Heart Panel's Conclusions Questioned

An NIH panel says that the entire U.S. population should lower its cholesterol; but the clinical trial evidence does not support such a strong statement, critics say

To many observers, the recent National Institutes of Health consensus panel report seemed merely to restate the conventional wisdom. The panel announced on 13 December, at the conclusion of a 2-day meeting, that high concentrations of blood cholesterol cause heart disease. In addition, said panel chairman Daniel Steinberg, who is director of the specialized center of research on arteriosclerosis at the University of California in San Diego, "lowering cholesterol can reduce the incidence of coronary artery disease and save lives." The panel recommended that all Americans, from age two onward, reduce their consumption of saturated fats and cholesterol and suggested a diet like the American Heart Association's prudent diet, which emphasizes fruit and vegetables, restricts egg yolks to no more than two a week, and specifies lean meat, skim milk, and low-fat cheeses.

These conclusions sound so familiar that many commentators did not even mention that they are actually quite strong. But despite what the panel said, there is no irrefutable evidence from clinical trials that cholesterol-lowering saves lives. And it is not as though no one has tried to get evidence.

Over the past 20 years, there have been nearly two dozen clinical trials of cholesterol-lowering. These trials involved at least 50,000 people at high risk for heart disease, selected so that they would be most likely to benefit from lowered blood cholesterol if it helps at all. But these trials failed to show that cholesterol-lowering prevents deaths from heart disease. Moreover, even if you lump all the trials together and look for an effect, you still do not see one.

This does not necessarily mean that the diet-heart disease hypothesis is wrong, nor that the consensus panel's conclusion is unjustified. Clinical trials are not the only evidence that links cholesterol and heart disease and by far the majority of investigators believe it is prudent for those with very high cholesterol levels, say 250 milligrams per deciliter and above, to attempt to reduce them. The argument really is about the strength of the clinical trial data and about whether the clinical trials indicate that low-fat diets might be risky for people whose cholesterol concentrations are already low and who have no other risk factors that might predispose them to heart disease. The question is not whether people at high risk for heart disease should be concerned about their cholesterol levels. It is about whether the data are strong enough to recommend that the entire population, including children, go on low-fat diets.

The critics are concerned that the panel exaggerated the evidence at hand and, in doing so damaged their own credibility. In addition, they fear that once the cholesterol issue is said to be settled, it will become increasingly difficult to get research funds to study the matter further.

This is the 47th consensus panel report from the National Institutes of Health, and agency spokesmen say that these reports do affect the practice of medicine. It is anticipated that one consequence of the cholesterol report will be national programs to educate the public and physicians about the need for everyone to have cholesterol measurements taken and to cut back on dietary fats.

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Since the consensus panel report is expected to have such wide-ranging effects, it is not entirely surprising that it is being criticized. After all, as Salim Yusuf of the heart institute notes, "the cholesterol question is very difficult. Many people have already made up their minds that cholesterol-lowering helps, and they don't need any evidence. Many others have decided that cholesterol-lowering is not helpful, and they don't need any evidence either."

But in this case, the critics of the consensus panel report include responsible scientists including Thomas Chalmers of Mt. Sinai Medical School and Paul Meier, a statistician at the University of Chicago who frequently sits on the data monitoring committees of the National Institutes of Health trials. These researchers say they have not prejudged the issue. Yet they and other charge that the report is misleading. "I think they made an *unconscionable* exaggeration of all the data," Chalmers remarks.

In recommending that the entire U.S. population lower its cholesterol levels, the panel cited epidemiological studies that compare Americans to the populations of countries such as Japan, Greece, or Italy, where the diet is very low in saturated fats and cholesterol, the average blood cholesterol concentration is about 180 to 200 milligrams per deciliter (it is about 210 milligrams per deciliter here) and the death rate from heart attacks is only about one-third to one-sixth what it is here. When people from these countries migrate to the United States, their blood cholesterol levels rise and they are more likely to develop heart disease. The panel also noted as evidence for the diet-heart disease hypothesis that animals that are fed high-fat diets develop heart disease. Another type of evidence comes from studies of people with certain inherited deficiencies in cholesterol metabolism. These people have unusually high blood cholesterol levels and die young from heart disease.

But as suggestive as these studies are, they do not show that *lowering* cholesterol makes a difference. And that was the reason the National Institutes of Health has waited so long to take a position on the diet-heart disease hypothesis. Others, such as the American Heart Association, have not been so reticent. The heart association came out with its prudent diet 20 years ago on the basis of the comparisons between populations and the studies of migrants. Now, however, said Steinberg of the consensus panel, they have "the keystone in the arch"—a recent study by the National Heart, Lung and Blood Institute (NHLBI) on the effects of cholesterol-lowering in men at high risk for heart disease.

The study, called CPPT for Coronary Primary Prevention Trial, was to be the crown jewel of the heart institute. It was lavishly funded and its results were anxiously awaited. But the results, despite the keystone metaphor, were not what they were hoped to be. "It was a very

good study. It just had weak findings," says Meier.

The study began in 1973 when the NHLBI began a 3-year screening project, evaluating nearly half a million middle aged men to find the approximately 4000 participants. The men who were selected had blood cholesterol levels of at least 256 milligrams per deciliter, which put them in the upper 95th percentile in the United States, and were initially free of heart disease. Half of the men followed a moderate cholesterol-lowering diet and took a drug, cholestyramine, that reduces their cholesterol. The rest followed the diet and took a placebo.

Last year, the results of the CPPT were announced with great fanfare. The cholestyramine group lowered its average cholesterol by 13.4 percent, as compared to an average of 4.9 percent in the placebo group and this lower cholesterol, the study investigators said, resulted in a decreased incidence of heart disease. The CPPT was hailed as an unprecedented success and the CPPT researchers wrote that its results should be "extended to other age groups and women and . . . to others with more modest elevations of serum cholesterol levels."

Frequently lost in the praise for the CPPT was the disappointing finding that there was essentially no difference in the death rates between the cholestyramine treated group and the placebo group. Sixty eight men in the cholestyramine group died and 71 in the placebo group died. The CPPT researchers argue that the mortality results were unfortunate, but they were most likely a fluke. More men in the cholestyramine group died of accidents and suicides. "Our most educated guess is that it's a chance occurrence," says Basil Rifkind, director of the CPPT.

But, say the statisticians, you cannot simply explain away results like that. "Any statistician would turn in his badge if he couldn't find an excuse like that for any outcome. It's just too easy to do," says Meier. "If you look at total mortality—the end point we're all really most interested in—you just don't find it," he remarks.

Of course, maybe it is asking too much to demand that the CPPT or any other such trial demonstrate that cholesterol-lowering saves lives. After all, atherosclerosis is thought to build up over a period of years, or decades, and these studies focus on middle aged people, in whom damage may already have occurred, and they intervene for only a few years. It may be too little and too late to reduce the death rate.

Then again, maybe the intervention studies are telling us something. In nearly every clinical trial, the treated group did reduce its death rate from heart disease, but the members of the group died of something else—frequently cancer—instead. Perhaps cholesterol-lowering is not always entirely safe for everyone.

Epidemiologists have carefully scrutinized the data on cardiovascular and noncardiovascular deaths in these clinical trials, hoping to find some explanation. But it is not yet clear what is going on. Says Yusuf, "I can't fully explain it and it worries the hell out of me."

Total mortality, however, was not the only end point in the CPPT. The investigators also looked at nonfatal heart attacks, analyzing cholestyramine's ability to reduce the incidence of heart attacks. But the results were not statistically significant by conventional tests.

But there is no dissenting voice on whether cholesterol should be reduced in high-risk people.

Rifkind argues, however, that the CPPT results are nonetheless impressive because all the trends in the data are in the same direction. The incidences of angina, bypass surgery, and abnormal exercise electrocardiograms all came down in the cholestyramine group, although the numbers were not statistically significant. Says Meier, these trends "do not appreciably strengthen the evidence." And Rifkind counters by saying, "Biostatisticians, I think, take a somewhat narrow approach. They say, 'We will judge you pass or fail purely on a *t*-test.' You don't do a trial in a vacuum."

Despite the fact that the CPPT failed, as every other trial did, to prove that lowering blood cholesterol saves lives and despite the fact that its results on nonfatal heart attacks were only marginally significant at best, the study maintains its reputation as the final proof of the cholesterol hypothesis. Largely as a result of the CPPT, Rifkind says, the cholesterol arguments are dying down. "The focus of the debate has shifted," he remarks. "A year or two ago, people would have been arguing about whether cholesterol should be reduced in high-risk people. Now there is no dissenting voice on whether cholesterol should be reduced in high-risk people."

There are dissenting voices, however, about the consensus panel's recommendations that cholesterol be lowered in the population as a whole. Chalmers, noting the lack of evidence that cholesterol-lowering saves lives, says "The American public might be more interested in whether they will live longer than in how they will die."

Chalmers emphasizes that, "there is absolutely *no* evidence that it's safe for children to be on a cholesterol-lowering diet. I don't think that anyone believes people start laying down plaques before puberty and then [it happens] only in males. So why subject children to the diet starting at age two? The [consensus panel's] argument that you have to start the diet early to make it a habit is fatuous," Chalmers remarks. "I am not against taking measures to lower cholesterol if you are in a high-risk group. But if you are at high risk you have something to gain. If you are in the low-risk category, the side effects become more significant."

Others believe that the panel's recommendations will not make much difference anyway because the diet they recommend—30 percent fat down from 40 percent—is not stringent enough. Edward Ahrens of Rockefeller University who has been doing metabolic ward studies of cholesterol-lowering since 1951, says that, based on his experience, very little would happen to the cholesterol levels of the population were we to adopt such a diet. To really effect a change, he says, we would have to move to 20 percent fat, which may not be entirely safe, especially for the young and the elderly. Such a very low fat diet, Ahrens says, changes the composition of cell membranes, making them more rigid and making red blood cells less deformable. Plasma becomes more viscous. Lymphocytes do not respond well to mitogenic stimuli, indicating that the immune system is less effective. The health effects of these changes are unclear. "There are a variety of unanswered questions that ought to be addressed," Ahrens remarks.

And then others, including Meier, believe that the panel's dietary recommendations make sense for adults, but not because there is any persuasive new evidence from recent clinical trials. Meier says that for 20 years, he has been swayed by the evidence from cross-cultural comparisons and studies of migrants. "My view—and I feel it very strongly—is that the dietary recommendations for adults are sound public policy," he says. "But none of this excuses misrepresenting the evidence. Our first obligation is to be honest and forthright."—**GINA KOLATA**