HIGH BLOOD PRESSURE

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By

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PREFACE

FIFTEEN years ago, my late chief, Sir Thomas Lewis, asked me to write a book on high blood pressure, pointing out the need for a critical review of the subject. At that time I felt that, while I could be critical, I could not be constructive, because I lacked a theme. Since then, however, chance encounter with new facts has stimulated new ideas which provide a theme around which many of the known facts concerning high blood pressure seem to fall into place.

The central purpose of this book is thus to explain these views on the pathogenesis and course of essential hypertension and to relate them to established knowledge. New ideas come when a newly discovered fact throws unexpected light on an old problem. I have therefore thought it right to treat the problem of high blood pressure broadly, reviewing all those aspects which the reader might expect to find in works on physiology, pathology and medicine. The advancement of knowledge resembles the siege of a fortress in that a constant search is made for a weak place in the defences through which a decisive attack may be launched. In thus attempting to encircle the objective, it is my hope that the reader may see an opportunity for attack that has been hitherto overlooked.

The book is addressed to all those who are interested in the problem of high blood pressure, whether they are students, scientists or practitioners of medicine. To do so is, in a sense, to declare an article of faith, namely that the antithesis sometimes made between the science and practice of medicine is false and mischievous. Good practice depends on exact knowledge, and exact knowledge is most quickly and certainly won by the scientific method. Conversely, good science depends on familiarity with the material investigated. Although work on animals may point the way, the decisive evidence concerning human disease must always come from a study of the patients themselves.

G. W. PICKERING.

ACKNOWLEDGMENTS

THIS book would not have been written had it not been for the hospitality of the President and Fellows of Magdalen College, Oxford, who received me into their society during the Hilary term of 1954 during which Professor L. J. Witts and I changed places. They enabled me to live, for a while, a life designed through the ages for scholarship. To them I express my deep gratitude. I would also like to thank my colleagues at St. Mary's for their friendship ; a book like this demands peace of mind and that they have given me. I am especially indebted to the team who have helped me. First, to Miss W. Gallagher, Librarian to St. Mary's Hospital Medical School for her unflagging help in tracing and obtaining original papers ; she prepared and checked the bibliography and checked the references and quotations in the text. Second, to my secretary, Miss Ursula McHale, to whom fell the major task of preparing the manuscript in its various stages and who always seemed to find time to do so in the midst of an exacting post. Third, to Miss Joyce Hollobon, Mrs. Heyworth and Miss Wenham, who assisted with the manuscript and proofs. I owe much to their accurate work. The manuscript and proofs were read critically and constructively by my friends Dr. Maurice Sokolow of San Francisco, Dr. Alvin Sellers of Los Angeles, Dr. Paul Rothschild, Dr. Clive Sowry and Dr. Stanley Peart of London. All of them made numerous suggestions for improving the presentation as well as drawing attention to errors and omissions. For help with individual chapters I am indebted to Drs. P. H. Sanderson, R. R. H. Lovell, G. A. Rose, R. H. Heptinstall and I. A. Bush.

My deepest debt is to those who have worked in this field, and particularly to those with whom I have myself worked. Most of these receive acknowledgment through references in text, tables and figures. But I am well aware that many who should have been included have been omitted, and I have not always succeeded in giving credit for priority when it was due. To them I offer my apologies. Authors and publishers have been generous in making available published figures and tables which are acknowledged as they occur. I am also indebted to Drs. N. Ashton, E. T. Bell, F. Byrom, R. H. Heptinstall, E. Neumark, R. Porter, H. Spencer and Professor C. Wilson for original micrographs. For advice and assistance with illustrations I am indebted to Dr. Cardew and his staff. Finally, I find it hard adequately to express my gratitude to Dr. Poul Bechgaard and his colleagues, Drs. Kopp and Nielsen, and to Drs. Cleland, Counihan and Goodwin for allowing me to quote and illustrate so extensively from their most important contributions before publication.

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CHAPTER 1

INTRODUCTION

The Importance of High Blood Pressure

Within the last 100 years, the implications of Pasteur's germ theory of disease, together with improvements in the social conscience and standards of living, have greatly increased expectation of life, particularly through reduced mortality from infectious diseases. In England and Wales the expectation of life for a child at birth rose from forty and forty-two years for males and females, respectively, in 1841, to forty-eight and fifty-two years in 1901, and to sixty-six and seventy-one years in 1951. Similar figures might be quoted for most of Western Europe and North America, and less strikingly elsewhere. The chief causes of death in Western Europe and North America are now cardiovascular disease and cancer. Thus, in England and Wales there were nearly half a million deaths in 1952. Of these about 18 per cent. were due to cancer, 14 per cent. to vascular lesions affecting the central nervous system, 12 per cent. to coronary and arteriosclerotic heart disease, 15 per cent. to "chronic endocarditis and other myocardial degeneration," and 4 per cent. to hypertension with or without heart disease. These figures must not be examined too closely since the errors involved in certification of death are well known. But they do suggest that vascular disease is now the commonest cause of death in this country. Though both cancer and cardiovascular diseases are predominantly affections of an ageing population, and for that reason may be regarded as of less biological importance, they not infrequently terminate life at what civilized society would regard as its most productive period. These two groups of diseases are, therefore, often regarded as the two greatest contemporary challenges to medical science.

The investigation of the degenerative vascular diseases affecting ageing subjects is hindered by the fact that it is usually difficult, and sometimes impossible, to detect the presence of these lesions until a major vascular disaster has occurred, while the full extent and nature of the vascular change is often only revealed *post mortem*. Many of these patients with vascular lesions do, however, have relatively high arterial pressure. Moreover, the experience of insurance companies has shown that mortality is related to arterial pressure, and that the excess mortality of those with the higher pressures is largely due to cardiovascular renal disease (page 180). Since arterial pressure is

easily and quickly measured, high blood pressure has become one of the conditions most frequently diagnosed by the doctor and dreaded by the patient. It has also been the chief focus of research into vascular disease partly, at least, because it seemed to be a problem that could be solved by the methods and techniques so successfully developed by physiology.

The Problem of Ætiology

The challenge to medicine of vascular diseases and high blood pressure may be resolved into two questions: what can be done to prevent these conditions, and what can be done to mitigate their evil effects if they exist already? This brings us at once to the question of ætiology or the search for causes, for the success of modern science in controlling the forces of nature is based not on empiricism but on an understanding of what these forces are. What are the successive links in the chain of causation which bring about a raised arterial pressure or a particular kind of vascular disease? To what extent does the mere possession of this elevated arterial pressure prejudice the wellbeing of the individual, and do measures designed to reduce the arterial pressure improve the wellbeing or expectation of well-being? These are some of the questions which will be examined in later chapters of this book. Here we may consider briefly the problem of the ætiology of disease in general and some of the difficulties peculiar to our present topic.

The General Nature of the Problem

It is generally believed that the characteristics of any living creature are due to the interaction of two components, namely what he was born with and what has happened to him since he was born, or more strictly his genetic constitution as determined at the time of the conjugation of the germ cells and the impact on it of subsequent events; in other words, inheritance and environment. Reduced in this way to its bare essentials, the problem seems simple enough, but in fact each component is extremely complex, and their interaction even more so. To take a simple example, there are several thousand combinations of the known hereditary factors responsible for the phenomena of the blood groups, and new factors are still being discovered. As for environment, any incident, or combination of incidents, that have happened to us during our existence may be the relevant factors so far as a particular disease is concerned. If we remember, too, that our state may be determined not only by environmental agencies that operate on the body but also by those that operate on the mind, then we begin to realize the dimensions of the problem. We very seldom deal with anything so simple as a single cause or a single effect, but

nearly always with a succession of happenings ; the object that is the focus of our attention at some instant is merely the expression of the causal sequence at that time.

To investigate such complex problems, we have the classical method of natural science : first, the accurate description of facts or events ; second, their arrangement ; and third the invention of a hypothesis to explain the relationship between them. This hypothesis is then tested by experiment, and by its ability to predict correctly other events. If the hypothesis withstands this test it achieves the status of a theory and finally, the dignity of a law. This process has been remarkably successful in dealing with the phenomena exhibited by inanimate objects, and in recent years with those exhibited by animate objects. But it has only had a limited success in elucidating the ætiology of disease. One cause of this comparatively limited success is the enormous complexity, already noted, of the factors concerned. Another consideration that is generally overlooked is that medicine does not begin, as it were, with a blank page. An organized system of beliefs concerning the origin of disease, and of practices designed to prevent or cure it, existed long before the advent of what we now call natural science. Modern medicine has been fashioned by the scientific method out of an earlier creation deriving from magic and religion. To our ancestors disease was the reward of sin, and it is no accident that many of my teachers believed that high blood pressure and arterial disease were the result of eating too much, of drinking too much and of smoking too much. So far as I am acquainted with the evidence, it would seem that their treatment, which they firmly believed to be life saving, was quite ineffective in prolonging life in this world, but as it implied the mortification of the flesh, it is to be hoped that it met with greater success in the next.

Each step forward in science represents a simplification. Complex and hitherto apparently unrelated phenomena begin to fall into place after the development of an idea or hypothesis. It may be noted in passing that the actual hypothesis often represents an oversimplification, and subsequent work has to extend or modify it to relate it more closely to observed facts, just as a sculptor will first rough out the broad mass of his conception in stone and later refine the details.

The nearer a causal chain approaches to the final event, the more influential do individual factors seem to be until, when we reach the terminal stage, the causal agent seems to be in unique relationship with the ultimate effect. So may be portrayed the philosophy of a unique cause. But there is another way in which this philosophy operates. In attempting to isolate from the vast array of possible factors those that chiefly determine a particular happening, in this case a disease, we attempt to assign some estimate of importance, as it were a value,

to each. We can do this most confidently when we can pick out one and say this alone is important or, with less assurance, this is of major importance, these others are only contributory. Here we see the doctrine of unique cause, not so much as a description of the final event, but as a selection of the more relevant from the less relevant. Advances in our understanding of the mechanism of disease in the last century have been chiefly along these lines. Thus the germ theory of disease envisaged as the unique or causal event the invasion of the body by a particular microbe. To suppose, however, that the sole event determining infection is contact between microbe and host is a gross oversimplification. We now know that infection is caused not merely by the contact of the microbe and host but also by the number and virulence of the organisms, on the one hand, and by the inherited constitution, the emotional and nutritional state and degree of fatigue of the host on the other. Any of these may be the determining factor. To take a simple example, Pasteur showed that the fowl was naturally resistant to anthrax, yet if the body temperature of the fowl was reduced it might easily be infected and succumb to the microbe. Here we may regard exposure to anthrax as the unique cause, and yet it was the change in body temperature that was the determining factor in the result. The values that we assign to the various factors have thus no fixed and immutable character, but depend on circumstances.

The Special Difficulties presented by Vascular Disease and High Blood Pressure

It would seem that we understand causation only in those diseases in which a single factor is so clearly demonstrable and of such outstanding importance that it can be picked out with some certainty. Thus we know a good deal about those diseases that are due to the inheritance of a gene which behaves as a simple Mendelian dominant (e.g. Huntington's chorea) less about those that depend on recessive inheritance (perhaps Wilson's disease, hepato-lenticular degeneration, may be cited). We know much of the diseases due to invasion by the larger micro-organisms (protozoa and bacteria), less about those due to ultramicroscopic microbes or viruses. We know something about diseases due to the action of chemical substances taken in excess (e.g. lead poisoning) and to necessary bodily components ingested in defective amounts (scurvy, iron deficiency anæmia). When, however, we have discerned the unique cause, as in iron deficiency anæmia, we find a considerable variety of inherited and environmental factors (gastric secretion, diet and blood loss) whose conjunction is necessary to bring it about.

In some of the commonest diseases of civilized society, the rheumatic diseases, cancer and vascular diseases, we have as yet been unable to

discover the ultimate cause or mechanism. Nor have we been able to segregate these environmental and hereditary factors that may be concerned in setting into motion the causal sequence. It is for this reason, if for no other, that an essay of this kind must treat the subject broadly, for it is the spice of scientific enquiry that no one can foretell whence will come that vital fact or energizing idea that will enable those that have hitherto "seen through a glass, darkly" now to see "face to face."

In dealing with high blood pressure we meet other considerations which add greatly to the difficulty of our task, and which should be faced from the outset. I refer to the fact that high blood pressure is a symptom, not a disease. It is the resultant of a complex set of factors, and the resultant may be the same even though the relevant factors differ greatly in their individual magnitude. Moreover, it is not only the height of his blood pressure that is important to the present or future wellbeing of the individual; the associated organic vascular disease is of equal, and in many cases of greater, moment. These organic vascular diseases are also of various kinds; some seem to be the result of hypertension; in others, hypertension is the result of the vascular disease; and in yet others the relationship is even more complex.

It seems of some importance to emphasize these general considerations at the outset for two reasons. In the first place, understanding of the causal sequence has been hindered by the uncritical transfer of ideas gained from a study of one set of processes to another that is totally different; or by the supposition, as in essential hypertension, that we are dealing with a specific morbid process to which the philosophy of unique causation can be applied. In the second place, three hypotheses are presented here that represent attempts at simplification. This is not the first time that each has been presented separately; but I believe it is the first time that they have been presented together. And the reader is invited to consider to what extent they exchange some kind of order for the disorder that has hitherto prevailed, and to what extent they require modification in the light of existing knowledge that has been overlooked, or whose importance has been underestimated, and to what extent they will stand the test of future observation and experiment. These hypotheses will be fully presented in the relevant chapters of this book in the context of the matrix of evidence from which they crystallized. It does, however, seem worthwhile mentioning them at this stage before the reader becomes immersed in detail.

Some of the more important Propositions to be Presented

The first proposition concerns the nature and pathogenesis of essential hypertension. Arterial pressure, like height, weight and other

measurable characteristics, shows a curve of continuous variation [1] in the population at large. Unlike height, the distribution curves are very different at different ages after adolescence is finished, and the average values for arterial pressure tend to rise steeply in the older ages. It seems that essential hypertension represents little, and perhaps nothing, more than the upper end of the distribution curve, designated as essential hypertension at some arbitrary level such as 150 systolic, 100 diastolic. On this view, the difference between subjects with essential hypertension and those with lower pressures is quantitative and not qualitative, a matter of degree, not of kind. And it is suggested that essential hypertension is the resultant of the interaction of genetic and environmental factors that operate in the population at large. Of these, the influence of age and inheritance can be defined approximately. Environmental factors are probably of even greater importance, but their rôle individually remains uncertain.

The second proposition is that, when arterial pressure is raised for long enough by some specific interference, then the arterial pressure may remain relatively high when the original specific interference is removed. This proposition is derived from experiments with animals and is supported by the results of experiments done in man in the form of therapeutics. This proposition may be of great importance particularly in relation to the possible rôle of environmental factors in essential hypertension.

The third proposition is that the malignant phase of hypertension is a consequence of the degree to which arterial pressure is elevated and the speed with which that elevation was attained. The malignant and benign phases of hypertension thus express differences in degree, not of kind. The occurrence of the malignant phase probably partly accounts for the observed fact that there is a ceiling above which arterial pressure does not rise. The importance of this hypothesis to therapeutics needs no emphasis.

These three propositions form, as it were, the skeleton of a concept of essential hypertension about which many of the previously discovered characteristics seem to achieve some orderly arrangement. It is to be emphasized, however, that they are in the stage of hypothesis and may require revision, amendment or total repeal in the light of future knowledge.

Terminology

High blood pressure has a number of equivalents in the technical jargon of the day: hyperpiesia, hypertonia, and hypertension. Of these, the last is by far the most prevalent in the English-speaking

[1] In the case of arterial pressure, this is not a "normal" curve. For fuller discussion see Chapter 8.

countries, and will be used frequently in this book. The temptation to use it as a title was, however, deliberately resisted for two reasons. First, it is not a very well chosen word, a bastard of Greek and Latin parentage, and signifying not high blood pressure but over-much stretching. Secondly, the use of the term has led to the practice of distinguishing between normal blood pressure and hypertension, and thus by easy stages to the assumption that those subjects with hypertension necessarily differ qualitatively from the rest of mankind ; a conception which has been fatal to an appreciation of the factors concerned in the pathogenesis of essential hypertension.

CHAPTER 2

MEASUREMENT OF ARTERIAL PRESSURE IN MAN

THIS book is concerned with arterial pressure in man. It seems important therefore to consider what it is that we measure when we estimate the arterial pressure, and how accurate these measurements are.

TRANSMISSION OF THE ARTERIAL PRESSURE PULSE : SYSTOLIC, DIASTOLIC AND MEAN PRESSURES

The sudden distension of the aorta at the beginning of the ejection phase of ventricular systole produces a pressure wave which travels along the aorta and its branches, both in the wall of the vessels and the fluid inside. After this wave, the pressure falls to a minimum. As the wave traverses the subdividing vascular tree, it becomes smaller and finally dies out in the capillaries, unless the pulse pressure is high and the arterioles dilated, when it reaches the venules as so-called capillary pulsation (Lewis, 1924). The rate of propagation of this wave is used to measure elasticity of the arterial wall (Bramwell, Downing and Hill, 1923).

At any point in the arterial system it is possible with a manometer of high frequency and small displacement to record two values of pressure, a minimum, or diastolic, and a maximum, or systolic. By choosing a manometer of very low frequency, such as a wide-bore mercury manometer, it is also possible to measure a mean pressure. In clinical medicine what we measure ordinarily as arterial pressure are approximations to the systolic and diastolic values. What the physiologist measures with his arterial cannula and wide mercury manometer is an approximation to mean pressure. So far as the flow of blood is concerned, mean pressure is probably a more useful figure than either the systolic or diastolic values. Mean pressure cannot be simply deduced from the systolic and diastolic figures. It is necessary also to know the shape of the pulse wave and to integrate pressure in respect of time. Mean pressure would only be half the sum of systolic and diastolic values if the pulse curve was of triangular shape. In fact, it is always concave upwards, but the shape of the concavity is not uniform, and there are many component smaller waves and curves. As a rule, mean pressure is nearer diastolic than systolic.

While it is probably true to say that mean pressure falls steadily, though not uniformly, as the blood passes along the aorta and through its branches, the relation of systolic and diastolic pressures is much more complex, owing to the fact that at each subdivision a pressure

wave is reflected back and may summate or interfere with the oncoming wave. Thus, it has been suspected by indirect measurement in man that the systolic pressure recorded from the femoral artery may be higher than that recorded from the brachial, even though leg and arm are at the same level. This is particularly true in aortic regurgitation (Hill and Rowlands, 1912). Direct measurements of arterial pressure with high frequency optical systems show that in the dog the systolic pressure is usually higher in the brachial artery than the aorta.

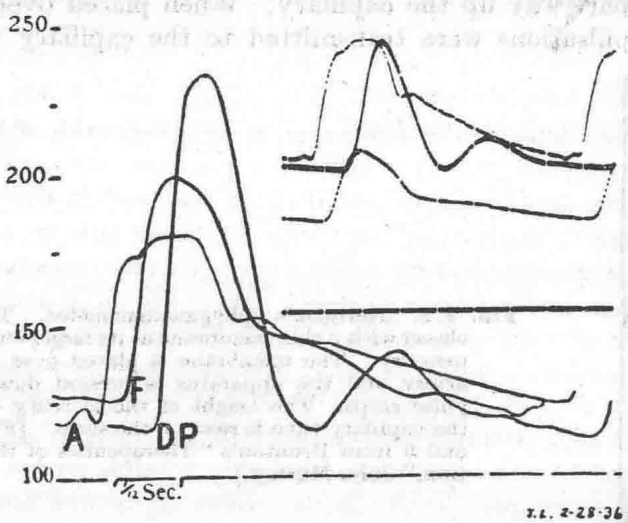

FIG. 2.1. Arterial pressure curves, recorded simultaneously in a human subject by optical manometers from needles in axillary (A), femoral (F) and dorsalis pedis (DP) arteries. The original record (right) has been replotted so that the pressures in the arteries are shown on the same scale (Hamilton and others (1936), *J. Amer. med. Ass.*, **107**, 853, Fig. 2).

Fig. 2.1, from Hamilton, Woodbury and Harper (1936), shows three simultaneous optical records of blood pressure from the axillary artery, femoral artery and dorsalis pedis artery in man. The systolic pressures were severally 165 mm. Hg[1] in the axillary, 200 mm. Hg in the femoral and 235 mm. Hg in the dorsalis pedis artery. In fact, as Hamilton (1944) has pointed out, the form of the pulse, and thus the systolic and diastolic pressures, differ greatly in the various arteries of the same animal at a given instant, due to the complex summation and interference of waves and reflected waves. In the dog, the aorta shows a great standing wave whose node oscillates around a point in the lower thoracic aorta. The reflected wave and therefore the systolic and diastolic pressures in an artery are much influenced by the state of contraction or dilatation of its branches.

[1] This is the figure given by these authors, but I should judge from Figure 2.1. that 180 mm. would have been more nearly correct.

Indirect Methods of Measuring Arterial Pressure

Almost the whole of our present knowledge of arterial pressure in healthy and diseased man is based on determinations by indirect methods. The last century witnessed a long succession of instruments designed for this purpose, beginning with that of Hérisson in 1834 (Fig. 2.2). Hérisson's apparatus consisted of a metal hemisphere sealed on its plane surface with a flexible membrane and carrying a graduated capillary tube at its summit. The apparatus was filled with mercury to part way up the capillary. When placed over the radial artery, the pulsations were transmitted to the capillary where they

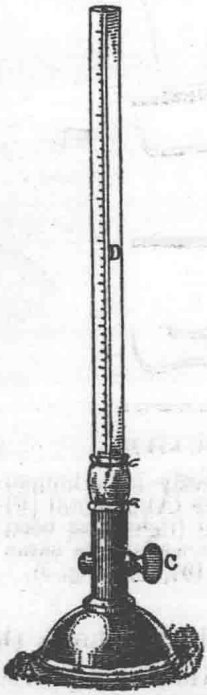

Fig. 2.2. Hérisson's sphygmomanometer. The funnel closed with a thin membrane at its larger end contains mercury. The membrane is placed over the radial artery and the apparatus is pressed down till the pulse stops. The height of the mercury column in the capillary tube is read on the scale. [Figs. 2. 2, 4 and 5 from Brunton's "Therapeutics of the Circulation," John Murray.]

could be measured. Although the purpose of this instrument was to measure the amplitude of the pulse, it could be used incidentally to measure the arterial pressure and was so used by later workers.

The first apparatus specifically designed to measure arterial pressure was that of Vierordt in 1854, in which weights were applied to a scale pan until the pulse compressed by a button was obliterated as shown by cessation of the movement of a writing point. Mahomed's instrument (Fig. 2.3) was a modification of Vierordt's and is of great interest because it enabled that luminous mind to appreciate the main features of what we now know as essential hypertension some twenty years before his time (see Chapter 6). In this instrument, the pressure on the button compressing the radial artery was adjusted by a

thumbscrew, the pressure itself being recorded in ounces of troy weight on the adjacent dial. These clumsy instruments were also very inaccurate. They were, however, the forerunners of several others

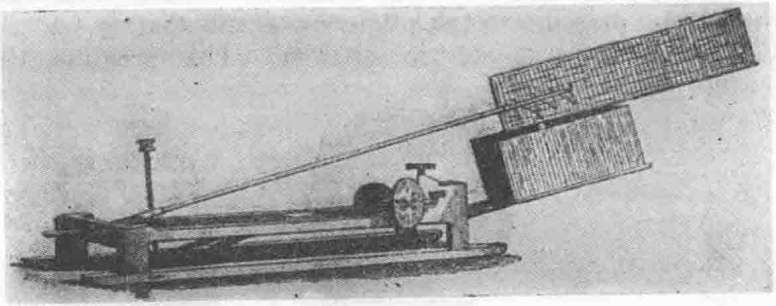

FIG. 2.3. Mahomed's sphygmomanometer. The pulse is inscribed by a lever writing on the clockwork drum to the right of the figure. Next to the drum is a thumbscrew which adjusts the pressure required to obliterate the pulse, the pressure being recorded on the dial in ounces of Troy weight.

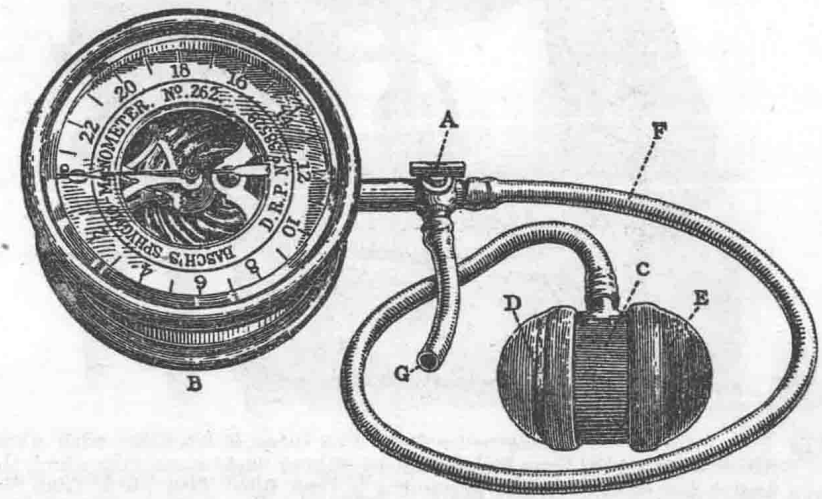

FIG. 2.4. Von Basch's sphygmomanometer as eventually developed for use at the bedside. A is a stopcock by which the aneroid B, reading in cm. Hg, can be put in communication either with the bulb C or the atmosphere. The bulb C is covered at one end by a thin membrane E, which is placed over the radial artery ; the other end is covered with a thick membrane D, on which the finger is pressed until the pulse is stopped.

designed to compress the radial artery until the distal pulse could no longer be felt. Of these, by far the most practicable and generally used was that of von Basch (Fig. 2.4). The intervening instruments are described and discussed by Brunton (1908), Master, Garfield and Walters (1952).