

Thematic review series: *The Pathogenesis of Atherosclerosis*

An interpretive history of the cholesterol controversy, part IV: The 1984 Coronary Primary Prevention Trial ends it—almost¹

Daniel Steinberg²

Department of Medicine, University of California—San Diego, La Jolla, CA

Abstract As of the early 1980s, despite the wealth of evidence from experimental animal models, the extensive epidemiologic evidence, the powerful genetic evidence, and the strongly suggestive clinical intervention trial results, most clinicians still remained unpersuaded regarding the relevance of the lipid hypothesis. What was needed was a well-designed, large-scale, long-term, double-blind study demonstrating a statistically significant impact of treatment on coronary heart disease events. The National Institutes of Health (NIH) had laid the groundwork for such a study as early as 1970, but the study was not completed and the results published until 1984. This study, the Coronary Primary Prevention Trial, showed that treatment with a bile acid binding resin reduced major coronary events in hypercholesterolemic men by 19%, with a *P* value of 0.05. The NIH followed this up with a national Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease. For the first time, the NIH now went on record advocating screening for hypercholesterolemia and urging aggressive treatment for those at high risk. The Institute initiated a national cooperative program to that end, the National Cholesterol Education Program. For the first time, preventing coronary heart disease became a national public health goal.—Steinberg, D. The pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part IV: The 1984 Coronary Primary Prevention Trial ends it—almost. *J. Lipid Res.* 2006. 47: 1–14.

Supplementary key words cholestyramine • National Cholesterol Education Program • coronary heart disease

As early as 1970, many of the country's experts in atherosclerosis and preventive cardiology, and the American Heart Association, were already convinced that there was a causal connection between blood cholesterol and coronary heart disease, as discussed in the earlier installments

of this series (1–3). However, no one could be certain how firm that connection was or how much impact treatment to decrease cholesterol levels would have. As a result, almost no nonspecialists, and in fact very few practicing internists or cardiologists, were paying very much attention to their patients' high blood cholesterol levels in 1970, and coronary heart disease continued to be the number one cause of death. What to do?

The National Institutes of Health (NIH) realized that launching a national program to treat high blood cholesterol levels would be enormously complex and expensive. They could not justify that expense without first having iron-clad proof that treatment would work. In any case, the medical community would have to be convinced before it could be expected to make serious efforts to implement any proposed treatment programs. Even though the cumulative evidence was impressive, the direct clinical intervention trials were individually weak. What was missing was an air-tight study, a “clincher,” that would bring the skeptics into the fold and mobilize the medical community. The first step toward the realization of such a study had already been taken in 1970.

THE CORONARY PRIMARY PREVENTION TRIAL

The keystone in the arch of evidence linking blood cholesterol to heart disease

In June 1970, Theodore Cooper, Director of the National Heart and Lung Institute, asked Donald S. Fredrickson, then Director for Intramural Research, to convene an expert panel, the Panel on Hyperlipidemia and Atherosclerosis, to advise him on how the Institute should proceed with respect to the prevention of heart

Manuscript received 13 October 2005.

Published, *JLR Papers in Press*, October 15, 2005.
DOI 10.1194/jlr.R500014-JLR200

Copyright © 2006 by the American Society for Biochemistry and Molecular Biology, Inc.

This article is available online at <http://www.jlr.org>

¹ Based in part on the author's book in preparation, *The Cholesterol Wars*.

² To whom correspondence should be addressed.
e-mail: dsteinberg@ucsd.edu

disease related to hypercholesterolemia. At the time the Panel was convened, Fredrickson and his colleagues, Robert I. Levy and Robert S. Lees, had just published a highly influential series of reviews in the *New England Journal of Medicine* (4–6). They proposed a classification of abnormalities of serum lipids based on total cholesterol and triglyceride levels plus the lipoprotein pattern revealed by paper chromatography. Despite the pioneering lipoprotein work of Gofman and colleagues (7, 8), the concept of lipoproteins and the classification of patients based on these lipoprotein patterns were still foreign to most practitioners, and there were technical problems still to be resolved. One question the Panel was asked to address was whether the Institute should establish a network of lipid centers of excellence across the country that could standardize methods of lipid and lipoprotein analysis. These centers, to be designated Lipid Research Clinics, would consult with local hospitals and clinics and help them train their own staffs in the use of these new methods. The Panel unanimously endorsed this proposal.³

Equally important, or possibly even more so, the Panel was also asked, “Do you believe the evidence is sufficient to warrant the detection of and some form of individual treatment of hyperlipidemia?” Of the 21 experts, 20 answered yes. However, they recognized that the evidence that such treatment would reduce heart attack rates, and by how much, was still limited. Therefore, they went on to recommend that the program must include a randomized intervention trial to determine the effect of the treatment of hypercholesterolemia on atherosclerotic complications.

As a member of that Panel, I remember that some, including Fredrickson himself, felt strongly that the establishment of the network of Lipid Research Clinics should not wait until the nature of the randomized trial was agreed upon. Fredrickson was concerned that the intervention trial would be so costly that it might drain away funds from the other parts of the program. Others, including Levy, felt strongly that a definitive intervention trial should be an integral part of the package and get a very high priority. As it turned out, fortunately, the Lipid Research Clinics program was approved and funded with almost no opposition. A new branch of the Heart and Lung Institute, the Lipid Research Branch, was established to oversee the implementation of these recommendations, and Levy was given the responsibility of heading it. Twelve

³ The panel included Fredrickson, Chair; Edwin L. Bierman, Professor of Medicine, University of Washington; David H. Blankenhorn, University of Southern California; William Castelli, Framingham Heart Study, National Heart and Lung Institute (NHLI); William E. Connor, University of Iowa; Gerald R. Cooper, Communicable Disease Center; Theodore Cooper, Director, NHLBI; Seymour Dayton, VA Medical Center, Los Angeles; Howard Eder, Albert Einstein College of Medicine; Ivan D. Frantz, University of Minnesota; William Fridewald, NHLBI; DeWitt S. Goodman, Columbia University; Frederick T. Hatch, University of California Berkeley; Richard J. Havel, University of California San Francisco; Peter Koo, University of Pennsylvania; Robert S. Lees, Massachusetts Institute of Technology; Robert I. Levy, NHLBI; Robert P. Noble, Sharon Research Institute; Isidore Rosenfeld, Cornell University; and Daniel Steinberg, University of California San Diego.

university centers were successful in the competition for Clinic grants, and these were up and running within a year or so.⁴

Planning for the randomized trial [the Coronary Primary Prevention Trial (CPPT)] was deferred, but, fortunately, for only about a year. It was then proposed that each of the Lipid Research Clinics would participate in a multicenter trial to definitively test the “lipid hypothesis.”

The CPPT

The decision to launch such a complex study was not easy. It would be painfully expensive and it would take an enormous amount of planning and years of detailed implementation, but it had to be done. Fredrickson (9) voiced his own ambivalence in a witty 1968 article entitled “The field trial: some thoughts on the indispensable ordeal.” He began by suggesting that the first-ever field trial was actually carried out in the Garden of Eden. Like so many subsequent field trials, he went on, it was roundly criticized because 1) the experimental protocol had received inadequate prior consideration; 2) the population sample was too small; and 3) the study consumed too large a fraction of the then available gross national product. Despite his tongue-in-cheek misgivings, he committed the National Heart and Lung Institute to a program that included a clinical trial as a major component.

In 1971, I was asked along with John W. Farquhar from Stanford University to cochair an NIH Committee⁵ that would design the protocol for the CPPT. Our Committee ran into many knotty problems, some theoretical, some ethical, and some just very difficult pragmatic problems. The discussions of the Committee spanned almost 2 years. The study would be named The Coronary Primary Prevention Trial of the Lipid Research Clinics. The final result would not become available until 1984, 13 years and about \$150 million later.

⁴ The participating centers were at Baylor College of Medicine under Antonio M. Gotto; University of Cincinnati Medical Center under Charles J. Glueck; George Washington University Medical Center under John C. LaRosa; University of Iowa Hospitals under William E. Connor and, later, Francois Abboud and Helmut Schrott; Johns Hopkins Hospital under Peter O. Kwiterovich; University of Minnesota under Ivan D. Frantz, Jr., and Donald B. Hunninghake; Oklahoma Medical Research Foundation under Reagan H. Bradford; Washington University School of Medicine under Gustave Schonfeld; University of California San Diego under W. Virgil Brown and Daniel Steinberg and, later, Fred H. Mattson; University of Washington under William R. Hazzard and Edwin L. Bierman and, later, Robert H. Knopp; Stanford University under John W. Farquhar; and University of Toronto and McMaster University under J. Alick Little.

⁵ The original Intervention Committee appointed in 1971 included Daniel Steinberg and John W. Farquhar, cochairs; William R. Hazzard; Edmond A. Murphy; Al Oberman and Richard D. Remington, members at large; Dale Williams and James E. Grizzle as Data Coordinating Center representatives; and Robert I. Levy and Basil Rifkind, National Heart and Lung Institute staff. Membership was later expanded to include William E. Connor; G. William Benedict; C. E. Davis; Ronald W. Fallat; Antonio M. Gotto; Richard C. Gross; Donald B. Hunninghake; John C. LaRosa; Maurice Mishkel; Gustav Schonfeld; L. Thomas Sheffield; Thomas F. Wayne, Jr.; and Richard J. Havlik representing the Program Office.

Designing the trial

The first thing the planning committee had to do was decide on the mode of intervention (10). From one point of view, diet would have been the preferred treatment because then the issue of toxicity would not arise. However, diet was not really a viable choice. The degree of cholesterol lowering would be limited, and unless huge numbers of subjects were studied (which would almost certainly make the costs unacceptable), the effects might wind up as marginal. Furthermore, a double-blind diet study would be all but impossible to design and fund. An NIH committee of consultants under the chairmanship of Edward H. Ahrens, Jr., had previously done an intensive, year-long study of the feasibility of a double-blind diet trial in the general population (11). They even considered an elaborate design in which fat-containing foods (meats, spreads, and dairy products) would be specially processed so that neither participants nor investigators could tell whether they contained saturated or polyunsaturated fats. The foods would carry bar-coded labels and be issued to participants from a central warehouse. This would have enabled a double-blind study design. However, Ahrens' committee concluded that such a design, although feasible in principle, would be out of the question in practice because it would simply be forbiddingly expensive. The double-blind diet-heart design was a nonstarter.

What, then, were the alternatives? The only effective drugs in use at the time were clofibrate, nicotinic acid, and cholestyramine, and none of these was ideal, as discussed below. In fact, some researchers seriously doubted that the lipid hypothesis could ever be proved definitively using drug treatment. This pessimistic outlook led Henry Buchwald, a surgeon at the University of Minnesota, to explore the feasibility of a surgical approach (12). He and his colleagues showed that cholesterol levels could be decreased by 20–25% using a modified intestinal bypass operation, and they initiated a long-term study to test whether this would decrease the risk of coronary heart disease. Obviously, this intervention would hardly lend itself to a double-blind study. Also, asking volunteers to undergo major abdominal surgery with no absolute guarantee that there would be a benefit seemed daunting. Nevertheless, it was briefly considered. Parenthetically, it should be noted that Buchwald stuck with his program for the surgical correction of hypercholesterolemia and eventually showed that treated subjects did have a significant decrease in coronary heart disease events and a decrease in total mortality compared with age-matched controls (13).

How did the candidate drugs look?

Clofibrate was quite effective, decreasing blood cholesterol by ~20%, and it had already been reported to significantly reduce cardiac end points in high-risk men (14). However, it was more effective in decreasing VLDL than LDL, and its use had been associated with significant increases in gallstones (15) and other diseases of the gastrointestinal tract. Later studies would show that the drug,

although having a favorable effect on cardiac events, actually increased overall mortality (16). Our decision to pass up clofibrate was a fortunate one.

Nicotinic acid was effective but not an easy drug to take. In the formulations available at the time, it caused uncomfortable flushing and itching in a large fraction of patients. More seriously, it could impair liver function, and although such a side effect was relatively uncommon, our committee was unwilling to expose patients in the study to any unnecessary risks. Furthermore, the flushing would disclose which subjects were getting nicotinic acid and which were getting placebo. So nicotinic acid might not be safe and the study could not be effectively double-blinded. Pass again.

Cholestyramine was effective. At full dosage (24 g/day) it reduced total blood cholesterol by 20–25% and LDL cholesterol by 30–35% (17). Because it was totally non-absorbable, it would predictably be free of systemic toxic side effects. However, it was at the time only available as a sandy powder that needed to be stirred in water or juice and gulped down. To be fully effective, it had to be taken in doses of 24 g/day. That meant bravely downing two packets three times daily. Moreover, a significant percentage of patients taking large doses experienced bloating, constipation, or diarrhea as a result of local irritation of the intestinal wall.

So here was a drug that some patients would predictably find almost intolerable, yet it was both safe and effective. Could we expect to persuade 3,800 men to take this gritty stuff regularly for 7 years? We elected to go with it, based mainly on its freedom from systemic toxicity. We would just have to grapple somehow with the problem of patient compliance and come up with imaginative ways to get the cholestyramine down and keep the morale up for 7 years.

Another tough problem was that of manufacturing a placebo that could not be distinguished from the active drug. Mead Johnson and Co., the makers of Questran, came through with polymer beads the same size and color as the active cholestyramine but with no ion-exchange groups on it. At the end of the trial, the men were asked to say whether they had been in the treatment group or the placebo group. Almost exactly 50% of the men got it right, as expected by chance alone. They could not tell the difference.

Study design

Our committee, after many meetings, with input from clinicians, statisticians, epidemiologists, and lipid specialists, settled on a protocol after ~2 years, and a green light was given to start the recruitment of patients. The study cohort would consist of ~3,800 men, ages 35–59 years, with no history of coronary heart disease and no signs of current disease. However, these men would be at high risk because of total blood cholesterol levels of 265 mg/dl or higher (men with cholesterol levels in the 95th percentile for this age group).

Recruiting 3,800 men fitting this description and willing to volunteer for a minimum of 5 years seemed straight-

forward, but it proved to be a formidable undertaking. The original plan was that each Clinic would ask community physicians to refer patients who met the protocol requirements from their private practices. In addition, clinical laboratories and blood banks would be asked to identify (with permission) patients whose blood cholesterol was >265 mg/dl. These approaches failed miserably. Practitioners simply were not measuring cholesterol levels, and the number of blood donors was much lower than had been expected. The plan had optimistically called for completion of the recruitment phase in 18 months. Ten months into the study, only 74 of the required 3,800 participants had been recruited and started on the protocol. First, men seeing a physician probably already had coronary heart disease and therefore were not eligible for the study. Second, cholesterol levels were not yet routinely measured, so there was no large existing database to draw on. There was a bit of a panic in the central office. Each year added to the recruitment period meant an additional year added to the length of the overall study...and another \$25 million dollars or so. Radically different recruitment strategies were going to be needed.

It became clear that the CPPT would have to resort to mass public screening. It was going to be necessary to "go public" and measure blood cholesterol levels in a random screening. The Lipid Research Clinic in St. Louis led the way. The Director, Gustave Schonfeld, and the CPPT Director, Joseph L. Witztum, enlisted the help of a professional public relations firm to plan their campaign. This firm also handled public relations for McDonnell Douglas, and the company agreed to let Witztum's recruiting team come in and draw blood samples from >10,000 employees. The firm also provided entrée to some department stores they represented. Later, recruiting booths were set up at Cardinals games and Rams games. The "come on" was a free cholesterol measurement, and there were a goodly number of takers. Other Lipid Research Clinics adopted similar mass screening strategies. Still, it took almost 3 years before the last subject was randomized. Eventually, almost 500,000 men nationwide had to be screened over the 3 year period from 1973 to 1976 before the full cohort of 3,800 participants was finally recruited.

Potential ethical problems associated with the placebo group

All of the men in this study had extremely high cholesterol levels and were, if the lipid hypothesis were correct, at high risk of having a heart attack. This posed the sticky ethical issue, common to all such intervention studies, of whether it would be justifiable to leave the placebo group untreated. The answer today would be a definite "No," because today the lipid hypothesis has been proved. At the time, however, the lipid hypothesis was still just that, a hypothesis in the process of being tested. In fact, at the time, the volunteers for this project, even if they had consulted with their internist, would either have received no treatment at all or, at most, would have been given advice about diet. It was decided to have all participants

follow a modest cholesterol-lowering diet such as their practitioners might have recommended. That diet was deliberately designed so that it would reduce total cholesterol only by ~5%. This would weaken the study by reducing the difference in cholesterol levels between the two groups and thus dilute the effect of the cholestyramine. However, based on the clinical experience available at the time, cholestyramine at full dose was expected to decrease cholesterol levels by ~30%. That would be more than enough to give a definitive result even though the diet reduced the cholesterol level somewhat in both groups. In any case, diet treatment was felt to be called for because some practitioners (although not many) were already recommending diet modification to patients with very high cholesterol levels.

The trials and tribulations of the CPPT directors

From the very beginning, the CPPT was not only a trial of the lipid hypothesis but also was a trial for those running it. Many had had little previous experience with large-scale trials. Some, more interested in bench science, were actually a bit resentful of the time the trial would take away from their laboratory research programs. However, they were prepared to put their shoulders to the wheel because they recognized that the trial was of pivotal importance. The central Program Office at the NIH in Bethesda was headed initially by Robert I. Levy and then by Basil Rifkind. That central office played an absolutely essential role, taking the trial directors and staff members of the 12 collaborating centers by the hand and leading them through the thickets of clinical trial research. It was a complex operation. Each center employed physicians, nurses, dietitians, laboratory personnel, adherence counselors, and clerks, a total of about 30 full-time employees. The annual budget at each center was close to \$2.0 million. Because many of the trial directors were in the program mainly out of a sense of obligation "to help get the job done," they sometimes lost patience with this monotonous year-after-year routine. The clinic staff worked tirelessly to improve compliance, but taking six packets of cholestyramine every day for >5 years was more than most of the men could manage, however good their intentions. Some brave souls managed it, and in that group the final results were quite dramatic. But overall compliance was disappointing. Yet, as discussed below, the study proved to be statistically significant, although barely so.

Rifkind and the other administrators in the Bethesda Program Office had the responsibility to see that every "i" was dotted and every "t" crossed. After all, the outcome of this trial might determine whether or not the NIH would join the battle against cholesterol as a cause of myocardial infarction. Moreover, it was predictable that the results would be examined with a fine-tooth comb, especially by the cholesterol skeptics. And it was going to cost about \$150 million overall, so it better be of the highest quality. All of these factors helped account for a certain amount of tension between the central Program Office and the individual trial directors on the front lines.

The directors chafed under the rigid insistence of the Program Office on strict adherence to protocol, the frequent joint meetings that meant travel sometimes far from home, and a sometimes “no-discussion-allowed” approach. At the same time, the trial directors recognized and applauded Rifkind for his outstanding job at the Program Office and, ultimately, for bringing the ship safely into port.

The CPPT comes in with the proof

When the CPPT ended (**Fig. 1**), the 3,806 participants had been followed for an average of 7.4 years. The degree of cholesterol lowering achieved with cholestyramine was, disappointingly, much less than had been expected, only a 13.4% reduction in total cholesterol and a 20.3% reduction in LDL cholesterol. Still, the number of events (definite coronary heart disease death and/or nonfatal heart attack) was 19% lower in the treated group, with a P value of <0.05 , statistically significant although barely so (18). It was a narrow squeak. The CPPT came frighteningly close to joining the early dietary trials as “case not proved.” In fact, some criticized the investigators for employing a one-tailed t -test, because testing a treatment that might have serious adverse effects does require the use of a two-tailed t -test (19). However, cholestyramine was not being evaluated as a new drug; it was being used as a means of decreasing cholesterol levels to test the lipid hypothesis. So the use of the one-tailed statistic was appropriate. In any case, the results of the CPPT were considerably strengthened by the concordant and highly significant decreases in secondary end points: development of anginal pain decreased by 20% ($P < 0.01$), and development of a positive exercise electrocardiogram decreased by 25% ($P < 0.001$).

Another important point is that the published final results were reported, according to the standard practice for such studies, on all of the men randomized without respect to whether they had or had not actually taken the prescribed six packets of cholestyramine daily (24 g). In fact, a large number of the men readily admitted that they

simply could not handle the drug and stopped taking it altogether within weeks of the start of the trial. Others stayed with it but reduced the number of packets from the prescribed six daily to as few as two or three daily. At each clinic visit, the men were given a large supply of packets, more than they would need to carry them until the next visit. One of the staff nurses would count the number of packets that had been used, the “packet count.” During the first year, the average daily packet count, which should have been 6, was only 4.2. By the end of the study it had decreased to less than four. This undoubtedly accounted for the discrepancy between the expected decline in cholesterol levels and the much more modest decrease actually observed. When the event data for those men who had taken the full dose of six packets daily were analyzed separately, it was found that they had a 35% decrease in total cholesterol and a 49% decline in event rate (**Fig. 2**). For the study as a whole, the reduction in risk was proportional to the reduction in cholesterol level, as predicted by the lipid hypothesis. Despite the poor compliance and the smaller than expected decrease in cholesterol levels, the study had made its point.

The relationship between the percentage decrease of cholesterol level and the percentage reduction in the incidence of coronary events was consonant with the results in previous intervention trials (**Fig. 3**). This was despite the fact that the data compared included both drug and diet trials and both primary and secondary trials. The outlier H in **Fig. 3** represents the data for the dextrothyroxine-treated group in the Coronary Drug Project (20), in which there was manifest cardiotoxicity, including some fatal arrhythmias. The outlier D represents the extraordinary reduction in events achieved in the Newcastle clofibrate trial (21). The data suggested, but by no means proved, that no matter what the interventional modality, the determinant of response was the degree to which cholesterol levels were decreased. Later trials using the more potent statins would add points to the right of this graph, and some of those points have been appended to **Fig. 3**. The

Reprinted from the *Journal of the American Medical Association*
January 20, 1984 Volume 251
Copyright 1984, American Medical Association

Original Contributions

The Lipid Research Clinics Coronary Primary Prevention Trial Results

I. Reduction in Incidence of Coronary Heart Disease

Lipid Research Clinics Program

Fig. 1. This 1984 paper presenting the results of the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT) was a landmark (18). Here was the first truly large, double-blind, placebo-controlled trial showing unambiguously that decreasing cholesterol levels in high-risk men (using cholestyramine) could significantly reduce the risk of myocardial infarction. (Reproduced from *J. Am. Med. Assoc.* 1984. **251**: 351–364, with permission.)

RELATION OF REDUCTION IN LDL CHOLESTEROL TO REDUCTION IN CORONARY HEART DISEASE (Cox Proportional Hazards Model)

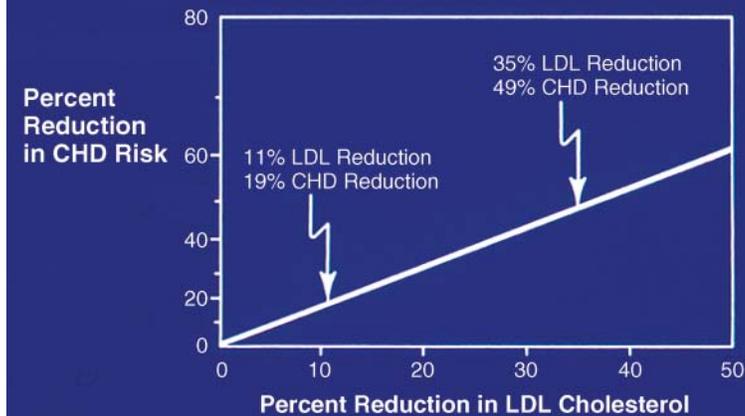


Fig. 2. Percentage risk reduction versus percentage decrease of total serum cholesterol in the CPPT. The arrow to the left indicates the relationship in the cohort as a whole. However, as discussed in the text, many of the men stopped taking the drug almost from the first day, and very few men were able to take the full prescribed dose of 24 g/day. The arrow to the right indicates the relationship for those men who did manage to take the full dose. CHD, coronary heart disease; LRC, Lipid Research Clinics. [Data from *J. Am. Med. Assoc.* 1984. 251: 351–364 (18), with permission.]

degree of cholesterol lowering was greater in the later studies and the reduction in risk was greater, but, at least to an approximation, the fit of the new data to the slope was rather close. A formal comparison of the prestatin clinical trial results and the statin trial results suggests that the slope for the statin trials is slightly steeper but that the bulk of the benefit can be attributed to the decrease in cholesterol levels rather than to pleiotropic effects (22).

There was joy in 12 Mudvilles: the 12 participating Lipid Research Clinics. At each clinic, the men who had unselfishly volunteered and stayed the course were invited together with their families to join the staff in celebration of the outcome. These men had persevered for 7–10 years in a very demanding regimen with a decidedly unattractive medication. Their contribution deserved and received appropriate recognition.

Reception by the profession and by the press

The major medical journals around the world hailed the results of the trial as finally providing the rationale for treating hypercholesterolemia. The *Medical Journal of Australia* featured a lead article by Leon A. Simons titled “The lipid hypothesis is proven” (23). He concluded with this: “The LRC-CPPT has given a new respectability and credibility to the dietary and pharmacologic management of hypercholesterolemia.” *Postgraduate Medicine* featured a Nutrition Highlights article by Richard N. Podell titled “Coronary disease prevention: proof of the anticholesterol pudding” (24). Even Michael F. Oliver, perhaps the most vocal skeptic over the years, wrote an editorial for the *British Medical Journal* titled “Hypercholesterolaemia and coronary heart disease: an answer” (25). However, with characteristic pessimism, he warned that these results only applied to men with very high cholesterol values, that there was no guarantee that other drugs would be of benefit, and that the study did nothing to really settle the diet-heart problem.

Other researchers were also decidedly underwhelmed. George W. Mann, Associate Professor of Biochemistry at Vanderbilt University College of Medicine, had this to say about the CPPT directors: “They have held repeated press conferences bragging about this cataclysmic breakthrough which the study directors claim shows that lowering cholesterol lowers the frequency of coronary disease. They have manipulated the data or reached the wrong conclusions.” And later: “The managers at NIH have used Madison Avenue hype to sell this failed trial in the way the media people sell an underarm deodorant” (26).

What was the nature of the criticisms?

Although the cholestyramine group in the CPPT showed significantly fewer fatal and nonfatal heart attacks, there was no decrease in total mortality. Was the treatment increasing mortality from some other diseases? What’s the point of preventing heart attacks if you just die of something else? This was perhaps the most troublesome criticism of the report and had to be taken seriously. However, three considerations made it most unlikely that this was the case. First, there was no statistically significant difference in total mortality. All-cause mortality was actually 7% lower in the treated group, but that difference was not significant. Second, the number of patients studied would have had to be considerably larger before one could have expected to see a statistically significant decrease in total mortality. Finally, there was no statistically significant increase in deaths from any single disease or disease category. If cholestyramine itself or the lowering of blood cholesterol were toxic, it would be expected to show up as an increased death rate in one or a few categories, but that was not the case. Most of the noncoronary deaths were attributable to cancer, and the numbers were almost identical in the two groups: 15 versus 16.

Much was made of the category of deaths in the CPPT that were lumped together (for reasons not entirely clear)

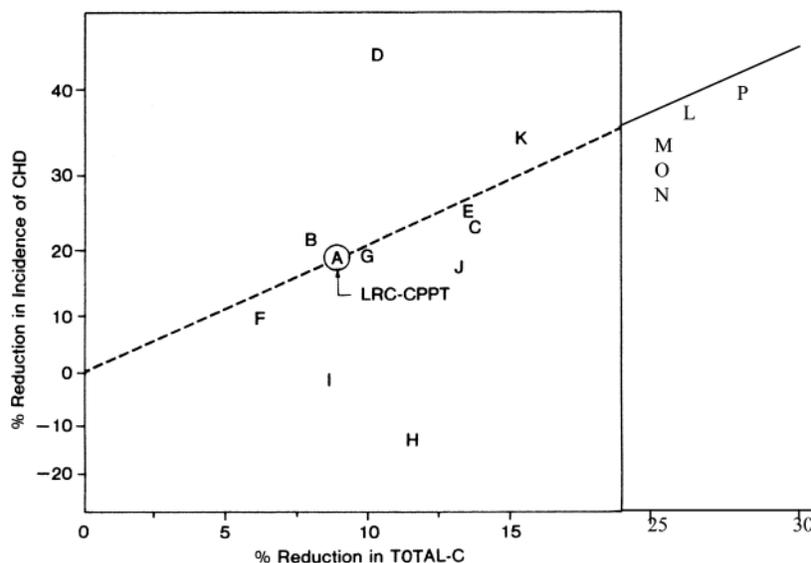


Fig. 3. This is a modified version of Fig. 3 from the CPPT report (18) showing that the results in terms of percentage risk reduction versus percentage reduction in total cholesterol level in the CPPT were comparable to the results in previous studies, whether using drugs or diet to decrease the cholesterol level. The outlier H represents the data for the dextrothyroxine-treated group in the Coronary Drug Project (20), in which there was manifest cardiotoxicity, including some fatal arrhythmias. The outlier D represents the extraordinary reduction in events achieved in the Newcastle clofibrate trial (21). The data suggested, but by no means proved, that no matter what the interventional modality, the determinant of response was the degree to which total cholesterol levels were decreased. (Most of the earlier studies did not include LDL cholesterol data.) Points representing results from three of the early statin trials and the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial (ileal bypass to decrease cholesterol level) have been added. L, Scandinavian Simvastatin Survival Study (31); M, West of Scotland study (43); N, Cholesterol and Recurrent Events study (44); O, the British Heart Protection Study (33); P, POSCH study (13).

as “traumatic deaths.” These included accidents, homicide, and suicide. Again, the difference was not statistically significant, but the difference was large enough to be disturbing: only 4 in the placebo group but 11 in the cholestyramine group. A similar small (but nonsignificant) excess of deaths attributable to violence was reported in a study using gemfibrozil to decrease cholesterol levels (27). Concern was expressed that any intervention that decreased blood cholesterol might affect cellular levels of cholesterol, especially in the brain, and in this way somehow induce aberrant behavior leading to violence (28, 29). Wysowski and Gross (30) looked into the details of the deaths in these studies and made a persuasive case that there was really no evidence to support such an hypothesis. First of all, the serum cholesterol levels in the accident victims were not particularly low, averaging 250 mg/dl at their last clinic visit. The one homicide death in the CPPT was actually not the murderer but rather the victim, surprised and shot by a burglar. Does taking cholestyramine or decreasing your cholesterol level make you a more likely victim? Later studies with larger numbers of subjects and even more effective cholesterol-lowering drugs would establish definitively that decreasing cholesterol levels actually reduces both coronary events and total mortality (31–33), but that was not yet firmly established in 1984. If decreasing cholesterol levels was to become a national public health policy, literally millions of people might be

treated. Even a small toxic effect might have drastic consequences. So these concerns had to be taken seriously.

The CPPT studied only men aged 35–59 years, all of whom had extremely high cholesterol levels. Many difficult decisions would have to be made about the extent to which the CPPT findings, together with the totality of evidence available from earlier studies, justified extrapolation to other subsets of the population.

THE 1984 NIH CONSENSUS DEVELOPMENT CONFERENCE ON LOWERING BLOOD CHOLESTEROL TO PREVENT CORONARY HEART DISEASE

With the results of the CPPT in hand, the NIH needed to decide what specific actions, if any, it should take. As one Australian lipid expert wrote, it was “time to treat cholesterol seriously” (34). Even if it were accepted that increased blood cholesterol was an important causative factor, what levels called for treatment? Using which drugs and/or diets? A key question not directly answered by the Lipid Research Clinics trial was whether decreasing cholesterol levels to a comparable degree by dietary means rather than by cholestyramine treatment would give a comparable decrease in events. This seemed likely because the decrease in risk in this study was similar to that in the early

studies using dietary treatment, but it could not be assumed. What were the potential hazards? At what age should treatment be started? In both men and women? What shape a national policy would take depended on the answers to these questions. Only if there were a true consensus would the NIH be prepared to establish new policy. The NIH had never before taken a position on how to deal with hypercholesterolemia, except in the rare, very severe genetically determined forms. The NIH had a well-established mechanism for getting such advice, the Consensus Development Conference.

Early in 1984, Basil Rifkind, Chief of the Lipid Metabolism-Atherogenesis Branch of the NHLBI, called and asked me if I would chair and help plan a Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease. As with other such NIH conferences, one of the Institutes proposes such a Conference but the overall responsibility for planning it and appointing the panel of experts is vested in an independent NIH office, the Office of Medical Applications of Research. That Office is independent of the individual Institutes, both in budget and in function. This independence is critical in keeping the Consensus Development Conferences as free of bias as possible. If the issue is important and if there might be a chance for a consensus position, the Office of Medical Applications of Research puts its machinery into operation to plan and organize the Conference. Rifkind's proposal had been accepted, and they had agreed on my appointment to chair the Conference.

It may be appropriate to record some of the details of how this conference was planned and by whom, because the objectivity of the panelists and the correctness of their conclusions were publicly questioned by some (35–37).

Our Conference followed the pattern common to all such NIH Consensus Development Conferences. A Planning Committee⁶ proposes the specific scientific questions to be addressed, lists the kinds of expertise that should be represented on the consensus panel, and nominates a Chair. The final approval of all aspects of these proposals rests with the Office of Medical Applications of Research, which at the time was headed by Dr. Itzhak Jacoby. The Chair then works closely with the Planning Committee to refine the questions to be addressed and to select the experts invited to sit on the panel. The Committee also selects topics and speakers for a day-and-a-half symposium in Bethesda at which the scientific data relevant to the questions are presented and discussed. Presentations at this symposium are made by experts not on the Consensus Panel itself. The symposium is widely publicized, and attendance is open to all interested parties: researchers, clinicians, other health professionals, food and drug

⁶ The Planning Committee was made up of Basil M. Rifkind, Chair; Susan Clark, Michael J. Bernstein, and Larry Blaser, representing the Office of Medical Applications of Research; Charles Glueck, Cincinnati General Hospital; William Hazzard, Johns Hopkins Medical School; Kenneth Lippel, Program Coordinator of the Atherogenesis Branch of NHLBI; and Albert Oberman, University of Alabama Medical Center.

manufacturers, lawyers, and the general public. Generally, more than 500 attendees come and participate in the discussion.

The specific questions to be addressed by our Panel were as follows. 1) Is the relationship between blood cholesterol levels and coronary heart disease causal? 2) Will reduction of blood cholesterol levels help prevent coronary heart disease? 3) Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started? 4) Should an attempt be made to reduce the blood cholesterol levels of the general population? 5) What research directions should be pursued on the relationship between blood cholesterol and coronary heart disease?

Fourteen experts were invited to join the Panel, and all accepted. They represented a wide span of disciplines, including biochemistry, endocrinology, cardiology, pathology, epidemiology and statistics, preventive medicine, and family medicine. Because our recommendations might have significant economic and legal implications, we also had two lawyers on the Panel, one who was a past Chairman of the American Heart Association, and one who was a public interest attorney.⁷ Over the summer and fall of 1984, I was in frequent contact with the panelists, assigning to each of them the responsibility for one or two facets of the material we would have to review before the Conference itself, which was scheduled for December 10–12 at the NIH Clinical Center in Bethesda, Maryland. The symposium was stimulating, the coverage was extensive, and without exception the speakers were outstanding authorities in their fields. The Panel members and the audience enjoyed an up-to-date survey of the data bearing on the question at hand. The program was as follows.

1) Evidence from pathology and animal models. Thomas B. Clarkson, DVM, Professor of Comparative Medicine, Bowman Gray School of Medicine.

2) Metabolic and genetic evidence: how LDL receptors influence cholesterol metabolism and atherosclerosis. Joseph L. Goldstein, MD, Paul J. Thomas Professor of Genetics, University of Texas Health Science Center.

3) Evidence from prospective and other epidemiologic studies. Jeremiah Stamler, MD, Professor and Chairman, Department of Community Health and Preventive Medicine, Northwestern University Medical School.

⁷ The Consensus Development Panel members were Daniel Steinberg, MD, PhD, Chair, University of California San Diego; Sidney Blumenthal, MD, Columbia University; Richard A. Carleton, MD, Brown University; Nancy H. Chosen, AB, JD, public interest attorney; James E. Dale, MD, MPH, University of Massachusetts Medical School; John T. Fitzpatrick, Esq., Attorney at Law and past President of the American Heart Association; Stephen B. Holley, MD, MPH, University of California San Francisco; Gregory O'Keefe III, MD, Islands Community Medical Center, Vinalhaven, Maine; Richard D. Remington, PhD, University of Iowa; Elijah Saunders, MD, University of Maryland School of Medicine; Robert E. Shank, MD, Washington University School of Medicine; Arthur A. Spector, MD, University of Iowa; and Robert W. Wissler, MD, PhD, University of Chicago.

4) Does lowering blood cholesterol prevent heart disease? A critique of the evidence. Robert E. Olson, MD, PhD, Professor of Medicine and Pharmacological Sciences, State University of New York, Stony Brook.

5) Summary of results from dietary and drug intervention studies. Richard Peto, MSc, Reader in Cancer Studies, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford University.

6) Evidence from the CPPT. Basil M. Rifkind, MD, FRCP, Chief, Lipid Metabolism-Atherogenesis Branch, NHLBI.

7) Relationship of clinical trial findings to epidemiologic data. Herman A. Tyroler, MD, Professor of Epidemiology, University of North Carolina School of Public Health.

8) The nature of plasma cholesterol and the population distribution of cholesterol levels. Robert I. Levy, MD, Professor of Medicine, Columbia University College of Physicians and Surgeons.

9) Efficacy of dietary management and associated risks. Scott M. Grundy, MD, PhD, Professor of Internal Medicine and Biochemistry and Director, Center for Human Nutrition, University of Texas Health Science Center.

10) Maximal cholesterol lowering from diet. William E. Connor, MD, Professor of Medicine, Oregon Health Sciences University.

11) Efficacy of drug management and associated risks. W. Virgil Brown, MD, Professor of Medicine, Mount Sinai School of Medicine.

12) Identification and management of individuals with markedly elevated cholesterol. DeWitt S. Goodman, MD, Tilden-Weger-Bieler Professor of Medicine, Columbia University College of Physicians and Surgeons.

13) Screening for hypercholesterolemia. Michael F. Oliver, MD, FCRP, Duke of Edinburgh Professor of Cardiology, University of Edinburgh.

14) What are the optimal cholesterol levels toward which we should aim for the American public at large? Antonio M. Gotto, Jr., MD, DPhil, Chairman, Department of Medicine, Baylor College of Medicine.

15) Identification and management of individuals with moderately elevated cholesterol. Edwin L. Bierman, MD, Professor of Medicine and Head, Division of Endocrinology and Nutrition, University of Washington.

16) The appropriateness of public health measures to change American dietary habits to reduce blood cholesterol. Henry Blackburn, MD, Professor and Director, Division of Epidemiology, University of Minnesota School of Public Health.

17) The lack of appropriateness (at this time) of public health measures to change American dietary habits. E. H. Ahrens, Jr., MD, Professor, The Rockefeller University.

18) The role of public education regarding cholesterol and heart disease. Kristen McNutt, PhD, JD, Associate Director, Good Housekeeping Institute.

19) The role of the food industry. Walter M. Meyer, Associate Director, Food Product Development, The Procter and Gamble Co.

20) What research directions should be pursued on the relationship between blood cholesterol and heart disease? Howard A. Eder, MD, Professor of Medicine, Albert Einstein College of Medicine.

No attempt will be made to summarize the proceedings except to say that the presentations were scholarly and there was lively discussion from the floor. Three points, however, deserve special comment.

First, Dr. Richard Peto from Oxford University (now Sir Richard) gave an electrifying presentation that included what may have been his first application of the method of meta-analysis, which he is generally credited with introducing into epidemiology. His analysis included all 17 of the appropriate diet or drug intervention studies available at the time. He concluded that when all of the diet studies were lumped together, there was a statistically significant decrease in coronary heart disease risk when blood cholesterol was decreased. He found the same to be true for the pooled drug intervention studies. This novel way of pooling results from several different studies in a formalized way shed new light on the meaning of the intervention data and had an important effect on the Panel's deliberations.

Second, there was ample opportunity for those who had strongly negative positions regarding the lipid hypothesis to voice their opinions, and they took advantage of that opportunity. Three of the formal presentations were made by on-record skeptics with respect to intervention: Edward H. Ahrens, Jr., Michael F. Oliver, and Robert E. Olson.

Third, the panelists did not draw their conclusions on the basis of the CPPT results alone. As reviewed by the outstanding speakers, there was already an impressive body of evidence of varying kinds that supported the lipid hypothesis. The Panel emphasized this, using the slide shown in **Fig. 4** to characterize the CPPT results as the keystone in an arch of evidence supporting the lipid hypothesis.

The Consensus Conference has been described, with some justification, as a "pressure cooker operation." Our Panel members arrived in Bethesda on Sunday and, after a dinner at which Dr. Jacoby briefed us on the *modus operandi*, we got right to work. We were still working at midnight. At 8:30 AM Monday, the scientific program in the Clinical Center began and ran, with only a brief break for lunch, until 5:00. The Panel members had dinner together and again worked until close to midnight, comparing notes on the day's presentations and hearing reports from members assigned particular topics for in-depth research. On Tuesday morning at 8:30 AM, we were back at the Clinical Center and listened to papers on the public health aspects of the problem until noon.

Then we went into Executive Session, and now we really had to get down to work, because we had to have a more or less final draft statement ready to present for review the following morning at 8:30 AM. On the very first straw vote, there was complete consensus on the first two questions: Was blood cholesterol causal? and Would reducing it help prevent heart disease? On these, the Panel voted, un-animously, yes (**Fig. 5**).

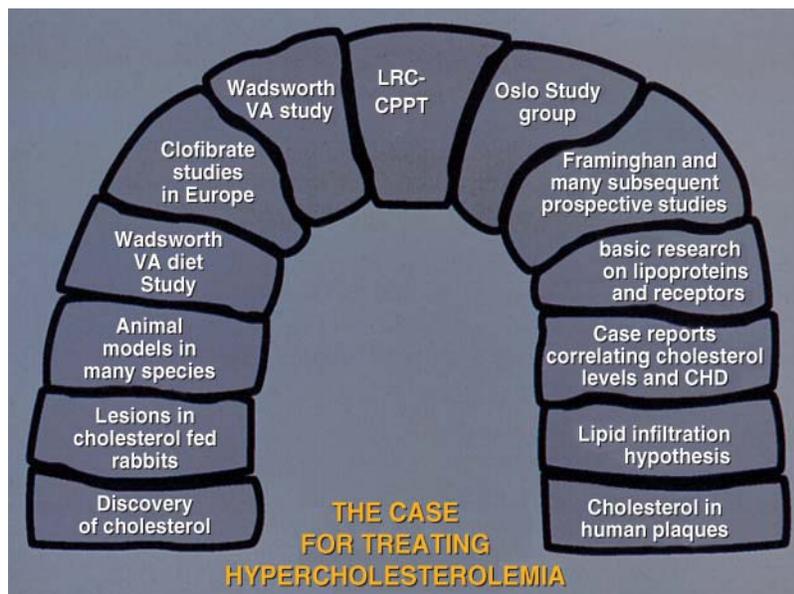


Fig. 4. A slide used in the 1984 Consensus Panel presentation to underscore the point that the Panel's conclusions were based not solely on the results of the CPPT but rather on all of the many lines of available evidence, an "arch of evidence," to which the CPPT results provided the all-important keystone.

Most of the next 11 h were devoted to animated discussion of what constitutes a significantly high level of blood cholesterol and how it should be managed. Many panelists felt that the so-called "normal" cholesterol levels in the United States were much too high and that we should set a goal of 200 mg/dl (or even less) for everyone. However, we had to be realistic. A recommendation that seemed too radical might be a turn off. Also, we wanted to keep things simple. If we set up too many categories and there were too many numbers to keep in mind, the practicing physician, somewhat skeptical to begin with, would just tune us out. Robert W. Mahley came up with a simple set of numbers that satisfied everyone. We proposed "desirable" levels of <200 for persons younger than 20 years; <220 for those 30 to 39 years; and <240 for those older than 40 years, and we proposed the same guidelines for men and women. A few years later, the National Cholesterol Education Program, discussed below, would issue more detailed guidelines but along similar lines (38). The other tough issue

was what dietary recommendations to make. After much discussion, we came up with guidelines very much like those adopted previously by the American Heart Association, namely, to exercise and reduce total calories to maintain normal body weight; decrease total calories from dietary fat to 30% (<10% from saturated fat); and reduce total daily cholesterol intake to <300 mg.

We also advised that, under the guidance of the NHLBI, there be established a national program, involving all of the major medical and public health associations, to educate both physicians and the public on the importance of controlling cholesterol levels. That program was officially launched the next year as the National Cholesterol Education Program. As discussed below, under the leadership of Dr. James I. Cleeman it has become a highly successful mechanism for providing education and guidance on management to physicians and patients alike (39, 40).

The response of the profession and of the press

The report of the Consensus Conference was published in the *Journal of the American Medical Association* and in several other major journals at the beginning of 1985. By and large, the reception was gratifyingly positive. Within a year or two, the Europeans and the Canadians had proposed cholesterol guidelines that were really quite similar, although differing slightly in cut-off points and treatment recommendations. But the Cholesterol Wars were by no means over yet.

The most widely read general scientific journal, *Science*, covered the Consensus Conference, but the published article was entitled "Heart panel's conclusions questioned." It dwelt as much or more on the points of view of a handful of vocal dissenters as on the unanimous views

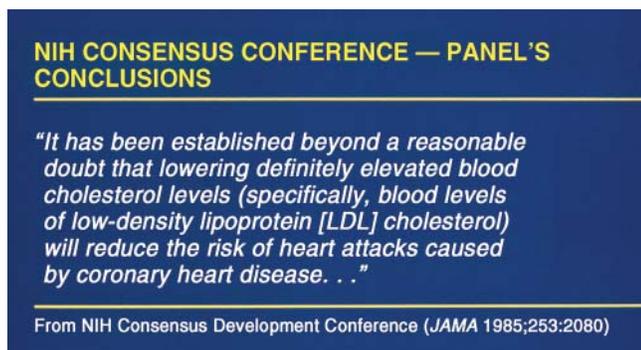


Fig. 5. The major conclusion of the 1984 Consensus Panel.

of the expert panel and the supporting views expressed by the majority of the invited participants who spoke from the floor. Did the dissenters quoted in this *Science* piece have access to different data? No. Did they have broader and deeper relevant experience? No. Did they poke holes in the rationale by which the expert panel reached its conclusions? No. Did they actually represent a larger number of professionals in the field than did the expert panel? No. It is simply that dissent is always more newsworthy than consensus. This is especially true if the dissenters are highly vocal and even more so if they claim to be exposing flaws in the establishment position. If they can in addition imply malfeasance and conspiracy, so much the better. That's news.

To be sure, science reporters are in a tough spot. In the absence of any formal polls, it is easy for convinced investigators to persuade them that their own views represent the majority position. The reporter from *Science*, Gina Kolata, was and is knowledgeable, accurate, and, justifiably, widely respected. But she was being told by several highly credentialed experts that the conclusions of the Consensus Panel were wrong. She may have assumed that she was dealing with an issue that had two sides and tried to give them equal weight. What she probably did not know is that the small group that talked with her after the conference represented a rather small minority of the experts in the field. Most of the time, reporters have no way of knowing which point of view represents the majority view. They can hardly be expected to take their own poll or contact all of the relevant experts for a head count. In this particular case, however, just such a poll had already been conducted and the results published in 1978, although it was not given much attention and the *Science* reporter was undoubtedly unaware of it. Dr. Kaare R. Norum, of the University of Oslo, conducted a survey to determine whether there was a consensus among experts on atherosclerosis with respect to the role of blood cholesterol (41). He sent a questionnaire to 211 epidemiologists, nutritionists, geneticists, and others doing research on lipids and atherosclerosis. The list included almost every prominent researcher in the field at the time. More than 90% of those contacted responded, so the results were representative. In answer to the question, "Do you think there is a connection between plasma cholesterol level and the development of coronary heart disease?," 189 of those responding said "Yes," 2 said "No," and 2 were "Uncertain." To the question, "Do you think that our knowledge about diet and coronary heart disease is sufficient to recommend a moderate change in the diet for the population in an affluent society?," 176 of those responding said "Yes," 16 said "No," and 1 was "Uncertain." Norum's paper was lost sight of. It is true that his questionnaire did not probe deeply into the many complexities of the cholesterol/heart attack problem, but it clearly showed that even 6 years before the NIH Consensus Conference, >90% of the experts in the field found the evidence linking blood cholesterol causally to heart attacks already very strong, strong enough to warrant recommendations that people should modify their diets to try and

decrease their blood cholesterol. Most recommended a decrease in saturated fat intake and a decrease in total calorie intake, exactly what the 1984 Consensus Conference recommended.

So here was an example of the fallacy of the oft-quoted but misleading aphorism that "There are two sides to every story." The aphorism implies that the two sides both have about the same validity, that experts are more or less evenly divided on the issue, and that both sides are equally persuasive.

In this case, there were indeed "two sides to the story"—cholesterol does or does not have anything to do with atherosclerosis—but the two sides were anything but equal. In Norum's survey, 189 of the experts said it does and only 2 of them said it does not. The reporter from *Science* was giving too much emphasis to the views of the <1% not yet convinced. *Science* accepted for publication a letter from me pointing out the skewed nature of the report and one from Dr. Jakoby on behalf of the Office of Applications of Medical Research, but follow-up letters are fairly ineffectual. Some damage had already been done.

A few months after the Consensus Conference, Michael F. Oliver published in *The Lancet* a piece entitled "Consensus or nonsensus conferences on coronary heart disease" (35). He wrote, "The panel of jurists...was selected to include experts who would, predictably, say...that all levels of blood cholesterol in the United States are too high and should be lowered." Oliver was, and still is, a major figure in British cardiology who had been involved in many vanguard studies relating to coronary heart disease and atherosclerosis. His opinions needed to be taken into account. So how does the bedeviled reporter know how to weigh his strongly worded dissent? In my published response to Oliver's piece in *The Lancet*, which I titled "Consensus minus one?," I gently pointed out that the panel of 14 experts reached its conclusions unanimously and that "...there were no more than a handful among some 600 conferees who appeared to disagree with the general terms of the recommendations." Oliver was himself an invited participant and duly had his say from the floor, as did two other well-known dissenters quoted in the *Science* article, Dr. Thomas Chalmers and Dr. Paul Meier.

Things got even worse. A few years after the Consensus Conference, *The Atlantic* published and featured on its cover (Fig. 6) an article by Thomas J. Moore entitled "The cholesterol myth" (37). Moore, a journalist covering science, wrote: "...the dissenters have been overwhelmed by the extravaganza put on not just by the heart institute but by a growing coalition that resembles a medical version of the military-industrial complex. This coalition includes...the 'authorities'...the heart institute [The National Heart, Lung and Blood Institute] itself...and the American Heart Association." Moore then went on to name explicitly five investigators very active in the lipid field at the time who had offered to make themselves available to answer questions about the statins, which had just been introduced by Merck for clinical use (Antonio Gotto, Scott M. Grundy, John LaRosa, Robert I. Levy, and Daniel

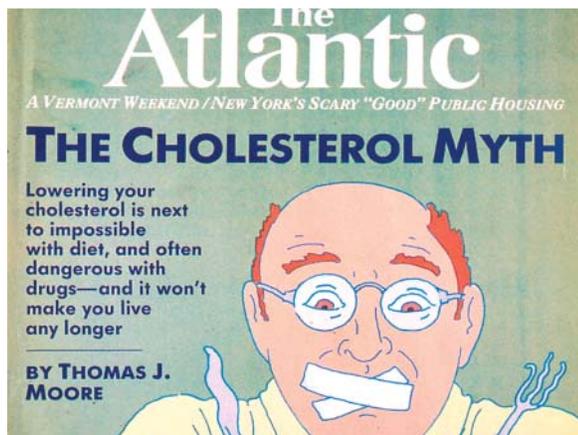


Fig. 6. Cover of *The Atlantic*, September 1989, featuring an attack by journalist Thomas J. Moore on the Consensus Conference, its members, and the proposition that decreasing high cholesterol levels would reduce cardiac morbidity and mortality. See text for details. (From *The Atlantic*, September 1989, with permission.)

Steinberg). There followed a series of short paragraphs about this “Gang of Five” (my term) and the arguably actionable conclusion that “It is likely that one reason these physicians consented to such an arrangement is that their laboratories were heavily involved in research funded by Merck.” Finally, borrowing from Marc Antony, “There is no reason to doubt the honesty, sincerity, and expertise of any of these men.” Yes, the cholesterol controversy has seen its share of vitriol.

The position of the Food and Drug Administration

The question of whether or not decreasing cholesterol levels would reduce coronary event rates was one the Food and Drug Administration (FDA) had already dealt with to some extent. For the FDA, this was a very pragmatic issue: should it approve drugs for marketing solely on the basis that they were safe and effectively decreased cholesterol levels? Or must the manufacturers first provide direct evidence that the cholesterol lowering actually reduced the frequency of clinical events?

There were good reasons for the agency to be wary about approving drugs in this category. Two of the drugs in the Coronary Drug Project, D-thyroxine and estrogenic hormone (in men), had not only failed to confer benefit but had actually increased mortality (20). Clofibrate, used in extensive clinical trials in Europe, had reduced nonfatal myocardial infarction but had proved to be toxic, increasing diseases of the gastrointestinal tract, including cancer, and marginally increasing overall mortality. Triparanol had been approved by the FDA for cholesterol lowering but proved to have serious side effects, including cataracts and hair loss, and was withdrawn from the market (42). Key personnel at Merrell were indicted by a grand jury but pleaded *nolo contendere*. A large number of lawsuits were filed, involving settlements of millions of dollars.

With this background of experience, there was understandably little enthusiasm either in the pharmaceutical industry or at the FDA for new drugs to treat hypercho-

lesterolemia. Nicotinic acid and cholestyramine were already on the market in 1984, but the package insert indications did not include cholesterol lowering. Nicotinic acid was for use as a nutritional supplement for its action as a B vitamin, and cholestyramine was to be used in the management of biliary atresia. Of course, many physicians were using them to decrease blood cholesterol levels, but they were prescribing off-label. It was not until the late 1980s that the FDA decided that the evidence linking blood cholesterol levels causatively to coronary artery disease was strong enough to justify the approval of cholesterol-lowering therapy without requiring the manufacturers to submit, at the time of application, clinical trial data demonstrating efficacy. According to Dr. Solomon Sobel, head of the Division of Metabolic and Endocrine Drugs at the time Merck’s lovastatin came up for review, the results of the Lipid Research Clinics CPPT and the conclusions of the 1984 Consensus Conference figured very large in the adoption of such a policy and smoothed the way for the later approval of the statins.

THE NATIONAL CHOLESTEROL EDUCATION PROGRAM

Armed now with the results of the CPPT and a consensus among the leaders in the field, the NIH decided to go into high gear. It accepted for the first time the need to make decreasing blood cholesterol levels a high-priority goal. Implementation would be difficult and expensive, but it would be well worth the effort and the cost. So in 1985, the NHLBI, Claude Lenfant, Director, took the lead by formulating plans for a national cooperative program to educate both health professionals and the public, the National Cholesterol Education Program (NCEP). A Coordinating Committee was established that included representatives from 24 important national health professional organizations, including the American Medical Association, the American Public Health Association, the American Heart Association, and so on. It also included representatives from 10 other federal agencies. This was going to be a full court press, and everyone was going to be on the team. James I. Cleeman was put in charge of the program and has continued to run it effectively and imaginatively to this day (39, 40).

One measure of the impact of the program is the increase in recognition by physicians of the importance of high cholesterol levels. The level of total cholesterol at which physicians would consider offering dietary advice decreased from 260–279 mg/dl in 1983 to 200–219 in 1995. Between 1986 and 1995, the percentage of physicians who rated LDL as a very important marker for heart disease increased from 34% to 75%. Of course, the increasing press and television coverage over the years and doctor-patient interactions contributed as well, but the NCEP played a key role in this sea change in “cholesterol awareness.”

Probably the most important contribution of the NCEP was to propose guidelines for diagnosis and treatment. At

22. Gould, A. L., J. E. Rossouw, N. C. Santanello, J. F. Heyse, and C. D. Furberg. 1998. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation*. **97**: 946–952.
23. Simons, L. A. 1984. The lipid hypothesis is proven. *Med. J. Aust.* **140**: 316–317.
24. Podell, R. N. 1984. Coronary disease prevention: proof of the anticholesterol pudding. *Postgrad. Med.* **75**: 193–196.
25. Oliver, M. F. 1984. Hypercholesterolaemia and coronary heart disease: an answer. *Br. Med. J. (Clin. Res. Ed.)*. **288**: 423–424.
26. Mann, G. V. 1985. Coronary heart disease—“doing the wrong thing.” *Nutr. Today*. **August/September**: 12–14.
27. Frick, M. H., O. Elo, K. Haapa, O. P. Heinonen, P. Heinsalmi, P. Helo, J. K. Huttunen, P. Kaitaniemi, P. Koskinen, V. Manninen, et al. 1987. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N. Engl. J. Med.* **317**: 1237–1245.
28. Virkkunen, M. 1979. Serum cholesterol in antisocial personality. *Neuropsychobiology*. **5**: 27–30.
29. Virkkunen, M., and H. Penttinen. 1984. Serum cholesterol in aggressive conduct disorder: a preliminary study. *Biol. Psychiatry*. **19**: 435–439.
30. Wysowski, D. K., and T. P. Gross. 1990. Deaths due to accidents and violence in two recent trials of cholesterol-lowering drugs. *Arch. Intern. Med.* **150**: 2169–2172.
31. The Scandinavian Simvastatin Survival Study. 1994. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. **344**: 1383–1389.
32. Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group. 1998. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N. Engl. J. Med.* **339**: 1349–1357.
33. MRC/BHF Heart Protection Study. 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. **360**: 7–22.
34. Nestel, P. J. 1984. Time to treat cholesterol seriously. *Aust. N. Z. J. Med.* **14**: 198–199.
35. Oliver, M. F. 1985. Consensus or nonsense conferences on coronary heart disease. *Lancet*. **1**: 1087–1089.
36. Kolata, G. 1985. Heart panel’s conclusions questioned. *Science*. **227**: 40–41.
37. Moore, T. J. 1989. The cholesterol myth. *Atlantic*. **September**: 37–70.
38. Expert Panel. 1988. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch. Intern. Med.* **148**: 36–69.
39. Cleeman, J. I., and C. Lenfant. 1998. The National Cholesterol Education Program: progress and prospects. *J. Am. Med. Assoc.* **280**: 2099–2104.
40. Cleeman, J. I. 1989. National Cholesterol Education Program. Overview and educational activities. *J. Reprod. Med.* **34**: 716–728.
41. Norum, K. R. 1978. Some present concepts concerning diet and prevention of coronary heart disease. *Nutr. Metab.* **22**: 1–7.
42. Fine, R. A. 1972. *The Great Drug Deception: The Shocking Story of MAR/29*. Stein and Day, New York.
43. Shepherd, J., S. M. Cobbe, I. Ford, C. G. Isles, A. R. Lorimer, P. W. Macfarlane, J. H. McKillop, and C. J. Packard. 1995. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N. Engl. J. Med.* **333**: 1301–1307.
44. Sacks, F. M., M. A. Pfeffer, L. A. Moye, J. L. Rouleau, J. D. Rutherford, T. G. Cole, L. Brown, J. W. Warnica, J. M. Arnold, C. C. Wun, et al. 1996. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N. Engl. J. Med.* **335**: 1001–1009.