Getting to the Heart of the Cholesterol Debate

Government recommendations about diet provoked familiar songs of praise and protest, but there's a new voice chiming in

WHEN the National Cholesterol Education Program recommended sweeping changes in the national diet last week, there was a strong sense of what Yogi Berra refers to as "déjà vu all over again." Proponents said that the scientific data justify a massive, government-sponsored effort to lower saturated fat and cholesterol intake in order to reduce coronary heart disease. Critics gave the customary riposte: not only do the data not justify these efforts, but the campaign to lower cholesterol intake is misguided, possibly counterproductive, and perhaps downright dangerous.

If any further evidence were needed, the cholesterol debate is a perfect example of the difficulty in translating a controversial scientific issue into public policy. This particular debate has been fulminating for years (see *Science*, 4 January 1985, p. 40). Despite clinical trials and epidemiological studies involving tens of thousands of patients, no single study has convinced the warring factions that the scientific questions are settled. Will there ever be such a study? Perhaps not. But while the latest version of the debate was being played out in the international media last week, one eminent scholar, Richard Peto, was preparing an innovative examination of the data already at hand that he thinks will yield answers so clear and compelling that they will go a long way toward resolving the scientific debate.

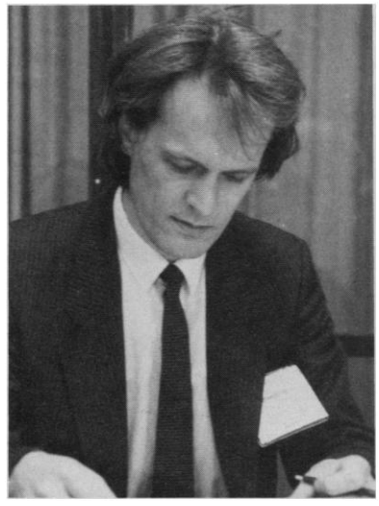
Peto, a statistician from Oxford University, has performed a new type of analysis on the cholesterol question. While he has yet to submit a paper for peer review, Peto says that he has concluded that nearly everyone has misinterpreted the existing data. "The old risk factors, things like blood pressure and blood cholesterol, have been underestimated even by those who are trumpeting their importance rather loudly in the public press," he says. (See box, p. 1171.)

Trumpeting is just what National Cholesterol Education Program (NCEP) was doing last week as it announced its dietary guidelines for the populace. With as much media fanfare as they could muster, NCEP officials made broad, if familiar sounding recommendations for how all Americans over the age of 2 should alter their diet to limit their risk of heart disease. According to NCEP they should reduce total fat, especially saturated fat, not eat more than necessary to maintain ideal body weight, and limit cholesterol to no more than 300 mg per day.

To change the habits of a fat-loving nation, NCEP proposes a broad education program. It would give governmental and nongovernmental groups as well as health professionals a role in explaining how to construct this healthy diet. The food industry would be encouraged to get on the bandwagon and provide "heart healthy" choices for consumers so that following a healthy diet will be easier.

NCEP bases its rationale for recommending a diet lower in saturated fat and cholesterol on a variety of epidemiological, clinical, and experimental evidence. One of the largest trials, the Multiple Risk Factor Intervention Trial (MRFIT) involving nearly 362,000 middle-aged men, showed a clear relationship between increasing serum cholesterol and increasing risk of heart disease.

But critics are quick to point out that the most compelling evidence for reducing cholesterol is restricted to a small segment of the population. "There are no data to support intervening in the diets of children or women or for that matter young men," says Robert E. Olson, a medical nutritionist at the State University of New York at Stony Brook and one of the population panel's scientific reviewers. "Boys do begin to make plaques [signs of heart disease in the arteries] at puberty. But the idea of trying to extrapolate that to children—well, I call that child abuse," he says.



A fresh approach. *Richard Peto brings a new analysis to an old argument.*

Nor does it make sense to enforce strict, low-cholesterol diets on older people, according to Paul Meier, a biostatistician from the University of Chicago. "Neither the epidemiology nor the trials support doing that," says Meier, "and those are the people who are going to have the hardest time meeting this standard."

Meier also faults the NCEP report for an oversight. He claims it should have explained an apparent paradox: even studies that show a decline in heart disease with lowering cholesterol fail to show a reduction in deaths from heart disease. The failure to detect a drop in mortality rates is so important, he says, "you really can't put [it] aside."

But for every piece of evidence that critics claim is missing or equivocal, proponents point to other studies that they claim will show that they are on the right course. James I. Cleeman, NCEP coordinator, says the National Health and Nutrition Examination Surveys conducted by the National Center for Health Statistics has already shown that serum cholesterol levels are dropping in the population at the same time coronary heart disease has been going down. It makes good sense to help that trend along, he says.

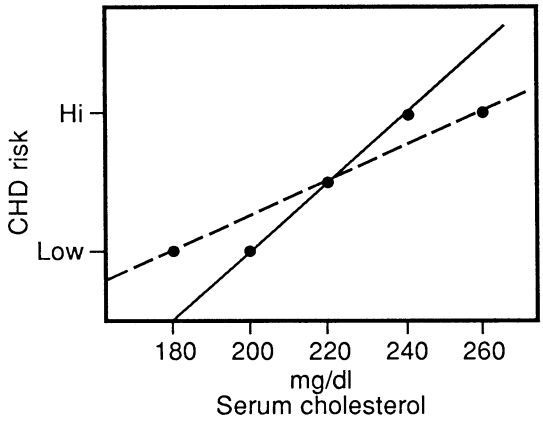
After the scientific debate is exhausted, the dispute begins to sound more like name-calling. Although Cleeman readily admits that competent scientists have disputed NCEP's program, he adds, "it's the same small group of critics everywhere you go." Olson responds that this is true also of the advocates of low-cholesterol diets—a small, tight-knit group of zealots. Cleeman retorts that some critics will never be satisfied until a conclusive clinical trial has been performed. "The trouble is there isn't enough money in the universe to conduct clinical trials on every question you want answered."

So how does Richard Peto cut through this thicket of scientific squabbling? Part of the answer is that the Oxford statistician is bringing a different analysis to the multitude of trials already conducted on the cholesterol question. The newly emerging technique called meta-analysis, or what Peto calls overviews, uses all the data from many different trials in a single analysis. Taking all available data into account vastly adds to the statistical power of the analysis and makes it possible for subtle patterns to emerge from the background variability. Although many epidemiologists are skeptical about the practice of merging data from disparate trials to form

Why Statistics May Understate the Risk of Heart Disease

Why does Richard Peto believe he has a fresh insight into a debate over cholesterol that has raged for years? Part of the answer is that the Oxford statistician has looked at the way researchers have analyzed their epidemiologic data—the data that argue both for and against a strong correlation between serum cholesterol and heart disease, depending on your point of view—and says he has found a crucial flaw in this methodology.

Even in the best of circumstances, there will be some random error when making serum cholesterol measurements. Most epidemiologists will assume that such random errors will wash out in the final analysis, especially in a study involving thousands of subjects. But Peto says it doesn't work that way. The staunchest proponents of cholesterol reduction say a 1% drop in the population's cholesterol will result in a 2% drop in heart disease, Peto goes even further, saying the drop will be closer to 3%, and he offers the following scenario to explain why this is the case.



"Imagine a country where everything is dead easy. There are only two types of people: high cholesterol and low cholesterol, 240 mg/dl and 200 mg/dl. And epidemiologists really have it easy because the high person is always high and never varies at all. And, what's more, no laboratory in that country ever makes a mistake. So if you draw blood from somebody, you can be sure that the result is going to be 240 mg/dl or 200 mg/dl.

"Now let's say you do a study of 100,000 people. There will be 50,000 with the higher figure, and 50,000 with the lower figure. Watch them for 5 years, and you'll finish up with the real relationship between cholesterol and heart disease."

Now, Peto turns to a graph he's devised (see illustration). "The true relationship between cholesterol and coronary heart disease (CHD)," he says, "is shown by the solid line on the graph. But suppose we introduce some random error. In each blood testing laboratory we're going to have a gremlin. The true serum cholesterol is either 200 mg/dl or 240 mg/dl, but the gremlin takes a coin, flips it, and adds or subtracts 20 depending on the toss. So it's purely random error—no bias. If the true value is 200 mg/dl, then the reported value will either be 180 mg/dl or 220 mg/dl. If the true value is 240 mg/dl, the reported value will either be 220 mg/dl or 260 mg/dl. So now we have three groups when we do our epidemiological study: 25,000 low cholesterol, 50,000 middle, and 25,000 high." Although the true slope goes up at one rate—say 1 to 3—the slope that results from the random error goes up less rapidly—perhaps 1 in 2 or less. "That demonstrates how purely random error generates systematic weakening of the slope," he says. "It's not a random error in the slope, it's a systematic dilution of the strength of the relationship. This has been happening in cholesterol and blood pressure studies for 40 years, and nobody has bloody well noticed it."

Peto says the same measurement bias can be found in other studies, and in an upcoming paper in *The Lancet*, he and his colleagues propose some statistical fixes. ■ **J.P.**

a unified picture, the technique is growing in popularity. And Peto is one of meta-analysis's staunchest advocates.

Despite the decades of accumulated data on cholesterol, Peto agrees that individual clinical trials to date have not definitively answered the question of whether it is possible to reduce the risk of fatal heart disease. But, he argues, part of the reason studies have not shown a decrease in mortality following a reduction in cholesterol is that they have been too weak in design. "The trials have been inadequate," he says. "They haven't been long enough; they've been examined in isolation."

Compounding weakness in study design, Peto says, is the fact that standard analytical methods tend to dilute the apparent strength of the relationship epidemiological studies have shown exists between cholesterol and heart disease (see box). For example, while most experts—including the NCEP population panel—would say that for every 1% decline in cholesterol there is a 2% decline in coronary heart disease, Peto says his analysis reveals that the true ratio is closer to 1:3 because people fail to correct for the measurement error.

A final confounding factor is that unlike smoking, a habit that people either do or do not indulge, in America there is no "normal" or unaffected group when it comes to fat and cholesterol. "If you take Americans and split them into 'American low-', 'American middle-', and 'American high-for-cholesterol', and then say, 'If only all Americans could have an American low cholesterol, we could avoid half of all American heart disease,' that's not the point." Explains Peto, "The real thing to do is compare Americans with the people who have got the sort of cholesterol that carries a really low coronary heart disease risk, like, for example, the rural Chinese peasants," who have virtually no heart disease, compared with Americans.

Indeed, this is what Peto has done, and although he has yet to publish his analysis, his work has been presented at scientific meetings and is already having an impact on the way researchers think about the problem. Richard Carleton, chairman of the NCEP population panel, says the panel was aware of Peto's arguments, but chose to take a more conservative figure than he uses for their report. The use of Peto's 1:3 ratio for cholesterol reduction and heart disease benefits is "arguable," Carleton readily admits.

Even critics of Peto's analysis respect his ability to forge a consensus. "He's a remarkable phenomenon," says Meier. "He's been able to get people together to do all kinds of things that a priori I would have said just can't be done."

So should the NCEP be recommending a change in everybody's diet? You might think Peto would be all for it. But, no, Peto says that's not a question his analysis can really answer. "There are two questions: first, what does cholesterol reduction do to you, and second, is it a good idea to go for cholesterol reduction," he says. Peto says his data will help answer the first question, but the second one is up to all of society to answer. "I want to avoid mixing [the two questions], which is what people are doing at the moment."

■ **JOSEPH PALCA**