PATHOLOGY OF ATHEROSCLEROSIS

Neville Woolf, PhD, MB ChB, MMedPath, FRCPath

PATHOLOGY OF ATHEROSCLEROSIS

Neville Woolf, PhD, MB ChB, MMedPath, FRCPath

Bland-Sutton Professor of Histopathology,
Middlesex Hospital Medical School, London
Honorary Consultant Pathologist,
Middlesex Hospital, London

Butterworth Scientific
London Boston Durban Singapore Sydney Toronto Wellington

First published, 1982

British Library Cataloguing in Publication Data

Woolf, Neviille
Pathology of atherosclerosis.–
(Postgraduate pathology series)
1. Atherosclerosis
I. Title II. Series
616.1'36 RC692

ISBN 0-407-00125-5

Photoset by Butterworths Litho Preparation Department
Printed and bound in England by Butler & Tanner Ltd, London and Frome.

Foreword

Previous volumes in this Postgraduate Pathology Series have dealt with the pathological features, including pathogenesis and functional changes, of diseases affecting specific organs or parts of organs. In the first volume a single disease entity (ischaemic heart disease) formed the subject matter; in the second and third volumes all the disease processes affecting the kidney and the heart valves respectively were covered. The fourth volume covered the histopathology of that most frequently biopsied tissue of all – the endometrium – in health and disease, while the fifth volume reverted to the earlier pattern of encompassing the complexities of a single type of heart disease (congenital malformations).

The present volume sets a new pattern by dealing with a single 'disease', and one which, by virtue of its involvement of the arterial system, is the pathological basis for several of the most important killing diseases as well as for less common clinical syndromes affecting the nervous system, eyes, and gastrointestinal tract. Indeed, hardly any tissue or organ of the body can be regarded as immune from the risk of damage due to ischaemia which is basically the result of atherosclerosis.

Whether atherosclerosis is a disease in its own right is a semantic argument that I would not care to enter into here: however, the fact that it is a progressive arterial lesion that forms the original trigger for an enormous range of 'diseases' in other organs cannot be doubted. It follows, therefore, that the pathogenesis of atherosclerosis is a matter of outstanding importance to all concerned with the promotion of health, and certainly every clinician should keep in touch with the progress that is slowly being made in the understanding of how atherosclerosis develops and how its development may be modified. Professor Neville Woolf's experience more than qualifies him to accept the task of surveying the present state of research on this outstandingly important facet of pathology.

Sir Theo Crawford

Preface

Unlike other volumes in the Postgraduate Pathology series, this one will do little or nothing to improve the diagnostic expertise of the trainee pathologists for whom it has been written.

I do not believe, however, that the devotion of a whole volume to this single pathological lesion requires any apology since atherosclerosis constitutes the basis for a variety of extremely common clinical syndromes that have a potentially lethal or crippling course.

The proper study of atherosclerosis involves disciplines as disparate as biochemistry, morbid anatomy, cell biology and epidemiology and I have tried to convey some idea of how a multi-disciplinary approach has improved our understanding of the nature of atherosclerosis, though it must be emphasized that this understanding is still very far from being complete.

The literature in this field grows apace and it would have been impossible in a book of this size to provide an exhaustive bibliography. I have not attempted to do so but trust that the references are sufficient in number and range to provide a useful guide for those who seek to read further.

Neville Woolf

Acknowledgements

I am grateful to the editors and publishers of *Haemostasis and Thrombosis* (edited by A.L. Bloom and D.P. Thomas, published by Churchill Livingstone) for permission to use the text of a chapter written for their book substantially unchanged in this work (Chapter 10).

I am also deeply grateful for permission to reproduce the following illustrations.

By courtesy of Professor M.J. Davies and Blackwell Scientific Publishers: *Figures 2.9, 2.10, 4.5, 4.11, 4.17, 6.1, 6.3, 9.7, 10.2, 10.3, 10.4, and 10.5.*

By courtesy of Professor Henry C. McGill, editor of *The Geographic Pathology of Atherosclerosis* and its publishers, The Williams and Wilkins Company of Baltimore: *Figures 7.1, 8.1, 8.2, 8.3, 8.4a and b, 8.5, 8.6, 8.7, 8.8, 8.9, 9.3 and 9.4, and Tables 5.2 and 7.3.*

By courtesy of Professor Margot Roach and the editor of *Atherosclerosis*: *Figures 9.5a and b, 9.6a and b.*

By courtesy of Dr Charles Levene and the editor of the *Journal of Pathology*: *Figure 2.7.*

By courtesy of the editor of the *Journal of Pathology*: *Figures 4.23, 4.24, 10.7, 10.10, 10.14, 10.15b, 10.16, and 10.17.*

It is a pleasure to acknowledge the advice I have received from Dr T. Powell of the Department of Physics as Applied to Medicine at the Middlesex Hospital School in relation to aspects of haemodynamic factors and atherosclerosis, and the invaluable help I have received in the preparation of illustrations from my colleagues, Peter Rowles, Niall Carey, Steve Bottoms, Mike Pittilo, and Ray Phillips.

My sincere thanks go also to my secretaries Mrs B. Dickson, Mrs L. Webster, and Mrs M. Green, who have coped with the onerous task of typing the manuscript.

Neville Woolf

Contents

1

Introduction

What is atherosclerosis?

'"When I use a word" remarked Humpty-Dumpty rather scornfully, "it means just what I choose it to mean: neither more nor less."' (Dodgson, 1872).

Atherosclerosis is one of the topics in pathology which seems fated to evoke prolonged, heated and often sterile controversy. This has extended even to its existence as a nosologic entity since an eminent authority (Pickering, 1963) attacked the propriety and usefulness (on both semantic and scientific grounds) of the term atherosclerosis, which he translates perfectly correctly as 'porridge-like hardness'.

In the study of atherosclerosis, as indeed in the study of all disease, the aim of the pathologist should be to delineate as accurately as possible not only the characteristic lesions but also the pathogenetic steps that constitute their base. However, our knowledge of the processes involved in atherogenesis is still inchoate and the relevance and relative importance of the various mechanisms, which have been canvassed as playing a role in the initiation and progression of atherosclerotic lesions, are still largly unknown. For this reason current definitions of atherosclerosis tend, for the most part, to be expressed in terms of descriptive morphology despite the obvious limitations inherent in such an approach.

On this basis Crawford (1960) has defined atherosclerosis as 'the widely prevalent arterial lesion characterized by patchy thickening of the intima, the thickenings comprising accumulations of fat and layers of collagen-like fibres both being present in widely varying proportions'. This straightforward morphological definition has the virtue, in addition to its succinctness, of emphasizing certain absolutely fundamental features of the general pathology of atherosclerosis. These are the focal distribution of the lesions; the predominant though not exclusive intimal manifestations; and the

complex, indeed heterogeneous, nature of the plaque constituents. Adams (1964) has adopted a somewhat different approach and has attempted in a rather general way to define atherosclerosis in terms of the basic pathological processes that are expressed in the lesions. His description is of 'a multifocal proliferative and degenerative condition that affects the lumen, intima and inner part of the media both of large elastic arteries and certain muscular arteries in the senescent individual. The proliferative feature of the disease is essentially an organizing or sclerotic reaction of tissues in the tunica intima, while the degenerative element is manifested by lipid accumulation, by fragmentation of connective tissues, by calcification and by ischaemic necrosis of the centre of the lesions'.

Both these definitions are essentially helpful. Not so, in my view, is that of the World Health Organization in its *Technical Bulletin* of 1958. This begs the whole question of the pathogenesis of atherosclerosis and seeks to protect every flank by offering a definition of atherosclerosis as 'a variable combination of changes of the intima of arteries consisting of focal accumulations of lipids, complex carbohydrates, blood and blood products, fibrous deposits and calcium deposits associated with medial changes'.

As we shall see in this brief review of the pathological basis of the largest single cause of death in the Western world, the key expressions of the processes concerned in atherogenesis are as follows:

1. Proliferation of smooth-muscle cells within the arterial intima and elaboration of extracellular connective tissue elements such as collagen and elastin by those cells.
2. Accumulation of intracellular and extracellular lipid, most of which appears to be derived from the plasma.

On these twin foundations, which may well be causally linked, occur later events in the natural history of the plaque. These include phenomena such as death of intimal smooth-muscle cells, hyalinization of intimal connective tissue, calcification, necrosis and softening of the plaque base which may ultimately lead to ulceration and last, but by no means least, mural or occlusive thrombosis.

AN HISTORICAL NOTE

Despite its comparatively short existence as a nosologic entity (Marchand coined the term atherosclerosis in 1904), the process does not appear to belong to our time alone. In 1909 Shattock described plaque-like lesions in the arteries of the mummy of an eighteenth dynasty pharaoh – Menephthah. He was, allegedly, the pharaoh of the Exodus and the existence of the mummy suggests that his death did not come about by drowning in the Red Sea after all. Marc-Armand Ruffer (1911), who was for some time associated with the Medical School in Cairo, had the opportunity of dissecting several mummies and often saw calcified lesions in the aorta, external carotid, brachial, femoral and posterior peroneal arteries. At least some of the lesions showed features that justify their being regarded as atherosclerotic.

As far as medical literature is concerned, there is no clear account of atherosclerosis and its clinical associations much before the beginning of the eighteenth century although Fallopius (1575), whose name is much better known for other reasons, described 'degeneration of arteries into bone'; and William Cowper (quoted by Long, 1967), who died during the reign of Anne, percipiently noted that 'the passage of blood is impeded in thickened arteries'. A striking picture of an aorta severely affected by atherosclerosis appears in a posthumous edition of J. J. Wepfer's *Observationes Medico-Practicae de Affectibus Capitis Internis et Externis* (1727) and is reproduced in Florey's *General Pathology* (French, 1958). The diseased vessel – which is described as containing 'bone-like plaques throughout' and having 'its internal coat ruptured, lacerated and rotten' – was derived from the necropsy performed on the author himself, who had succumbed in 1695, 32 years prior to the publication of his work. Fortunately, prepublication delays of this order must now be rare and there seems little, if any, call nowadays for such close identification of an author and his work.

Johan Friedrich Crell (1740; quoted by Long, 1967) emphasized the pultaceous or 'atheromatous' elements in some arterial lesions although he did not use the term atheroma. He held the view that the basal pool in atherosclerotic plaques was akin to pus and represented the end point of an inflammatory process. Albrecht von Haller (1755; quoted by Long, 1967) made similar observations, and it is to him that the credit must go for applying the term 'atheroma' to the arterial lesions. This was a new use of an existing word rather than the coining of a new one, since 'atheroma' appears in ancient Greek medical literature as a term descriptive of any cystic space or sac containing a gruel-like material (Mitchell and Schwartz, 1965). Descriptions of coronary artery lesions encountered at necropsy on patients who had exhibited clinical features referable to the heart occur in the writings of Senac (1749) and Morgagni (1761) [both quoted by Morgan (1956)]. Senac, one of the court physicians of Louis XV, described thickened and hardened coronary arteries in a monk who had been subject to 'palpitations'. He compared the affected vessels to 'branches of coral', a felicity of expression for which one would search in vain in a necropsy protocol of the present day. Morgagni in his *De Sedibus et Causis Morborum* described the clinical course of and necropsy findings in a Venetian woman whose symptoms would today be interpreted as indicative of myocardial ischaemia by any first-year clinical student. The coronary arteries were recorded as showing hardening and early 'bone formation' and similar features were noted in the aorta.

The credit, however, for first divining a direct causal relationship between lesions in the coronary arteries and the symptoms of myocardial ischaemia is usually given to Edward Jenner (Herrick, 1942; Morgan, 1956). Heberden had described angina pectoris as a clinical entity in 1768 and 2 years later Jenner wrote to him putting forward his views on the correlation between anginal symptoms and coronary artery disease. The writing of this letter was prompted by the illness of Jenner's mentor, John Hunter, who had begun to have attacks of severe precordial pain often precipitated by attendance at hospital committees (Home, 1794). A short time before, Jenner had noted the presence of coronary artery stenosis in

two patients who had died with clinical histories suggestive of angina and he considered that the symptoms were due to impairment of normal coronary circulation. In view of Hunter's clinical state Jenner sought Heberden's advice as to whether this hypothesis should be communicated to Hunter himself. In the event the letter was never sent and was many years later found among Jenner's papers. When Hunter died in 1793 his coronary arteries were found to be severely diseased and his aorta was described in the following terms: 'The internal membrane of this part had entirely lost the natural polish and was studded over with opaque white spots raised higher than the general surface'.

Further contributors to the British literature (Hodgson, 1815; Baillie, 1793) make it clear that by the reign of William IV an association between lesions in the coronary arteries and at least one of the classic syndromes of myocardial underperfusion was well recognized. Although clearly valid, this appreciation was based on very crude morphological observations. In the 100 years that followed these observations gave way to the scrupulous and detailed studies of the great German school of pathology in which we can descry the birth of a number of apparently conflicting theories as to the origin and progression of atherosclerosis. In one form or another some of them are with us still.

Von Rokitansky and the thrombogenic theory

A relatively early and important contribution to our ideas of pathogenesis came from Carl von Rokitansky, who in 1844 outlined his concept of the nature of what we now call atherosclerosis. His views on atherogenesis are explicit in the very title of the relevant chapter in his *Handbook of Pathological Anatomy*, i.e. 'Excessive Deposition of an Inner Vascular Membrane'. In the introduction Rokitansky stated that '. . . this deposition is by far the most frequent disease of arteries and embodies the foundation of aneurysm formation and of many spontaneous [arterial] obliterations . . . It consists of excessive building up and deposition of an external vascular membrane from the blood mass'. He mentioned that 'the deposit is an endogenous product derived from the blood, and, for the most part, from the fibrin of arterial blood,' and regarded the underlying cause of this fibrinoid encrustation as being some form of 'blood crasis'. He envisaged the mural deposits as increasing in thickness 'by the addition of new strata' and described them as undergoing atheromatous transformation which could be followed by 'ossification'. In such atheromatous lesions he described 'pultaceous softening associated with fatty globules, cholesterin crystals and calcium salts' and stated that such softened plaques were likely to rupture through the force of the blood, a process which was likely to be followed by the formation of fresh 'fibrinous vegetation on the surface'.

Rudolf Virchow and the 'imbibition' theory

Rokitansky's main thesis that there was deposition of some blood constituents on the luminal surface of the arterial wall during the formation and growth of atheromatous plaques was severely criticized by Virchow in

1853. His chief objection, as also that of Risse (1853), was that the material that Rokitansky had described was clearly subendothelial in position and this could not be derived from any surface encrustation. We shall, in a later section of this book, examine the question of arterial mural thrombosis in some detail, but whatever the contribution of mural thrombosis to atherogenesis may or may not be, it is now obvious from many experimental studies that this caveat at least was not securely founded. However, backed by Virchow's enormous and well-deserved prestige, it served to bring von Rokitansky's hypothesis into long-lasting disfavour.

Virchow considered that the early lesions of atherosclerosis were based on a 'loosening' of the connective tissue ground substance of the intima as a result of 'imbibition' of constituents of the passing blood. This was followed within a short time by an almost neoplastic proliferation of connective tissue cells and an increase in connective tissue ground substance and only then did 'degenerative' changes supervene. These consisted essentially of a 'fatty metamorphosis' of intimal connective tissue cells and an associated softening of the intimal connective tissue matrix. In due time these processes led to localized thickenings which were prone to erosion as a result of the interaction of continued plaque softening and 'alteration of the surface by the passing current of blood'. We see from this that the keystone of Virchow's concept of atherogenesis was that all the structural changes were initiated by an invading stream of plasma or some moiety of the plasma. This is the origin of the so-called 'infiltrative' theory of atherosclerosis which certainly, in so far as lipid accumulation is concerned, appears even now to have much truth in it.

Primary medial changes as a factor in atherogenesis

The basic ideas embodied in the writings of Virchow and his adherents for the most part went unchallenged, but a notable dissenter was Thoma (1883). Thoma drew attention to the thinning which we see so often in the media underlying atherosclerotic plaques and suggested that the primary fault was localized weakness of the media and that the aneurysmal dilatation consequent on this evoked a secondary and compensatory connective tissue proliferation in the overlying intima. Similar views were expressed by Adami and Nicholls (1909). In a study of aortic and iliac artery plaques after fixation at a pressure equal to the recorded systolic blood pressure of the patients, Crawford and Levene (1953) confirmed that fact that medial thinning of some degree is an almost constant accompaniment of the atherosclerotic plaque. In their preparations the plaques, instead of bulging into the lumen, were more or less flush with the surrounding intimal surface. While these data are certainly valid, there are mechanisms other than primary defects in the media which would account for them as we shall see later from the results of certain experimental studies relating to the natural history of experimental mural thrombosis.

LIPIDS AND ATHEROSCLEROSIS

It seems right to conclude this brief sketch of some of the landmarks in early studies of atherosclerosis by referring to two observations which have

had a profound effect on research and thinking in the field of atherogenesis. One was the finding by Vogel in 1847 that atherosclerotic plaques contained relatively large amounts of cholesterol. The other, which came 66 years later, was the production by Anitschkow and Chalatow (1913) of fatty lesions in the rabbit aorta by feeding these animals a diet rich in egg yolk. This association thus adumbrated – between plaque lipids, plasma lipids and diet – has been a dominating factor in much of the research in the field of atherosclerosis and its clinical complications that has been undertaken in the last 65 years and must be considered in some detail in later chapters.

References

ADAMI, J.G. and NICHOLLS, A.G. (1909). *The Principles of Pathology, Vol. 2*, p. 182.

ADAMS, C.W.M. (1964). Arteriosclerosis in man, other mammals and birds. *Biological Reviews*, **39,** 372–423.

ANITSCHKOW, N. and CHALATOW, S. (1913). Über experimentelle Cholesterinsteatose und ihre Bedeutung fur die Enstehung einiger pathologische Prozesse. *Centralblatt fur Allgemeine Pathologie*, **24,** 1.

BAILLIE, M. (1973). *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*.

CRAWFORD, T. (1960). Some aspects of the pathology of atherosclerosis. *Proceedings of the Royal Society of Medicine*, **53,** 9–12.

CRAWFORD, T. and LEVENE, C.I. (1953). Medial thinning in atheroma. *Journal of Pathology and Bacteriology*, **66,** 19–23.

CRELL, J.F. (1740). De arteria coronaria instar essis indurata. Cited by E. Long. In *Atherosclerosis* (1953). Ed. by E.V. Cowdry. New York; MacMillan.

COWPER, W. (approx. 1700). Development of our knowledge of atherosclerosis. Cited by E. Long. In *Cowdry's Arteriosclerosis* (1967). Ed. by H.T. Blumenthal, pp. 5–20. Springfield; Charles C. Thomas.

FALLOPIUS, G. (1575). Lectiones de partibus similaribus humani corporis. Cited by E. Long. In *Cowdry's Arteriosclerosis* (1967). Ed. by H.T. Blumenthal, pp. 5–20. Springfield; Charles C. Thomas.

FRENCH, J.E. (1958). In *General Pathology*. Ed. by H.W. Florey, pp. 351–377. London, Lloyd-Luke.

HERRICK, J. (1912). Clinical features of sudden obstruction of the coronary arteries. *Journal of the American Medical Association*, **59,** 2015–2020.

HERRICK, J. (1942). *A Short History of Cardiology*. Springfield; Charles C. Thomas.

HODGSON, J. (1815). *Treatise on the Diseases of Arteries and Veins*.

HOME, E. (1794). A short account of the life of the author. Cited by R.H. Major (1939). In *John Hunter's Treatise on the Blood, Inflammation and Gunshot Wounds*.

JENNER, E. (1778). Letter to Heberden. In *Dr Jenner of Berkely*. Ed. by D. Fisk (1959), p. 68. London; Heinemann.

MARCHAND, F. (1904). Über Arteriosklerose. *Verhandlung der Kongres für innere Medizin*, **21,** 23–59.

MORGAGNI, G.B. (1761). *De Sedibus et Causis Morborum pis Anatomen Indigatis*.

MORGAN, A.D. (1956). *The Pathogenesis of Coronary Occlusion*. Oxford; Blackwell.

PICKERING, G. (1963). Arteriosclerosis and atherosclerosis. *American Journal of Medicine*, **34,** 7–18.

RISSE, A. (1853). In *Arteriosclerosis* (1933). Ed. by E.V. Cowdry. New York; MacMillan.

ROKITANSKY, C. (1844). In *Handbuch der PathologischenAnatomie, Vol. 2*. Vienna; Braunmuller and Seidel.

RUFFER, M.A. (1911). On arterial lesions found in Egyptian mummies. *Journal of Pathology and Bacteriology*, **15,** 453–462.

SENAC, J.B. (1749). Traite de la Structure du Coeur de son Action et de ses Maladies. Cited by A.D. Morgan (1956). In *The Pathogenesis of Coronary Occlusion*. Oxford; Blackwell.

SHATTOCK, S.G. (1909). A report upon the pathological condition of the aorta of King Menephthah, traditionally regarded as the Pharoah of the Exodus. *Proceedings of the Royal Society of Medicine, Pathological Section*, **2,** 122–127.

THOMA, R. (1883). Über die Abhangigkeit des Bindergewebsneubildung in der Arterienintima von der mechanischen Bedingungendes Blutumlaufs. *Virchow's Archiv*, **104,** 209.
VIRCHOW, R. (1856). *Phlogose und Thrombose im Gefass-System. Gesammelte Abhandlungen zur wissenschaftlichen Medizin*, p. 458. Frankfurt; Meidinger.
VOGEL, J. (1847). *The Pathological Anatomy of the Human Body*. Cited by T. Crawford (1955). Philadelphia; Lean and Blanchard.
VON HALLER, A. (1755). Opuscula pathologica. *Observatio*, **L1**.