Atherosclerosis and Occlusive Arterial Disease

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Abstract:

This selection of research papers, reviews, books and book chapters is considered representative of the works by the author over the years 1958-1993. Perceived important or novel research contributions have impacted an understanding of the nature of atherosclerosis and myocardial infarction, emphasizing mechanisms implicated in atherogenesis and thrombogenesis. Attention has been directed to the interactive roles of the focal hemodynamic environment, endothelial and smooth muscle cell function, blood monocyte-derived macrophages, and inflammatory cytokines/chemokines involved in intimal leukocyte recruitment. Studies have employed the classical techniques of pathology augmented by the diverse methodologies of cellular and molecular biology. An early thrust of the work, commenced in Oxford in the Department of the Regius Professor of Medicine, under the aegis of Sir George Pickering FRS, Dr. R.G. McFarlane FRS, and Dr. A.H.T. Robb-Smith has been a detailed description of the nature, extent and distribution of human atherosclerosis, and an elucidation of the pathogenesis of myocardial infarction. The Oxford Study clearly established the causal relationship between occlusive thrombosis and acute transmural (Q-wave) myocardial infarction. Related studies characterized the strong relationship among lesions in different arterial sites, the predictably focal topography of lesions, the significant role of episodes of mural thrombosis in the later stages of plaque progression, and the inflammatory component of advanced lesions as reflected by a striking adventitial lymphocytic infiltration. Work in Oxford culminated in the book "Arterial Disease" written jointly by the author and his friend and colleague, the late Prof. JRA Mitchell. Subsequent studies in Australia established that the "early" lesions of atherosclerosis are universal by the age of one year. Others described further the natural history of coronary atherosclerosis, and the clinico-pathological significance of renal artery stenosis and aneurysms of the renal artery.

In the years 1962-67, studies included the comparative arterial pathobiology of Australian reptiles and Antarctic seals, but most effort was directed to platelet biology and thrombosis. Highlights include demonstration that the methyl xanthines (phosphodiesterase inhibitors) inhibit platelet aggregation, while catecholamines markedly potentiate ADP - induced aggregation, findings which anticipated the role of cyclic AMP in platelet physiology. Other studies showed a distinct propensity to *in vitro* thrombosis in diabetics, and in post-operative and post infarction subjects emphasizing the role of hyperfibrinogenemia. Animal studies clearly established that platelet-rich artificial thrombi undergo *in vivo* changes leading to atheroma-like lesions.

During the North American years (1968 to present) considerable effort was devoted to characterization of arterial lesion-prone areas. These studies provided a rational basis for the predictably focal distribution of lesions, with emphasis on endothelial permeability and turnover, and the focal hemodynamic environment. Coupled with *in vitro* fluid mechanical studies exploring the influence of differing modalities of shear stress on endothelial cell structure and function (orientation, geometry), signal transduction, LDL-receptor function, endothelial leukocyte adhesion, and the gene expression of monocyte chemotactic protein-1 [MCP-1] and vascular cell adhesion molecule-1 [VCAM-1], we have concluded that atherosclerosis develops preferentially in areas of low hemodynamic shear stress, with a heightened expression of adhesion molecules and microdomains of reversing flow, where the residence time of cells and molecules is prolonged.

With our observation of an enhanced intimal monocyte recruitment to lesion-prone areas with a cholesterol-fat dietary challenge, thus began a major new research thrust pioneering the then unfashionable role of the monocyte-macrophage in atherogenesis. Transitional sequences between the monocyte and cholesteryl-ester rich foam cell were established in the carrageenan granuloma model. Additionally we were fortunate to describe, isolate and characterize for the first time the powerful monocyte-specific 14 KD chemoattractant synthesized by both endothelial and smooth muscle cells, the expression and synthesis of which is augmented by oxidatively modified low density lipoproteins.

Author's Statement:

This work contains no material which has been accepted for the award of any other degree or diploma to the author in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I happily give my consent to this copy of my thesis, when deposited in the University Library, being available for loan and for photocopying.

Signed,

Professor Colin John Schwartz Date 2 — IX — 94

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The author is particularly happy to recognize the collaboration of colleagues. One such colleague and friend, the late J.R.A. Mitchell, Professor of Medicine, University of Nottingham was a significant collaborator in the Oxford Study, and co-author of the book, "Arterial Disease". More recently (1977 to present) Professor Robert M. Nerem, Ph.D. has actively participated in the conceptual and ongoing development of our hemodynamics/fluid mechanics program with research arms in both the University of Houston and the Georgia Institute of Technology. This rewarding collaboration has made substantial contributions to the field of cardiovascular hemodynamics and the pathogenesis of thrombo-atherosclerosis.

Another active collaborator was the late Professor James C. Paterson of London, Ontario. During a sabbatical year in the author's laboratory in Australia Dr. Paterson and the author undertook studies on the development of atherosclerosis in infants and children. They also established that intramural hemorrhage does not ante-date the development of lesions, thus negating the long-time hypothesis of intramural hemorrhage as an initiating event in atherogenesis.

Finally, the author wishes to acknowledge a number of fellows, students and graduate students who have worked under his guidance over the years, together with some younger faculty who have also been valuable members of his research team.

These include Dr. Raelene Kinlough, Professor Neville G. Ardlie, Dr. Ian H. Craig, Dr. B. Schultz, Dr. Bernard Caplan, Dr. John B. Somer, Dr. Peter Gillies, Dr. Frank P. Bell, Professor Ross G. Gerrity, Dr. Ian Adamson, Professor K. Prathap, Dr. A. Jankus, Dr. Ellen Edwards, Dr. J. Jauchem, Associate Professor E.A. Sprague, Dr. M. Rozek, Dr. A.J. Cayatte, Dr. S. Logan, Dr. B. Steinbach, Dr. R. Delgado, and Dr. J. Kerbacher. Collaborating faculty include Dr. A.J. Valente and Dr. Jim L. Kelley.

The estimated percentage contribution of the author (CJS) to publications involving any of the above is shown in parenthesis [ ].

Preface and Author's Annotations:

The author is greatly honored to have this opportunity to submit his selected published works to the University of Adelaide, his alma mater, for the Degree of Doctor of Science in the Faculty of Science. As indicated in the Abstract, his research has focused to a very great degree on the etiology, and pathogenesis of atherosclerosis and occlusive arterial disease.

It would appear that this three volume submission requires no specific explanatory comments. Estimating the author's contribution to each of the publications was a difficult task, and has been purposefully conservative, not fully reflecting his intellectual and conceptual input into the planning and conduct of studies by his young fellows, students, and junior colleagues.

To make this submission somewhat more manageable, all material has been bound as a three volume set, Volume I, containing research manuscripts and reviews, Volume II, copies of the book "Arterial Disease" and Volume III, a selection of book chapters, together with originals of the book, "New Horizons in Coronary Heart Disease". Wherever possible originals have been incorporated in the submission, except where size and or discoloration due to aging have precluded this.

The author's assembly of this collection of published works was made possible only with the help of his secretary, Ms. Anna Juiel, and the staffs of the University of Texas Library, and print-shop. Their help is most gratefully acknowledged.

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ARTERIAL DISEASE

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TO OUR WIVES
MURIEL and JENNY

FOREWORD

The subject of this book is an important one for three reasons. First, many people, particularly men, die in middle age after the abrupt onset of pain in the chest and with manifestations before and after death suggesting infarction of the heart. Second, the cause of this disease is not understood, and therefore no preventive measures can be undertaken. Finally, a vast number of man-hours of scientific research, and a corresponding amount of wealth is being consumed in trying to answer this riddle. Unfortunately, the elementary facts concerning the disease in man are by no means clearly established. The critical onlooker may therefore be forgiven if he is a little doubtful whether some of this effort will have great relevance to the human problem just outlined.

It was because of this important consideration that Mitchell and Schwartz undertook the work that is set out in the first part of this book. I myself am delighted with this work for several reasons. It represents the joint effort of a physician and a pathologist to illuminate what happens during life by what can be seen after death, an effort that is nowadays too rare. They have compared the changes found in the coronary arteries with those in other arteries of comparable size and in the aorta. They have used the best methods yet described. They have avoided unnecessary and unverified assumptions. They have used the same methods to investigate patients dying with clinical or post-mortem evidence of infarction of the heart, and an unselected sample of those dying in hospital in the same city. Thus although this is not the first study of this subject it is in many ways the most complete. The story seems to be this.

The immediate cause of infarction of the heart is in most cases, though possibly not in all, a thrombus occluding a branch of a coronary artery, particularly the left anterior descending. The thrombus has a characteristic structure—clumps of platelets fringed with leucocytes and interlaced with a fibrin meshwork which often contains red cells or the ghosts of red cells. As the thrombus ages the nuclei disappear, and it becomes more uniform in composition. Later it becomes organized and recanalized. The longer the interval between the clinical attack and death, the less likely is there to be a fresh thrombus and the more likely is there to be a characteristic plaque of intimal thickening producing coronary stenosis. A unitary view

would imply that most stenosing plaques in coronary arteries represent the remnants of past thrombi of similar composition. An extrapolation of this hypothesis would be that most stenosing intimal plaques that occur in other arteries arise similarly.

A working hypothesis of the nature of this disease is thus that it is a disease in which leucocyte-platelet-fibrin thrombi occur episodically in arteries, especially at certain sites. These become organized and are incorporated into the intima as raised plaques. The media atrophies and the adventitia becomes vascular and infiltrated with cells. In this stage the disease is symptomless. Eventually a thrombus occludes a coronary artery, and the well known syndrome occurs which may or may not be fatal. This hypothesis resembles that of Rokitansky and Duguid, but differs in stressing that arterial thrombi contain platelets and leucocytes as well as fibrin. This is no more than a working hypothesis, but is as well substantiated as any other. If it is correct then the platelet, much neglected by current research projects, would seem to occupy a key position.

Finally, may I record my pleasure in being asked to write a foreword. As I have tried to indicate, this is careful, methodical work on an important subject which comes to a relatively novel, and I think probably correct, view of the nature of the disease. It is beautifully illustrated and presents new knowledge against a background of the old. It should make a substantial contribution to the advancement of knowledge in an important and hitherto poorly understood field.

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Some of our material has already appeared in scientific journals, and we are grateful to the following for permission to reproduce photographs, diagrams and data:

Figures 2.23, and 2.25, and the data on adventitial cellular infiltration—the Editor of *Circulation*, by permission of the American Heart Association.

Figures 3.1 to 4, 3.10 to 13 and the line diagrams in that chapter—the Editor, *Circulation Research*, by permission of the American Heart Association.

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We are also grateful for permission to use material which did not form part of our own survey, and we are indebted to Dr J.R.Casley-Smith of Adelaide for the electron micrographs which appear as Figures 14.3 and 14.4; to Professor R.C.Buck and the Editor of the *British Journal of Experimental Pathology* for Figures 14.5 and 14.6, and to Doctor A.J. Honour for Figures 15.7 and 15.8.

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