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THE EPIDEMIOLOGY OF CORONARY HEART DISEASE--FEBRUARY 1972

Address by Ancel Keys

Council on Epidemiology, American Heart Association

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Mr. Chairman, officers and members of the Council on Epidemiology, guests:

When Bill Kannel wrote asking me to speak at this dinner he said, "We think it fitting at the time of your retirement to give us your thoughts on the contribution of epidemiology to our understanding of cardiovascular disease--" I am glad to respond but first a word on my own status beginning in July.

My "retirement" will mean a large reduction in pay but no end of work. However, much of that work will be done at our home in Italy where the sun shines most of the days, where snow is used only to beautify the nearby mountains, where we eat well and stay very well indeed, and where we are glad to welcome colleagues.

Now let us examine the question, where are we? What is the status of the epidemiology of cardiovascular disease? I put the question simply to insist that I narrow the field. For it is not useful to lump together the several cardiovascular diseases and attempt an overall appraisal. Congenital, rheumatic, coronary, the various myocardial diseases, and so on--each has its separate epidemiology and its different degree of progress.

Currently, coronary heart disease accounts for nearly four-fifths of all cardiac deaths in the United States so it is reasonable that most of the present effort in cardiovascular epidemiology is devoted to this one disease.

And since I have so long concentrated on this subject and don't know much else I shall deal only with the coronary story.

So where are we? I think we are near the end of a phase that began about 25 years ago in response to stimuli from three main sources. First was appreciation of numbers. Realization of the tremendous incidence of this disease was dawning in the 1940s. With so many persons affected, the need for mass consideration was obvious and it was easy to appreciate the associated research opportunities. Even modest-scale surveys would give indications of prevalence and any follow-up would shortly produce incidence cases.

The second spur to epidemiology was the increasing acceptance of the idea that populations differ in the frequency of the disease and that the mode of life must be involved. A great boost came from the evidence from World War experience that the incidence of the disease could change in association with changes in the way of life. Confirmation came soon from the Yemenites and other Jews in Israel, then from Japanese in Japan, Hawaii, and California.

The third stimulus for epidemiological work came from consideration of the concentration of cholesterol in the blood. If the cholesterol level is as important as suggested by experiments on animals it should be revealing to compare populations in this respect and to observe the follow-up of persons differing in their habitual level of cholesterol in the blood.

So, 20-plus years ago, some of us started prospective studies in the United States, explorations of populations abroad, analyses of mortality rates of men of different occupations or ethnic origin. The awakening of interest in epidemiology coincided with the start of public support for research in heart disease.

Research grants from the new National Heart Institute started in 1947--mine was number ten--and the American Heart Association "went public" the next year, meaning that the AHA started to raise money and aid research.

Naturally, as more and more people entered the field, controversies developed; persons and ideas competed for the center of an increasingly popular stage. Because serum cholesterol was the first variable proposed as what we now call a risk factor, repeated assaults on its role were made by claiming greater importance for other things: the cholesterol-phospholipid ratio, the flotation pattern in the ultracentrifuge, the beta lipoproteins or the pre-beta band in electrophoresis, the triglycerides, lately the lipoprotein pattern. Those of us who had been measuring cholesterol for a long time still do not believe that we were measuring the wrong thing.

The importance of the diet, especially of the dietary fats, was challenged on the basis of some quickie surveys and travelers' tales. Accusingly we were asked, "What about the Eskimo?", "the happy Hunza?", the Navajo Indian?", the Masai?" And then came the pronouncement that dietary sugar is the real villain.

The importance of serum cholesterol has been subject to a variety of attacks. Because practically all tissues can synthesize at least a little cholesterol it was proposed that the cholesterol in the atheroma is a local product unrelated to the cholesterol in the blood. It was even proposed that a fall in the concentration of cholesterol in the blood means a deposition of that cholesterol elsewhere in the body.

Such diversions along the road are often exasperating but they provoke some useful responses; a hard look at even a false trail can teach us something.

Where we are today reflects what has been accomplished in the last 25 years, in what I suggest is the first great phase, nearing an end, of the epidemiology of coronary heart disease. So what is the progress? I can only suggest some highlights.

First, we rose to cope with complexity; we got rid of the urge to over-simplify and seek the cause, a single and sufficient reason for the result we recognize as clinical coronary heart disease. The primordial cause is the innate nature of the arterial wall, everybody's arterial wall. We now realize that what happens to it over time, how much and how fast, depends on several influences. Much of the effort in coronary epidemiology has gone to the discovery and evaluation of these influences, now commonly called risk factors.

Age itself is a risk factor because the underlying pathology of the disease takes a long time to develop. Sex is a risk factor although we don't know why nor how to measure it. But age is beyond control, and sex should be, so we turn to influences that can be manipulated. Outstanding here are the arterial blood pressure and the concentration of cholesterol-rich lipoproteins in the blood plasma. The incidence of heart attacks under age 65 could be cut perhaps to one-fourth if systolic pressure were always under 130 and cholesterol under 220.

A bad family history of heart attacks is also a risk factor but it is unknown to what extent genetic constitution operates <u>independently</u> from expression in blood pressure and the blood lipids. Conceivably it could contribute by controlling the architecture of the arterial system of the individual;

The kinks and bends of the arteries pinpoint sites of predilection for atherosclerosis and more kinks from genetic endowment could mean more locally severe atherosclerosis.

Undoubtedly other variables beyond this short list influence atherogenesis but they are only speculative or as yet entirely unknown. Some experiments on animals suggest effects of infections and of toxins on the intima but these may have no frequent counterpart in man. Duguid and his followers made much of the coagulation-fibrinolysis system of the blood but nobody has identified any part of that system as atherogenic in animals or as a risk factor in man. Duguid's own experimental evidence proved mainly that diet-induced hypercholesterolemia is atherogenic!

So far I have said nothing about smoking because I have been concentrating on atherosclerosis. Smoking is a risk factor for coronary heart disease but there is no proof that smoking is atherogenic. Perhaps an effect on the irritability of the myocardium is responsible. But it is time to make the point that, in general, epidemiological studies do not reveal mechanisms and only rarely do they deal with pre-clinical pathology in the classical sense. In epidemiology people talk a lot about atherosclerosis when actually all they know are clinical events that allow the diagnosis of coronary heart disease.

So epidemiology has identified some risk factors and thereby offers the prospect of preventive programs. The case is air-tight for attacking blood pressure, serum cholesterol, cigarette smoking, diabetes, and these are things that people and their doctors can do something about. If the family history is bad, that is all the more reason to pay attention to these risk factors.

And now, what about overweight and lack of exercise? Personally I deplore obesity and physical indolence but I pause at the claim that these two characteristics, of themselves, promote coronary heart disease. By any standard we are a nation of fat and sedentary people but there is no evidence that this explains our pandemic of coronary heart disease. Every time I go to Finland I am reminded that getting a lot of exercise and staying thin offers small protection against heart attacks. And I recall that the prognosis in both angina pectoris and myocardial infarction is better for fat than for thin people.

The evidence is now overwhelming that overweight in the absence of high blood pressure is not a significant risk factor for coronary heart disease, at least not for middle-aged men in the United States or in Europe. Hypertension is more common in fat than in thin people and when fat hypertensives reduce they often have a fall in blood pressure. But the majority of overweight people are not hypertensive and there is no justification to tell that majority that they are at undue risk of heart attacks. Incidentally, in all of our surveys the prevalence of hypertension among American men is no higher than it is among men of the same age in populations where overweight is far less common. Some statements about overweight in the American Heart Association pamphlet, "Reduce Your Risk of Heart Attack," fly in the face of the evidence.

This is not the occasion for detailed examination of the claim that regular exercise will prevent the development of coronary heart disease. I am all in favor of physical activity and I should be delighted if someone would only produce some solid evidence. But the more carefully this question is examined the more it seems unlikely that good evidence will come from the epidemiological approach. When men in active versus sedentary categories are compared, what

justification is there for concluding that differences in disease experience are caused by the difference in habitual activity. Besides the fact that men who aren't well tend to be concentrated in the less active class, commonly the two kinds of men also differ in other respects that may influence their likelihood of developing coronary heart disease. When the men contrasting in activity are fairly similar in other respects, as in the case of our railroad switchmen and clerks, they show little or no difference in susceptibility to heart attacks. Finally, in our society and time at least the men in different classes of activity have self-selected themselves into those classes; the differences in activity are not accidental.

But I would lean over backwards to give credence even to poor epidemiological evidence if it were consistent in different samples and populations and if there were reasonable support from experiments and plausible biomedical theory. We had hope in the theory that exercise builds collaterals and these could be protective. Alas! further experiments and clinical observations seem to have completely demolished that idea.

And there was the idea that exercise could be protective by lowering blood pressure and serum cholesterol. But closer scrutiny shows that where such changes in risk factors were reported they were always associated with a negative calorie balance. Well, for many years I have been advising fat people to increase their physical activity as well as to cut down on the groceries--which is not quite the same as saying that heart attacks will be prevented by exercise, period.

More data and more critical analyses also de-emphasize some other variables proposed as risk factors--resting pulse rate and vital capacity, for

instance. On the other hand, there is increasing reason to think that susceptibility to coronary heart disease may be influenced by the personality or emotional type, though I'd like to know why. Anyway, some of us are asking how we can change from Type A to Type B. I like to think that our home in Italy may be my personal answer.

But single variables are no longer fashionable; multivariate analysis, greatly aided by new models and computer programs, is in. No more excuse for clumsy cross-classifications and the loss of information from making dichotomies and trichotomies out of continuous distributions. Now we can automatically expose confounded variables and evaluate interactions.

Theoreticians may argue which multivariate method is best but in regard to the multiple regression and the two methods for solving the multiple logistic the argument seems academic. At least in no published material I have seen nor in any of the many parallel runs we have made is there any indication that the several methods differ significantly in the accuracy of predicting the distribution of cases into classes of estimated relative risk.

And I should like to know what theory says we should accept conclusions about the relative importance of variables from comparisons of t values and F ratios calculated with variables whose distributions do not remotely approach normality. As a matter of fact, next to the danger of burial in computer output the chief hazard of modern multivariate analysis is the temptation to over-interpret the meaning of the coefficients found. They are not necessarily applicable to any other sample or population and they do not necessarily have anything whatever to do with ultimate causes.

The application of multivariate solutions from one population to another is just beginning to be tested but already the result is fascinating. Relative risk in middle-aged men is remarkably well predicted. But predicted total incidence in the population is grossly in error when the incidence among men in Europe is predicted from multivariate solutions from data on men in the United States. The error is just as great, but in the opposite direction, when the reverse prediction is made. Numerically, the indication is that about half of the incidence in the United States remains unexplained when account is taken of age, blood pressure, serum cholesterol, cigarette smoking, relative body weight, body fatness, pulse rate in rest, vital capacity of the lungs, and habitual physical activity.

Something of great importance is being missed, is not represented in our list of potential risk factors for which we have data. What is it? Unrecognized variables? Long-time longitudinal data on the variables studied? Do we need a better model for multivariate analysis? Should we look into non-linear functions? Here is a big challenge and the discovery that there is this challenge represents progress.

There are many other plus marks to our situation in epidemiology as of today. I think a big item of hope is the finding that it is possible to have a very low incidence of coronary heart disease without a compensating high death rate from other causes. A big plus is that we now have an objective and accepted method of classifying the electrocardiogram and this is in wide use in epidemiological studies.

The natural history of coronary heart disease after the myocardial infarction is being revealed--and much more is coming--from the Coronary

Drug Study. Apart from what will be learned about the effects of the drugs, that study is discovering the risk factors after the infarction and finding that they are not identical with the factors that predispose to the first heart attack.

The plan of the Coronary Drug Study took advantage of the fact that at last we are properly estimating the numbers of subjects needed to test hypotheses. The rub with this progress is that we see what large numbers are needed for many purposes, numbers too big for the independent investigator or small group of investigators.

This is one reason why I think we are nearing the end of the first major phase of the epidemiology of coronary heart disease. Another reason is the prospect that the main action will move away from simple observation, the exploratory survey, and the limited scale follow-up that has dominated the picture until recently. So what next?

The time is past when we could make major progress simply by making examinations and then standing by to count the cases. We need to examine some more variables and a few more populations but this is no big new deal. The real wave of the future is indicated by the fact that it is no longer defensible to hold still so we can measure more exactly the penalty, in heart attacks and deaths, of the risk factors. We now must enter, and I think we are entering, the era of preventive trials and demonstrations. And these will be followed, we trust, by prevention programs aimed at the entire public.

All this means much bigger operations involving far more people, far larger professional teams--and another order or two of magnitude of budgets--than anyone dreamed of until lately. But this necessarily means epidemiology by contract and by committee.

For many years some of us have been talking about the great day when we can actually start helping people by giving them some measure of prevention. While we now rejoice in the near approach of that day, some of you may feel, as I do, that we are glad we were in the game earlier, when we could draw up our own protocols and make our own mistakes.

Thank you