart J., *98*:409, 1979.
32. McMichael, J.: Fats and asheroma: an inquest. Br. Med. J., *1*:173, 1979.
33. McMichael, J.: Dietetic factors in coronary diseases. Eur. J. Cardiol., *5*:447, 1977.
34. McNamara, J. J., Molot, M. A., Stremple, J. F., and Cutting, R. T.: Coronary artery disease in combat casualities in Vietnam. J.A.M.A., *216*:1185, 1971.
35. Mann, G. V.: Diet-heart: end of an era. N. Engl. J. Med., *297*:644, 1977.
36. Maseri, A., et al.: Coronary vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study of "preinfarction angina." N. Engl. J. Med., *299*: 1271, 1978.
37. Maseri, A., et al.: "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am. J. Cardiol., *42*:1091, 1978.
38. Meijler, F. L.: Becel-reclame en Coronaire Hartziekten. Med. Contact, *40*:1236, 1980.
39. Meijler, F. L.: Voeding en Coronaire Hartziekten, een bouwvallig luchtkasteel? Ned. Tijdschr Geneeskd., *124*:1695, 1980.
40. Meijler, F. L.: Cholesterol en Hartinfarct. Twijfels rondom "Vethypothese." Med. Contact, *33*:339, 1978.
41. Meijler, F. L.: De preventie van Coronaire Hartziekten. Ned. Tijdschr. Geneeskd., *122*:261, 1978.
42. Meijler, F. L.: Genzen is beter dan niet voorkomen. Hart Bull., *9*:35, 1978.
43. Mieltinen, M., et al.: Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes. Lancet, *2*: 835, 1972.
44. Nichols, A. B., Ravenscroft, C., Lamphicar, D. E., and Ostrander, L. D.: Independence of serum lipid levels and dietary habits. The Tecumseh Study. J.A.M.A., *236*:1948, 1976.
45. Nora, J. J., et al.: Genetic epidemiologic study of early-onset ischemic heart disease. Circulation, *61*:503, 1980.
46. Olinger, G. N., et al.: Unstable angina: the case for operation. Am. J. Cardiol., *42*:634, 1978.
47. Oliva, P. B., and Beechinridge, J. C.: Arteriographic evidence of coronary arterial spasm in acute myocardial infarction. Circulation, *56*:366, 1977.

48. Oster, K. A.: Duplicity in a committee report on diet and coronary heart disease. Am. Heart J., *99*:409, 1980.
49. Puska, P., et al.: Changes in coronary risk factors during comprehensive five-year community programme to control cardiovascular diseases (North Karelia Project). Br. Med. J., *2*:1173, 1979.
50. Reinhold, R.: Academy's report sparks debate over its objectivity. New York Times, June 10, 1980.
51. Roos, J.: A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Lancet, *2*:979, 1980.
52. Ross, R., and Glomset, J. A.: The pathogenesis of atherosclerosis. N. Engl. J. Med., *295*:369, 420, 1976.
53. Salonen, J. T., Puska, P., and Mustaniemi, H.: Changes in morbidity and mortality during comprehensive community programme to control cardiovascular diseases during 1972-7 in North Karelia. Br. Med. J., *2*:1178, 1979.
54. Shaper, A. G., and Marr, J. W.: Dietary recommendation for the community towards the postponement of coronary heart-disease. Br. Med. J., *1*:867, 1977.
55. Stallones, R. A.: The rise and fall of ischemic heart disease. Sci. Am., *243*:43, 1980.
56. Stamler, J.: Lifestyles, major risk factors, proof and public policy. Circulation, *58*:3, 1978.
57. Stern, M. P.: The recent decline in ischemic heart disease mortality. Ann. Intern. Med., *91*:630, 1979.
58. Toward Healthful Diets. Food and Nutrition Board Division of Biological Science Assembly of Life Science National Research Council. Washington, D.C., National Academy of Sciences, 1980.
59. Turpeinen, O.: Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes. Circulation, *59*:1, 1979.
60. Unstable Angina Pectoris Study Group: Unstable angina pectoris: national cooperative study group to compare surgical and medical therapy. Am. J. Cardiol., *42*:839, 1978.
61. Wall Street Journal Staff Reporter: Report questioning link of cholesterol to heart disease is assailed at hearing. Wall Street Journal, June, 19, 1980.
62. Weidman, W.: Effect of change in diet on level of serum cholesterol. In *Primary Prevention in Childhood of Atherosclerosis and Hypertensive Disease* (Lauer, R. M., and Shalleke, R. B., Eds.). New York, Raven Press, 1978.
63. Werkö, L.: Diet, lipids and heart attacks. Invitation to discussion. Acta Med. Scand., *206*:435, 1979.
64. Yudkin, J.: Diet and coronary thrombosis: hypothesis and fact. Lancet, *2*:155, 1957.

PRINTED IN U.S.A.