HYPERTENSION*

The Coincidence of Conditions

Part I

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By hypertension is implied an elevation above normality of intra-arterial blood pressure, an increase of the pressure at which blood is forced through the arteries by the heart. Such an interpretation does not include the conditions often associated with it; diseases of the heart and arteries are no integral part of hypertension although in clinical medicine they usually form the most important aspect of the subject. The word hypertension (a hybrid of Greek and Latin origin) means over-stretching but in its inception it was intended to apply to excessive pressure and it is in this sense that it is here used. Thus far the definition is easy but the closer the scrutiny the more difficult does precision in definition become. Recognition, however, generally presents less obstacle than does definition and it is proposed for the moment to accept the situation where the subject is clearly recognized yet ill-defined.

That raised arterial pressure is associated with an adverse expectation of life and with impaired health is now well appreciated. It is worth recalling that nothing of this was known to the physicians of a century ago. Bright,³ it is true, in 1836 had postulated that an increased resistance to peripheral blood flow might have caused the hypertrophied hearts found in certain post mortem examinations where there was no evidence of valvular disease; whilst six years earlier measurement of arterial pressure in man had first been reported by Hérisson.¹⁵ It was not until 1879, however, that any accurate correlation between records of blood pressure in life and post mortem findings was attempted. In that year Mahomed²⁰ published his analysis of 100 cases who at post mortem were found to have granular kidneys. His observations in life that many had raised arterial pressure with no evidence of renal damage led him to question the views of Bright that the kidney

damage was primary in all such cases. Thus the first seeds of the concept of essential hypertension were sown and the idea emerged that high blood pressure should be recognized as important in its own right, with its own sequelae. Between that time and today, in the span of 80 years, hypertension has grown to occupy a leading place in the aetiology of disease processes. There are those who, perhaps with justification, question whether the role ascribed to it is now not greater than it deserves. There is a danger that myopia may have resulted from such intense scrutiny as has occurred in this one field, scrutiny which has led to the unfolding of a profusion of scientific knowledge. The risk exists of losing the ability to stand back and to see the whole problem in perspective.

It will be the purpose of this essay, therefore, to attempt just this; it is proposed firstly to note the many difficulties which lie in the way of a clear understanding of the subject; thereafter more closely to consider the definition; to pay particular regard to the aetiology and epidemiology; to consider the ill effects generally attributed to hypertension and to assess the validity of such attribution; and finally to consider the methods available for influencing both the condition and its natural history.

The Difficulties

Measuring blood pressure is now so much a part of medical routine that it has been accepted as a reliable observation; it is on a par with testing the urine for albumen or for sugar, and is deemed to provide as definite an answer. It is a salutary experience therefore to record simultaneously or consecutively the pressure in different limbs in the same individual. The variation from site to site is considerable; the femoral pressures, normally higher than the brachial, and the smaller pulse pressure in the left than in the right arm are examples which can be demonstrated readily in

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CORRECTIONS FOR ARM CIRCUMFERENCE TO BE APPLIED TO AUSCULTATORY MEASUREMENTS OF ARTERIAL PRESSURE (Based on data from Ragan and Bordley³²)

Arm circumference to nearest cm.	Systolic pressure, mm. Hg.	Arm circumference to nearest cm.	Diastolic pressure, mm. Hg.
15 to 18	Add 15	15 to 20	No correction
19 to 22	Add 10	21 to 26	Subtract 5
23 to 26	Add 5	27 to 31	Subtract 10
27 to 30	No correction	32 to 37	Subtract 15
31 to 34	Subtract 5	38 to 43	Subtract 20
35 to 38	Subtract 10	44 to 47	Subtract 25
39 to 41	Subtract 15		
42 to 45	Subtract 20		
46 to 49	Subtract 25		

From Pickering, Roberts and Sowry.²⁸

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man. These readings are at the best but approximations to the true intra-arterial pressures during the passage of the pulse wave, and measurements with manometers within the lumen show great variation in different arteries. Hamilton, Woodbury and Harper¹⁴ recorded in man simultaneous systolic pressures of 165 mm. Hg in the axillary artery, 200 mm. in the femoral and 235 mm. in the dorsalis pedis artery. Such observations are of value in calling attention to the inaccuracies of the methods of measurement and pose the question 'What pressures do we routinely measure?' So long as this aspect is kept in view, it is sufficient to say that the usual clinical record of blood pressure provides an approximation to the true systolic and diastolic pressures in the brachial artery, although Ragan and Bordley³² have shown that the diastolic end-point as generally measured in this country is of the order of 5 mm. Hg too high. A closer end-point is the final fading of the sounds; the location of this point is, however, more difficult than that of the commencement of fading generally adopted. In view of the other inaccuracies it seems perhaps wiser to adhere to the accepted and more easily defined end-point.

It has long been recognized that obesity is correlated with hypertension, albeit not closely. That some of the apparent rise of pressure is an artefact produced by increased arm circumference was demonstrated by Ragan and Bordley.³² Using their data, Pickering, Roberts and Sowry²⁸ calculated the corrections to be applied to pressures obtained by auscultation for arms of varying girth (see table). The corrections are small in comparison with the other sources of variation and error, being seldom more than 15 mm. Hg. They thus have little importance in clinical medicine. But in any study of epidemiology in hypertension they assume major proportions. Miall and Oldham²² have shown that the differences com-

monly observed between the arterial pressures of males and females below the age of 50 years are greatly diminished, if not abolished, by applying such a correction. In particular it would appear that the observed rise in systolic and diastolic pressures shown in males shortly after puberty is due in part to an artefact produced by the rapid growth in stature of males at that age.

A further difficulty introduced by this factor when considering the blood pressure of large populations is the fact that hypertensive individuals who are obese tend not to survive to the same age as their slimmer fellow hypertensive subjects. In effect there tends to be a selected survival amongst hypertensive subjects at older ages of individuals who are not obese and who therefore do not possess in their observed pressures so large a component due to this artefact. It is possible that this effect has not received sufficient attention in the interpretation of the mortality and morbidity statistics from insurance companies. The actuarial problem is relatively simple and, in a word, consists of correlating excess mortality and morbidity with the excess of weight and arterial pressure. The scientific interpretation of such correlation and the apportioning of responsibility to obesity per se and to hypertension per se is more difficult. For if the obesity has contributed an appreciable but false contribution to the hypertension in such cases, an excessively malignant influence may have been ascribed to the hypertension.

So far only the inaccuracies of measurement and the site to site variation of pressure have been considered. Significant though they be, they are of minor importance compared with the chronological variability of pressure in the same individual and in the same limb. Factors which affect the arterial pressure are multitudinous and are not readily amenable to control. Fear, exertion, pain and other discomforts are all of consequence. Three aspects of this problem require special consideration since they stem from the procedure of measurement itself.

Firstly the emotional disturbance caused by the procedure causes considerable elevation of pressure. Alam and Smirk¹ have employed 'emotional desensitization' to eliminate this effect in the determination of what they term basal blood pressure. To what extent the reduction of pressure which they observed was due to the emotional desensitization is not made apparent. That the effect was considerable is beyond question.

A second factor is the pain and discomfort produced by the procedure. No doubt a large part of this is concerned with emotion and will be removed by emotional desensitization; it seems

likely that some pressor effect is due to the sensory stimuli themselves.

These two factors are of significance when the meaning of basal blood pressure is considered. Many functions of the body are under reflex control and in the majority the control is multifactorial. Arterial pressure is no exception and, in broad terms, at any moment the level of pressure is determined by the sum of a number of different stimuli. The less the number and strength of these stimuli the less will be the reflex response and the lower the pressure. The extent, therefore, to which conditions are made basal will determine the level to which the pressure will sink. Physical rest and quiet surroundings will produce some lowering; familiarity with observer and procedure (which is emotional desensitization) will produce further depression; darkness, sedation and sleep will take the process still further. The best that can be derived from such manoeuvres in general is that the arterial pressure can be measured under standardized conditions of rest. To regard any rest, other than death itself, as absolute is to belie the significance of life.

The third aspect of the procedure itself which requires a moment's consideration is the mechanical effect upon the pressure within an artery of compression of that artery. Robinow, Hamilton, Woodbury and Volpito³³ showed that there was a marked rise in directly recorded systolic pressure proximal to the occlusion of a brachial artery in children, although none in diastolic. Compression of the brachial artery of the opposite arm, or of either femoral artery, caused a smaller but definite rise of both systolic and diastolic pressure in the brachial artery.

There are thus at least three factors inherent in the procedure of measurement of pressure which alter the pressure itself, all tending to produce elevation. The effects of these factors are not large but it is probable that they are greater in subjects with hypertension than in those without.

When arterial pressure is found to be elevated in an individual, that is, when hypertension is found, these artefacts and sources of error do not negate the finding. But it is wise for the observer to bear them in mind in assessing the significance of the departure from normal. Of all the factors considered, that of individual variability presents the greatest stumbling block to a clear understanding of hypertension. It complicates all aspects of the subject; insurance companies are well aware of it in assessing expectation of life and generally endeavour to reduce its magnitude by laying down standardized procedures of measurement of pressure; those engaged in epidemiological investigations find that it tends to minimize the effects of other factors in the aetiology of

hypertension; whilst the practising physician finds that his attempts at prognosis are at times brought to nought by its Puckish character and that his assessment of the value of a particular therapeutic agent is likewise obscured.

Before proceeding to consider the definition, brief mention must be made of a further factor which complicates the understanding of hypertension. It is in the nature of a mathematical or statistical hindrance and to introduce the subject here is to some extent to anticipate what follows. The story begins in 1834 when Hérisson¹⁵ first described his apparatus for estimating intra-arterial pressure. His manometer was, as today, a column of mercury and his readings on a linear scale. From then until now, blood pressure has been recorded in a linear fashion. There are, however, many facts which point to the conclusion that a linear scale is not the most suitable metric. Reference to curves showing the distribution of arterial pressure (Figs. 5. and 6) shows that such curves are not of normal distribution. Analysis of related curves for the distribution of pressure indicates that they are positively skewed and that they show other marked departures from normality. The increased scatter of arterial pressure, shown in the older age groups (Figs. 5 and 6) is explicable if it is noted that these older groups tend to have higher pressures. The greater range of systolic than diastolic pressure can be viewed similarly. It has already been suggested that the effects of pressor stimuli resulting from the procedure of measurement of pressure are greater in those with initially high pressures, and there is other evidence that similar stimuli produce greater changes in high than in low initial levels of pressure.²⁶ It seemed logical therefore to reassess the normality of the distribution of arterial pressure exposed upon a different scale. This has been undertaken by the author and his associates and it has been demonstrated that arterial pressure expressed upon a logarithmic scale shows a normal distribution. It is in keeping with many graded characteristics of a biological nature to show a log normal distribution.⁹ The bearing of this inappropriate measure of pressure upon certain aspects of hypertension will be noted.

The Definition of Hypertension

If hypertension is to be defined, then normality must be defined also. For at the outset the point was established that hypertension is an elevation of arterial pressure above normality. It follows from this that no examination of hypertension, and particularly of its epidemiology, can be complete without a study of arterial pressure levels in the population at large. That all such

FIG. 1

FIG. 2

Mean arterial pressures in different population samples. Present series refers to that of Hamilton, Pickering, Roberts and Sowry.¹¹ (Reproduced by kind permission of 'Clinical Science'.)

FIG. 3

FIG. 4

Mean systolic and diastolic pressures of the population sample, together with fitted curves. From Miall and Oldham.²² (Reproduced by kind permission of 'Clinical Science'.)

FIG. 5

Frequency distribution of systolic and diastolic pressures in the population sample. The histograms show the percentage having a given range of pressure, shown as the mean of the observed readings (e.g. 120 and 125, mean 122.5 mm. Hg). The number of subjects in each decade are shown in the centre. The dotted lines are at 150 mm. Hg for systolic and 90 mm. Hg for diastolic pressures, levels often adopted as the division between normality and hypertension. From Hamilton, Pickering, Roberts and Sowry.¹¹ (Fig. 5 reproduced by kind permission of 'Clinical Science'.)

FIG. 6

studies as are recorded have been made in circumstances which led to the introduction of the artefacts and sources of error already considered does not appreciably detract from their value in general. This is largely the case because it is in similar circumstances that the practising doctor routinely records his patient's pressures. It is, however, wise to bear in mind the particular circumstances of measurement, and the method of selection of each series when comparing one with another.

What is to be learnt from such studies of pressure in samples of the general population? Clearly it is wrong to predict for individuals behaviours of pressure similar to those recorded as averages at various ages in groups. Such groups are composed of individuals whose pres-

sures behave in fashions differing widely one from another. But general trends become apparent and it is of value to observe these trends in considering the concept of normality in blood pressure.

In Figures 1 and 2 are shown the results of a number of such population studies as presented by Hamilton, Pickering, Roberts and Sowry.¹¹ The divergences are considerable from one series to another and are presumably due to differing methods of population selection and differing circumstances of pressure measurement. In general, however, it can be seen that mean pressures, both systolic and diastolic, rise with age, more markedly so in females than in males, and in both more so in systolic than in diastolic pressures. Indeed, the curves for diastolic pres-

tures for males recorded from the data of Robinson and Brucer³⁴ and of Saller³⁵ suggests no rise over many years of middle life. Both, however, relate to highly selected populations, the former work being derived from cases accepted for life insurance whilst the latter was based upon patients attending medical clinics, but excluded all cases showing organic cardiovascular disease. In addition Robinson and Brucer selected the lowest reading of a series in the event of there being any undue elevation of pressure in any individual examined.

Further observations in this field are those of Miall and Oldham²² who made a study of arterial pressure in a randomly selected 1 in 90 sample of the population of the Rhondda Fach, a South Wales mining valley. The mean pressures together with their fitted curves are shown in Figures 3 and 4. Diagrams showing the distribution of arterial pressures at different ages should dispel any doubt as to whether it is usual for pressure to rise with age. Figures 5 and 6 are from the paper by Hamilton, Pickering, Roberts and Sowry¹¹ and show the percentage distribution of each 10 mm. Hg division of arterial pressure, for systole and diastole, for females and for males, in each decade. The gradually diminishing or disappearing number with low pressures, the increasing number with high pressures and the rising modal pressures are explicable most readily and most completely by the assumption that it is usual for pressures in any individual to rise with age. The authors inserted the dotted lines in each diagram at the pressures of 150 mm. Hg systolic and 100 mm. diastolic, levels commonly accepted as dividing lines between normality and hypertension. The arbitrary and artificial nature of such a selection is well demonstrated.

These and other observations make it abundantly plain that arterial pressure usually rises with age. Whether or not it is established by the same evidence that it is normal for this to happen is dependent upon the definition of words. The Shorter Oxford English Dictionary describes 'usual' as 'that commonly observed,' whilst for 'normal' it records 'according to or squaring with a norm.' For 'norm' it gives 'a rule or authoritative standard.' The controversy over normality in arterial pressure has continued for such a time that it is expedient to view it in this light. It resolves itself into the question of whether there is a 'rule or authoritative standard' in this measurement. To the author it is clear that there is none. Furthermore, it is apparent that to attempt to create one, irrespective of the use to be made of it, is unwise and that even when a division is arbitrarily created for a specific

purpose, its use is fraught with danger. There is thus no acceptable norm and therefore no definable normal. It must follow therefore that there is no acceptable definition, save in general terms, for hypertension. To adopt this position should cause no regret; to require a definition except for a specific end, is the trait of the obsessional.

The demand for a definition of hypertension arises from the desire neatly to pigeon-hole patients and conditions. Much of this desire is met when the problem under consideration is aetiological. A simple illustration is the elderly patient, for example a woman of 70 with a blood pressure of 200/100, who dies of cardiac failure. It is easier to ascribe her death to Hypertensive Heart Disease than to Heart Disease due to a variety of agents which include ischaemia, hypertension, endocrine and nutritional disorders and a multitude of factors concerned with ageing about which little is known. Easier, but not necessarily more accurate!

Tolstoy,⁴⁰ in 'War and Peace' makes much of this theme and if this essay, like a sermon, is to have a text, what follows is not inappropriate. Referring to the war of 1812 he writes:—

'To us who are not carried away by the process of research and can therefore regard the event with unclouded common sense, an incalculable number of causes present themselves. The deeper we delve in search of these causes the more of them we find.' Pursuing this further he draws the simile: 'When an apple has ripened and fallen why does it fall? Because of its attraction to the earth, because its stalk withers, because it is dried by the sun, because it grows heavier, because the wind shakes it, or because the boy standing below wants to eat it? Nothing is the cause. All this is only the coincidence of conditions in which a vital organic and elemental events occur.'

In such a patient as has been cited, a diagnosis of hypertensive heart disease is incomplete and may be misleading. It is, though, of no great consequence. Greater importance should be attached to the error of rigidly dividing populations into normal and hypertensive portions by fixed criteria. Once such a division is made, the assumption is inevitable that these two populations are distinct. On this assumption, false theses are constructed. Without such a basis, the hypothesis of a Mendelian inheritance in hypertension could never have been proposed. A further illustration of this particular fallacy is the fact that Weitz⁴³ so chose his dividing line that it best fitted the theory of a dominant gene for hypertension. Thus starting with a number of subjects having hypertension he found that 50 per cent. of their sibs were similarly affected, but only if he

chose 160 mm. Hg as the division for systolic pressure. From such a ratio of affected to unaffected sibs he propounded a dominant inheritance. A lower critical level would no doubt have given a greater number of affected than unaffected sibs; whilst a higher figure would have weakened the case by revealing a deficiency of affected sibs. This, and more, can be laid at the door of the rigid definition of hypertension.

It is perhaps surprising that such a desire exists or existed. It is not met elsewhere to the same extent. Few would wish rigid limits for dwarfs, normal men and giants; nor for the slim and the obese. It is widely appreciated that height and weight are graded characteristics and can be quoted in quantitative rather than qualitative terms, except for relative reference. An advance in medicine will occur when this attitude prevails in the sphere of blood pressure. The physician who enquires 'Is the patient hypertensive?' would do well to rephrase his question 'What is the patient's blood pressure?' For the diagnosis, the prognosis and the treatment can scarcely be influenced by the rigid answer to the former question but correct assessment of the situation is helped by an accurate answer to the latter.

The Aetiology of Hypertension

When all patients with hypertension are considered, there are found to be a number who show diseases other than the hypertension and its consequences and it is generally considered that in many such instances the disease found is 'the cause' of the hypertension. Bearing in mind the advice of Tolstoy, it would be as well to substitute 'an aetiological factor' or even 'an important' or 'the most important aetiological factor' for 'the cause.'

It is no part of this review to delve into the details of each and every condition thus associated with hypertension. It will be sufficient to mention those which have a bearing on the theme.

Of greatest importance are lesions of the kidney. Physiologically these appear to fall into two main categories in so far as they relate to hypertension. In the first category, by itself, is acute nephritis. This lesion differs from all other renal lesions in that in all probability it is not the cause nor even an aetiological factor in the hypertension that is associated with it. Both would seem to be due to a widespread vascular lesion.²⁴ This type of hypertension appears to be unique in that the vasoconstriction which is responsible for it is under nervous control, and is abolished by releasing vasomotor tone. It is of interest to note that the hypertension has often been observed to precede the albuminuria.¹⁸

The underlying mechanism for the hypertension associated with chronic nephritis is analogous to that found in most other forms of hypertension. For in chronic nephritis, and indeed in all other chronic renal lesions where hypertension exists, release of vasomotor tone does not appear to cause a vasodilatation in skin blood vessels.²⁴

The incidence of hypertension and its severity in the various renal lesions with which it is associated are of interest. In acute nephritis, some degree of elevation of pressure, generally fairly mild, is common. It is usually transient and more often than not is of little consequence, although at times over-whelming. In subacute nephritis (Type II of Ellis)⁷, hypertension is less common. Its occurrence in some early cases is associated with a rapid progression of the condition. Raised arterial pressure is found most frequently, amongst renal diseases, in chronic glomerulonephritis, of whatever cause. Here it is usually severe and terminally frequently in the malignant phase.

Other renal lesions with which high blood pressure is found include chronic pyelonephritis, amyloid nephrosis and the diabetic intercapillary glomerulosclerosis of Kimmelstiel and Wilson.¹⁶

Its incidence in chronic pyelonephritis has been the subject of considerable debate. Post mortem studies of patients with malignant hypertension show a high incidence of pyelonephritis; the figures are variously quoted as from 10 to 30 per cent. Viewed the opposite way, however, the incidence of high pressure in clinical pyelonephritis is less certain, and Goldring and Chasis¹⁰ have produced evidence from which they deduce that there is no correlation between the two conditions. The factors which determine its occurrence in some patients and not in others are by no means clear. Weiss and Parker⁴² claim that pyelonephritis is only associated with hypertension in the presence of hyperplastic arteriosclerosis in the kidneys or kidney (for the lesion may well be unilateral). This view is supported by others, notably Pickering and Heptinstall²⁵ and Kincaid-Smith.¹⁷

The matter is complicated by a personal, and as yet unpublished, observation, that the relatives of hypertensive chronic pyelonephritic patients show an elevation of arterial pressure comparable with the relatives of patients with essential hypertension; whereas the relatives of hypertensive patients who had coarctation of the aorta or phaeochromocytoma showed no such elevation. This observation, if confirmed, would seem to indicate that inheritance, known to play a considerable part in the aetiology of essential hypertension, is operative also in the hypertension found in pyelonephritis. Its method of operation is undetermined as yet but three

possibilities present themselves. Firstly patients with essential hypertension may more readily develop chronic pyelonephritis; this would not well explain the high incidence of pyelonephritis without hypertension. Secondly pyelonephritis or a predisposition to it may itself be inherited; this possibility cannot be discounted. Thirdly, it may be necessary for there to be the coincidence of an inherited predisposition to hypertension and of the renal arteriosclerosis of pyelonephritis before arterial pressure will rise appreciably. This last hypothesis seems on face value the most attractive, and accords with the multifactorial basis which it is suggested applies in the majority of hypertension.

Contrary to popular belief, hypertension is probably no commoner amongst diabetics as a whole than amongst normal people.²⁴ Its incidence amongst diabetics with glomerulosclerosis is considerable. It can be as severe as in any form of hypertension. In patients with amyloid nephrosis, arterial pressure generally remains normal until gross renal destruction has occurred, when it may soar. In diffuse disorders of collagen, such as polyarteritis nodosa and disseminated lupus erythematosus, renal involvement may bring hypertension in its wake, early or late, severely or in mild form.

The endocrine disorders closely associated with hypertension, namely Cushing's syndrome and pheochromocytoma, are of relevance to the theme of this essay in that the incidence of hypertension is extremely high and thus the likelihood of direct cause and effect high. Plotz, Knowlton and Ragan³¹ give an incidence of hypertension of 85 per cent. for the former condition. Elevated blood pressure must occur at some time or another in almost 100 per cent. of the latter.

These two lesions together with unilateral pyelonephritis and coarctation of the aorta are also of importance in that they represent conditions in which 'the cause' of the hypertension is removable. In none, however, does obliteration of the specific lesion result in invariable return of the blood pressure to normal. Indeed, the hypertension appears to persist, albeit often at a less severe level, in half, or more than half, such instances. Throughout the whole field of hypertension this phenomenon recurs wherein arterial pressure, once elevated by any factor, tends to remain high even when the original factor no longer operates. It is essential to the proper understanding of the subject. It is an integral part of the 'coincidence of conditions.'

When all the disease processes which are in aetiological relationship with what is termed secondary hypertension are put aside, there remains that large majority of persons with high

blood pressure for whom no definite aetiological agent can be found—that is, with essential hypertension. The size of this majority is difficult to assess. Indeed since a rigid definition of hypertension has been set aside, a numerical assessment of the incidence of the condition, secondary or essential, is impossible. If attempted, it is of no more value than the definition itself. What is of value is the observation that the younger the subject with hypertension, the greater is the probability that it will be of secondary aetiology.³⁰ It follows from this either that secondary hypertension is absolutely more common in youth or alternatively that essential hypertension is absolutely more common at older ages. It has already been shown that arterial pressure usually rises with age and thus it is reasonable to infer that the latter explanation is the most likely. An important conclusion is thereby reached; one that at first sight is somewhat obvious but which has far reaching implications. Namely, that the process of ageing is an important factor in the genesis of essential hypertension. If now 'the usual rise of blood pressure with age' is substituted for 'the process of ageing,' the inference is that essential hypertension is derived in part from the rise of blood pressure which usually occurs with ageing. The magnitude of this factor can in general terms be estimated. It is higher for women than for men. For systolic pressures an approximation to the factor can be gleaned from the old adage of '100 mm. Hg plus the age'; for diastolic pressure the factor is about half that for systolic.

When this factor is fully taken into account it is found to be responsible for only a modest proportion of the condition which is clinically of importance as essential hypertension. What are the other factors that are at work? It is important at this juncture to recall that the subject under discussion is hypertension, not the cardiovascular diseases so often associated. The agents to be unmasked are those which cause the arterial pressure to rise. The role of inheritance is a subject which has for a long while been debated. The occurrence of hypertension in several members of a family is a commonplace observation but in a condition so prevalent, one of no great importance. Studies of twins³⁹ are of greater interest and have supported the view that inheritance plays a part in the aetiology. Family histories further strengthened the case²⁹ but are open to one criticism, amongst others, that they record largely the incidence of cardiovascular disease. Observations of arterial pressures seemed likely to provide the answer but the difficulty of comparing pressures in subjects of different ages proved for a long time an obstacle to the correction

FIG. 7.—Systolic and diastolic pressures for each 5-year age-group of the population sample, together with fitted curves. The area of each circle (females) or square (males) is proportional to the number of subjects in that age-group. From Hamilton, Pickering, Roberts and Sowry.

interpretation of such results. Until recently all engaged on this work fell back upon the device of a rigid definition of hypertension. In every case the results, whilst confirming the presence of an inherited factor, were unable to show its magnitude. It has already been pointed out that the definition adopted greatly influenced the conclusion reached by Weitz⁴³ and that the mere presence of a rigid definition fostered the development of the thesis of a simple Mendelian inheritance, a thesis incompatible with the fact that arterial pressure is a measurable and therefore graded characteristic.

To advance further in this field it was necessary to devise a method of eliminating the effects of age. One approach would be a more extensive and detailed study of twins and it is probable that much will yet be learnt from this quarter. An alternative approach was that adopted by Hamilton, Pickering, Roberts and Sowry.¹² Using the figures obtained from their study of a sample of the general

population they constructed curves (Figure 7) for the expected arterial pressure at all ages from 10 to 80 years, for females and males. From these curves, simple deviations could be calculated for the pressures of any individual at any age. It was apparent, however, in their distribution curves (Figs. 5 and 6) that the scatter of arterial pressure increases with age (perhaps as a result of the inappropriate linear scale of measurement). It thus seemed logical to introduce a correcting factor to increase the significance of a simple deviation in youth in comparison with one at an older age. For reasons which were technical they corrected all deviations so as to represent the deviation which would be found in women at the age of 60. The resultant figures for each systole and diastole for each individual they termed the Age and Sex Adjusted Scores. Armed with this they were able to compare the pressures of individuals of differing age and sex and hence to proceed to the genetic analysis of the families whose arterial pressures they had recorded.¹³ Their conclusions were strengthened by their ability to utilize the data of Soby³⁷ who had made a similar study but who had been obliged to employ a rigid definition of hypertension (and thus had 'confirmed' the existence of a Mendelian dominant inheritance).

Hamilton and his colleagues found that an inherited factor did exist; that its magnitude was independent of sex and was of the same order for parents, sibs and children and for systolic and diastolic pressures; that it was of a size which could be expressed by a regression coefficient of rather more than 0.2. This figure represented the degree by which any individual tended to resemble his or her first degree relatives in arterial pressure: thus a deviation of pressure of 10 mm. Hg. from the expected by one member of a family would tend to be reflected by a deviation in the same direction of 2 mm., or rather more, amongst other members.

This work has been fully confirmed by Miall and Oldham²² in their studies in the Rhondda Fach. These workers, however, have been able to proceed further. They have been able to prove what was suspected but not confirmed by Hamilton and his fellows, namely that this factor of inheritance is of the same magnitude irrespective of the height of the pressure in the original subject studied. It had until then been possible to envisage that a degree of inheritance would operate at one extreme of the range of arterial pressure different from that at the other. This would have strengthened the view still widely, but probably erroneously, held that essential hypertension is a discrete entity. Miall's and Oldham's finding, however, demonstrates that, whatever its level, arterial pressure is

inherited as a graded characteristic, in a quantitative, and not a qualitative fashion. From this can be inferred that essential hypertension differs only from normality in degree and not in kind.

Miall and Oldham were able to take into account the effect of arm circumference. They considered the possibility that the factor of inheritance represented nothing more than an artefact due to the inheritance of arm circumference; and alternatively that it represented only an inheritance of the true elevation of pressure associated with obesity, itself inherited. In their original work they were unable entirely to dispose of either of these possibilities. But subsequent investigations have shown that at least the former explanation is invalid (personal communication); for even after correcting for arm circumference, the inherited factor is expressed by a regression coefficient of rather more than 0.2.

It thus transpires that three different studies, by Soby in Denmark, by Hamilton and others in London and by Miall and Oldham in South Wales, provide evidence of a factor of inheritance which accounts for between a quarter and a fifth of the variations of human blood pressure at any age. In the development of arterial pressure (and therefore at the upper end of its scale, in the development of hypertension) the factors of age, sex and inheritance have within broad limits been assessed. The place of certain disease processes has been considered, but with exceptions their role is imperfectly understood. Furthermore, none of them is operative, by definition, in the commonest, that is essential, hypertension. There remain the multitude of circumstances affecting the population which are termed environment. In this sphere must lie the remainder of the problem of the aetiology of hypertension.

The role of obesity, per se, as distinct from the artefact due to arm circumference has been mentioned, and it is established beyond doubt that there is a positive correlation between arterial pressure and weight. Prolonged and repeated

physical exertion might be thought to play a part and Miall and Oldham (personal communication) have shown that pressures are lower, age for age, in men employed in heavy physical work than in men of the same district in more sedentary occupations. This observation is of importance but its interpretation is far from simple. The possible explanations would appear to be that repeated exercise tends to lower arterial pressure and/or that some factor associated with a sedentary occupation tends to elevate it; such a factor could well be psychogenic in origin. When the magnitude of the component of arterial pressure removed by emotional desensitization is considered, it will be appreciated how real this psychogenic factor could be in the initiation of hypertension. Add to this the principle already enumerated, that arterial pressure, once elevated, tends to retain some part of that elevation when the original pressor stimulus has been withdrawn, and a possible method of development of hypertension becomes clearer.

From all this, one thesis emerges more strongly than ever. A person is not hypertensive solely by virtue of his age; nor as a result of an inherited factor or factors (for the inheritance itself is surely multifactorial). Nor is he hypertensive solely through obesity; nor through diet; nor through emotional lability of blood pressure; nor perhaps through lack of exercise; nor yet through an undue tendency to retain some part of transient hypertension. He is hypertensive because all or some of these factors combine in a 'coincidence of conditions'. Although such factors do not explain the mechanism of hypertension, do they not, taken together, explain most of the aetiology? Or is there still some large component of which there is as yet no comprehension? The answer to these questions lies ahead. It is probably in the realm of mathematics. For when the magnitude of each factor can be accurately assessed, then will it be known if the parts add up to form the whole.