Heart Institute Is Major Player in Clinical Trials

Clinical trials in heart disease have had a major impact on public health, but as money becomes tight, the heart institute is becoming more cautious about starting trials and is looking to private industry to help with funding

RESEARCHERS at the National Heart, Lung, and Blood Institute (NHLBI) are eager to start a new clinical trial to examine the benefits of lowering cholesterol in women and in older people. The trial would contribute answers to questions that may not be resolved for years, if at all, unless the study is done.

But Claude Lenfant, director of the heart institute, says the study is not likely to be funded because, at a cost of $60 million over 7 years, it is simply too expensive to consider in these days of fiscal restraint. Lenfant will approve the study only if he gets at least $20 million of its cost from the pharmaceutical industry, which he is hoping to do.

This funding strategy is a radical change for the institute and reflects the evolution of the clinical trials program as it approaches its second decade. Clinical trials in heart disease have gone from what Lawrence Friedman, acting chief of the clinical trials branch of the NHLBI, compares "the golden years of the 1960s," when the big questions about the prevention of heart disease were still open and when large, expensive clinical trials were begun with little hesitation, with the more cautious days of the late 1980s when, says Friedman, "we have to be more careful in deciding which trials should be done, and how."

The drug company money is the newest twist. The heart institute recently began asking companies to help pay for trials and has gotten funds for at least two studies so far. But the institute never before asked for as much as it is requesting for the proposed cholesterol trial. Nonetheless, says Lenfant, in the 1960s and 1970s the NHLBI "would never have thought of calling on the private sector for help. Today, if you don't call on the private sector, you are a lousy manager."

Clinical trials have always been controversial, and never more so than today when funds are limited. They are expensive and they are time-consuming. They also are risky. It is always possible that a treatment that seemed perfectly reasonable when a study started will be outdated when the study ends or that a study's results will be equivocal and the question the study was designed to address will remain unanswered. Moreover, says Friedman, no matter how strong a study's results, "there is no such thing as a definitive clinical trial. The results of a clinical trial alone are not necessarily persuasive, nor should they be." In other words, if a clinical trial says that lowering cholesterol saves lives, that result is only persuasive in the context of other sorts of evidence, from biochemical and genetic studies, epidemiology, and animal work, that point in the same direction.

Yet the NHLBI clinical trials in heart disease have had a substantial impact on public health, convincing many people that heart disease can be prevented and exploring whether treatments such as bypass surgery and beta blockers are effective. Moreover, once the results of a trial result are accepted, that study can become a "surrogate end point," making future studies easier. For example, everyone now agrees that reducing blood pressure in patients with hypertension saves lives. The clinical trial results, building on other evidence, were compelling. As a consequence, now a clinical trial of a new drug needs only to demonstrate that it lowers blood pressure.

"There is no question that surrogate end points are a big issue," says Lenfant. "Basically, in our clinical trials, we used to count dead bodies after 10 years. Today, we're trying to use morbidity end points and we can do this because we have developed much more sophisticated approaches."

The clinical trial on cholesterol lowering that Basil Rifkind of NHLBI wants to start illustrates many of the issues facing the heart institute today as it allocates money that Congress earmarks for such studies. According to Lenfant, the institute's extramural program has $800 million this year, of which $524 million is to go to individual grants for basic research; another $35 to $38 million will be spent on clinical trials.

The proposed cholesterol-lowering study is incredibly expensive by current NHLBI standards. Its $60-million cost over 7 years is about three times the cost of the typical NHLBI trial. Nevertheless, Lenfant says, "it is a very important study and we are committed to trying to do it."

The cholesterol trial is part of a continuing debate over the wisdom of lowering serum cholesterol levels in the general popu-

Drawing by Richter; © 1987 The New Yorker Magazine, Inc.

"Then we've agreed that all the evidence isn't in, and that even if all the evidence were in, it still wouldn't be definitive."

lation. Although the heart institute advises Americans to reduce their cholesterol levels, there is no agreement in the scientific community over the best cholesterol levels to aim for or about whether the advice should hold for children, women, and older people, as it does for middle-aged men.

As long ago as 1969, an institute advisory group met to decide whether a clinical trial could answer the cholesterol question once and for all. Epidemiological studies had indicated that populations eating low-fat diets tend to have lower cholesterol levels and lower incidences of heart disease. Animal studies had hinted that low-fat diets and lowered cholesterol levels can reduce the buildup of fatty plaques in the arteries. But no one could say for sure that if Americans were to change their diets and lower their blood cholesterol, there would be a reduced incidence of heart disease. The epidemiological and animal studies pointed to associations. A clinical trial might show cause and effect.

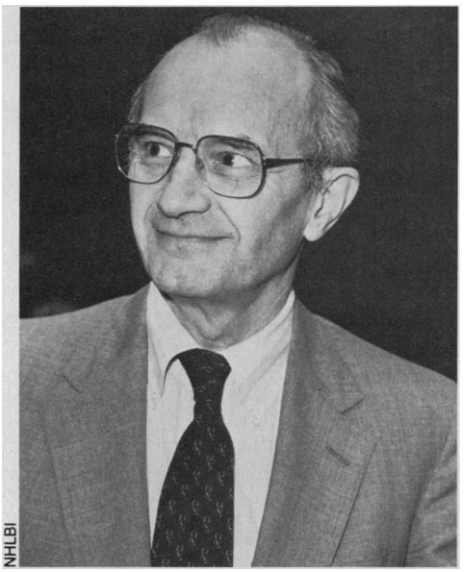
The heart institute group met to consider the feasibility of a diet-heart study. It would be a study consisting of two groups. One group would change its diet; the other would not. Then the study investigators would, in Lenfant's words, "count dead bodies after 10 years." If the cholesterol-lowering diet was effective in reducing heart disease, fewer members of the diet group would have died.

Such a study was infeasible, the advisers concluded. A national dietary study would have to involve as many as 50,000 to 100,000 people and might cost as much as $1 billion, in 1969 dollars. Robert Levy, a past director of the NHLBI, told *Science* that such a study would consume all of the institute's funds (*Science*, 21 November 1975, p. 764).

The NHLBI decided to compromise, to get at the diet-heart question in other ways. It initiated two studies whose results are still being debated. One was the Multiple Risk Factor Intervention Study, or MRFIT, a 10-year study that cost $115 million. It produced equivocal results (*Science*, 1 October 1982, p. 31). MRFIT was to determine what would happen if middle-aged men at high risk for heart disease did exactly what doctors were already advising—stopped smoking, went on a low-fat diet, and got their blood pressure under control.

The 12,866 MRFIT participants were divided into two groups. The "special intervention" group was intensively counseled to reduce its risk factors for heart disease by following the advice of doctors. The control group was left alone—its members were referred to their private physicians for care.

The result, reported in 1982, was that there was no difference in mortality between the two groups. Both groups lowered their risk factors for heart disease—although the "special intervention" group did better than the others—but the special intervention group lived no longer.



NHLBI

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The trial investigators were immensely disappointed, and, because so much time and money had been spent on the MRFIT study, the researchers were reluctant to present the results as completely equivocal. One investigator recalls coming to Washington to participate in the press conference to announce the MRFIT results and was startled to learn that he and the other investigators were to spend the weekend holed up in a hotel rehearsing what to say—how to put a good face on a discouraging result.

Because no one considers a trial result in isolation, the medical community did not retract their dietary advice because of the MRFIT results. Researchers do not seriously argue that MRFIT proved that risk factor reduction is not helpful. Instead, they say the usual care and special intervention groups were too similar for the results they all expected to show up, which raises the question of why a study like MRFIT should have been conducted in the first place. If researchers are so convinced that risk factor reduction saves lives, why did they do MRFIT?

William Friedewald, associate director for disease prevention in the office of the director at the National Institutes of Health, sees a lesson in the MRFIT experience. "You should do a pilot study first," he says. "If you don't get an intervention—in this case, a significant difference in cholesterol levels between the groups—maybe you shouldn't go ahead with a full-scale study. In the case of MRFIT, the argument was made that you could stop the study. But it had a momentum of its own and was impossible to stop."

The second big cholesterol study was the CPPT, or Coronary Primary Prevention Trial, that was designed to see whether taking a cholesterol-lowering drug would prevent heart disease. This 5-year, $150-million study was completed in 1984 (*Science*, 27 January 1984, p. 381), and its results were positive. All the middle-aged men in the study started with cholesterol levels above 265 milligrams per deciliter, which put them in the upper 5% in this country. Those men who took the cholesterol-lowering drug cholestyramine reduced their cholesterol levels by an average of 8.5% and had 24% fewer deaths from heart disease and 19% fewer heart attacks than a control group.

But even the successful CPPT had its problems. In this case, it was the difficulty that the study investigators had in recruiting study participants. It took 3½ years to find enough men who met the study criteria and were willing to participate. The reason for the delay, according to Friedewald, was that the study planners thought they could use the "medical model" for recruitment. They asked doctors and laboratories to refer middle-aged men with high cholesterol levels. This approach, says Rifkind, "nearly killed us. It just didn't work." Now they know that they have to try anything and everything they can think of to recruit patients. They have to air radio and television spots, set up shop in factories and shopping malls, and go to blood banks, for example. By cutting the recruitment time, they can substantially cut costs.

In the years since the CPPT, says Rifkind, "things have changed tremendously." There have been "shifting attitudes about cholesterol and heart disease" as more and more researchers and physicians have come to believe that, as a nation, we must reduce our cholesterol levels. When the heart institute followed up on the 356,000 men who were screened for the MRFIT study, it was learned that there is no lower limit to the benefits of cholesterol lowering—there is no level of cholesterol below which diminution in heart disease risk levels off. Essentially, the lower the cholesterol, the lower the risk, no matter how low the cholesterol level goes. Furthermore, a recent, if controversial, study showed that when cholesterol levels are reduced, fatty deposits in arteries actually shrink.

Yet, says Rifkind, "as always, there are

unanswered questions." One pressing question is whether the CPPT results apply to persons who reduce their cholesterol levels with a diet rather than with cholestyramine. Some preliminary evidence suggests that cholestryamine reduces heart disease risk more effectively than diet. So critics have asked whether there really is enough evidence to recommend dietary cholesterol lowering for the entire nation.

Heart institute administrators are so concerned by these questions that they recently convened a working group to resurrect the old diet-heart study that was dismissed in 1969 as too expensive and infeasible to boot. "We went in with a bias against it, but we asked again if we could do it," says Rifkind. The answer was still no. "The problem is even worse now than it used to be," he says. Because much of the population is now trying to eat low-fat diets, the entire population has reduced its cholesterol levels in the past 20 years, and so it would be enormously difficult to get statistically significant differences between intervention and control groups. Of course, such a study could not be double-blind, which would muddy its results. In short, the study would require even more people and be even more expensive than the 1969 estimates and still might give equivocal results.

On the other hand, there are additional questions about cholesterol lowering that the NHLBI and its consultants think urgently demand a clinical trial. There is a new class of cholesterol-lowering drugs, called HMG CoA reductase inhibitors, that dramatically reduce cholesterol levels with few side effects, and they are easy to take since they are tablets, as opposed to cholestyramine, which is a powder. To take cholestyramine, patients must mix it with juice or another liquid. It is a gritty concoction, and the CPPT participants used to joke that drinking it was like drinking Miami beach. Moreover, it leads to gastrointestinal side effects, including bloating and flatulence. It is not a drug that can be taken willingly by masses of people, whereas the HMG CoA reductase inhibitors apparently are.

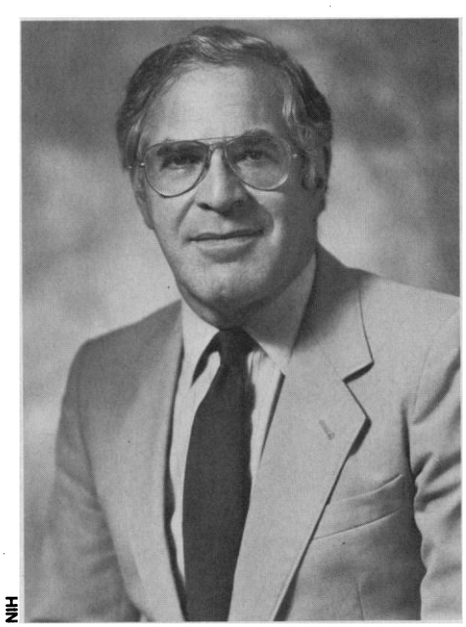
Enthusiastic researchers are talking about a new era in cholesterol lowering, analogous to what happened when effective drugs to lower blood pressure were introduced. "We have the potential to reduce cholesterol levels to below 200 milligrams per deciliter in everyone," Rifkind says. Pharmaceutical companies see a bonanza.

As for the long-term toxicity of the new drugs, says Rifkind, "so far, so good." Investigators worry primarily about two possible side effects. First, there is a 1% increase in liver enzymes, an effect that is common with cholesterol-lowering drugs but researchers want to be certain that it is not associated with liver disease. Second, they are worried about the lens of the eye. A drug called MER-29 which was briefly introduced in the 1960s, lowered cholesterol but had negative effects on the eye. Researchers do not expect that the HMG CoA reductase inhibitors, which block a much earlier step in cholesterol synthesis, will affect the lens, but according to Rifkind, when the drugs were given to dogs in very large doses, some of the animals developed cataracts.

Since the potential of the HMG CoA reductase inhibitors is so great, the NHLBI researchers saw an opportunity. "We got excited about these drugs and we asked what is our role," says Rifkind. "What are the outstanding questions in the cholesterol area?"

Rifkind and his colleagues decided that the time is ripe for studying older Americans, meaning people over age 60. "One of the things that became apparent is that most coronary disease is in people over age 60," Rifkind says. "If you have a mission to prevent coronary disease, you are talking about people over age 60. But from the public health standpoint, do you have to start reducing cholesterol at age 30 or 40 or can you start at age 60? That's an unanswered question. There are no definitive data."

There also is the question of lowering cholesterol in women. Women have not been included in the big clinical trials because they are less likely to have heart attacks than men. If women were included in the CPPT, for example, the study would need 7000 to 8000 participants rather than the 4000 middle-aged men it in fact included, according to Rifkind. But the frequency of heart attacks in older women is great enough to be studied. Rifkind and his colleagues estimate that they can include women who are at least 68 years old in their study.



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Basil Rifkind. *"If you have a mission to prevent coronary disease, you are talking about people over age 60."*

Finally, there is the question of the long-term safety of the HMG CoA reductase inhibitors. "Most of us feel that if you lower cholesterol, you probably get a benefit," Rifkind says. "But if you say that, then why not use the HMG CoA reductase inhibitors on everyone? The question is not so much benefit but risk. Every drug has a price attached. And lipid lowering has a special price because it is long term."

So what Rifkind and heart institute advisers are proposing is that a clinical trial be started with 55,000 older men and women who have moderately high cholesterol levels—about 240 to 260, which puts them in the 60th to the 85th percentile for their age group. Half the study participants would take an HMG CoA reductase inhibitor and the other half would take a placebo. The participants would be followed for 5 years to see if the cholesterol-lowering drug reduced their mortality from heart disease.

Now it is up to Lenfant, who says it is, in the end, up to the pharmaceutical industry. Officials at Merck and Squibb are talking with Lenfant about participation in funding a trial, and Sandoz may be approached. All three have an interest in cholesterol lowering drugs. Lenfant agrees with Rifkind and the NHLBI advisers that there are questions, such as those this study is designed to answer, that really are best addressed by large-scale clinical trials. "Some say that clinical trials can be resolved by a study of 20 patients," Lenfant remarks. "Of course, we take the view that that's not the case. Clinical trials are a real science. There is no question that it's a tool that has its place in medicine today."

And for the NHLBI, as it approaches its second decade of large clinical trials, the questions that it wants to answer are just as pressing today and the clinical trials just as compelling. But the NHLBI has gotten wiser and more frugal over the years and it is trying harder than ever to be sure that the money that is spent on clinical trials is spent prudently. ■ GINA KOLATA