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Contribution of the Risk Factor Concept to Patient Care in Coronary Heart Disease

FRITS L. MEIJLER, MD, FACC

Utrecht, The Netherlands

This article deals with the question of whether or not the risk factor concept, a principal aspect of preventive cardiology, has contributed to patient care in coronary heart disease. The risk factors considered are plasma cholesterol, high blood pressure, smoking, diabetes and marked obesity. With the exception of plasma cholesterol and diabetes, all of these factors enhance myocardial oxygen consumption and thus, in the presence of coronary insufficiency, promote myocardial ischemia. Their modification is therefore good general medical practice, even if not related to coronary atherosclerosis. Diabetes needs adequate medical treatment in patients both with and without coronary atherosclerosis.

Because of the occasional occurrence of spontaneous regression of coronary atherosclerosis and the morphologic and functional complexity of coronary artery pathology, it has never been and probably never will be demonstrated that lowering plasma cholesterol levels by diet or other means will cause regression of coronary atherosclerosis. It follows that modification or treatment of risk factors is implemented for good medical reasons but does not *demonstrably* or *predictably* affect coronary artery disease. It is concluded that the contribution of the risk factor concept to patient care in coronary heart disease has been, and still is, trivial.

Cardiology has witnessed great strides in the diagnosis and therapy of congenital and acquired heart diseases during the past 25 years. In the field of diagnosis many new techniques such as coronary arteriography, clinical electrophysiology, echocardiography and nuclear cardiology have been developed and have contributed to the diagnostic arsenal of clinical cardiology. Coronary arteriography (1) has dramatically improved our knowledge of and changed our approach to coronary heart disease. In the field of therapy we have seen progress in surgery for congenital, valvular and coronary heart disease and more recently for arrhythmias (2). Coronary bypass surgery has had a major beneficial impact on the life of many patients with coronary heart disease. Similarly, the pharmacologic approach to the treatment of coronary heart disease has changed significantly. A great number of people with coronary heart disease live symptom-free and fruitful lives, instead of being disabled or dead as a result of the introduction of beta-receptor blocking agents (3). In the last decade our arsenal has been further extended by a new group of drugs, the so-called calcium antagonists (4).

The recent development of percutaneous transluminal coronary angioplasty (5) and intracoronary streptokinase infusion for angina pectoris and acute or impending myocardial infarction, respectively (6,7), may add new dimensions to the therapy and improve the prognosis of patients with coronary heart disease. From its initial conception in 1958 by Chardack (8) to its present space technology form, the electronic pacemaker has secured its place in daily cardiologic practice. Not every technologic development is a medical improvement, as Parsonnet (9) recently indicated when he characterized the latest generation of pacemakers as "a treatment in search of a disease." But there can be no doubt that developments in diagnosis and therapy have had an enormous positive impact on the patient with heart disease, especially on those with coronary heart disease.

The sums of money and intellectual skill that so successfully developed new diagnostic techniques, drugs and types of surgical procedures for cardiovascular disease during the past 25 years have probably been equaled by the funds and efforts spent on the prevention of coronary heart disease. It is true that when a disease is prevented, the person affected does not become a patient and thus requires no care. However, preventive cardiology has delivered a set of rules and options for healthy persons that are also freely propagated for and applied to patients with coronary heart disease as if these rules had a specific significance of their own.

Because epidemiology and prevention of coronary heart disease have consumed so much of our funding and atten-

tion, and because modification of risk factors is being advocated as a guide to clinical decisions in coronary heart disease (10,11), it is important to reflect on the role and contribution of such a risk factor concept to patient care.

Definitions

Any discussion of preventive cardiology and risk factors calls for proper definitions of terms (12). Prevention of coronary heart disease can be divided into primary and secondary prevention. Primary prevention of coronary heart disease is any action or measure to forestall the occurrence of coronary artery disease (coronary atherosclerosis, for example). Secondary prevention of coronary heart disease is any action or set of measures taken to prevent coronary heart disease in the presence of coronary artery disease. Prevention is not the same as treatment of clinical signs and symptoms in patients known to have coronary heart disease. In practice it is difficult, if not impossible, to distinguish between primary and secondary prevention.

Coronary artery disease versus coronary heart disease. It is essential to differentiate between these two conditions. Coronary artery disease is any demonstrable functional or morphologic abnormality of the coronary artery system. Coronary heart disease is any clinical sign or symptom or combination of those due to myocardial ischemia and coronary insufficiency caused by coronary artery disease. Coronary artery disease can be present without coronary heart disease (13). Thus, angina pectoris in a patient with valvular aortic stenosis and normal coronary arteries should not be called coronary heart disease. Coronary atherosclerosis is atherosclerosis of one or more coronary arteries. The diagnosis of coronary atherosclerosis can be made only by inference from a coronary arteriogram, because the arteriogram gives no direct information about the causes of the obstructions or narrowings observed, although at autopsy the majority of cases prove to be due to atherosclerosis. As will be seen later, coronary atherosclerosis can present itself in so many forms that the uniformity of the underlying metabolic process is open to serious question.

Coronary insufficiency is the pathophysiologic mechanism resulting in myocardial ischemia. Coronary insufficiency occurs when the demand for coronary artery perfusion surpasses the supply. This may be due to morphologic or functional abnormalities of the coronary arteries and/or to small vessel disease, such as that thought to be present in the so-called syndrome X (14): coronary heart disease without demonstrable coronary artery disease.

Thus, four different terms should be differentiated. These are:

1. Coronary heart disease: the clinical syndrome
2. Coronary insufficiency: the underlying pathophysiologic mechanism

3. Coronary artery disease: morphologic or functional abnormalities of the coronary arteries that may cause coronary insufficiency
4. Coronary atherosclerosis: the polymorphic narrowing of the coronary arteries in atherosclerosis.

In recent years it has been demonstrated that so-called coronary spasm may occur in apparently normal coronary arteries or arteries narrowed by atherosclerosis, or both (15,16).

Risk Factors

The pillars of preventive cardiology are the risk factors. A striking feature of a risk factor is that hardly anyone is concerned about its proper definition. For instance, the recent report on the rationale of the diet-heart statement by an American Heart Association committee (17) fails to define a risk factor, although the term is used in the text many times.

When a definition of risk factors is given in a paper or a report, it often differs from the definition in another paper. One may find, "those factors found to be statistically associated with an increased incidence of the disease" (18), or "characteristics which are associated with an increased risk of developing coronary heart disease" (19). When one takes these definitions literally, one will soon notice that the most absurd variables such as the sale of nylon stockings or number of television sets become risk factors, as already suggested by Yudkin in 1957 (20). Ideally, a factor should be called a risk factor only if, on elimination of that factor, the incidence of coronary heart disease would decrease (12). But for a critical appraisal of the contribution of risk factors to patient care in coronary heart disease, one needs to conform to the broad concept as it is generally used and that is, "a relation between certain conditions or circumstances and the incidence of coronary heart disease."

As it is the purpose of this paper to discuss the contribution of the risk factor concept to patient care, an attempt will be made to analyze the pathophysiologic contribution of each factor to coronary heart disease symptomatology and therapy. In this context, it is important to remember the difference between primary and secondary prevention and thus between those (risk) factors that advance coronary *artery* disease and those factors that (also) contribute to coronary *heart* disease when coronary artery disease is present.
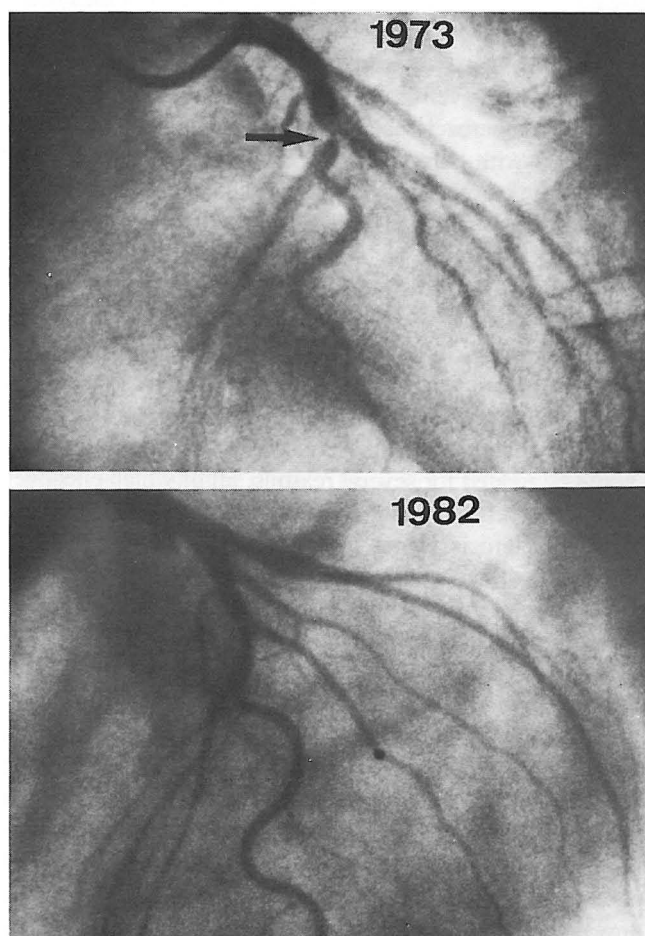
An extensive list of risk factors can be found in Blackburn's chapter in Progress in Cardiology (21). The two most prominent risk factors, the male sex and one's family history (22), cannot be manipulated. This leaves those risk factors whose modification according to the current recommendations of the American Heart Association should decrease the danger of coronary heart disease (17). These risk factors include: 1) elevated plasma cholesterol, 2) elevated blood pressure, 3) smoking, 4) diabetes mellitus, and

5) marked obesity. Suppose preventive cardiology had not come forth with these five factors. Would patient care have suffered?

Cholesterol and Coronary Artery Disease

There is scanty, if any, evidence that lowering the plasma cholesterol level by either diet or other means has a beneficial effect on the clinical status of a patient with coronary heart disease (23). Regression of atherosclerosis in general or of coronary atherosclerosis in particular by means of relatively drastic "therapeutic" interventions is still very much in doubt, but may perhaps become clinically relevant in the future (24,25). The optimists, however, should be aware that spontaneous regression of seemingly permanent stenosis in coronary arteries does also occur. This is supported by studies of coronary arteriograms in patients with coronary artery disease and coronary heart disease (Fig. 1).

Figure 1. Coronary arteriograms of a male patient born on September 6, 1926. The 1973 film **(top)** shows a severe stenosis proximally in the left anterior descending coronary artery. At that time the patient had an impending myocardial infarction. His serum cholesterol was 5.5 mmol/liter. In 1982 **(bottom)** there is almost complete regression of the stenosis; serum cholesterol was 5.2 mmol/liter. Both films were obtained in the left anterior oblique position with cranial angulation.

Regression of a lesion in one artery is often associated with progression of narrowing in other branches (26,27). Moreover, establishing the degree or severity of coronary atherosclerosis is a precarious undertaking. The endless variability of morphologic and functional abnormalities and the unpredictability of the degree of coronary artery disease in any given patient with symptoms of coronary heart disease (12,25) seem to defy a rational approach to the study of regression of coronary artery disease. Any true quantitative analysis, and thus comparison of different degrees of coronary atherosclerosis, is nearly impossible.

Wide spectrum of coronary artery abnormalities. Although in general, older people seem to have disease involving more vessels than do younger men and women, each clinical syndrome may be associated with a wide spectrum of anatomic arterial abnormalities (Table 1). For instance, one may find a single circumscribed stenosis in one coronary artery while the rest of the coronary artery tree seems to be perfectly normal. On the other hand, a seemingly totally different type of coronary pathology is formed by the so-called rosary type of abnormality in one or all of the major branches of the coronary system (Fig. 2). These and other forms of atherosclerotic coronary artery lesions may occur in patients of the same sex and age with the same symptoms and electrocardiographic abnormalities. Other patients may have a single fixed stenosis in each of the three major coronary arteries or may present themselves with spasm in one or more branches. Figure 3 illustrates multiple stenoses in all branches of the left coronary artery. The different types of coronary arteriograms that may be found in patients with coronary heart disease are summarized in Table 1.

In our experience, the appearance of a coronary lesion on an arteriogram cannot be predicted from the clinical picture. Severe and disabling angina pectoris may be accompanied by a single circumscribed narrowing in one ar-

Table 1. List of Anatomic and Functional Findings From Coronary Arteriograms in Patients With Clinical Signs and Symptoms of Coronary Heart Disease

1. Normal coronary arteries
2. Circumscribed solitary lesion in one artery
3. Circumscribed solitary lesion in two or more major branches
4. Diffusely narrowed arteries with or without local obstructions
5. "Rosary" type abnormalities in one, two or all three coronary arteries
6. Coronary spasm with or without anatomic lesions in one or more major branches
7. Findings 2 through 6 with coronary collateral vessels
8. Slow flow of dye in the coronary artery system
9. Aneurysmal dilations in one or more coronary arteries
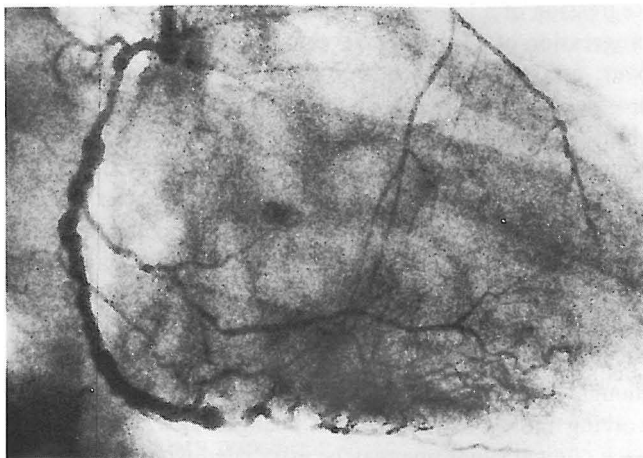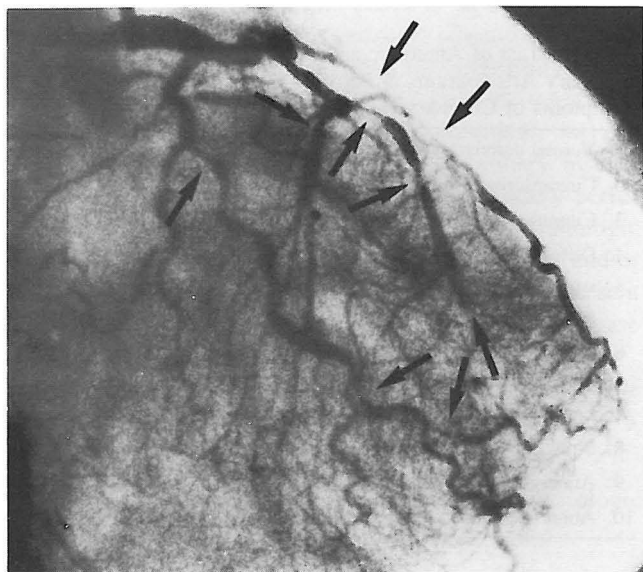10. Abnormal origin of one of the coronary arteries

Figure 2. Coronary arteriogram of a male patient born on September 24, 1931. The patient had an 8 year history of angina pectoris (class II, New York Heart Association) and progression of complaints for 3 months. The film shows the right coronary artery in the right anterior oblique position. The artery shows a so-called rosary type of abnormality with collaterals via the septum to the left anterior descending coronary artery.

tery while mild angina with a good exercise tolerance may be associated with multiple stenoses in all major branches. The undeniable conclusion is that a patient with *predictable* and *typical* abnormalities of the coronary arteries does not exist.

Lowering Blood Pressure

Increased blood pressure is an accepted risk factor for the development of coronary artery disease in patients with cor-

Figure 3. Coronary arteriogram of a female patient born on August 14, 1926. The patient had a 5 year history of angina pectoris (class III, New York Heart Association), nightly attacks since 6 weeks and electrocardiographic findings of an inferior wall myocardial infarction. All branches of the left coronary artery show multiple stenoses (**arrows**).

onary heart disease and hypertension, and reducing the blood pressure has a beneficial effect through a decrease in myocardial oxygen consumption (28,29). Treatment of elevated blood pressure in patients with angina pectoris is beneficial even if the hypertension was not contributing to the genesis of coronary atherosclerosis. Control of blood pressure is also important in the treatment of cardiogenic shock, and efforts to reduce the infarct size in patients with myocardial infarction with afterload reduction have become a more or less accepted form of therapy in selected patients (30–32).

Conclusion. Lowering blood pressure in patients with hypertension diminishes myocardial oxygen consumption, and therefore may restore the balance between oxygen demand and oxygen supply of the myocardium. Thus, lowering an elevated blood pressure is important in the care of patients with coronary heart disease, independent of its potential role as a risk factor for coronary atherosclerosis.

Smoking

Cigarette smoking is a major risk factor for coronary artery disease, and cessation of smoking reduces the risk of coronary heart disease (33). But this is not the only reason why a cardiologist will advise his patients with coronary heart disease to stop smoking. Cigarette smoking increases heart rate and arterial blood pressure and has a direct effect on myocardial oxgen consumption and coronary perfusion (34–36). Therefore, even if cigarette smoking should prove not to promote atherosclerosis, smoking should be discouraged in patients with coronary heart disease because of its potential for increasing the oxygen consumption of the myocardium.

Diabetes Mellitus

Diabetes mellitus is a major precursor of atherosclerosis and small vessel disease (37). This, however, is not necessarily the main reason for proper treatment of diabetes mellitus. Diabetes mellitus is an independent disease that should be treated for several reasons, all of which endanger a patient's well-being and longevity. Therefore, prevention of atherosclerosis is not the prime reason for control of diabetes mellitus. Although diabetes may promote atherosclerosis and consequently contribute to the incidence of coronary heart disease, we should be cautious about linking coronary heart disease to diabetes mellitus in all patients with coronary heart disease accompanied by diabetes. Because coronary heart disease due to coronary atherosclerosis often occurs in the absence of any carbohydrate metabolism abnormality, the combination of the two diseases does not necessarily reflect a cause and effect relation. This is supported by the fact that in societies where coexistence of coronary heart disease and diabetes is relatively rare, the prevalence of coronary atherosclerosis is also relatively rare (38).

Obesity

Whether or not marked obesity is an independent risk factor (17), fundamental laws of thermodynamics dictate that all weight, and certainly overweight carried by the body, requires physical energy that has to be provided by the myocardium. Moreover, excess weight contributes to hypertension which is an additional incentive for weight reduction (39). Thus, whether or not obesity is an independent risk factor, weight reduction is an essential part of medical treatment of patients with coronary heart disease.

Further Considerations

Rationale for making dietary recommendations for prevention. If we accept the notion that a relation between certain conditions or circumstances and the incidence of coronary heart disease is a risk factor, then the question whether the risk factor concept is applicable or of potential value to the individual patient with coronary heart disease is justifiable. Some risk factors can be avoided, such as cigarette smoking. Others can be alleviated, as for example, hypertension and obesity. There is no question that smoking and, when appropriate, intake of salt should be discouraged while antihypertensive treatment sometimes should be encouraged. The major unresolved issues are the role of plasma cholesterol and the question: Should patients with coronary heart disease change their eating habits to achieve regression of coronary atherosclerosis and lessening of their symptoms? Whether the available evidence linking the lipid composition of diets to the incidence of and death from coronary heart disease (40) is sufficiently convincing to allow governments to decide what one should or should not eat is not pertinent to the questions raised in this paper. Evidently much more proof is necessary to convince the population and their governments that they should change their eating habits. The rationale for making dietary recommendations for prevention of coronary heart disease has been questioned by prominent investigators (41–44) and groups (18). The Nutrition Committee of the American Heart Association has acknowledged the current difference of opinion on this subject (17).

If the rationale for prophylactic dietary changes in the population at large is not generally convincing, what about dietary recommendations for patients with coronary heart disease? The latter question, however, cannot be totally separated from the former because the arguments in support of dietary recommendations for patients are based on information obtained in epidemiologic and experimental studies. Consequently, one may question whether the end points used in those studies are valid or even transferable to clinical situations.

Establishing the diagnosis of coronary atherosclerosis. In the aforementioned American Heart Association's Committee report on the rationale of the diet-heart statement

(17), one may read that the fundamental goal is to prevent cardiovascular disease and, in particular, to reduce the incidence of coronary heart disease and other atherosclerotic diseases in our society. Suppose that atherosclerosis is a uniform process in the human organism and if the fundamental goal is to reduce atherosclerosis by means of changing the (American) diet, the question can be raised as to the existence of evidence that atherosclerosis is present in a given population. For instance, if the relative prevalence of atherosclerosis is defined by the number of heart attacks, as is done in some populations, one may raise the question as to the definition of a heart attack. Is it a myocardial infarction, sudden death, pulmonary edema or ventricular tachyarrhythmias? One cannot assume that even the most classic symptoms of coronary heart disease can be freely transposed to atherosclerosis. As early as 1972, thus before the coronary spasm "boom," Friesinger and Smith (45) demonstrated that, although unusual, normal coronary arteries could be present on arteriograms in patients with angina pectoris. This finding implies that clinical symptoms of coronary heart disease are not necessarily related to demonstrable coronary atherosclerosis.

Therefore, if we are to use epidemiology as a guide to clinical decision making in coronary heart disease, we need to be certain that the epidemiologic data are valid and applicable to daily cardiologic practice.

Myocardial ischemia in absence of coronary artery disease. Clinical symptoms of myocardial ischemia due to coronary artery disease can often be discovered by carefully taking the patient's history, rarely by physical examination, sometimes with the aid of an electrocardiogram obtained at rest, during exercise or during 24 hour ambulatory recording, sometimes with isotope imaging and, perhaps in not the too distant future, with adapted digital subtraction techniques, nuclear magnetic resonance, or both. If there is evidence of local myocardial ischemia, we may assume with confidence that coronary perfusion has been impaired. Nevertheless, we should be careful about assuming the presence of coronary artery disease, because subendocardial ischemia or injury may occasionally be a result of elevated left ventricular end-diastolic pressure (46) or small vessel disease.

Although Stamler (47) declares that, "In the overwhelming majority of cases (90% or more) clinical coronary heart disease (sudden death, myocardial infarction, congestive heart failure, unstable and stable angina pectoris) results from severe atherosclerosis of coronary arteries, often involving two or more vessels," James (48) warns against oversimplification. He states, "Finally, in recognizing that sudden death and severe coronary (artery) disease often coexist in men of middle age or beyond, we must not lose sight of the wealth of information to be had from many other forms of sudden death in which coronary disease plays little or no role."

Not only sudden death, but other symptoms of coronary

heart disease, such as myocardial infarction, can occasionally appear without demonstrable coronary artery disease as well (49). This implies that coronary heart disease, even in the presence of severe coronary atherosclerosis, need not always be caused by the atherosclerosis. The equalization of coronary heart disease and coronary atherosclerosis is an oversimplification at best and a scientific mistake at worst. Therefore, also for purely epidemiologic purposes, the concept that coronary heart disease and coronary atherosclerosis are interchangeable is probably overstretched.

Variability of pathologic patterns. Because the pattern of coronary artery disease is complicated and unpredictable, the application of epidemiologic rules to the clinical situation and especially to the individual patient is even more precarious. We learned from coronary arteriography that in patients with a variety of signs and symptoms of coronary heart disease, at least 10 different types of coronary abnormalities may be found, but their presence is unpredictable (Table 1). Not only is it possible to divide coronary artery disease into one, two and three vessel disease as well as left main stem disease, but the functional and anatomic abnormalities of each artery may differ significantly in patients with the same numbers of vessels involved and among patients with different numbers of vessels involved in the disease. All these different abnormalities may or may not be related to atherosclerosis.

It is difficult to understand that a single metabolic disorder can be responsible for such a variety of morphologic changes involving one, two or all of the coronary arteries. Moreover, there is no explanation why the lipid composition of the diet by way of serum cholesterol would affect one arterial system while doing no harm to the rest of the arterial vasculature. Although from an epidemiologic viewpoint there may be some logic in attempts to influence coronary artery disease by lowering plasma cholesterol levels by dietary means or with drugs, proof of a lasting and quantitatively significant regression of coronary atherosclerosis as a result of lowering the plasma cholesterol level in a patient with coronary heart disease has yet to be reported. Thus, simple rules, such as changing the diet to reduce symptoms of coronary heart disease or attain regression of coronary atherosclerosis, may not be applicable to patients with coronary heart disease.

Despite all this skepticism, general rules and common sense should prevail. The risk factors linked to primary prevention also play a role in secondary prevention and are part of a sensible therapeutic approach to patients with coronary heart disease. However, the contribution of the risk factor concept to patient care in coronary heart disease has been trivial. The scientific basis for the application of the risk factor concept per se to the individual patient has been severely overstretched.

No wonder that in his article, "The Rise and Fall of Epidemiology," Rothman (50) states that, "Among the legacies (of epidemiology) is the demise of major 20th Century epidemics attributable to tobacco, dietary fats, and some carcinogens in the work place and environment."

Conclusion

Considering the major risk factors linked with coronary heart disease and the contribution of their identification and modification to the care of patients with coronary heart disease, we can only conclude that their impact has been trivial. The factors, male sex and heredity, cannot be manipulated. Quantitative regression of coronary sclerosis by measures that lower cholesterol level has yet to be demonstrated; reduction of blood pressure, cessation of cigarette smoking, treatment of diabetes mellitus and weight reduction are reasonable and appropriate measures in patients with or without coronary heart disease, even if the idea of modification of risk factors had never entered the minds of cardiologists. On the basis of these considerations it must be concluded that the contribution of risk factors to the daily care of patients with coronary heart disease is like an elephant that has delivered a mouse.

Final Remarks

For a non-American member of the American College of Cardiology, it is an honor and a pleasure to contribute to this anniversary issue of the College's journal. As far as I may represent cardiology in The Netherlands, we wish the *Journal of the American College of Cardiology* every success on its way to spreading cardiologic knowledge and expertise among cardiologists all over the world. I thank the guest editor of this issue for giving me the opportunity to make this contribution.

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