

Thematic Reviews on the Pathogenesis of Atherosclerosis

This issue inaugurates a new Thematic Series that highlights one of the important clinical consequences of disturbances in lipid and lipoprotein metabolism, namely atherogenesis. Atherosclerosis and its complications are still the major source of morbidity and mortality in the industrialized world, and estimates have been offered that, at its present rate of growth, it will be the major cause of death from disease by the year 2020 in the entire world. Atherogenesis is a disease that, at its earliest phase, appears to be present even in fetal life, and it evolves slowly over decades, impacted by a myriad of environmental and genetic factors. Clearly, hypercholesterolemia is a dominant risk factor for this disease, and innumerable clinical trials of various hypolipidemic agents now document the efficacy of cholesterol-lowering therapy. For many years, some of us have argued that any LDL cholesterol level above ~50 mg/dl is not ideal, and that the risk for cardiovascular disease (CVD) increases proportionately as values exceed the ideal. Recent clinical trials have convincingly shown that lowering LDL cholesterol values below 100 mg/dl is desirable, and the ideal target values are being explored. Only in the past few months, the PROVE-IT trial has shown, for the first time in a high-risk population, that a target LDL cholesterol level of ~60 mg/dl is superior to 90 mg/dl, a target value that until recently had been considered to be appropriate. In the near future, we can expect further clinical trials to fully define the optimal goals for hypolipidemic therapy, both for secondary as well as primary prevention.

However, atherosclerosis is a complex and multifactorial disease, and even if one accepts the "new" dogma that any LDL value above 50 mg/dl is potentially atherogenic, it is not likely that this target will be achieved in a large percentage of patients, and, more importantly, will not be achieved in the population as a whole. Furthermore, there still remains an enormous degree of heterogeneity in disease expression among individuals with equivalent LDL values and even equivalent degrees of other known risk factors. This is emphasized by the two to three decade differences, or more, in expression of CVD that have been observed even among subjects with Homozygous Familial Hypercholesterolemia, who uniformly have exceedingly high LDL values. Even among populations treated with effective hypolipidemic agents, such as the statins, there remains a very large residual of disease activity, a point often lost sight of. Clearly, the complexities of lipid and lipoprotein metabolism, and the differing responses of vascular

wall cells to the interplay of lipoproteins and to the vast array of circulating cellular and blood elements, are enormous. Those factors that are involved in the initiation of disease, those involved in its progression and in its perpetuation and chronicity, and those that lead to radical changes in morphology that result in clinical events may in turn each have their own independent set of interacting factors. To add to the complexity, there is an enormous contribution of both environmental and genetic factors that individually and synergistically affect different aspects of the disease process, effecting both protective and proatherogenic consequences in the face of LDL values above the ideal.

In the current Thematic Series, we will begin to address a few of the current themes on which a large body of work has been developed to suggest that the particular topic plays an important role in the complexity of this disease. Over the ensuing years, we will try to cover many aspects of atherogenesis, with an emphasis on those aspects of lipid and lipoprotein metabolism that remain the preeminent focus of the *Journal of Lipid Research* (JLR).

In this initial series, we will explore a group of common themes that revolve around what might be considered to represent inflammatory aspects of atherogenesis. The initial paper in this series explores the "oxidation hypothesis," one of the most widely studied aspects of current atherogenesis research, which has made its way into the clinical arena, although early trial data provided disappointing results. This review will especially emphasize one of the dominant themes to emerge from the oxidation hypothesis, namely, the role played by a specific set of oxidized lipid moieties, oxidized phospholipids, and the role of HDL in this complex story. A subsequent thematic review will explore in depth the effects of infection and generalized inflammation on lipid and lipoprotein metabolism. That paper will provide a uniquely detailed review and a comprehensive bibliography of this timely subject. In future reviews, we will explore the role of nuclear hormone receptors on lipid and lipoprotein metabolism and their complex roles on inflammation and atherogenesis. Finally, we will explore how the use of genetic studies can help sort out the immense complexities that mediate these aspects of atherogenesis. Future series will focus on the many other biological factors that affect atherosclerosis, such as the role of immune function and the emerging evidence of the enormous contribution of adipose tissue to disturbances in lipid metabolism and inflammation.

We will shortly also inaugurate a unique and fascinating insight into the History of the Cholesterol Hypothesis, as seen from the perspective of one of the leaders in the “cholesterol wars,” who has played a pivotal role in bringing to recognition the now widely accepted notion that the “lower the cholesterol level the better.” Many of my young colleagues, both in the clinic and in the lab, do not realize and cannot imagine that our current emphasis on aggressive dietary and therapeutic programs to lower LDL cholesterol levels was a subject of deep controversy only a few decades ago. They are unaware of the intense scientific debate, and even public controversy, that ensued over the question of whether one should even lower cholesterol levels at all. This debate was marked not only by genuine scientific discourse but by personal attacks and extremism not commonly associated with what should be a scientific issue. Dr. Daniel Steinberg has a unique perspective on this controversy, from his leadership roles at both the NIH and at the University California, San Diego, where for decades he has been one of the preeminent international scientists involved in both the scientific and public aspects of this debate. Dr. Steinberg is not only a highly observant reporter, but he can tell a tale as can few others. His lectures have always been enjoyed not only for their scientific wisdom, but equally for the eloquence and humor of the presentation. He is currently engaged in writing a personal perspective of the cholesterol contro-

versy, from its origins to its current status. We are excited and privileged to have the opportunity to present some of this in serial fashion over the next few years. After reading the first chapter in this most revealing story, which will debut in a few issues, we are sure that each and every issue of the *JLR* containing one of these chapters will be eagerly awaited. We think these reviews will not only be entertaining, but, of more importance, they will sketch the birth and development of what is now recognized as one of the dominant scientific accomplishments of modern medicine, with enormous public health importance for the population as a whole. The lessons to be learned are important. A vital idea must be fought for and proven, and there will be controversy along the way. It is an important lesson for all of us in the scientific community, especially those of us interested in lipid research and its clinical applications.

We begin this new series in the current issue with a review of the current status of the relatively newly developed “oxidation hypothesis” of atherogenesis, a subject currently under considerable debate, as well it should be. The lessons to be learned from the long gestation of translating the cholesterol hypothesis from theory to practice should put into perspective what will be needed to determine the importance of this idea and others that arise.

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