Heart Study Produces a Surprise Result

A massive study of heart disease that seems to contradict conventional wisdom may have been skewed by drug toxicity

A 10-year, $115-million study of the causes of heart disease may have turned up an important but entirely unexpected result. Widely prescribed diuretics used to treat high blood pressure may be toxic, especially at high doses. Although the evidence is not conclusive, several researchers associated with the study believe that the drug's possible toxicity may have skewed the overall findings.

Called the Multiple Risk Factor Intervention Trial (MRFIT) and sponsored by the National Heart, Lung, and Blood Institute (NHLBI), the study was designed to answer the question of whether men who reduce their blood cholesterol, blood pressure, and cigarette smoking—the three major factors for heart disease—will live longer. But the results were not what was expected.

Briefly, the results are inconclusive. The group of men in the study who greatly reduced their risk factors did not have a lower mortality rate than the control group. So, on the face of it, it looks like risk factor reduction may not be beneficial, contrary to the current medical dogma.

But the MRFIT investigators think that something more is going on. Most of the study participants who reduced their risk factors were helped, they believe, but these positive results were canceled by negative ones in a group that appeared to be harmed by reducing their risk factors. The MRFIT participants who had high blood pressure, had abnormal electrocardiograms, and were given diuretics to control their blood pressure, had a higher death rate than expected. These participants were given either of two popular and widely prescribed diuretics, hydrochlorothiazide or chlorthalidone; the suspicion is that hydrochlorothiazide, or possibly each of these drugs, is toxic at high doses.

At a press conference, held on 16 September, and in their article on MRFIT which is in the 24 September issue of the *Journal of the American Medical Association*, the study investigators played down this suspicion. For example, in his prepared statement at the press conference, Oglesby Paul, chairman of the MRFIT steering committee, said, "The investigators suspect that some aspect of the regimen adversely interacts in participants with electrocardiographic abnormalities."

Questioned after the press conference about the possible hazards of the diuretics, William Friedewald, associate director for clinical applications at the NHLBI, said, "It's alarming. But it's hard to be dogmatic because our data are not that clear."

> "We've obviously got a problem and it's not a trivial problem."

The MRFIT participants were 12,866 middle-aged men, nearly all of whom were white, who were at high risk for heart disease because each had at least one of the three risk factors under consideration. The men were randomly assigned to two groups. One group of men, designated "usual care," received annual checkups at the MRFIT clinics but were referred to their own doctors for medical treatment. Members of the other group, called "special intervention," were intensively counseled to help them stop smoking, lose weight, and change their diets to lower their blood cholesterol. Their blood pressure also was carefully monitored and they visited MRFIT clinics every 4 months.

As expected, the group receiving special care reduced its risk factors. But so did the usual care group, although not to the same degree. The MRFIT designers had expected the usual care group to retain the same risk factors throughout the 10 years of the study, but during the 1970's the entire U.S. population reduced its risk factors for heart disease.

Since the usual care group also lowered its risk factors, the study was more difficult to analyze, but the MRFIT statisticians predicted that the special intervention group still would have a lower mortality rate. The finding, then, that the two groups had the same mortality rates was an immense disappointment, but it was not totally unanticipated.

About 3 years ago, the MRFIT data monitoring committee came upon some peculiarities in the death rates. Jeremiah Stamler of Northwestern University, a MRFIT principal investigator, explains, "The monitoring group got some signals that although reducing smoking and reducing cholesterol were clearly beneficial in the special intervention group, reducing blood pressure was not." This flew in the face of all that was known about hypertension and, in fact, contradicted the findings of another NHLBI study, called Hypertension Detection and Follow Up (HDFP). The MRFIT investigators assembled a special committee to analyze the data. Some of its members reported that they could not erase their suspicions that the MRFIT drug treatment was toxic.

The MRFIT investigators then took a look at their protocols and those of the HDFP and realized that HDFP used only chlorthalidone and at doses of no more than 50 mg per day, whereas MRFIT used both chlorthalidone and hydrochlorothiazide at doses up to 100 mg per day. Since they did not know if it was the drug or the dose that was causing the poor results in the MRFIT study, the investigators decided to play it safe and change both. They quietly switched all the trial participants to chlorthalidone and suggested that the clinical investigators lower the diuretic dose if at all possible. The MRFIT investigators did not inform the Food and Drug Administration of their suspicions that hydrochlorothiazide or both drugs may be toxic, particularly in high doses, because, says Friedewald, "the data were very weak."

Last March, the MRFIT analysts discovered the connection between electrocardiogram abnormalities and excess deaths after diuretic treatment. Twenty-eight percent of all the hypertensive men in the study had these cardiac abnormalities. In the special intervention group, this group of men had a 66 percent higher mortality rate than expected. It is presumed that most men in the usual care group who had hypertension and electrocardiogram abnormalities were given lower doses of diuretics or were not given diuretics at all. Drugs such as propranolol are increasingly popular as a

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first line of attack against high blood pressure but were not included in the MRFIT protocol, in part because they were not available 10 years ago.

The MRFIT investigators now are frantically reanalyzing their data and are looking at the HDFP data to see if there is any evidence of adverse effects of chlorthalidone in that population. One finding that stands out in the MRFIT data is that if the group of men with hypertension and abnormal electrocardiograms is eliminated, the special intervention group has almost exactly the predicted 22 percent lower mortality rate when compared to the usual care group. But this sort of subgroup analysis is statistically shaky.

One reason that high doses of diuretics might adversely affect men with abnormal electrocardiograms, Friedewald says, is that these men have damaged hearts to begin with and the diuretics are known to lower potassium concentrations in the body. The lower potassium levels could precipitate heartbeat disturbances leading to sudden death. The MRFIT investigators did find an unexpectedly high incidence of sudden death, according to Friedewald.

Asked how he would advise physicians and their hypertensive patients, Friedewald said, "We feel that routinely the patients should get an ECG. If abnormalities are found, and the patient is given a drug, he should get very low doses of a diuretic. If that doesn't lower his blood pressure, he should go to the next level of drugs [when diuretics were insufficient in the MRFIT trial, the men were given reserpine, a different kind of antihypertension drug]. Propranolol would also be logical."

As for now, says William Insull of Baylor College of Medicine, who is head of the MRFIT policy advisory board, "We're obviously very concerned about this. We've obviously got a problem and it's not a trivial problem. We are making every effort to find the exact dimensions of the problem and the exact cause of these deaths." But, if the diuretic toxicity can be conclusively demonstrated, the MRFIT study will have made a major and completely unanticipated contribution to American medicine.

—GINA KOLATA

Can the Administration Sell Reprocessing?

The unfinished nuclear fuel reprocessing plant at Barnwell, South Carolina, symbolizes Administration difficulties with plutonium policy

The Reagan Administration wants a pristine nuclear fuel reprocessing plant at Barnwell, South Carolina, completed and brought on-stream as part of its plan for a major revision of U.S. nuclear policy. In its campaign for reprocessing, however, the Administration is encountering the same conflicts that afflict its nuclear grand design.

To achieve its aim at Barnwell, the Administration will have to overcome industry's skepticism that reprocessing can be done at a profit and the fears of congressional critics that domestic reprocessing will encourage the international proliferation of nuclear weapons. These issues are expected to come to a head in coming weeks when the Administration issues two long-overdue policy statements affecting reprocessing.

Nearly $400 million was spent on the Barnwell plant by its private sector owners before work on it was stopped in 1977 as a result of a Carter Administration policy decision. President Reagan reversed that decision after he took office, but ruled out government purchase and operation of Barnwell, which had been suggested by Department of Energy (DOE) officials. The President told DOE to seek a formula to give a firm footing for commercial reprocessing in line with his free enterprise preferences.

Finding such a formula means making the terms attractive enough to induce private industry to undertake reprocessing while not violating Reagan precepts on the proper restraints on public expenditure. The Administration's problems are compounded because completion of Barnwell requires construction of additional facilities costing an estimated $700 million in mid-1980 dollars; a completed Barnwell would represent an investment of well over $1 billion. Needed are a facility for waste storage and solidification and another to convert plutonium nitrate yielded by reprocessing to plutonium oxide suitable for fabrication into fuel.

What makes Barnwell's operation highly controversial is this capacity to extract plutonium. For the critics, plutonium is synonymous with nuclear proliferation. They argue that domestic reprocessing would seriously weaken the U.S. position in international nonproliferation efforts. To bolster their case, they contend that reprocessing is not only dangerous, but that, in the present market for nuclear fuel, it is uneconomic and, therefore, unnecessary. In addition, the critics increasingly cite experience with commercial reprocessing to warn that it is technologically trouble-prone.

The debate over Barnwell is fired by differing visions of the nuclear future. The Administration is attempting to push through an integrated nuclear policy dominated by development of the fast breeder reactor, which both uses and produces plutonium; reprocessing goes in tandem with the breeder. The Administration position is that reprocessing is vital to the long-term development of American nuclear industry. Barnwell is the key to Administration plans to close the back end of the fuel cycle. In nuclear parlance, this denotes the reprocessing of spent fuel from light-water reactors so that a substantial part of it can be reused.

Proponents of reprocessing claim that a major point in its favor is that it would significantly reduce current problems with high-level radioactive wastes, since such wastes are converted by reprocessing into a form more readily disposed of. Spent fuel is now kept in indefinite storage on reactor sites and a large backlog is accumulating.

Internationally, the Administration view is that domestic reprocessing would strengthen the U.S. competitive position in nuclear commerce. It would also give the United States greater influence in nuclear nonproliferation efforts than provided by the Carter Administration policy, which Reagan officials describe as one of "technological denial."

The Carter Administration after 1977 followed a broad policy intended to discourage development of an international plutonium economy. As part of this policy, work was ordered deferred on Barnwell and the breeder. The Reagan Administration is already following a more flexible policy in international dealings

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