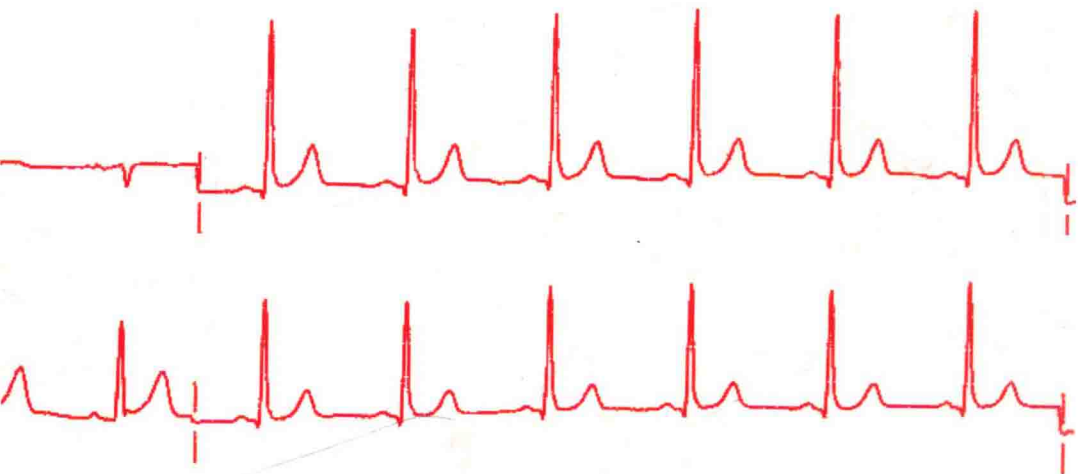


The **Cholesterol** **Wars**

The Skeptics vs. the
Preponderance of Evidence



Daniel Steinberg



THE CHOLESTEROL WARS

The Skeptics vs. the Preponderance of Evidence

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THE CHOLESTEROL WARS

To the hundreds of scientists, clinicians and associated research personnel who over many years amassed the evidence that hypercholesterolemia is a key causative factor in atherosclerosis; and to the thousands of volunteers who agreed to participate in the critically important clinical trials that closed the case, inaugurating a new era in preventive cardiology.

FOREWORD

The bravest are surely those who have the clearest vision of what is before them.

Thucydides, ~404 BC

The tradition of chronicling wars while they are being fought was initiated in the 5th century BC with the description of the Peloponnesian Wars by Thucydides, a general in the Athenian army. That noble tradition is extended in elegant fashion in this book by Daniel Steinberg, a general in the Cholesterol Wars. The Cholesterol Wars began nearly 100 years ago in Russia when a young pathologist, Nikolai Anitschkow, fed cholesterol to rabbits and produced atherosclerosis of the arteries. This experiment and subsequent epidemiologic studies triggered a passionate debate as to whether cholesterol is the root cause of human atherosclerosis, the disease process that underlies heart attacks and strokes. The stakes were high. Throughout the 20th century, while the cholesterol battles were raging, more people were dying of atherosclerosis than were killed in military combat.

Although the Cholesterol Wars are not over, major battles have been won by the anti-cholesterol forces, i.e. those who condemn cholesterol as the culprit. Like modern armies, the anti-cholesterol forces have been aided by powerful new weapons: (1) profound insights into the mechanisms by which lipoproteins such as low density lipoprotein (LDL) and high density lipoprotein (HDL) transport cholesterol in the blood; (2) unmasking of the regulatory mechanisms that control these processes; (3) molecular delineation of genetic factors that elevate blood LDL-cholesterol and accelerate atherosclerosis; and (4) development of relatively safe and effective drugs that lower LDL-cholesterol and reduce heart attacks. Steinberg replays all of these battles in succinct and compelling fashion. He names the protagonists and the antagonists. He supplies delicious quotations from skeptics of the “cholesterol hypothesis”. He quotes an eminent British epidemiologist who described English skepticism as follows: “Cholesterol

was something that Americans had; it definitely wasn't British. Anyone who talked about cholesterol was obviously suffering from American-style hypochondria." (see p. 8). The speaker was characterizing attitudes as recent as the 1990s.

While these battles were being fought, public health authorities in the U.S., U.K., and elsewhere hesitated to make the general recommendation of aggressive cholesterol lowering to society as a whole. This inexplicable delay resulted in widespread public confusion and cost many thousands of lives. For the anti-cholesterol forces, it is still too early to declare "mission accomplished". Although mortality from heart attacks and strokes has been reduced, these catastrophes are still major killers.

Where is the next battleground? We agree with Steinberg that the next battle will be fought over the issue of when to start LDL-lowering therapy. All of the epidemiologic data suggests that "the earlier the better" (see Chapter 9). This conclusion has been reinforced recently with the discovery of a common genetic trait in African-Americans that lowers blood LDL-cholesterol levels by only 28 percent throughout life, yet leads to an 88 percent reduction in coronary heart disease in the sixth and seventh decades despite contributory "risk factors" that include hypertension and diabetes. This 88 percent reduction in coronary events is much greater than the 30–40 percent reduction that is attained when LDL-cholesterol levels are lowered by diet or drugs that are started many years after the atherosclerotic process has developed.

Autopsy studies, such as those on young men who died in the Korean War, have documented that the earliest hallmarks of atherosclerosis begin before 20 years of age. While few would suggest aggressive LDL lowering for most teenagers, there must be a time between age 20 and 40 when it is appropriate to begin careful attention to plasma LDL-cholesterol in everyone. The standard intervention is a low-cholesterol, low-fat diet that is relatively rich in polyunsaturated fatty acids. When consumed faithfully over a lifetime, as it was in China and Japan before recent times, such diets lower plasma LDL-cholesterol sufficiently to reduce the incidence of heart attacks by more than 90 percent. Yet, as Steinberg suggests, it would take decades to change the dietary habits of Americans sufficiently to make such an impact. Moreover, the economic and social consequences would be great. Thus, it is likely that we will see more widespread use of LDL-lowering drugs such as statins and cholesterol absorption inhibitors. All evidence predicts that these drugs would lower markedly the heart attack burden if they were started early enough. Yet, as Steinberg documents, the remaining skeptics still challenge the wisdom of such widespread use.

When a scholarly book like this one is published, the question always arises as to who should read it. In our opinion, *The Cholesterol Wars: The Cholesterol Skeptics vs. the Preponderance of Evidence* should certainly be read by anyone who is in a position to influence public policy toward health issues. It should

also be read by all physicians who care for patients at risk for heart disease or stroke. Finally, it should be read by members of the general public who are puzzled by the conflicting claims about cholesterol that continue to be made. Armed with the facts outlined in this book, any individual will be fully equipped to stake out an informed position in the next Cholesterol War.

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PREFACE

The thesis of this book is that the importance of hypercholesterolemia in human atherosclerosis should have been and could have been appreciated decades earlier than it was. The opportunities that were missed and the findings that went unappreciated because of preconceived mindsets are reviewed and analyzed. The history of the controversy is intrinsically of interest. In addition, there may be lessons to be learned from that history that could provide guidance in dealing with controversies yet to come.

This book is largely confined to the key events that ultimately established dyslipidemia (elevated blood levels of low density lipoprotein or/and low blood levels of high density lipoprotein) as causative in atherosclerosis. Of course, many factors in addition to dyslipidemia contribute to the atherogenic process and help determine when and how aggressively it will express itself clinically. Cigarette smoking, hypertension, obesity, diabetes, and family history are among the critical ones. No attempt is made here to deal with these in any detail except as they bear on the evolution of the lipid hypothesis. That should not in any way be taken as a comment on their importance. They are also critically important. Nor does this book attempt to present a broad review of atherogenesis research or of lipid and lipoprotein research, again, except as they fed into the development and validation of the lipid hypothesis. The book is primarily an inquiry into how, after much controversy, cholesterol and lipoproteins were indicted, tried, and ultimately found guilty as major contributors to the development of the atherosclerotic lesion and its clinical consequences.

Having started my medical training in 1941 and having done research relating to atherosclerosis for more than 40 years, I have lived through the “cholesterol wars” myself – and have a few scars to show for it. In addition to carrying on my own clinical and laboratory research programs, I have always tried to do my part in national cooperative programs and policy-making committees. Specifically, the reader should know that I have been actively involved in both the research

and the public policy developments on the cholesterol front. I was chairman of the committee that designed the landmark clinical trial that, in 1984, demonstrated that lowering blood cholesterol levels with cholestyramine significantly decreased coronary heart disease risk (the Lipid Research Clinics Coronary Primary Prevention Trial) (1–3). I was also chairman of the 1984 Consensus Conference on Lowering Blood Cholesterol to Prevent Heart Attacks, sponsored by the National Institutes of Health (NIH) (4) and a member of the first Expert Panel asked by the National Cholesterol Education Program to issue guidelines for managing high blood cholesterol (5). On the positive side, this involvement means that I know first hand much of the scientific background and many of the players involved in this history. On the negative side, my close involvement with the events as they unfolded could have led to biases that help shape how I tell the history. I have tried my best to be objective but that is sometimes hard for warriors and I may not always have been successful. For errors, omissions, or imbalances that have crept in I apologize in advance.

Portions of this book first appeared in five excerpts published as invited reviews in the *Journal of Lipid Research*, a publication of the American Society for Biochemistry and Molecular Biology (6–10). The author is deeply indebted to the editors, Edward A. Dennis and Joseph L. Witztum, for inviting those reviews and to the Society for generously giving copyright permission for the inclusion of some of that material in this book.

The intended primary audience for the book is the biomedical community. However, there may be material here of interest to people in other fields. For that reason a glossary is appended that may be helpful to them.

This book might never have been written if Irvine H. Page had not suggested it to me almost 20 years ago. He wrote me a note shortly before his death in 1991, saying in essence that it was my duty “to write the history – so that people will remember the uphill battle it was to gain acceptance of the lipid hypothesis.” Page was one of the first cardiologists to recognize the plausibility of the hypothesis and to champion efforts to prove it at the clinical level (11;12). He and his long-time collaborator, Lena A. Lewis, published, in 1969, an article with the ingenuous title: “A long-time study of the blood lipids of two students of atherosclerosis” (13). In it he reveals that he himself had a total blood cholesterol over 300 mg/dl when untreated. With a diet low in saturated fat and high in polyunsaturated fat he managed to keep his cholesterol level between 230 and 270 mg/dl, which is not bad, but would hardly be considered satisfactory treatment by today’s standards. He had a strong family history of cardiovascular disease on his father’s side and, in June 1967, he had a myocardial infarction. He died 24 years later, 5 months after his 90th birthday. Whether that was because of his diet or in spite of it, we will never know. In one of his many charming discourses on the subject of atherosclerosis he acknowledged that the lipid hypothesis was at that time (late 1960s) not yet solidly proved. He went on,

however, to say that he personally was following a heart-healthy diet anyway – because he “didn’t want to be the smartest man in the cemetery.” Irv, thanks for your mandate to write the history.

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