almost total dependence on imported oil is being seriously considered. In South America, Brazil is reported to be already introducing ethanol-gasoline blends into general use. In the United States a variety of industrial organizations are considering plans to build coal- or wood-based methanol plants, but the oil and automobile companies appear to be holding back. A bill recently introduced into the California legislature that would have required methanol-gasoline blends to be sold in that state by 1980 was strongly opposed by oil and auto company spokesmen and eventually killed. No existing U.S. research efforts on methanol use are comparable in scale to the MIT fleet test, which might possibly have had considerable national impact, as Reed claims.

The alternative point of view—that methanol should be discounted for the present as an energy option because shortages of oil are not imminent and the United States can live very well on imported oil—does have supporters beyond the major oil companies. White and many of his colleagues at the energy laboratory subscribe to this argument. At issue in the MIT affair, then, is whether the decision to cancel the fleet test went beyond honest differences of opinion.

Reed certainly believes that it did, and although he continues to pursue research on synthetic fuels and to interact with the energy lab on some matters, he is obviously badly shaken by the experience. In recent correspondence with his Minnesota benefactor, Hawley, he received a second check, this time for $50,000, to further his methanol work. The check, however, was made out to MIT, and Reed, rather than risk a repeat of the whole affair, sent it back.

White, while rejecting any suggestion of improprieties, says that a more carefully designed test would probably have attracted the cooperation of Heywood and Longwell and have been approved. But this merely raises the question of why the test was not redesigned, rather than canceled. It would not appear to have been beyond salvaging. One energy lab scientist, who did not want to be named, says "the design may have been a little sloppy, but to say that it wasn't scholarly is ridiculous."

This ambiguous incident is troublesome because it raises the specter of universities adjusting their perspective as to what is important and their research programs to mesh more smoothly with government and industry. Even the suspicion of improper influence tends to weaken confidence in academic independence and hence the potential for university leadership in energy research matters.

—ALLEN L. HAMMOND

Prevention of Heart Disease: Clinical Trials at What Cost?

With the passage of the Heart, Lung, and Blood Act in 1972, several large-scale clinical trials were planned to see whether people can voluntarily decrease their risk of heart disease. Now, 4 years later, screening for participants in the two most extensive and most expensive of these trials is nearly complete, but the trials are turning out to cost far more than anyone anticipated and the National Heart and Lung Institute (NHLI) budget is far less than was projected in 1972.

Since corners cannot be cut on these clinical trials and since no knowledge of heart disease would be gained if the trials were terminated early, some critics are asking if it was a mistake even to begin these studies. In particular, many point out that the irreversible commitment to these clinical trials means that larger and larger portions of the NHLI budget are being drained away from basic research. Others contend that the cost of conducting such large-scale trials is minuscule in comparison with the social and economic costs of heart disease to this nation. Moreover, information gained from such large-scale trials can provide the best means, at present, to prevent heart disease, the major U.S. cause of death.

In 1972, there was promise of a vast increase in government spending for research on cardiovascular disease. At that time, the Lipid Research Clinic (LRC) Primary Prevention Trial and the Multiple Risk Factor Intervention Trial (MRFIT) were conceived and were expected to cost at most $80 million. Unfortunately, inflation and certain other costs were not anticipated, and now these trials are expected to cost at least $200 million. The NHLI budget, on the other hand, has been pared down so that instead of receiving $520 million in fiscal year 1975, as was expected in 1972, the NHLI received only $325 million.

Most investigators agree that there is a need for information on whether the variables affecting incidences of coronary heart disease can be controlled. Whether diet affects risks of heart disease, for example, is a major social and medical issue in this country. Few Americans are unaware of the statistical correlations between high concentrations of serum lipids and cholesterol and coronary heart disease. A national obsession with dietary fats and cholesterol seems to have developed despite the fact that there is as yet no conclusive evidence that people can voluntarily decrease their risks of heart attacks by changing their diets. Nor is there conclusive evidence that modifying other risk factors, such as smoking and high blood pressure, can affect incidences of heart disease. Until more is known about the biochemical etiology of heart disease, the only way to decide whether incidences of heart disease can be reduced is to conduct large-scale clinical trials.

The LRC Primary Prevention Trial and MRFIT concentrate on select high risk populations in order to reduce the number of people who must be studied and the length of time the trial must continue before statistically significant results can be obtained. Because, on the average in any year, only 1 middle-aged man in 100 suffers a heart attack, large numbers of people must be studied for years to see if the variables that influence heart attacks can be controlled. For example, an NIH group concluded, in 1969, that a national dietary study of the population at large would necessarily involve about 50,000 to 100,000 people and might cost as much as $1 billion. According to Robert Levy, director of the NHLI, such a study would take up all the funds allocated to the NHLI.

Although they are more modest than studies of the entire population, the LRC Primary Prevention Trial and MRFIT nonetheless involve formidable managerial problems, not all of which were anticipated when the studies were proposed, and these tend to escalate costs. For example, measurements of serum cholesterol must be carefully standardized. According to Basil Rifkind, director of the LRC, cholesterol

measurements vary significantly from laboratory to laboratory. Some people are referred to NIH for hypercholesterolemia, he claims, who, upon testing, turn out to have normal concentrations of cholesterol in their blood. Thus procedures for cholesterol measurements taken at the various clinics participating in the two trials had to be made uniform. To ensure that the cholesterol measurements at the clinics remain comparable, standards and related material must be sent from the Center for Disease Control in Atlanta to each of the participating clinics.

The LRC study is designed to determine whether men whose serum cholesterol concentrations fall in the upper 5 percent of the normal distribution of cholesterol concentrations in the United States can decrease their risk of heart disease if they decrease the amount of cholesterol in their blood. About 3600 men will be studied for 7 years. To find those men, as many as 400,000 people must be screened—a task that has taken 3 years.

Once chosen for the LRC study, the men are randomly divided into two groups. Members of the first group are given a diet low in saturated fats and cholesterol and are given a drug—cholestyramine—that should lower their cholesterol concentrations. (The drug has few side effects, and so planners of the trial expect that the men will not be harmed when they take it for 7 years.) Members of the second group are given the same diet as the first group but are given a placebo instead of cholestyramine.

Designers of the LRC Primary Prevention Trial expect about 9 percent of the subjects given a placebo to have heart attacks during the 7 years of the trial. They expect those who are given cholestyramine to attain cholesterol concentrations so low that, on the basis of their cholesterol concentrations alone, only 4 percent of the members of the group should have heart attacks during the course of the trial. Thus the trial should provide some indication of whether a person's past history of high cholesterol concentrations affects his risk of heart attacks when his cholesterol concentrations are decreased.

The second intervention trial, MRFIT, constitutes an attempt to alter more than one risk factor for coronary heart disease. Investigators at the NHLI estimate that about 80 percent of those who have coronary heart disease have at least one of three risk factors: namely, high concentrations of serum cholesterol, high blood pressure, and cigarette smoking. Data from the Framingham study indicate that men with one of these risk factors have a 1.9 times greater chance of contracting coronary heart disease than those with none of the factors, those with two of the factors have a 3.4 times greater chance, and those with all three of the factors have a 10.6 times greater chance.

In January 1974, screening for MRFIT began. About 375,000 men aged 35 to 57 will have been examined by 28 February 1976 when investigators hope that the screening will be complete. Of those screened, 12,000 who have at least one of the risk factors will be chosen to participate.

The men participating in MRFIT are divided into two groups. Members of one group are referred to their personal physicians for whatever care they choose to receive. Members of the second group enter a special intervention program designed to reduce their blood cholesterol concentrations through diet, reduce their blood pressure through weight reduction or drugs, and convince those who smoke to give it up. Each participant will be studied for 6 years.

Are Both Trials Worthwhile?

One objection to the LRC Primary Prevention Trial and MRFIT, voiced by Harriet Dustin, vice-chairman of the Research Division of the Cleveland Clinic Foundation and an NHLI council member, is that criteria for deciding who has heart disease are not precise enough. Investigators are counting incidences of strokes or deaths from coronary heart disease when what ideally should be measured is the progress of atherosclerosis, according to Dustin. To measuring the progress of atherosclerosis however, a noninvasive technique to determine the presence of atherosclerotic plaques must be developed and no one knows whether such a technique will be developed in the near future.

Since clinical trials such as the LRC Primary Prevention Trial and MRFIT are so expensive and time consuming, Dustin believes that the question of whether this is the best time to do the projects should be addressed. If noninvasive techniques for measuring the progress of atherosclerosis were developed, far fewer people need be studied for shorter times in order to obtain the results now anticipated by the designers of the LRC program and MRFIT.

Richard Havel, the Director of the Cardiovascular Research Institute of the University of California at San Francisco, believes that neither the LRC Primary Prevention Trial nor MRFIT is optimally designed. Participants in the LRC study include people with genetic disorders that cause them to have high cholesterol concentrations. Since these people are not distinguished from individuals in the trial, without such a genetic "impairment," results of the study may tend to be confused, Havel speculates.

Despite the difficulties with the LRC program, Havel is still biased in favor of it as compared to MRFIT. He feels that results from MRFIT, although useful, cannot provide a clear answer to the question of whether heart disease can be prevented in the population at large by modifying one risk factor alone.

Richard Ross, a member of the National Heart and Lung Advisory Council from Johns Hopkins University, disagrees with Havel. He favors MRFIT because, although it is not as scientifically clean as the LRC trial, it reflects the way the world really is. Any patient will be told by his doctor to stop smoking, attempt to reduce high blood pressure, and reduce his serum lipid and cholesterol concentrations. Thus it is vitally important to ask: Will following this treatment do anything to prevent heart disease?

Havel and others state that their discomfiture with the two programs and other similar clinical trials arise because they seem to be taking up a larger and larger portion of the NHLI budget and thus they are draining money from other programs the NHLI could support. If inflation continues, these investigators predict, the situation will become much worse. In particular, Havel is concerned that the NHLI is in danger of investing too much money in applied programs at the expense of basic research.

Levy is also concerned about the costs of the two programs and states that if he had known in 1971 what he knows today about the cost of the LRC program and MRFIT, he would not have recommended funding them. He describes the uncontrollable costs of the two trials as a noose around his neck. However, he says he is glad he didn't have the foresight to recommend the two programs not be funded.

Studies of how to prevent cardiovascular disease are actually cost effective, Levy points out. He quotes estimates that the cost to this country of cardiovascular disease is more than $40 billion a year. Research on how to treat people once they have had a heart attack can be of at most limited use because 25 percent of those with cardiovascular disease die from their first heart attack. It is clear that a serious investment in preventive medicine has the potential to alleviate much of the human suffering or economic loss caused by cardiovascular disease. A first step in a program in preventive medicine is to discover which factors can contribute to the incidence of heart disease.

—GINA BARI KOLATA