MEDICINE IN OLD AGE

ARTERIAL DISEASE IN THE ELDERLY

Edited by
R.W. Stout

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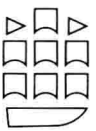

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Arterial Disease in the Elderly

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Introduction

To a great extent the medicine of today and tomorrow is the medicine of old age. In every hospital in the Western World old patients predominate. In the past it was too readily assumed that either the medicine of old age was confined to degenerative disease and was uninfluenced by diagnosis and treatment; or that it was identical with the medicine of young and middle age and required no special study. Neither view is correct. It is now becoming clear that the diseases which strike old people, the symptoms and the signs which are induced, and the response to treatment are distinctive. Years of growth, maturation and decline alter the response of the host to disease and to its management in ways which require special study. As this fact has been grasped medical science and research-minded clinicians have embarked on the study of the diseases of late life and have documented their characteristic features. Progress has been slow, partly because of an initial lack of sense of urgency, and difficulty in attracting research workers and funds; partly because of the complexities of defining normal values in old age and of attributing deviations from the normal to any one cause. Methodological and statistical problems have compounded the difficulties. But over the years there has been a very real and impressive growth of knowledge of the medicine of late life.

Some years ago the idea was conceived of collecting this new knowledge, system by stystem, in a series of volumes to be entitled 'Medicine in Old Age'. These books were addressed to physicians in all Western countries and in all medical disciplines who dealt with elderly patients. The contributors included physiologists, pathologists, epidemiologists and community physicians, as well as general internal physicians, geriatricians, psychiatrists and specialists in the various systems of the body. The response accorded to the first few volumes in the series was most encouraging, and the publishers are continuing and expanding the series.

This enterprise is supervised by an Editorial board composed of practising clinicians and academics on both sides of the Atlantic. The Board selects the topics and appoints the guest editors for each volume and has been fortunate in its choice as editors of leaders in each field. These have been able in turn to attract contributions of high merit from many countries, thus putting into the hands of the reader a series of highly authoritative volumes. These bring together

a wealth of knowledge and the best of modern practice in the care of elderly patients, retaining the critical spirit in the evaluation of the data which is characteristic of medicine in all age groups. The volumes are intended to stand mid-way between the immediacy of the scientific journal and urbanity of the standard text book, combining freshness with authority. It is hoped that the profession will find them of value.

Birmingham, 1984 Bernard Isaacs

Preface

The state of the arterial system is a major determinant of health, particularly in old age. Ischaemic heart disease, cerebrovascular disease and arterial disease in the lower limbs inflict a massive toll of disease, disability and death causing pain and distress to patients and their families, and consume a large proportion of the health budget.

This book discusses two important topics related to arterial disease. The first section deals with atherosclerosis, the predominant cause of arterial insufficiency in adults. After a description of the pathogenesis of the atheromatous lesion, the relationship of atherosclerosis to ageing is discussed. The following chapters describe three major risk factors for atherosclerosis and how they relate to ageing. In the last chapter of the section, Dr Hazzard tackles the difficult and controversial topic of prevention of atherosclerotic cardiovascular disease.

Hypertension is one of the major risk factors for cardiovascular disease. It is the only 'intrinsic' risk factor for which there is good evidence of beneficial effects of therapeutic intervention. Although the question as to whether treatment of hypertension is indicated in old age must remain unanswered at present, a review of the current state of knowlede of hypertension is appropriate in a book devoted to medicine in old age. Dr Atkinson discusses modern views on the pathogenesis of hypertension and his chapter is followed by a description by Dr Miall of the epidemiology of hypertension in the elderly. The remaining three chapters cover practical aspects of managing the elderly patient with hypertension — the comprehensive assessment of the patient, the choice of drugs, and the question of whether treatment is necessary.

The aim of this book is to present the current state of knowledge of two common and important conditions. It is hoped that the book will interest doctors who treat older patients and that it may stimulate some to try to answer many of the questions that are raised.

Belfast, 1984 R.W. Stout

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Atherosclerosis

INTRODUCTION

Atherosclerosis with its complications of ischaemic heart disease, stroke and peripheral arterial disease is by far the most important disease in the developed part of the world. It is the commonest cause of death in adults and is also a major cause of disability. It affects not only life expectancy but also the quality of life. For example, in 1977 atherosclerosis caused 873 000 deaths in the United States, almost half of all deaths in that country and in the same year cost an estimated $39 billion in health expenditure and lost productivity (Arteriosclerosis, 1981).

A considerable amount of research effort has been put into atherosclerosis, and our understanding of the disease has increased in the last decade. These achievements and the problems that remain to be solved have been summarised in a recent report from a working group on arteriosclerosis of the National Heart Lung and Blood Institute of the National Institutes of Health in the United States (Arteriosclerosis, 1981).

Atherosclerosis is a universal disease. It appears to start in adolescence and quite advanced disease has been found in young men killed in war or as a result of accidents (Enos et al, 1953). Although the disease progresses for many years, it does not become clinically apparent until blood flow through an affected artery is impeded. It is of course impossible to examine the progression of human atherosclerosis except by complicated and invasive means, and our knowledge of the natural history of the disease is therefore incomplete.

Atheromatous lesions are usually classified as fatty streaks, fibrous plaques and complicated lesions. It is assumed that the lesions progress through these stages. Although there is evidence that fatty streaks may progress to become fibrous plaques (Pearson et al, 1980), it seems that not all fatty streaks will eventually become complicated lesions. It is also likely that different factors play a part at different stages of the disease and that the advanced complicated lesion is the final common pathway for a variety of different aetiological and pathological influences.

As atherosclerosis is universal after middle age, it may be conveniently regarded as a condition closely related to the ageing process but which may be

modified by environmental and perhaps genetic factors. Thus rather than considering cause or prevention of atherosclerosis, it would be more accurate to consider factors which accelerate or delay the condition. The final step that leads to a reduction in blood flow through the atheromatous vessel is usually a thrombus on the atheromatous plaque. The cause of this thrombosis is unknown — it may be related to changes in the blood or changes in the fibrous plaque itself.

RISK FACTORS

Epidemiological studies have introduced the concept of risk factors for atherosclerosis. Risk factors are characteristics which identify individuals or groups of people who are at risk of developing early or premature ischaemic vascular disease. Risk does not necessarily imply causation. Risk factors may be associated with other factors which may be involved in causation, they may be markers of a genetic or other predisposition to the disease, they may be secondary to the disease or an early feature of the disease. The risk factors which have been identified are shown in Table 1.1. Combinations of risk factors are often present in the same individual. In these circumstances the risk of developing atherosclerosis is greater than the combined effect of single risk factors.

Table 1.1 Risk factors for atherosclerosis (from Arteriosclerosis, 1981)

Hypercholesterolaemia
Hypertension
Cigarette smoking
Diabetes mellitus
Obesity
Familial and genetic influences
Exercise
Behaviour patterns
Age
Sex

THE NORMAL ARTERY

The arterial wall is conventionally divided into three layers: the intima, media and adventitia. The adventitia consists of adipose and connective tissue, and its function is to relate the vessel to the surrounding tissues. It appears to play no part in the development of atherosclerosis, which is a disease of the intima and the inner media. The media consists of smooth muscle cells concentrically and longitudinally arranged. The media is the main structural support for the artery and also provides the artery with its contractile properties. The intima lines the luminal surface of the artery. It consists of a single layer of epithelial-like cells, the endothelium and a layer of connective tissue. The connective tissue contains a small number of smooth

muscle cells which tend to increase in number as the artery ages. The intima is bounded by the internal elastic lamina, a distinct fenestrated structure.

Endothelial cells have at least three functions (Gimbrone, 1979) (Table 1.2). They act as a blood compatible container allowing the free flow of blood and preventing clotting within the vessel. This is accomplished by both the physical characteristics of the endothelial cells and by the synthesis and secretion of a potent platelet anti-aggregatory agent, prostacyclin. Endothelial cells also act as a selective permeability barrier allowing entry into the inner parts of the artery of selective plasma constituents and excluding others. This is an active process requiring energy. Endothelial cells synthesise, metabolise and secrete a number of important substances. Factors influencing proliferation of endothelial cells are shown in Table 1.3.

Table 1.2 Functions of endothelial cells (from Stout, 1982)

1. Blood compatible container
2. Selective permeability barrier
3. Synthetic/metabolic/secretory tissue
   - angiotensin-converting enzyme
   - factor VIII
   - plasminogen activator
   - von Willebrand factor
   - prostacyclin
   - thromboxane
   - fibronectin
   - collagen (type IV)
   - α-2-macroglobulin
   - lipoprotein lipase
   - hormone receptors
     - adrenergic
     - insulin
     - oestrogen
     - thrombin
4. Binding and internalisation of lipoproteins

Table 1.3 Factors affecting proliferation of endothelial cells (from Stout, 1982)

1. Serum
2. Platelet factor (inhibits)
3. Cyclic AMP (inhibits)
4. Glucose (inhibits)
5. Cell and tissue derived growth factors

Arterial smooth muscle cells also have a variety of functions (Chamley-Campbell et al, 1979) (Table 1.4). As well as providing the main structural support and contractile properties of the artery, they also have major synthetic functions. As smooth muscle is the only cell type in the arterial media, these cells are responsible for the synthesis of all the constituents of the arterial wall, including its connective tissue. Smooth muscle cells are also capable of endocytosis of foreign material and lipoproteins. Evidence has

Table 1.4 Function of arterial smooth muscle cells (from Stout, 1982)

1. Structural support
2. Contractile responses
3. Synthetic/metabolic/secretory tissue
   - actin
   - myosin
   - collagen
   - elastin
   - microfibrillar proteins
   - proteoglycans
   - lipids
4. Endocytosis

recently been presented that arterial smooth muscle cells can exist in one of two forms, a contractile form or a synthetic form, and that proliferation is only possible in the synthetic form (Chamley-Campbell et al, 1979). Under certain cultural conditions, smooth muscle cells can be observed to change from one form to another (phenotypic modulation) (Chamley-Campbell & Campbell, 1981). Factors influencing the proliferation of arterial smooth muscle cells are shown in Table 1.5.

Table 1.5 Factors affecting the proliferation of arterial smooth muscle cells (from Stout, 1982)

1. Serum
2. Hyperlipidaemic serum and lipoproteins
3. Diabetic serum
4. Growth hormone
5. Insulin
6. Platelet factor
7. Prostaglandins (inhibit)
8. Cyclic AMP (inhibits)

A major development in atherosclerosis research has been the description of ways of growing both endothelial and smooth muscle cells in culture. Endothelial cells of human origin can be conveniently grown from umbilical vein or artery (Jaffe et al, 1973; Gimbrone et al, 1974) and of animal origin from appropriate vessels (Schwartz et al, 1981). Human arterial smooth muscle cells have been grown from small pieces of arterial tissue obtained at surgery (Bierman & Albers, 1975) and they may also be cultured from primates and other animals (Ross, 1971). Cell culture allows investigation of the biology of arterial cells, and their ability to react to external stimuli can be studied under carefully controlled laboratory conditions. Caution must be exercised in the interpretation of results from cell culture experiments, as the environmental conditions are different from those which occur *in vivo*. Nevertheless, cell culture experiments in the last decade have provided a considerable amount of information on possible mechanisms in the development of atherosclerosis.

THE ATHEROSCLEROTIC LESION

The earliest identifiable change in the development of the atherosclerotic lesion is an accumulation of smooth muscle cells in the arterial intima (Fig. 1.1). These cells may result from replication of cells already in the intima or may come from proliferation and migration of smooth muscle cells from the media. In more advanced stages of the disease the smooth cells are seen to contain lipid, and later extracellular lipid is found. As this process continues, extracellular connective tissue is formed. Eventually calcification, haemorrhage, ulceration and superimposed thrombosis, the characteristics of the complicated lesion, occur. The characteristic cell of the advanced atherosclerotic lesion is the lipid engorged foam cell. The exact origin of foam cells is uncertain, but they may originate from smooth muscle cells which have become laden with lipid or from circulating monocyte-macrophages (Ross, 1981).

While the different stages of the lesion can be identified and it is assumed that lesions progress from one stage to the next, the fundamental basis of the

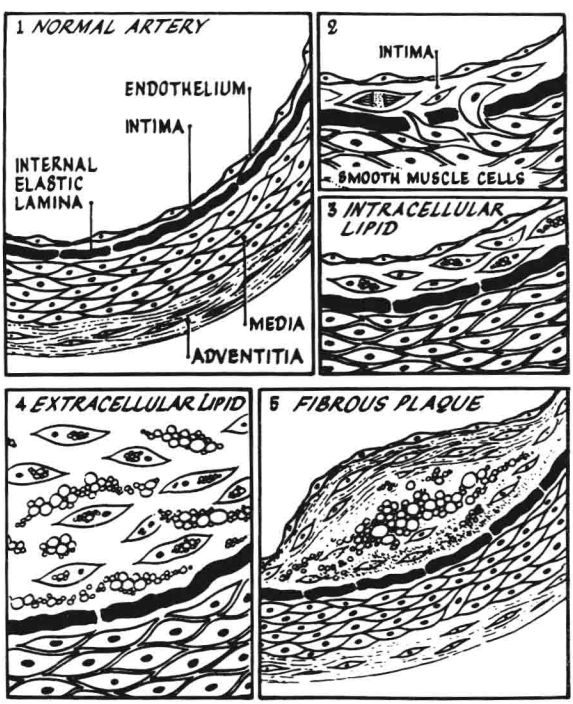

Fig. 1.1 The development of the atherosclerotic plaque. The normal artery (1) consists of an epithelial-like endothelium, the media consisting of smooth muscle cells and the connective tissue adventitia. An early change in atherogenesis (2) is an accumulation of smooth muscle cells in the intima. These cells become filled with lipid (3) which also accumulates extracellularly (4). The complicated lesion (5) also contains fibrous tissue, calcification and superimposed thrombus. (From Stout, Bierman & Brunzell, 1975 by kind permission of MTP Press.)

development of atherosclerosis is less clear. Theories on the pathogenesis of atherosclerosis have been proposed for many years (Haust & More, 1971). These theories have obtained varying degrees of experimental support and some have lapsed to reappear later in slightly altered forms. Early theories include the thrombogenic theory which suggested that lesions develop from thrombus deposited on the arterial wall and incorporated into the artery; the inflammatory theory which proposed that the lesion is an inflammatory response to degeneration of the arterial wall; the lipid theory which suggested that the major cause of the lesion was infiltration of circulating lipids, particularly cholesterol, into the arterial wall; and the insudation theory which proposed that an early change is accumulation of serous fluid derived from the blood. The detailed cytological and biochemical studies that have been carried out in the last decade have resulted in a number of new theories or modifications to the older theories (Table 1.6). These theories are not mutually exclusive and, while each has experimental support, none can be regarded as conclusive.

Table 1.6 Theories of the cause of atherosclerosis

Response to injury
Monoclonal
Lysosomal
Clonal senescence

The response to injury hypothesis

The response to injury hypothesis has recently been revived, having originally been suggested by Virchow (Ross, 1981). The theory suggests that the earliest stage in the development of the lesion is an injury to the integrity of the endothelial barrier. This results in a sequence of events leading eventually to the atherosclerotic lesion. These are:

1. Altered endothelial integrity or endothelial injury
2. Intimal smooth muscle cell proliferation
3. Synthesis and deposition by the smooth muscle cells of connective tissue matrix proteins including collagen, elastic fibres and proteoglycans
4. Accumulation of lipids within the proliferating smooth muscle cells and macrophages as well as in the newly formed connective matrix

Endothelial cell injury may result from mechanical stresses including for example, hypertension, chemical agents and toxins, immunological stimuli and viruses. The initial effect of endothelial injury is exposure to the circulation of sub-endothelial connective tissue. Endothelial collagen reacts particularly strongly with platelets which adhere to the intima and aggregate on its surface. The platelets release a potent mitogen, the platelet-derived growth factor which acts on smooth muscle cells to start a cycle of proliferation. Other substances in the plasma, including hormones such as