Clinical Hypertension

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Preface

There is little doubt that high blood pressure is one of the major sources of chronic ill-health and premature death in modern society. Although the concept of the 'disease' of hypertension has been thoroughly demolished by Pickering, scientific study of high blood pressure and its management has proved extraordinarily fruitful since the last war. The aim of the present work is to transmit this information to post-graduate doctors in a simple and concise fashion. It is also hoped that the interested undergraduate who wishes to study an important topic in depth will derive benefit from this book.

Hypertension does not readily fit into one of the accepted 'subspecialties' of medicine: it does not lie snugly in a specific area in the way in which glomerulonephritis or disseminated sclerosis fit into the subspecialties of nephrology or neurology. Rather hypertension lies astride several areas. Relevant research has involved the skills of the cardiologist, the nephrologist, the endocrinologist, the metabolic physician, and the epidemiologist. This is no disadvantage: nature has long recognized that cross-fertilization produces the strongest stock. This may not continue to be the case. The need to regulate training in medicine is putting an end to free movement between specialties. The physician of the future, with his 'training' behind him, his certificate in nephrology, cardiology or endocrinology duly stamped, will be in a weak position to pass a critical judgement over several disciplines. It is to be hoped that the present work to a small degree will help to set back the clock in this respect at least, and that practising specialists in several fields as well as doctors studying for higher qualifications will find new and relevant information.

I have attempted to cover the major facts relevant to hypertension, to describe briefly the areas of discussion and debate and, where possible, to give a balanced judgement. Rather than break up the text with a large number of references, I have included a reading list of reviews at the end of each chapter, from which primary sources can be identified. Exceptionally, I have provided references in the text to original work where specific experiments or points of view seemed to demand that this be done.

In the first six chapters, I have summarized the physiological background to blood pressure control and described the changes which occur as a result of elevated blood pressure and the abnormalities which

will produce such an elevation. The remainder of the book presents the clinical features of hypertension and its management. I have sought to emphasize important clinical lessons with figures illustrating features of particular cases. In a few instances, I have used original data from groups of patients to stress a particular point.

Two areas, (surgical and obstetric aspects of hypertension) could not satisfactorily be classified under the headings used elsewhere and, in order to avoid scattering references to these important topics throughout the text, I have discussed them separately in a final chapter.

I am grateful to my wife and my secretaries, Miss Anne Taylor and Mrs Val Crozier, for typing the manuscript, to Dr Derek James for the X-rays, to the Department of Medical Illustration at Leicester Royal Infirmary and to the Wellcome Trustees for permission to publish the portrait of Stephen Hales.

The financial generosity of CIBA laboratories made it possible to include the colour plate of fundal changes.

Contents

CHAPTER ONE

Introduction

Whilst the unpleasant consequences of high blood pressure (hypertension) have been recognized from the earliest times, the recognition of high blood pressure demanded the means to measure it. This was first achieved in horses by Stephen Hales (1733) who measured the height of a column of blood in a vertical tube inserted into an artery (Fig. 1.1). Richard Bright (1836) made the next major stride forward when he

Fig. 1.1 Stephen Hales, an eighteenth century clergyman and a pioneer of experimental physiology.

described cardiac hypertrophy in glomerulonephritis and postulated that this was secondary to an increase in renal vascular resistance produced by distorted blood vessels. Sir Clifford Allbutt in 1896 also made a fundamental advance when he recognized the distinction between hypertension due to renal disease and hypertension in which no evidence of renal disease could be discovered (essential hypertension). Thus, the recognition of renal hypertension preceded that of essential hypertension by many years, although the latter is by far the more common. It is, perhaps, not too fanciful to recognize in this historical sequence a pattern which has been repeated in the twentieth century, when renal mechanisms of hypertension have attracted an interest out of all proportion to their clinical importance.

At the turn of the 20th century, two observations of critical importance were made. Tigerstedt and Bergman (1898) isolated a pressor substance from the renal cortex, to which they gave the name renin. Ambard and Beaujard (1904) studied hypertensive patients and observed that a positive chloride balance was associated with a rise in blood pressure and *vice versa*. Accordingly, they ascribed a role to the chloride ion. Their interest in chloride was of course due to the fact that the chemical assay of chloride was simple, whilst the assay of sodium was exceedingly difficult at the time. As technology improved, emphasis was shifted to the sodium ion, although this trend reflects sophistication of laboratory method more than biological insight. It is undeniable that 'salt' can cause hypertension in some clinical states (such as end-stage renal disease). It is uncertain whether salt is a factor in causing more common forms of hypertension, although such a view has its persuasive advocates.

Both the study of renin and of the role of salt in hypertension fell into abeyance until it became possible to establish reproducible hypertension in animals. Goldblatt achieved this in 1934 by constriction of the renal artery of dogs. A second major tool was placed in the hands of medical researchers with the development of dialysis in the management of chronic renal failure: this enabled the study of changes in electrolyte and fluid balance to be carried out in the presence and in the absence of the kidneys and a more precise understanding of the role of the kidneys was thereby achieved. The difficulty with both the experimental model of hypertension devised by Goldblatt and his colleagues and the clinical model studied by nephrologists is that the mechanism of hypertension may well be different in the most common form of hypertension in man – essential hypertension. Thus, whilst it is probably valid to extrapolate some of the effects of hypertension from experimental models to man, it is much more difficult to use animal models to define the cause of hypertension in man. To apply knowledge culled from animal experiments to the elucidation of the pathogenesis of essential

hypertension demands the demonstration that the mechanism is the same in the two cases. If there was convincing evidence of that one would not need the animal model. The most that can be done with experimental models is to demonstrate that, in certain situations, some biological systems give rise to sustained blood pressure elevation. One then needs to examine the various forms of clinical hypertension to establish whether any of these systems are likely to be responsible, bearing in mind that there are major species differences in the ease with which one particular physiological abnormality (renal ischaemia for instance) can cause hypertension in animals.

Another revolution in understanding hypertension was achieved with the development of potent drug treatment, beginning with the ganglion-blocking agents which came into clinical use in the early 1950s. Since then the benefits of effective drug therapy have been amply demonstrated in moderate and severe hypertension, although the need for therapy in milder hypertension is still debatable. Before modern drugs were available, the only effective way of securing a sustained fall in blood pressure was the use of a strict salt-free diet (Kempner rice-fruit diet) which was intolerable for most patients over any substantial length of time. Apart from this, the treatment regimes advocated for hypertension before modern drugs came into use were uniformly ineffective. Nevertheless a wide variety of medical and even surgical procedures were authoritatively advocated (see, for instance Halls Dally's book *High Blood Pressure*, 1926) – a powerful testimony to the placebo effect in the management of hypertension.

While the past 25 years have seen the development of more potent drugs with progressively less unpleasant side-effects, selection of drug treatment for hypertension in man remains quite empirical i.e. a drug is chosen because it is the most effective drug for lowering blood pressure and is tolerated by the patient. A particular drug is not used because it enjoys a specific locus of action which is relevant to the pathogenesis of the hypertension: indeed, in some cases, the specific site of action is unknown. The treatment of hypertension therefore differs from, say the treatment of an infection when selection of an appropriate antibiotic is determined after analysis of the characteristics of the infecting agent. Attempts to achieve a similar degree of matching in anti-hypertensive therapy have not been convincing. The precise clinical consequences of long-term therapy with different drug regimes are also largely uncharted. Thus, whilst understanding has progressed enormously, the mechanism(s) of essential hypertension and the relative merits of long-term treatment using different drugs with different sites of action are still largely unknown.

In addition, the scientific analysis of yield in terms of patient benefit is still in its infancy. Thus, only recently has attention been directed

towards the *net* value of diagnosing the comparatively rare case of renal hypertension, or of attempting to detect and treat all hypertensive subjects within the population. Science has all to often been identified with the excessive use of laboratory investigations: scientific method should correctly be applied to the improvement of health at every level of care. This should include the actual balancing of harm and benefit and the assessment of priorities and relative needs, as well as the development of new laboratory techniques. It is to be hoped that the next 20 years will resolve some of these problems.

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CHAPTER TWO

Blood pressure control

SYSTOLIC AND DIASTOLIC PRESSURE

The pressure of blood within the circulation is created by the contraction of the heart expelling blood against vascular resistance. Flow is therefore pulsatile with a peak (systolic pressure) being achieved with each contraction of the left ventricle. Since systole occupies only about 0.3 s of each 0.8 s cardiac cycle, the *mean* pressure of the circulation over a period of time is not the mid-point between systole and diastole but a value closer to the diastolic pressure (conventionally taken as a third of the difference between systolic and diastolic pressures added to the diastolic pressure).

Fundamentally, there are therefore two components which create the pressure of fluid within a vessel – the force propelling the fluid and the resistance to flow. In the simple physical system in which fluid moves along a tube as a result of applied pressure, this relationship is expressed by Poiseuille's formula.

$$Q = \frac{\pi r^4 (P_1 - P_2)}{8L\eta}$$

Where Q is the volume of fluid moving in unit time, r the radius of the vessel, P_1—P_2 the pressure difference across it, L the length of the tube and η the viscosity of the fluid. It is of note that Poiseuille, a clinician, made his observations as a result of his interest in blood flow (his other major contribution to medicine was his construction of the mercury manometer). Whilst the same fundamental factors determine blood flow resulting from the pulsatile contraction of the heart, the circulation is enormously more complex than simple models would suggest. The relevant factors can best be considered by following blood flow down the arterial tree.

Aorta and large arteries (Windkessel vessels)

The walls of these vessels are composed of elastic tissue, collagen and smooth muscle. The elastic tissue gives distensibility to the vessel wall, whilst collagen prevents over-distension and smooth muscle contraction changes the degree of distensibility. Contraction of the heart in systole expels blood into these vessels, which therefore distend. After

systole has finished the elastic pressure exerted by the vessel wall forces blood down the arterial tree since blood cannot reflux back through the closed aortic valve. Pulsatile expulsion of blood from the heart is therefore converted into a more continuous flow through the distal arterial bed ('damping' of pulsations, Fig. 2.1).

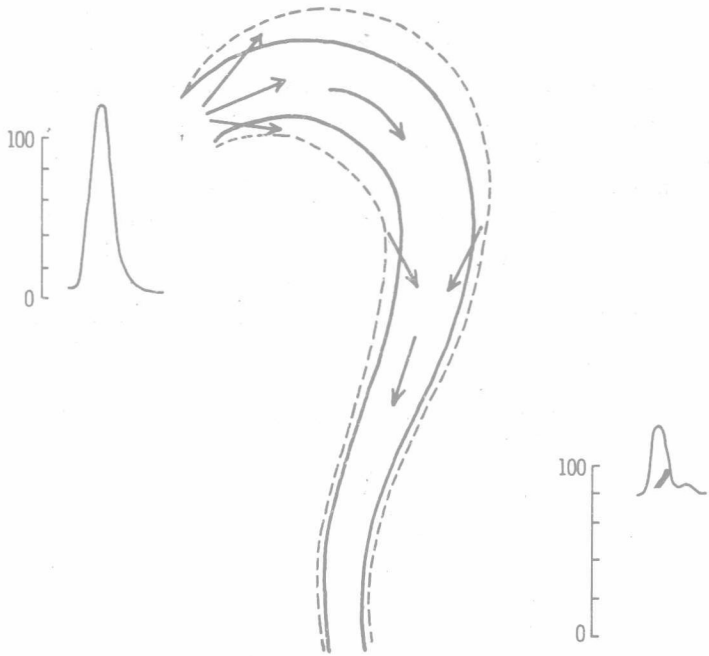

Fig. 2.1 Effect of systolic pressure wave upon the aorta (exaggerated) to show damping effect.

Small arteries and arterioles (precapillary resistance vessels)

These determine the resistance to the forward flow of arterial blood: the state of arteriolar vasoconstriction is therefore one of the critical determinants of blood pressure, since according to Poiseuille's equation, resistance to flow is proportional to the fourth power of the radius. Arterioles also have a sphincter function, occluding or permitting the flow of blood through sections of the capillary plexus. Constriction of the arterioles is under the influence of myogenic tone, locally generated metabolites, the sympathetic nervous system, local and circulating hormone systems.

Capillaries (exchange vessels)

Fluid exchanges across the capillary bed between plasma within the capillaries and the interstitial fluid (i.e. the fraction of extracellular fluid

which lies outside the blood vessels). This exchange is determined by the Starling equilibrium (Fig. 2.2) i.e. filtration occurs as a result of (a) the hydrostatic pressure gradient between the capillary and the interstitial fluid and (b) the osmotic pressure gradient across the capillary bed. The hydrostatic pressure gradient results from the difference between the pressure of blood within the capillaries and that in the interstitial fluid (which is probably slightly negative). The pressure within the capillary bed is determined by the degree of constriction of the vessels entering and leaving the bed. Vasodilatation of the precapillary vessels will increase capillary pressure and so increase filtration, whilst vasodilatation of the postcapillary vessels will reduce capillary pressure and hence filtration. The osmotic pressure gradient across the capillary bed is a consequence of the fact that the capillary pores are largely (but not entirely) impervious to plasma proteins. Most of the protein osmotic pressure (oncotic pressure) is accounted for by plasma albumin concentration: the remaining plasma proteins only account for a fifth of the oncotic pressure. In looking for a cause of oedema therefore, serum albumin concentration is much more important than total serum protein.

It should also be remembered that changes in capillary permeability or in lymphatic drainage of fluid are important in determining the partition of fluid between plasma and interstitial fluid spaces

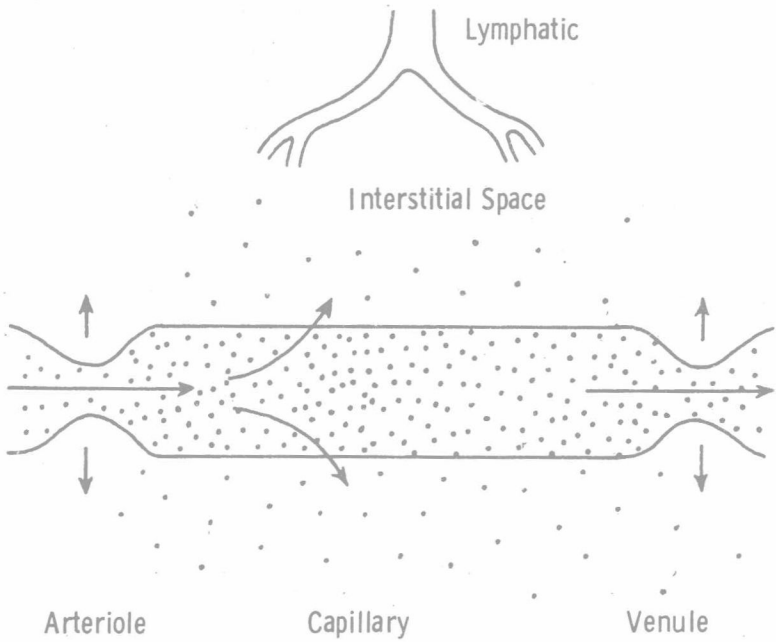

Fig. 2.2 Starling equilibrium. Distribution of fluid is determined by oncotic pressure gradient (represented by dots), hydrostatic pressure gradient (arrows) and capillary permeability.

Venules (post-capillary resistance vessels)

Constriction and dilatation of these vessels is important in determining pressure within the capillary bed and, hence, filtration of fluid.

Large veins (capacitance vessels)

The importance of these vessels is as reservoirs of variable capacity, which supply venous blood to the heart and so are important in determining cardiac output since the heart can only put out what it receives. Homeostatic control of the veins is largely exerted by noradrenergic sympathetic fibres. Their capacity increases with increase in venous pressure, as their cross-sectional configuration changes from a rather flattened ellipse to a circle.

PHYSIOLOGICAL AND PATHOLOGICAL CONSEQUENCES

Ageing

Ageing produces degeneration of the arterial wall. The spiral elastic fibres become uncoiled and broken. In addition, calcium is deposited. Consequently, collagen plays a greater role in determining the physical properties of the arterial wall. The aorta, and large arteries become moderately dilated but much less elastic. The buffering function of the distensible tube provided by these vessels is thus partially lost and the systolic rise and diastolic fall in pressure is greater both within these vessels and distally. Thus a wider pulse pressure is transmitted to the periphery. In the aged therefore, the systolic blood pressure is higher, the diastolic blood pressure lower (other things being equal) and the upswing and downswing of the pulse wave of shorter duration.

Vasodilator drugs

Vasodilator drugs (such as minoxidil and diazoxide) produce oedema. Arteriolar vasodilatation without commensurate venodilatation produces increased filtration pressure by raising capillary hydrostatic pressure.

Other anti-hypertensive drugs

Other anti-hypertensive drugs such as methyldopa, guanethidine and reserpine inhibit constrictor tone in the venules and so reduce capillary hydrostatic pressure. Thus, oedema is not usually produced. Changes in fluid volume may be produced, of course, by other actions, either upon the heart or upon the kidneys.