

ATHERO— SCLEROSIS V

Proceedings of the
Fifth International Symposium

Edited by

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PREFACE

The objective of the program committee of the Fifth International Symposium on Atherosclerosis was to bring together experts in many disciplines to broaden the scope of the attack on this disease and to foster interaction. Our hope was that such interaction would accelerate the eradication of the disease. The symposium achieved that objective and continued the tradition of the previous symposia in providing a forum for summaries of recent research developments in the study, treatment and prevention of atherosclerosis. The leading authorities and researchers in this field and in the related areas of interest have presented the newest information, concepts and ideas that have evolved in the past three years since the previous meeting in Tokyo. The most promising fields for future investigation are clearly identified, as are the nature of the controversies that persist in some highly important aspects of treatment of this disease. The appearance of these proceedings so soon after the meeting will greatly enhance the impact of the symposium on current research in atherosclerosis.

The program committee is particularly indebted to the excellent response of the investigators for their willingness to participate in the symposium and for their successful efforts in bringing high quality to their presentations. Their cooperation in the expeditious delivery of manuscripts for this volume has been particularly gratifying. The efforts of Ms. Barbara Allen in preparing this volume bear special note. The Chairman and the General Secretary gratefully acknowledge their debt of gratitude to Ms. Jean King, whose extraordinary skill and effort provided a pleasant, superbly organized and well-managed context for this symposium.

Antonio M. Gotto, Jr.
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Louis C. Smith
General Secretary

November 23, 1979
Houston, Texas

INTRODUCTION

Baylor College of Medicine and The Methodist Hospital hosted the Fifth International Symposium on Atherosclerosis in Houston, Texas, November 6-9, 1979. The honorary co-sponsors of the Symposium were Mrs. Mary Lasker of New York and Princesse Lilian of Belgium, two distinguished supporters of biomedical research. Because of their long interest in programs for the treatment and prevention of cardiovascular disease, the Fifth International Symposium conferred distinguished service awards on Mrs. Lasker and Princesse Lilian. Distinguished service awards were also given to Dr. Michael DeBakey, President and Chancellor of Baylor College of Medicine, for his contributions to the surgical treatment of atherosclerosis; to Mr. Ted Bowen, the President of The Methodist Hospital, for his vision, foresight, and administrative leadership in providing the facilities for a comprehensive cardiovascular center; and to Professors Gotthard Schettler of Heidelberg and Yuichiro Goto of Tokyo for their long and dedicated work in the field of atherosclerosis. At the meeting, Professor Schettler announced the establishment of a new organization called the International Atherosclerosis Society. The Fifth International Symposium on Atherosclerosis was the first to be held under the auspices of the new International Atherosclerosis Society.

The Symposium demonstrated the dynamic growth of the field, the progress that has been made since the previous symposium in Tokyo, and the fact that atherosclerosis has become a remarkably interdisciplinary activity. One of the most gratifying aspects of the Symposium was the degree of interchange between basic and clinical scientists, epidemiologists, biochemists, nutritionists, cardiologists and cardiovascular surgeons.

The opening session of the Houston Symposium honored Dr. DeBakey's contributions to the surgical treatment of atherosclerosis. As it presents to the surgeon atherosclerosis may follow a number of different patterns. One is the primary distribution of the lesions, for example, whether the coronary, the carotid or the peripheral arteries are involved, or a combination thereof. Another characteristic feature is whether the disease involves primarily distal or proximal blockage. A third characteristic relates to the rate of progression of the disease: rapid, slow or intermediate. It has not yet been possible to establish correlations between several of the patterns and any known constellation of risk factors. Another type of pattern, of which the frequency is unknown, are those individuals who may have coronary artery spasm, usually superimposed on underlying coronary artery obstruction, but in some instances without significant underlying coronary atherosclerotic lesions.

A workshop was devoted to the topic of coronary bypass surgery. Both the cardiologists and cardiovascular surgeons exhibited a considerable degree of enthusiasm for the procedure. There was even some note of optimism that the procedure may prolong life. Regardless of this last point, which remains a controversial one, the overall consensus of the participants in the workshop was one of enthusiasm for coronary artery bypass surgery as a treatment for obstructive disease of the coronary arteries. The relatively new procedure of coronary angioplasty may also prove to be beneficial to patients with certain types of coronary artery obstruction. This subject was to be extensively discussed at the annual meeting of the American Heart Association and one under intensive investigation.

The question of treatment of hyperlipidemia continues to be spiced with controversy. A

number of different methods of reducing blood lipids discussed at the Symposium included diet, the subject of the second plenary session, drugs, ileal bypass surgery, portacaval shunt and plasma exchange procedures. Some preliminary evidence from human studies suggests that atherosclerosis may be reversible in man. The majority of individuals in intervention trials for relatively short periods of time will probably show failure of progression rather than clear-cut evidence of regression. What is needed is a way of achieving more than a marginal reduction of cholesterol or low density lipoproteins (LDL). For example, if it were possible to lower the cholesterol to less than about 150 mg/dl with a concomitant reduction in LDL, then extensive long-term intervention trials might not be required in order to show a clear-cut effect on morbidity and mortality. Some promising new drugs described at the Symposium include a new inhibitor of HMG CoA reductase.

A distinguished group of scientists could not agree on what information should be conveyed to the general public about diet. The fields of nutrition, platelet biochemistry, thrombosis prostaglandin chemistry, and cardiovascular disease are merging, as was illustrated by the plenary sessions on diet and on the vessel wall in which prostaglandin metabolism was discussed. In the platelet membranes from the Eskimo, an increased proportion of phospholipids containing unsaturated C-20:5 eicosapentanoic acid has been found. This most likely occurs as a consequence of ingesting the preformed fatty acids from fish in the Eskimo's diet. The Eskimo has been found to have a prolonged bleeding time. Several reviews claim that the Eskimo has a decreased incidence of coronary artery disease. Firm evidence for this latter point appears to be lacking, and it should be more intensively examined by epidemiologic studies. There is no evidence that consuming larger amounts of the C-20:3 fatty acid homo- γ -linolenic acid would increase the arachidonic acid content of platelets since administration of lipid emulsions containing homo-linolenic acid results in a replacement of arachidonic acid by the homo-linolenic acid. Thus, the role of polyunsaturated fats continues to be a controversial one. Depending upon the polyunsaturated fatty acid composition of the diet, the cholesterol and LDL concentrations may be lowered and bleeding time may be prolonged. It seems likely that the fluidity of the platelet and other cellular membranes may be altered by the specific fatty acid composition and this in turn may affect associated membrane properties.

One of the most encouraging reports at the meeting was that of a positive beneficial effect upon morbidity and mortality from treatment of mild hypertension in Australia. There continues to be much less controversy associated with efficacy of the treatment of hypertension than that of hyperlipidemia. Among the information concerning hypertension presented at the meeting was the report of a possible new marker for essential hypertension, the measurement of an abnormality in the mechanism of potassium transport across the erythrocyte. The use of drugs to affect the renin angiotensin axis also holds promise as providing new avenues for the treatment of hypertension.

The importance of cell biology in atherosclerosis was again emphasized by the presentation of important fundamental work at plenary sessions and at the workshops and oral sessions. The roles of the platelet growth factor of collagen and of glycosaminoglycans were discussed along with a number of other important topics. The study of the arterial wall has focused on the crucial cellular elements, viz., the endothelium, the smooth muscle cell and macrophage. No longer is atherosclerosis viewed as a disease of degeneration but rather one of proliferation. The role of hyperlipidemia in the proliferation of the cellular elements of the arterial wall is an important subject but remains to be defined.

A panel of expert epidemiologists, cardiologists and internists could not agree on an explanation for the declining death rate for cardiovascular disease in the United States, although there was agreement that such a decrease has occurred. The overall decline in the death rate for cardiovascular disease for the past 15 years has been approximately 30% as

compared to 17% for noncardiovascular disease. A number of potential contributing factors have been suggested, including more effective detection and treatment of hypertension; a decline in the consumption of tobacco, a decrease in the use of saturated fats with a concomitant increase in consumption of polyunsaturated or vegetable fats, an apparent decline in the concentration of serum cholesterol and a national enthusiasm for exercise. Other countries, particularly European ones, have not shown a decline in death rate, although favorable trends may now be occurring. Despite these encouraging results, cardiovascular disease remains the number one cause of death and disability in Western society, accounting for over one-half the deaths in the United States each year. Approximately one million die each year in the United States from cardiovascular disease, of which about two-thirds are from myocardial infarctions. Thus, there is an enormous challenge yet awaiting physicians and researchers in the field of atherosclerosis and the end of this problem is far from visible at the present.

The results of the World Health Organization study on clofibrate have been reported since the last symposium. These results have been variously interpreted. For those who want to interpret the study in a favorable way, the group receiving clofibrate experienced a 20% lower rate of nonfatal myocardial infarctions, which accompanied a 10% reduction in the concentration of serum cholesterol. For those who wish to interpret the study in a different light, the group taking the clofibrate had a higher mortality as compared to the placebo control group. It is hoped that the results of the Multiple Risk Factor Intervention Trial in the United States and of the Lipid Research Clinics intervention with cholestyramine will give a more clear-cut resolution of the lipid hypothesis.

Regardless of the difficulties in proving or disproving the lipid hypothesis, interest in hyperlipidemia has lead to an explosion of research and knowledge concerning the structure and metabolism of plasma lipoproteins. This subject was extensively discussed in plenary sessions, workshops and in the oral sessions of the Symposium. An awareness of the complexity of the plasma lipoproteins has developed as more knowledge has evolved. Subclasses and subgroups have been identified, some of which may have important metabolic implications. For example, do HDL₂ and HDL₃ differ in their ability to protect against atherosclerosis? A causal relationship between concentrations of HDL and coronary artery disease has not been established, although a strong negative correlation exists. Different subgroups of LDL may exist due to differences in carbohydrate composition or other chemical properties. Work presented at the Symposium showed that some patients treated with drugs such as clofibrate responded with a reduction in LDL, while others exhibited an increase. Such findings illustrate the importance of performing careful metabolic studies of lipoprotein subclasses and apoproteins. Knowledge from such studies may form the basis of clinical tests that can be applied to patients and that can provide a more precise indication of who is likely to respond to a given hypolipidemic drug.

Knowledge of the chemistry of the lipoproteins has greatly expanded with the identification of apoprotein groups extending from A through E. The primary amino acid sequence of five of the apoproteins is known. In addition to binding lipids, certain of the apoproteins have been shown to have other specific functions, for example, the activation of lecithin:cholesterol acyltransferase by apoA-I and apoC-I and lipoprotein lipase by apoC-II. ApoD, also called the thin-line peptide and apoA-III, may be identical to the cholesteryl ester transfer protein. Specific regions of the apoC-II have been identified which activate lipoprotein lipase and which are involved in lipid binding. Extensive evidence now exists to support the role of hydrophobic surfaces in the binding of apoproteins to phospholipids in the plasma lipoproteins. The specific lipid binding sites are located in certain regions of the apoprotein called amphipathic helices.

Often a great deal of valuable information concerning lipoprotein metabolism can be gained by the study of mutants, as was illustrated at the Symposium by work on abetalipop-

roteinemia, LCAT deficiency, hypobetalipoproteinemia, Tangier disease, a form of type I hyperlipoproteinemia which is due to the complete absence of apoC-II, and familial hypercholesterolemia. An outstanding example is the knowledge gained about LDL and cholesterol metabolism from the discovery of the LDL receptor; these investigators rested heavily on the use of patients with familial hypercholesterolemia, who either have a deficiency or a complete absence of the receptor. Evidence was presented at the Symposium to support the occurrence of the receptor in vivo employing chemically modified LDL. Just how much LDL under normal conditions goes through the non-LDL receptor pathway has not been established. While a deficiency of the LDL receptor can explain the elevation in levels of LDL, additional factors are required to explain why elevation of LDL produces atherosclerosis. If the receptor were working normally in the endothelial cell or smooth muscle cell, the system should be self-regulating. Evidence was reviewed that chemical modification of LDL can enhance its uptake by cells. Whether such mechanisms operate in vivo is not known.

The purpose of my summary is not to list the most important or most significant work discussed at the Symposium, but rather to give a flavor of a few of the subjects discussed in order to indicate the interdisciplinary nature of the research and the great amount of progress that has been made since the last Symposium three years ago. The Symposium highlighted the hope that this progress will one day lead to the elucidation of the basic cause or causes of atherosclerosis and will point the way towards the development of solutions for the problem.

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