Lowered Cholesterol Decreases Heart Disease

A clinical trial shows, at last, that reducing blood cholesterol reduces the risk of heart disease, providing the missing link in the cholesterol hypothesis

The National Heart, Lung, and Blood Institute (NHLBI) has just completed a clinical trial designed to test the cholesterol–heart disease hypothesis. The results confirm it dramatically. A group of middle-aged men with high cholesterol levels took a drug that reduced their blood cholesterol by an average of 8.5 percent. The men had 24 percent fewer heart disease deaths and 19 percent fewer heart attacks than a control group. These findings have already been hailed by the American Heart Association and are expected to affect profoundly the practice of medicine in this country.

The reason for the trial, says NHLBI director Claude Lenfant, is that the institute has never felt comfortable advocating that people reduce their blood cholesterol without good evidence that cholesterol lowering will reduce their heart disease risk. Although many physicians and organizations such as the American Heart Association and the Department of Agriculture were satisfied that the evidence in hand was conclusive enough to recommend that the entire population follow cholesterol-lowering diets, the NHLBI remained to be convinced.

To the NHLBI, the evidence for the cholesterol hypothesis has been only suggestive. Researchers have established that populations with high average cholesterol levels have high incidences of heart disease. They know that cholesterol is a major component of atherosclerotic plaques and that animals fed diets that give them high cholesterol levels get heart disease. In addition, individuals with inherited diseases causing very high blood cholesterol concentrations die at an early age of heart disease. But there was still a missing link to the hypothesis. It could be that cholesterol concentrations are correlated with heart disease risk in humans but do not cause the disease. Some investigators had tried but no one had ever shown that people who lower their blood cholesterol lower their incidence of heart disease.

The NHLBI's original plan was to test the effects of cholesterol-lowering diets on heart disease by dividing volunteers into two groups. One would follow a cholesterol-lowering diet and the other would follow any diet they chose. But diets only reduce cholesterol by 10 to 15 percent in the best cases, and it is notoriously difficult to get people to rigorously follow a restricted diet for the years and years of a clinical trial. Thus the group that was supposed to lower its cholesterol by diet would probably reduce it far less than 10 percent. A reduction of 3 or 4 percent would be more realistic. For that reason, an enormous group of study participants—millions of people, the NHLBI estimated—would be required to have a chance of seeing a statistically significant reduction in heart disease. The study would also cost more than $1 billion. For that reason, in 1971, the NHLBI devised an alternate plan to test the cholesterol-heart disease hypothesis.

The idea was to select men with very high blood cholesterol and give half of them a potent cholesterol-lowering drug as well as a diet. The other half of the men would be given a placebo and a diet. The study would be double-blind. Thus the NHLBI established 12 Lipid Research Clinics across the country to design and implement the trial. They recruited 3806 men, aged 35 to 59, whose blood cholesterol levels were above 265 milligrams per deciliter—placing their cholesterol levels in the upper 5 percent in this country. The men had no evidence of heart disease when the study began and normal blood pressure.

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It took 3 years to recruit the men for the study. At first the clinics requested that doctors and clinical laboratories recommend patients for the trial. But by April of 1974, they had spent 9 months trying to find participants in this way and had recruited only 74, or 2 percent of the number they wanted, so the clinics decided to go public. They advertised for volunteers, asked that blood banks help them find people with high cholesterol levels, set up screenings at factories and at community events, and sent out mass mailings. They ended up screening over 400,000 men to find 18,000 with high enough blood cholesterol for the study. But most of these men were disqualified because they had high blood pressure, evidence of heart disease, or evidence of some other major disease.

Even a study of 3806 men was an immense undertaking. The men were studied from 7 to 10 years, and during that time they made a total of 193,000 visits to the clinics, gave 341,000 blood samples, had 72,000 electrocardiograms, and generated over 1 million data forms.

In the beginning of the study, all the men were treated with diet alone. Their cholesterol levels fell an average of 3.5 percent. Then the men were given cholestyramine or a placebo and it became apparent immediately that cholestyramine significantly reduced blood cholesterol. The cholestyramine group had an 8.5 percent lower cholesterol level than the placebo group, even though compliance with the drug therapy was by no means 100 percent. By the end of the trial, the cholestyramine group was consuming an average of 4.1 packets a day of the drug, although 6 were prescribed. The men in the placebo group were instructed to take 6 packets a day of an inert substance, but they averaged only 4.8 packets a day by the end of the study. Twenty-seven percent of the men in both groups were taking no packets at all by the study's end.

But, strikingly, the cholestyramine group nonetheless had significantly fewer heart attacks and deaths from heart disease, less bypass surgery, and fewer heart disease symptoms. These symptoms included the development of electrocardiogram changes with exercise and angina. Moreover, the more scrupulous the men were in taking the cholestyramine, the better they did. Those who averaged 0 to 2 packets of the drug a day had a drop in cholesterol concentration of only 4.4 percent and a reduction in heart disease risk of less than 11 percent. Those who averaged 5 to 6 packets a day had 19 percent reduction in their cholesterol level and a nearly 40 percent reduction in their heart disease risk. In general, the NHLBI investigators say, a 1

percent reduction in cholesterol concentration translates into a 2 percent reduction in heart disease risk.

The side effects of the cholestyramine treatment were minor. The cholestyramine group did not have an increased incidence of cancer or any other major disease and the study participants complained mostly of bloating, heartburn, and constipation. Sixty-five percent of the men taking cholestyramine complained of such symptoms—but so did 45 percent of the men taking the placebo.

The NHLBI is so encouraged by the study results that it is willing to go quite far in extending them. As might be expected, the institute suggests that the 1 to 2 million middle-aged American men who have cholesterol levels of 265 milligrams per deciliter and above might want to take cholestyramine or a similar drug. In addition, says Basil Rifkind of the NHLBI, "the trial's results could and should be extended to younger men with high blood cholesterol." Rifkind also believes that women with high blood cholesterol levels should try to reduce them. "High," to Rifkind, means 230 or 240 milligrams per deciliter, which is the upper 15 to 20 percent of the American cholesterol distribution. There are 35 to 40 million Americans with cholesterol levels in this range.

But, stress Rifkind and Robert I. Levy, who was director of the NHLBI when the study began and who is now at Columbia University, the preferred way for anyone to reduce their blood cholesterol is with diet. For persons with cholesterol levels of 240 or so, a diet might get them down to the American average of 210 milligrams per deciliter, which the NHLBI group recommends as a goal to aim for. Diet can, for some people, reduce cholesterol by 10 to 15 percent. For those who cannot get their cholesterol down far enough with diet, cholestyramine or a similar drug could be tried. In addition to the inconvenience and possible discomfort of taking cholestyramine, the drug is quite expensive. It costs about $150 a month for the doses used in the NHLBI trial.

Is the NHLBI ready at last to recommend that the general public try to reduce its blood cholesterol levels? Well, says Rifkind, they are still considering the matter. "Before making categorical recommendations we plan to bring experts together to reflect on the results of the study and link them to other evidence," he says. Besides, he remarks, there is no pressing reason to wait for the NHLBI. "Many experts have already made recommendations," he says.

—GINA KOLATA

Another Oil Resource Warning

In a recent U.S. Geological Survey (USGS) report,* government researchers specializing in the estimation of oil resources issued a strong warning—the amount of oil left to slake the world's thirst for energy is smaller than some optimists would like to think and may be even smaller than conservative estimates. A total of 1718 billion barrels of oil (BBO) will ultimately be recovered by conventional means, according to the report by Charles Masters and David Root of the USGS in Reston, Virginia, and William Dietzman of the Energy Information Administration in Dallas. This USGS estimate is near the lower end of the range of recent estimates, most of which have tended to fall slightly above 2000 BBO. Their estimate of the most uncertain portion of ultimate recoverable resources—undiscovered resources—is 550 BBO. That compares with another recent estimate of 987 billion barrels yet to be discovered made by oil consultant and sometime Reagan adviser Michel Halbouty and consultant John Moody. Their estimate is the most likely value in a range of 280 to 2415 billion barrels.

The USGS report finds no support for such large estimates of the maximum amount of oil left to be found. To find 2415 BBO, the report says, industry would have to locate another oil province with the mammoth resources of the Middle East, "and our studies indicate no possibility for such an occurrence." After considering such frontiers of exploration as the Arctic, the deep sea floor, and other relatively untested basins, they note that "most of these basins are untested for good geologic or economic reasons . . . our analysis suggests the likelihood that most of the new oil will come from the established provinces," predominantly the Middle East. This new oil, plus reserves known to exist in the ground, would last the world about 60 years at present rates of consumption. The estimated U.S. supply from undiscovered resources and demonstrated reserves is 36 years at present rates of production or 19 years in the absence of imports.

Things may be worse than they appear. Since the mid-1960's, the amount of oil discovered each year has dropped—from about 38 BBO in the early 1960's to about 10 BBO in the late 1970's, according to the report. At the same time, world consumption was increasing so that, beginning in the early 1970's, more oil was consumed from reserves each year than was added by new discoveries. Reserves declined despite the drilling of more wells in more places. This decrease in the finding rate is evident outside the United States, Canada, and Communist countries, where each wildcat well drilled in search of a new field discovered an average of about 23 million barrels of oil in the early 1950's but only about 10 million barrels in the recent past, according to Root. Within the United States, the cycle of depletion is much farther along, reserves having peaked in the 1950's.

The increasing difficulty of discovering each additional barrel of oil may bode ill for future discoveries. The report's 550-BBO estimate of undiscovered oil in the world is actually the most likely value in a range of possible values. There is a 5 percent probability that as much as 1417 BBO will be found and a 95 percent probability that, on the low side, at least 321 BBO will be found. "[T]he general level of exploration, as measured by numbers of wells, has increased over time," the report says, "yet annual discoveries are declining, suggesting the possible reality of low-side assessments. If the low side be reality, the need for alternate energy sources becomes increasingly critical for most of the world's countries."

Dependence on subjective geologic interpretation, as in the USGS study, has already resulted in unduly optimistic expectations (*Science*, 24 April 1981, p. 427). In U.S. frontier areas, drilling experience has been discouraging enough of late that Root and Masters "strongly suspect" that the USGS's 1981 estimate of U.S. undiscovered resources is too high. Early last month, for example, the much touted Mukluk wildcat well in Alaska's Beaufort Sea, the frontier province that greatly buoyed the 1981 estimate, came up dry. By Christmas, the first well drilled into the buried reef off New Jersey, one of the last hopes of the U.S. Atlantic outer continental shelf, was being abandoned.—RICHARD A. KERR

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