DEATH RATES attributed to cardiovascular disease, especially arteriosclerotic heart disease and stroke, are decreasing among all races and sex groups and most age groups in the United States.1,2 Recent reports suggest that the incidence of stroke also decreased, particularly in the older age groups.3 Diets high in cholesterol and saturated fat remain the cornerstone of the experimental atherosclerotic model. Numerous analytical epidemiologic studies have shown the relationship between plasma cholesterol, especially low-density lipoprotein cholesterol, cigarette smoking, hypertension and the risk of heart attack. Populations in which the total cholesterol is very low have extremely low death rates from arteriosclerotic heart disease and minimal atherosclerotic disease at postmortem examination. The geneticist and lipid biochemist have identified several types of familial hyperlipoproteinemias that are clearly related to atherosclerosis. More recent studies have shown an inverse relationship between high-density lipoprotein cholesterol and the risk of heart attack.4 New risk factors, such as type A and B behavior, physical inactivity and perhaps abnormalities of clotting and thrombosis, have also been identified. However the “big three” — plasma cholesterol, blood pressure, and smoking — still have the center stage.

National programs have been launched by voluntary agencies such as the American Heart Association and by the federal government to urge everyone to modify risk factors. The National High Blood Pressure Education Program had apparent great success in screening persons for high blood pressure and increasing the percentage being treated for their high blood pressure.5 Cigarette smoking has decreased among adults.6 Some reports suggest that dietary habits have been changing and that the mean cholesterol in the population is also decreasing. People are clearly exercising more. Jogging has become a great new fad and obesity has become a “bad word.” Stress management is a thriving industry. Preventive cardiologists are joining the faculty of medical schools. We all should be pleased with these great accomplishments. The research dollars appear to be well spent.

But there remains a small cloud in this beautiful picture. We lack the experimental evidence that modification of the risk factors, except perhaps at the extreme ranges, reduce the incidence and mortality from heart attack. The agonist and antagonist have lined up month after month in numerous journals to profess their views about the concept of primary prevention of heart attack based on dietary modification, reduction of cigarette smoking and treatment of high blood pressure. In the middle there appears to be a great absence of solid scientific evidence.

A series of important experimental or clinical trials are now being conducted in the United States and other countries to establish the effectiveness of primary prevention through modification of the risk factors. These clinical trials of primary prevention should be separated from the previously reported secondary prevention trials that attempted to modify risk factors after a heart attack or stroke in order to reduce the risk of a second heart attack or death after the initial heart attack.7 The primary prevention trials select subjects who are free of clinical heart disease or stroke at entry to the study.

The primary prevention trials can be subdivided into those limited to a single risk factor, e.g., plasma cholesterol reduction,8 and multiple risk factor intervention.9 Most of the single risk factor intervention trials are double blinded and include a pharmacologic agent to lower either the cholesterol or the blood pressure compared with a placebo. Many of these studies are further limited to very high risk subjects, that is, subjects with plasma cholesterol levels in the highest 10-15% of the population that are difficult or impossible to modify by dietary intervention.10 The studies are also generally limited to relatively small sample sizes. The trials such as the Lipid Research Clinic Study and the National Heart, Lung and Blood Institute Type II Intervention Study are of great importance in determining the efficacy of lowering plasma cholesterol on the risk of a heart attack or changes in the degree of coronary atherosclerosis. However, they will not determine the efficacy of primary prevention for the majority of people or the efficacy of lifestyle changes independent of pharmacologic therapy.

Many of the primary prevention trials are not double blinded. Trials to reduce cigarette smoking obviously cannot be blinded. Although it was possible to blind nutritional intervention trials, the cost and practicality has ruled them out, and almost all nutritional trials are nonblinded. Trials to lower blood pressure, especially using drugs, can be double blinded, but many investigators believe that it is unethical to allow subjects with markedly elevated blood pressure to go untreated in a blinded placebo trial, so the majority of blood pressure trials, at least in the United States, including the Hypertension Detection and Follow-up Program, have been unblinded.11
Ideally, we should treat each risk factor independently, but modification of one risk factor often results in changes in other risk factors. Cigarette smoking cessation often causes weight gain and the weight gain may result in an elevation of blood pressure. In a good primary prevention program there would be an effort to reduce the weight gained, and if this failed certainly to treat the elevated blood pressure with drugs. Although we recognize that the multifactorial approach is less precise and perhaps somewhat less likely to give solid scientific information, it is probably a more rational approach to the problem.

Two types of multifactorial primary prevention trials are underway. The first type of study, exemplified by the Multiple Risk Factor Intervention Trial (MRFIT), selected subjects at high risk of heart attack based on a combination of blood pressure, cigarette smoking history and plasma cholesterol level. Subjects were then randomized into either a special treatment group or a comparison group.

The second type of study is exemplified by the Belgium Heart Disease Prevention Project, discussed in the current issue of Circulation. In this type of study communities or groups, rather than individuals, are randomized into a treatment or control group. The Belgium study has randomized men by the factory where they work. A similar type of study recently reported by the Stanford Heart Disease Prevention Program randomized three communities in California. Similar studies are being done in other countries, including Finland and Holland.

The primary hypothesis in these studies is that reduction of the risk factors will reduce the incidence of and mortality from heart attack. The successful test of this hypothesis requires that subjects or groups be successfully recruited and categorized at entry to the study, baseline, and that a very high percentage be successfully followed for the duration of the study. The Belgium Heart Study was able to recruit 83% of the eligible participants. However, no data were presented about the number of participants in the intensive health education program or how many remained for the full 2 years of the follow-up.

The Stanford experience noted that at the end of 2 years, 62% of the individuals in the control group and approximately 73% in the intervention group remained for follow-up examination. This percentage may be too low for careful evaluation of some end points, especially morbidity and changes in the risk factors.

The second step in testing the hypothesis requires the successful reduction of the major risk factors, smoking, blood pressure and cholesterol. Both the Belgium and the Stanford Three Community Study selected a subsample of high-risk subjects for more intensive individual intervention, while the rest of the treatment group received only community health education approaches. We do not know how large a reduction in risk factors is necessary to observe a decrease in heart attacks. The larger the reduction in risk factors the greater the chance for observing a decrease in heart attacks. MRFIT set specific goals for reduction of risk factors, based on the presumption that such reduction would result in a statistically significant decrease in the incidence of heart attack. So far, the results in the health education phase of the Belgium and Stanford Three Community Studies have been disappointing. The Belgium study failed to show any difference in cigarette smoking, a modest difference in cholesterol due almost completely to an increase in cholesterol in the control group, probably due to laboratory drift, and a small difference in systolic blood pressure. The Stanford Study had more promising results — fewer cigarettes smoked per day, but very minimal changes in systolic blood pressure and plasma cholesterol levels. The Belgium study reported better results for the high-risk subsample given more intense intervention. In the Stanford study the more intensive intervention group did better only in terms of the reduction of the number of cigarettes smoked. Both studies reported an impressive reduction in the risk score. However, the risk score is markedly influenced by modest changes in both systolic blood pressure and number of cigarettes smoked.

The relationship between the reduction of this risk score and actual reduction in the frequency of disease is, of course, the hypothesis being tested. Comparison of reduction in risk factors between the special-care and usual-care groups have not been published by MRFIT.

The third and most critical step depends on the first two — that is, measurement of outcome, changes in the incidence or death rate due to arteriosclerotic heart disease. The ability to measure the incidence requires careful and unbiased monitoring of the sample. It is difficult to determine whether any of the major studies will include a complete enough follow-up for a sufficient duration to be able to measure the change in the incidence of heart attack. The determination of total and cardiovascular mortality will be much simpler, since it only depends on minimizing the number of participants lost to follow-up. The community studies will be attempting to compare the death rates between two or several communities. The power of such a statistical test is obviously very weak. If we were just comparing two communities there would be a 50–50 chance that either community would have a lower death rate than the other. The individualized trials, such as MRFIT, have a much better chance of demonstrating the difference in death rates between the so-called special- and usual-care groups and also specific subgroups within the study. This type of study, in which subjects are randomized, has a much more powerful statistical base and may offer the only true scientific measure of the efficacy of multiple-risk-factor intervention.

Studies such as MRFIT have an added problem. The control group may be receiving intervention advice to change behavior because the people in this group are seen every year and referred to their physicians.
Both the community and the individualized studies are also confounded by the uncertainty of the interval between risk-factor change and reduction in risk of disease. We have already pointed out that those subjects most likely to die or have a heart attack in the first few years of the study are subjects with the most extensive disease at baseline, e.g., more extensive coronary artery stenosis and poor left ventricular function. Such subjects may obviously also be least likely to benefit from risk-factor reduction because they may be considered to be in a terminal stage of their subclinical disease. Unless the population is followed long enough to include both the lag period and the effects of the initial selection of those with advanced subclinical disease, a spurious interpretation of the study results is possible. We might conclude that there is no benefit due to risk-factor reduction, at least within the first 4-5 years of the study. This obviously does not tell us whether such risk-factor reduction will be beneficial later on. We do not know the length of this interval nor the number of susceptible and non-susceptible to intervention. Because of the costs in dollars and the difficulties of maintaining both the staff and the participants for a long period of time there is a definite time limit to these studies.

Other investigators, realizing these problems, have suggested that we use intermediate end points, such as a change in the extent of coronary atherosclerosis or atherosclerotic disease at other sites as measured by radiographic or other techniques. However, it is hard to believe that the scientific community would accept a 10-15% reduction in the size of an atherosclerotic plaque as solid proof of the efficacy of risk-factor reduction for the prevention of coronary heart disease mortality. Sadly, we might accept lifestyle changes as good preventive medicine without solid scientific proof of efficacy. We can only hope that quitting smoking, lowering the blood pressure, modifying the diet to reduce the plasma cholesterol, exercising more, and reducing stress is a better health policy than having a hot dog and beer and then smoking a cigarette while sitting in front of a television on a Saturday afternoon.

References

L H Kuller

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