George Lyman Duff Memorial Lecture

Cholesterol Revisited
Molecule, Medicine, and Media

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The past year has been truly extraordinary. Not only has there been astonishing medical and public health interest in cholesterol, but the term cholesterol has been brought by the media into common culture and consciousness in quite surprising ways. How did this happen? And what are its implications for science, for medicine, and for public health and policy?

This evening I will try to address some of these issues—not in a thorough and systematic way, but from the vantage point of someone who has been caught up and tossed aloft by the tidal wave of cholesterol concern, and who has been trying to remain afloat and perhaps even channel the wave in desirable directions.

When Arthur Spector invited me to give this year’s Duff Lecture, I was faced with a quandary. Previous Duff Lecturers have generally provided a scholarly and state-of-the-art review of a scientific topic that embodies their own research. In my case, however, such a review would deal with retinoids and retinoid-binding proteins and would be neither sufficiently entertaining nor really appropriate for this occasion. Accordingly, I will speak tonight more as an essayist and journalistic observer than as a scientist—and will adopt the stance of the Roman god for whom our month of January is named, by looking both backward and forward—and even at times straight ahead.

Nullius in Verba. That is the motto of the Royal Society of London, a motto that proclaims that experiments, not words, are the test of truth. An obvious concept, you say; yet not so obvious in 1662, when Charles II first chartered the Royal Society of London for Improving Natural Knowledge. Among the founders were such great scientists as Isaac Newton, Robert Boyle, and Robert Hooke, and also nonscientists such as Christopher Wren, John Locke, John Dryden, and Samuel Pepys. Their guiding philosophy was that we are “beholden to Experiments; which though they have not yet completed the discovery of the true world, they have already vanquished those wild inhabitants of the false world that us’d to astonish the minds of men.” Enlightened thinking, yes indeed—a product of the scientific revolution of the seventeenth century, a revolution that I. Bernard Cohen describes as being “in many ways... more radical and innovative than any of the political revolutions of the seventeenth century” with effects that have “proved to be more profound and lasting.”

What has this to do with cholesterol? One connection is that in modern times, the media is the message. Nullius in Verba implies that actions and programs should be based on data and stand on a floor of facts. Our risk is that, given the interest of the media and the public, programs will be launched and promoted that are not based upon solid data and facts. Perhaps this is not surprising in a society where astrology is acceptable as a help to guide decisions and behavior. As scientists, we would be wise to be alert to this risk.

The Molecule: Past History

Cholesterol, the molecule, was first identified as a specific substance roughly a century after the founding of the Royal Society. It was found that gallstones were largely soluble in organic solvents, such as alcohol or ether, and that the main component of gallstones could be obtained as waxy, white leaflets from organic solutions. In 1816, the French scientist Chevreul gave this substance its original name, cholestereine, from the Greek words, chole (bile) and stereos (solid). And after it was found to have a reactive hydroxyl group, the name was changed to cholesterol.

During the past century, research on cholesterol, the molecule, has been paralleled by that on the role of cholesterol in atherosclerosis. In the early 1900s, extensive efforts were focused on the structure of the sterol molecule. This work, successfully completed by the early 1930s in the laboratories of Wieland in Munich and of Windaus in Goettingen, was recognized by the award of the 1927 and 1928 Nobel Prizes in Chemistry to Professors Wieland and Windaus. As described by Konrad Bloch, “after decades of effort... with this achievement one of the most brilliant chapters of organic chemistry came to a close.”

At the time these structural studies were in progress, remarkable findings about atherosclerosis were also being made. In 1906 Aschoff first drew attention to the high content of cholesterol in atheromatous aortas, and in 1910 Windaus, already working on the chemistry of the molecule, showed that the cholesterol deposited in atheromatous aortas is present chiefly as cholesteryl esters. The significance of these human observations was high-
lighted by experimental work in rabbits. In 1908 Ignatowsky reported in St. Petersburg that rabbits fed on milk and egg yolk developed severe atherosclerosis. And five years later in 1913, Anitschkow and Chalatow also produced atherosclerosis by adding pure cholesterol to rabbit food.

The cholesterol saga illustrates well the important links between basic science and medicine. Many of the major molecular advances were made by men with a powerful interest in atherosclerosis and heart disease. I have already mentioned Windsa’s early work on atheromatous aortas. In the 1920s, Rudolf Schoenheimer conducted chemical studies on aortas, and found that total lipid and particularly cholesterol increased with atherosclerosis. The same Rudolf Schoenheimer subsequently left Germany to escape the Nazis and came to Columbia University, where he pioneered in the use of isotopes to study intermediary metabolism and inaugurated the modern era of biochemistry and of cholesterol research. George Popjak, who contributed so much to our understanding of cholesterol biosynthesis, began his career as a pathologist interested in experimental and in human atherosclerosis. And in the present time, the Dallas group, with their brilliant work on the low density lipoprotein (LDL) receptor, have stressed the connection between their molecular studies and our understanding of atherosclerosis and disease.

I will return later to the links between basic research and advances in medicine.

**Medicine: Past History**

Let us now turn more fully from molecule to medicine and consider the disease that we connect with cholesterol. It has been argued that the first case history of coronary heart disease (CHD) appears in the Bible in the first book of Samuel. The case is that of Naval, a heavy eater and drinker, who had come into conflict with King David. Naval’s wife, Abigail, learned of David’s intention to assail their house. The story in the Bible (as quoted) goes as follows:

And Abigail came to Naval; and behold, he held a feast in his house, like the feast of a king; and Naval’s heart was merry within him, for he was very drunken; wherefore she told him nothing, less or more, until the morning light.

But it came to pass in the morning, when the wine was gone out of Naval, and his wife had told him these things, that his heart died within him, and it became as a stone. And it came to pass about ten days after, that the Lord smote Naval, that he died.

It has been suggested that: “Naval was perhaps prone to coronary disease because of his nutritional habits; which, coupled with... anxiety of a man harbouring guilt feelings because of his ingratitude towards King David, may have been responsible for his cardiac death. In this case death overcame him after ten days of great tension, perhaps as the result of a second, and fatal, heart attack.”

The science base for the study of CHD includes the great Renaissance scholar, Leonardo da Vinci, and the pioneering work of William Harvey. Among Leonardo’s many anatomical drawings are admirable studies of the coronary vessels, with fascinating notes in mirror writing. Leonardo demonstrated for the first time the origins of the coronary vessels from the coronary sinus and explored the details of the coronary branches. Leonardo was very much interested in blood vessels and in changes produced by the aging process. His drawings are probably the first to pictorially show sclerotic vessels.

In 1628, William Harvey published his famous book, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise Concerning the Movement of the Heart and Blood in Animals). Harvey proposed and demonstrated that there was a single, closed circulatory system, an idea that represented a revolution in biology in the 17th century. *De Motu Cordis* was published in Frankfurt-on-Main in a poorly printed volume of only 72 pages with two plates, and has been said “to contain a greater amount of important material in small compass than any other medical work ever published.”

Harvey’s work led to a radical reform of biology and of the physiological basis of medicine. According to I. Bernard Cohen, this radical reform resulted in “the firm establishment of experiment and careful direct observation as the means of advancing biology and of establishing knowledge in the life sciences.” Nullius in Verba, indeed.

It was decades—in fact, centuries—after the publication of the *De Motu Cordis* before CHD was fully recognized as a clinical entity. In 1772, William Heberden reported the clinical picture of angina pectoris, and during the following hundred years, there developed the coronary theory of this disease and the early concept of atherosclerosis. The idea that coronary occlusion and myocardial infarction could be a clinical event, however, rather than one for the autopsy table, did not appear until the early 20th century.

In 1912, James Herrick authored a classic paper entitled, “Clinical Features of Sudden Obstruction of the Coronary Arteries.” This paper began as follows: “Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious accident. Several events contributed towards the prevalence of the view that this condition was almost always suddenly fatal.”

“No one at all familiar with the clinical, pathological, or experimental features of cardiac disease can question the importance of the coronaries. . . . But there are reasons for believing that even large branches of the coronary arteries may be occluded—at times totally occluded—without resulting death, at least without death in the immediate future. Even the main trunk may at times be obstructed and the patient live. It is the object of this paper to present a few facts along this line, and particularly describe some of the clinical manifestations of sudden yet not immediately fatal cases of coronary obstruction.”

And so a newly recognized clinical entity was launched, which within a few decades would become an epidemic.
Why bother with historical rambling, you might say? What has this to do with modern times? It has been said that, “Those who cannot remember the past are condemned to repeat it” (Santayana) and that “What’s past is prologue” (Shakespeare). While the past is certainly prologue, I doubt that anyone today, regardless of whether or not they had heard of Anitschkow, would think it novel to feed cholesterol and produce atherosclerosis in rabbits.

No, the value of the historical perspective and point of view is party like the value of a liberal education—it broadens perspective and philosophy and permits us to better understand how we arrived at the present and how to best engage the future. This perspective is needed today in biology, where graduate students and postdocs often seem to think that useful science began with reverse transcriptase and the genetic code. Cloning, codons, and consensus sequences constitute language, literature, and life. But shouldn’t we remember that organic chemistry does matter and that language and art can be enriched beyond bare ingredients? Campbell soup cans are not the same as the still lifes of Cezanne. The poetic prose of Marquez and Bellows, let alone Thomas Hardy and Proust, adds worlds to the language of DNA.

This summer, in Woods Hole, Massachusetts (where I am often found on the tennis court), the Marine Biological Laboratory (MBL) held its centennial celebration with a series of lectures, concerts, and other events. Centennial celebrations also occurred this year at the Pasteur Institute in France, and at our own National Institutes of Health. In fact, a profound development in science at the end of the nineteenth century was the founding of major research institutes, both within and separate from universities, and a new commitment by universities to graduate study and research. Self-trained scientists—amateurs like Faraday and Darwin—were replaced by scientists with specialized and advanced training working in institutional settings with technical support. To again quote Cohen: “The nineteenth-century image of a Charles Darwin, who could live for decades in the country outside of London... and there study and think in privacy while occasionally conducting significant experiments at miniscule cost, must seem as foreign and strange to today’s scientists as the concept of scientific research done by Martians.”

What was happening a century ago? Yes, technical discoveries were being made, but there was also a flowering of reductionist philosophy. Thus, in Woods Hole, the MBL celebration particularly honored one of its founders, Jacques Loeb. Loeb was a leader of a school of scientists that believed that biological phenomena could be explained by—could be reduced to—the principles of chemistry and physics. That’s obvious, you say. Yet not so obvious a century ago, when vitalism was a widely held philosophy, and what we would call antiscientific thinking was even more powerful than it is today. And let us not forget that antiscientific thinking, which would be hostile indeed to Jacques Loeb, is far from disappearing or unpopular today. Consider our problems with the animal rights and welfare people, the so-called right-to-life folks, the creation science movement in education, and all those other groups that distrust science and scientists and enliven the American scene. Isn’t it amazing, therefore, that the science surrounding cholesterol has been able to generate such a large and positive public impact?

**The Molecule: Recent History**

Let us now return to cholesterol, the molecule, and briefly review its history in the past half century. In the 1940s, 50s, and 60s, the pathway and details of cholesterol biosynthesis were brilliantly elucidated. In 1937, using deuterium-containing water, Rittenberg and Schoenheimer showed that newly synthesized cholesterol must have arisen from the coupling of many small molecules, and in 1942, Bloch and Rittenberg demonstrated the synthesis of cholesterol from acetate. In the years that followed, amazing surprises occurred as the biosynthetic pathway was unraveled. To quote George Popjak’s Harvey Lecture in 1970: “Who could have predicted that vinegar and mevalonic acid, both products of fermentation, squalene, discovered in shark liver oil, lanosterol, found in wool fat, and cholesterol were all linked in precursor-product relationships? Or who would have dared to imagine that squalene—chemically a rather dull and symmetrical molecule—was synthesized by unique stereospecific processes through the intermediary of an asymmetric molecule?”

The highlights of this work included the discovery of the role of mevalonic acid and the identity of the key isoprene unit and the earlier discovery of the role of squalene and its cyclization to lanosterol, in Konrad Bloch’s laboratory at Harvard, and the structural and later mechanistic studies of the pathway by Cornforth and Popjak in England. The stereospecificity of the pathway, which between 5-phosphomevalonate and squalene included 2^18, or 262,144 possibilities, was fully worked out. And as you all know, these achievements were recognized by Nobel Prize awards to Bloch in 1964, in Physiology or Medicine, and to Cornforth in 1975 in Chemistry.

In the past 15 years, research on the molecule has shifted to a different arena, with its focus on regulation and roles. In his 1928 Nobel lecture, Windaus asked, “What is the biological role of cholesterol itself?” Many experiments have been designed to answer this question. Even today, although so much is known, we still have much to learn about the biological roles of cholesterol. I will not comment here in any detail on the discovery of the LDL receptor, and the recognition of its critical roles—except to say that one of my great pleasures as Chairman of the Council on Arteriosclerosis was the opportunity to host Joe Goldstein and Mike Brown in their Duff Lecture in 1981. We expect soon to hear the full details of the regulation and role of genomic sterol response elements in the intracellular control of cholesterol homeostasis. The discovery of the LDL receptor has had a profound impact on cell biology, on clinical investigation and therapeutics, and on the field of atherosclerosis. The acclaim and publicity given to this work and to their 1985 Nobel Prize contributed keenly to the cholesterol saga of the past year.

**Medicine: Recent History**

When we turn from molecule to medicine, we are confronted with the remarkable rise and fall of ischemic
heart disease, of CHD, that has occurred in the 20th century. The description of the dramatic changes in disease rates that occurred since 1920 is complicated by several changes that were made in the classification and reporting of heart disease. The overall pattern is clearly shown, however, by the changing mortality rates for the entire category of diseases of the heart, as shown in Figure 1.

Between 1900 and 1920, the death rates attributed to diseases of the heart were relatively stable. An abrupt change came in 1920, when an upward trend that continued for 30 years was established. As pointed out by Stallones, "the abruptness of the change was accentuated by a deficit of deaths in 1919, the year that followed the excessive mortality of the influenza pandemic of that time." By the 1950s and 1960s, the mortality rate for CHD had risen so high that the preface of a monograph on Coronary Heart Disease would open with the sentence, "Coronary heart disease may well be termed 'the black plague' of the 20th century." A strong statement indeed—and one that might have gone uncontested, except for the unforeseen appearance of a viral plague in our midst in the 1980s.

In the late 1960s, a downturn began in the rates of CHD, and, in the past 20 years, CHD mortality has decreased by well over 35%. The reasons for this decline have been analyzed and discussed and really cannot be conclusively determined. It is clear that primary prevention, due to beneficial changes in risk factors in the population, has played an important role and that improved medical care has also contributed. I like to think that the black plague of the 20th century has been transformed medical practice and public health with regard to the risk factor of hypertension.

Part of the motivation for development of the NCEP was the realization that cholesterol was a risk factor whose time had come. In 1984, there had emerged a broad consensus that the evidence concerning cholesterol in the cause and prevention of CHD was so substantial that action to lower elevated levels of cholesterol should no longer be delayed. And in 1985, the Nobel Prize award gave added authority and acceptability to this approach.

In 1983, the Institute had carried out a survey of knowledge and attitudes about cholesterol in a sample of physicians and of the public. This survey showed that only 64% of the public and only 39% of the physicians recognized that lowering elevated levels of cholesterol would have a large impact on the risk and incidence of heart disease. The survey was repeated in 1986. Between 1983 and 1986, there were three major events that each generated considerable publicity about cholesterol. These were: the report of the results of the Upjohn Coronary Primary Prevention Trial (LRC CPPT) in early 1984, the cholesterol consensus development conference in December 1984, and the 1985 Nobel Prize award. As a result of this publicity, by 1986, cholesterol awareness had risen to 72% in the public and to 64% among physicians. These numbers were still sadly deficient, however, compared to the level of awareness of the importance of hypertension in cardiovascular disease, where both physicians and the public much more fully recognized that lowering elevated levels of blood pressure would have a major impact upon cardiovascular disease.

The NCEP was launched to deal with this deficit and to change awareness, practice, and behavior on the part of both physicians and the public with regard to cholesterol.

The goal of the NCEP is to reduce the prevalence of elevated blood cholesterol in the United States and thereby contribute to reducing CHD morbidity and mortality. The Program serves as a vehicle for cooperation among a broad base of interests: practitioners, public health officials, community and voluntary organizations, state and local government officials, health care administrators, and industry representatives. The program receives overall direction from a Coordinating Committee that is composed of representatives of the many nonprofit national organizations that are participating in the program, with liaison representatives from 10 government agencies.

There are two general strategies that can be used in disease prevention: the high-risk or patient-based strategy, and the public health or population-based strategy. Each of these approaches has its advantages and disad-

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Figure 1. U.S. mortality by gender for diseases of the heart (redrawn from Stallones).

Figure 1. U.S. mortality by gender for diseases of the heart (redrawn from Stallones).
vantages, and these are particularly well discussed by Geoffrey Rose in his 1985 article, "Sick Individuals and Sick Populations."  

The high-risk strategy seeks to identify persons who have high-risk levels of cholesterol and to enroll them in programs aimed at lowering their levels of cholesterol and of coronary risk. A major advantage of this approach is that the intervention is appropriate for the individual. This leads to enhanced motivation both for the subject and for the physician. This strategy does, however, also have disadvantages. Perhaps the most important is the fact that the potential benefit for the population is limited. The point is that a large number of people at small risk may give rise to more cases of disease than the smaller number who are at high risk. This limits the utility of the high-risk strategy for prevention.

The population-based strategy aims to lower the levels of cholesterol in the population at large and to shift the entire population distribution curve for cholesterol to the left. This strategy attempts to remove the underlying causes that make the disease common. As a result, the potential benefit for the population is large. However, the benefit offered to most individuals in the population is relatively small. This leads to a situation that has been called the "prevention paradox," namely that a preventive measure that brings much benefit to the population may offer but little to each participating individual. As pointed out by Rose, however, this has been a feature of several successful public health prevention programs—for example, mass immunization, the wearing of seat belts, and now the attempt to change life-style characteristics.

Fortunately, the high-risk and the population-based strategies are complementary to each other. Together they represent a coordinated strategy for reducing cholesterol levels and coronary risk.

The NCEP has been developing its program through committees called expert panels. The first panel, the Adult Treatment Panel, was convened to develop recommendations for the high-risk strategy and completed its report one year ago. A laboratory standardization panel has been dealing with the clinical chemistry issues involved in the measurements of lipids and lipoproteins. Its second report, "Recommendations for Improving Cholesterol Measurements," will soon be available. A population-based panel is currently working to prepare recommendations for the development of the population-based strategy. A fourth panel is being formed to deal with questions about the treatment of high-risk children.

The official name of the Adult Treatment Panel was the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The panel consisted of 22 members and seven ex officio members. Little did I realize, when Claude Lenfant asked me to chair this panel in early 1986, what a large impact this activity would have on my life.

The development of the report of this panel proved to be an interesting challenge. Not only did we have to reach agreement, to hammer out a consensus among the 29 members of the panel, but we had to try to satisfy, and ultimately to obtain formal voted approval from, the 24 members, representing many different kinds of constituencies, and the many liaison representatives of the Coordinating Committee. Fortunately, the panel was an outstanding one, fully equal to the task at hand, with an outstanding coordinator, James Cleeman, and by October, 1987, the final report was ready for approval.

I do not intend, this evening, to provide a summary or review of the recommendations of this report. I have done that many times, perhaps far too many times, during the past year. For you few in the audience who are not familiar with the report, however, I would like to say just a few words about the contents of the report.

As already stated, the report is concerned with the high-risk strategy, and represents a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive medical intervention. The goals of the report are 1) to establish criteria that define candidates for medical intervention and 2) to provide recommendations on how to detect, set goals for, treat, and monitor these patients over time.

In developing the report, our panel tried to follow certain basic principles. One was simplicity, to make the guidelines as simple as possible consistent with current knowledge. Another was to provide enough specific details to assist an individual physician in dealing with an individual patient.

The report deals with two basic questions: Who should be treated for high blood cholesterol? and, How should they be treated? Therefore, the report is organized into guidelines for classifying patients based on total cholesterol and on LDL cholesterol levels and guidelines for treating patients with diet or with diet and drugs.

Individuals are classified according to total cholesterol as follows: levels below 200 mg/dl are classified as desirable blood cholesterol; those of 200 to 239 mg/dl, as borderline-high cholesterol; and those 240 mg/dl and above are classified as high blood cholesterol.

A corresponding LDL classification that determines the risk status of the patient is provided. Levels of LDL cholesterol below 130 mg/dl are classified as desirable LDL cholesterol; those of 130 to 159 mg/dl, as borderline-high-risk LDL cholesterol; and those of 160 mg/dl and above, as high-risk LDL cholesterol.

Some of the major general features of the guidelines can be summarized as follows: Total blood cholesterol levels are used for initial case finding and classification. LDL cholesterol, however, is the key index for decisions about treatment. Total cholesterol is used for monitoring dietary therapy. Repeat cholesterol tests are used to confirm values before action. Cholesterol cutpoints and goals as recommended in the report are not age- or sex-specific. The presence of CHD or other major risk factors influences the treatment plan. And finally, the cutpoints for drug treatment are set so as to provide a protective barrier for the inappropriate overuse of cholesterol-lowering drugs.

The Adult Treatment Panel Report was published in the Archives of Internal Medicine in January 1988. It was subsequently also published in a more handsome and colorful format by the NHLBI.

The NCEP strategy for implementing the recommendations in the report has been to involve the many organi-
zations that participate in the cholesterol education program in the development of physician and patient educational programs and materials. It is not quite the philosophy of "let a hundred flowers blossom," but during the past year, an amazing number of programs have begun to bloom.

On October 6, 1987, the day after the formal approval and release of the Adult Treatment Panel report, the American Heart Association (AHA) launched its Physicians Cholesterol Education Program, aimed at using AHA affiliates throughout the country to teach and implement the Adult Treatment Panel guidelines. The AHA has prepared a large number of excellent and useful materials for patients, particularly about nutrition and diet, under the overall rubric of Heart Rx.

In the NHLBI the NCEP prepared a physicians' kit about cholesterol, containing a variety of informative materials for both physicians and their patients. This kit has been sent to more than 175 000 physicians throughout the country.

In addition to the AHA, many other professional organizations have developed or engaged in educational programs aimed at implementing the Adult Treatment Panel recommendations. These include the American Academy of Family Practice and organizations of cardiologists, nurses, and nutritionists. Recently, the American Medical Association has launched a major cholesterol education program.

Last week, the First National Cholesterol Conference was held in Virginia, in the Washington area. This conference demonstrated an astonishingly strong interest in the implementation of the Adult Treatment Panel guidelines on the part of practitioners, public health professionals, dietitians, and other kinds of health workers, as well. It is extremely gratifying to see that our report and recommendations are being widely accepted and adopted as useful and appropriate for good medical care. It truly seems that we are engineering a qualitative and irreversible change in medical thinking and practice concerning cholesterol.

In addition to physician education, the NCEP has also engaged in a variety of public education activities. A national campaign is underway to encourage every American adult to "know your cholesterol." This campaign is being promoted through public service announcements on radio and TV, advertisements in newspapers and magazines, posters in airports, and a number of other publications and fact sheets.

The Media

Public education has been greatly enhanced by the media—newspapers, magazines, TV, and radio—all of which have grasped with glee and gusto the concept of cholesterol as a critical public issue. This is not the first time the media has flirted with cholesterol. Four years ago, for example, there was a flurry of publicity about cholesterol after the report of the LRC CPPT, but somehow the media's interest proved fickle and was not sustained. Of course, the American public has long shown a strong interest in nutrition, but over the years, this interest has tended toward food faddism, non-science (which pronounced rapidly sounds like nonsense), and variable degrees of misinformation. Lecithin and garlic; fiber and fish oils; megadoses of vitamins A, C, and E; high protein and even high fat diets; the litany of misinformation, and sometimes dangerous misinformation at that, is long indeed.

The wave of media attention first tossed me aloft the day the Adult Treatment Panel report was officially approved and made public. The next day, newspapers throughout the country, and in fact throughout the world, carried cholesterol as front page news. In the New York Times, the report on cholesterol shared the front page with an article indicating that the nomination of Robert Bork to the Supreme Court was doomed. This same happy conjunction of topics had also been featured the evening before on the McNeil-Lehrer Newshour. And with this wide array of front page articles, the public campaign against cholesterol was firmly launched.

In the weeks that followed, to my astonishment, the media interest in cholesterol as "hot news" did not seem to slacken. Newspapers, magazines, TV, and radio all continued to carry the campaign, which was now beginning to acquire a life of its own. And, in fact, cholesterol as a media topic was showing signs of star status. Articles appeared in Time magazine, in Newsweek, and in many other major publications. Diet and heart disease became an increasingly popular topic in the media.

The element of interest was also fueled by hints that appeared in some reports of a possible commercial dark side to the cholesterol campaign. The Wall Street Journal carried articles about the billion dollar market that was being created for cholesterol-lowering drugs and hinted softly at manipulation by Merck. Advertising Age, a major publication of the advertising industry, reported that low cholesterol claims are going to be extremely hot in food advertising—a report which has been proved amply true.

In fact, throughout the entire past year, and right up to the present, media and public interest in cholesterol has continued and has been sustained at a very high level.

The media attention to diet and foods in connection with cholesterol has been astounding. Many articles have appeared this year in the New York Times. When the Surgeon General's Report on Nutrition and Health was issued in July, it received extensive front page coverage, and all of the articles showed some focus on cholesterol and heart disease.

This publicity has had a broad impact. This summer, for example, I was astonished by the intense interest and concern—often quite excessive concern—by scientists and their spouses in the Woods Hole community. Instead of books, or music, or art, or even science, my friends amazingly wanted to talk about fiber, fat, and fish oil. Fortunately, they did not persist in keeping this a burning topic of conversation for too long.

Cartoons concerning cholesterol have been carried continuously in newspapers and magazines throughout the year, so that quips on cholesterol have become quite favorite.

A surprising result of the continuing media attention is that the term, cholesterol, is taking on new meaning in common culture and consciousness. Cholesterol is become-
ing a buzzword for something to be avoided, something undesirable, perhaps even dangerous. As a consequence, the term has appeared in all sorts of surprising contexts. Earlier this year I was listening to a radio concert program, when the announcer described a new string quartet series that was coming to New York. He ended by saying, "If you want to do something really good for yourself, next to lowering your cholesterol, subscribe to this concert series." A few days later, a radio financial review made the same kind of point: investing in this fund, next to lowering your cholesterol, will be good for you. Amusing examples even found their way into the recent political campaign. In May, George Bush, in Maine, said "I'll tell you, I'm getting a little bit of a cholesterol rise. My frustration level is going up in terms of sitting around and listening to Michael Dukakis and Jesse Jackson dump all over me and the administration."32 In August, the New York Times described a jazz brunch in New Orleans as "a mix of cholesterol and music that seems to be the preferred form of entertainment at the Republican Convention."33 And finally, in November, a summary of George Bush's vital statistics on the front page of the New York Times, and of Michael Dukakis' the next day, prominently featured—you guessed it—cholesterol.34

So cholesterol has moved beyond being a lipid to being a symbol. Even Daniel Koshland, a talented editor, could not resist using this symbol in an editorial on the economic problems of our country: "Here is a nation with lots of jobs and a good standard of living, but also one with a serious economic arteriosclerosis filling up its fiscal arteries.... 'Eat dessert first, life is uncertain.' That T-shirt slogan expresses the fiscal policy of the United States at the moment. It is a prescription that can make the system fat, happy, and dangerously clogged with cholesterol."35

Finally, in August Jane Brody wrote a not unreasonable or uninformative article about sexual impotence in men that ended with the sentence, "A high-fat, high-cholesterol diet can speed the development of atherosclerosis, impairing blood flow to the penis."36 So cholesterol has moved beyond its connection to CHD, to many areas, including fiscal failure and sexual impotence.

The Cholesterol Campaign

As for myself, the tidal wave that tossed me aloft has tossed me again and again into an airplane, traveling to talk about the report's recommendations and the cholesterol campaign. Many of the members of the Adult Treatment Panel have had the same experience. It has been both exhilarating and exhausting, and I have, at times, almost wished that the cholesterol campaign would start to dwindle. I have felt like the author described by the poet W. H. Auden, in his personalized poem "On The Circuit":

Spirit is willing to repeat
Without a qualm the same old talk,
But Flesh is homesick for our snug
Apartment in New York.

The public education campaign and the high level of media attention have generated a huge groundswell of enthusiasm for public screening for cholesterol. Despite the fact that our current knowledge may not be sufficient to know how to develop truly successful public screening programs, the momentum for such programs cannot be contained.

On May 4, 1988, the Voluntary Hospitals of America, the largest chain of private not-for-profit hospitals in the country including well over 600 hospitals, carried out a one-day nationwide screening program called Count-Down USA, in which more than 400 000 American adults had their cholesterol measured. In my own medical center, a program that offered cholesterol screening to staff and students was overwhelmed by the level of interest and screened several thousand people over the course of several days. Both the NCEP and the AHA have been trying to thoroughly examine the issue of screening and to develop information and guidelines for those who wish to engage in such programs.

The public education, media attention, and screening programs move the cholesterol campaign from the high-risk strategy to the public health strategy, that is, to the population-based approach. Recommendations for a population-based approach to the problem of cholesterol and atherosclerotic heart disease are, of course, not new. In 1957, Irvine Page and colleagues published a report37 to the AHA and to the American Society for the Study of Arteriosclerosis, the society that would soon join the AHA as its Council on Arteriosclerosis. This led to formation by the AHA of an Ad Hoc Committee on Dietary Fat and Atherosclerosis, also led by Irvine Page, which issued its report in 1961.38 This report stated that "current knowledge is sufficient to warrant a general statement regarding the relation of diet to the possible prevention of atherosclerosis," and made recommendations for the public and for coronary-prone persons about calories and fat. In the years that followed, the AHA has periodically updated its recommendations in the form of reports and statements from the AHA Nutrition Committee. The most recent such update occurred in 1988.39 These recommendations have pioneered and led in the public health strategy, and yet their impact has been limited.

Now, however, we appear to be on the verge of an effective population-based approach to the issue of cholesterol that could lead to a major public health benefit. The Surgeon General's report of July 198840 aroused a great deal of interest and finally put the government clearly and squarely in the arena of urgent changes in the American diet to prevent and reduce disease. The population-based panel of the NCEP is working to generate a strong and effective report that will both contain recommendations for the public and discuss strategies for implementing these recommendations. Finally, a committee of the National Research Council—Institute of Medicine (the Committee on Diet and Health) has been working for more than two years to prepare a comprehensive and scholarly review of all of the evidence relating diet to the major chronic diseases. The report of this committee is now being finalized and is scheduled for official release in March of 1989. This report will put the prestige and authority of the National Academy of Sciences and the Institute of Medicine behind public recommendations to Americans to change their diet to promote health and...
reduce disease. The implementation of these recommenda-
tions will not be simple and will require actions on the part of many sectors of society, including the food industry, government at several levels, the advertising industry, the education field, the medical and health fields, and others as well. Another National Research Council committee is already at work on the problems of implementation of the diet—health recommendations. And so I think that we are going to see a great deal of activity and excitement in the public arena with regard to diet and disease prevention in the next two years. As an optimist, I think that the possibility for truly changing the American diet and having a major impact upon heart disease is now very real.

Lessons for the Future

So, where do we stand? What lessons can we learn that might be useful in the future?

In the final few minutes of this lecture, I’d like to comment on some lessons and issues that I find of interest and that might be worthy of more general consideration.

My first lesson is the need to continue to emphasize the vital links between basic research and advances in medicine, and the importance of maintaining and increasing our national investment in support of basic science. This is not merely providing platitudes of praise about motherhood and morality. Advances in the diagnosis, treatment, and prevention of cardiovascular disease are dependent upon advances in knowledge, and these, in turn, often come from basic, nontargeted research. Julius Comroe documented in 1976 that of 529 key articles that were essential for clinical advances in ten broad areas, 37% could be considered as basic and not clinically oriented research, and another 25% as basic but clinically oriented research. To quote Comroe on the delivery of health care, "There are two ways to improve the nation’s health: one is seeing to it that we deliver what we already have in hand, and do it fairly, evenly . . . intelligently . . .; the other is to find something better to deliver—earlier diagnosis, preventive measures, more effective treatment—and to recognize that these come through research and not through Madison Avenue slogans."41 If “the price of liberty is eternal vigilance,” then the price of biomedical excellence is to grasp every opportunity to emphasize the importance of support of basic research. The cholesterol campaign and the attendant interest of legislators, bureaucrats, and the public provides such an opportunity. To again quote Comroe: “We forget that we will never have anything better or completely new to deliver—another disease to prevent, another disorder to cure—until we discover something new, and that is what we call research.”41 This is obvious, you say—yes, but I think it bears repetition.

A second issue is the growing need for social science research that will tell us how to effectively implement programs of prevention. We want to move forward effectively, but do we really know how to do so? Activism, energy, and enthusiasm in the development of prevention and education programs are clearly not enough. There are many slogans that can be brought to bear on this issue. “Primum non nocere,” “cost-benefit analysis,” and “save the whales” are but a few. But the issue should not be one of slogans, opinions, and energy, but of information, tested techniques, and evaluation. We need to develop and establish methods and mechanisms to evaluate programs and approaches for lowering cholesterol and coronary risk. I personally think that at the present time, this issue—how to effectively implement and evaluate programs—may be the most urgent issue in the national cholesterol campaign.

A related issue is the question: How much of a change in the American diet can we really hope to achieve? There seems little doubt that major changes in diet can occur in populations, as is strikingly illustrated by studies such as the Ni-Hon-San Study42 on the effects of emigration. The issue is, how can we direct change in the way we deem desirable in our highly pluralistic and laissez-faire society? I have already mentioned that analysis and recommendations concerning implementation strategies will be forthcoming in the coming year or two, from both the Population-Based Panel of the NCEP and the Diet-Health Implementation Committee of the National Research Council. These strategies will have to go far beyond just education of the public if they are to be effective.

A fourth issue concerns the media. How can we properly enlist the media to participate in accurate and thoughtful cholesterol education efforts? We have seen how cholesterol, the molecule, has moved beyond its role in medicine to become a star symbol in the media. The possibility that this process will go too far, or has already gone too far, is very real indeed. We want the public to become aware and informed about cholesterol and diet, so as to promote changes in behavior and reductions in coronary risk. We do not want people to be misinformed about the health risks and benefits that pertain to cholesterol and diet so that they become excessively anxious about the dangers of borderline-high, or even high blood cholesterol levels or so that they have unreasonable expectations about the health benefits that will derive from a lowered cholesterol level. Media messages often tend to simplify, to exaggerate, to distort in the drive to be more lively, more exciting, or more visible. The need to optimize the role of the media in the evolving cholesterol campaign represents a major challenge.

A final lesson worth noting is that the current cholesterol campaign represents a rare concordance of interests on the part of many constituencies. The health professions, the pharmaceutical industry, government, the public—all should benefit from efforts to promote and implement the recommendations and guidelines in the Adult Treatment Panel report. Physicians will benefit because they will be providing better medical care to their patients and incidentally will have available a new and expanded market of patients for preventive medical care. The pharmaceutical industry will benefit from the greatly expanded market for cholesterol-lowering drugs that will result from even the most careful application of the guidelines on a national scale. The public will benefit from reductions in coronary risk and disease. And government will benefit from better health of its citizens and from reduced national expenditures that should result from reductions in coronary risk and disease. Sounds naive and pollyanna-ish, you say. Perhaps so, but I think the phenomenon is real.
Moreover, this concordance of interests should promote cooperation—even collaboration—on the part of these various constituencies, something that is indeed occurring in part in a quite gratifying way.

In closing, I'd like to acknowledge the pleasure I've had in playing an active role in the national cholesterol campaign. It has been a most exciting year—and a great pleasure this evening to be able to share some of my thoughts with friends and colleagues in the cholesterol and cardiovascular communities.

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