Hypertension and Coronary Artery Disease

The Proceedings of a Symposium held in Chelmsford under the auspices of the Chelmsford Medical Society and the Mid-Essex Branch of the British Medical Association

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FOREWORD

In recent years physicians have been increasingly concerned with the management of patients with hypertension as new drugs have become available to lower the blood pressure and to improve the prognosis. It is therefore important that the practising doctor, whether in consultant or general practice, should have the opportunity from time to time to review what is known of this disease, to get the latest ideas on aetiology, incidence, treatment and complications, and to meet and discuss various matters of common interest with experts in the field.

Over the past five years the Chelmsford Medical Society has developed a very active programme, with regular meetings and hospital rounds to which general practitioners are welcomed, and this has led to a lively interest in clinical and academic medicine in the area. As a result the more ambitious project of a two day Symposium on Hypertension and Coronary Artery Disease was organised by the Medical Society in conjunction with the British Medical Association. We were fortunate in that a number of physicians of the highest distinction agreed to present papers on subjects of special interest, and to take part in panel discussions.

The success of this Symposium reflected not only the more formal meetings and discussions but also the opportunities for social and professional contact between the individual speakers and participants. We only regret that some who wished to attend could not be accommodated because of the limited size of the conference hall. However it is hoped that the availability of these published Proceedings will be of some help to those who missed the occasion or would like to review it.

The burden of organisation fell heavily on a few members of the Society and they are to be congratulated on its outcome. We are indebted to CIBA Laboratories for the production of the Proceedings, and in particular to Dr. J. H. Fryer for his role of Editor and to Mrs. M. McCulloch who did all the secretarial work.

Peter Martin, V.R.D., M.Chir., F.R.C.S.

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Hypertension: Consideration of Aetiology and Treatment

CHAIRMAN: J. F. GOODWIN

The Nature of Essential Hypertension

G. S. C. SOWRY

By definition, essential hypertension is an elevation of arterial pressure for which no tangible major causative factor can be detected. With such a definition, I should avoid discussion of all other types of hypertension. But I want for a moment to remind you of some of the factors which are associated with hypertension and which hence may be said to give rise to secondary hypertension.

These include a number of pathological conditions of the kidney:-

Glomerulo-nephritis; acute and chronic

Chronic pyelonephritis - pyogenic or tuberculous

Renal lesions of diabetes and amyloid disease

Collagen disorders, such as polyarteritis and lupus erythematosus

Specific endocrine disorders, such as phaeochromocytoma, Cushing's Syndrome and hyper-aldosteronism (Conn's Syndrome) are closely associated with hypertention, as are coarctation of the aorta and toxaemia of pregnancy.

This is not an exhaustive list of the conditions which may be associated with the development of hypertension. But I mention them to show the diverse nature of the factors involved and to draw attention to the fact that any of these conditions can exist in patients without hypertension. If you accept this fact, then you must accept that none of these conditions is a true cause of high blood pressure but that they merely condition the patient so that arterial pressure is likely to be higher than in the rest of mankind. From this it must follow that more than one factor is concerned in the development of hypertension. This may appear obvious but it is a fact which is so often forgotten that I make no apology for reminding you of it.

I will draw one further point from the list of "causes" of secondary hypertension. Quite a number of them are removable, as for example unilateral renal lesions, adrenal tumours, coarctation of the aorta and toxaemia of pregnancy. It is a well recognised fact that in many patients where such a specific "cause" has been removed the blood pressure may never fall to what may be regarded as a normal level for the patient's age and sex. If one accepts this as a fact, then there emerges the concept, advanced and advocated by Pickering (1961) and others, that arterial pressure, once elevated for any reason, tends to remain higher than is normal, even after removal of the original factor.

Now let us turn from these secondary types of hypertension to essential, primary or idiopathic hypertension (call it what you will) and consider the factors which may or may not play a part.

It is common knowledge that emotion may cause a rise of blood pressure. Of all the known types of emotion, anger, frustration and fear are perhaps the most important in this connection. This is the basis of the method of obtaining basal, rather than casual, readings of blood pressure and has been developed with the technique of "emotional desensitization". Many workers have shown that the business executive class, who may be regarded as being more exposed to such tensions, have higher pressures than their fellows. One cannot, of course, regard this as any more than an indication that such strains may play a part in initiating hypertension, a process which once initiated may be self-perpetuating. For it is possible that such classes of mankind differ environmentally in other ways. A lesser amount of physical exercise may, for example, be the more important factor, since it is generally accepted that blood pressure is statistically lower in those who perform more physical exertion in their daily lives than in those who perform less.

Weight and body build come into the picture and cannot easily be dissociated from occupation (and hence class), exercise, or inheritance. Diet is involved too, and closely bound up with social status, both of the individual and of the society to which he belongs. Specific factors within the diet have from time to time come under review, but none has been found to provide a major clue to the understanding of the aetiology of hypertension.

With so much detailed research upon this subject, and with so little profit to show as a result of the effort, it is not surprising that sympathy should grow for a concept which provides for a unique specific cause for hypertension as yet undiscovered. Attempts to define environmental factors having largely been unconvincing and inadequate to account for the condition as seen, could there not be a large inherited factor? And if there is such a factor, could it not be unique and specific in determining whether or not an individual will develop hypertension? In its simplest form, such a factor could be inherited as a Mendelian dominant characteristic whose existence could be proved by the demonstration of

certain manifestations. These would include the transmission of the condition through three or more generations, an equal proportion of affected and unaffected offspring of a sufferer and the clear division of such offspring into affected and unaffected.

Now severe hypertension is rare in the young. The simple pattern of Mendelian inheritance as seen in other conditions, such as albinism, may therefore need to be qualified by the proposition that possession of the gene may lead to development of the condition only after a certain age.

Such indeed is the hypothesis put forward successively by Weitz (1923) in Germany, by Platt (1947) in this country, by Sobye (1948) in Denmark, and subsequently supported by many others. To summarise, their evidence is that essential hypertension may be found in three or more successive generations of many families, that approximately equal proportions of siblings of affected subjects will be affected and unaffected and that examination of the distribution of pressures of these siblings shows bimodality, that is peaks of incidence above and below the critical pressures which can be used to divide hypertension from normality. There are other points made by these protagonists, but these are the most important.

A differing view has been put forward by a group led by Sir George Pickering (1960) in which Dr. Hamilton, to whom we are all indebted for this meeting, and myself were fortunate to be included. Again to summarise, we do not dispute the opposition's evidence. We agree that hypertension may often be found in three or more generations, but we place a different inference upon this fact. We agree that an equal number of affected and unaffected offspring can be demonstrated by choosing a particular dividing line between normality and disease. And finally we agree that if the distribution of pressure of the siblings (within certain age ranges) of affected persons is examined, evidence of bimodality, of peaks above and below the critical evidence can be seen. Indeed we owe it to Sir Robert Platt (1959) that it was he who first demonstrated this from data compiled and published, amongst others, by ourselves.

You will note that the first two of these three sets of evidence require the assumption that it is possible to divide arterial pressure into two groups, those below and those above a certain line, i.e. into normal and abnormal. The third method itself provides evidence for such a line and, indeed appears to add justification to the assumption that pressures of 160 mm.Hg. for systolic and 90 mm.Hg. for diastolic are justifiable points upon the scale at which to make such a division.

It may be profitable for a moment to consider what other evidence exists for such a division. Certainly none is justified by inspection of distribution curves of casual pressure in the population as a whole (Figures 1 and 2).

A commonly advanced reason for accepting a division between normal and abnormal is that cardiovascular morbidity acquires an accelerated relationship to arterial pressure once such levels as 160 for systolic

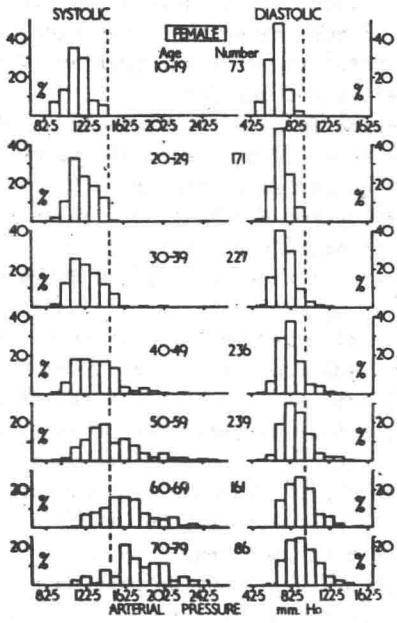

Figure 1. Frequency distribution of systolic and diastolic pressures for females of the population, arranged by age in decades, from Hamilton et al.

Reproduced from Clin. Sci., 13, 11 (1954)

or 90 mm.Hg. for diastolic pressure are passed. But while it is true that the morbidity does increase more steeply above such figures the whole process is smooth.

The most that can be deduced from these considerations is that by the time such levels of pressure are reached, morbidity is beginning to appear in a sizeable manner.

Let us reconsider, then, the evidence on three affected generations. It happens that these pressures of 160/90 are the levels that can be recorded or exceeded in some 25% of the male population in this country by the age of 60 years and in 40% of the female population of the same age. It can be shown from this that even if there were no inherited factor in hypertension, as many as 30% or more of families chosen at random would contain three generations where these pressures would be exceeded by the age of sixty. The argument from three-generation incidence of the disease rests upon its occurrence in less than 10% of studied families; this evidence therefore is scarcely convincing. It is

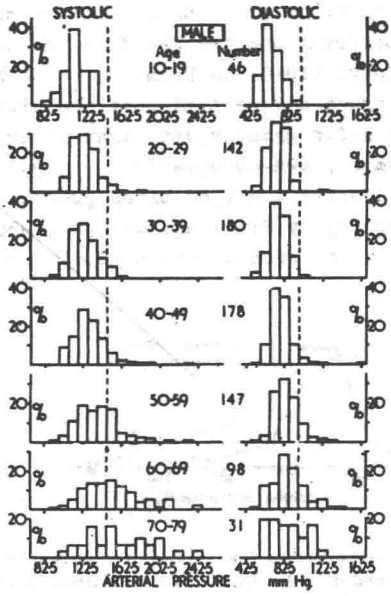

Figure 2. Frequency distribution of systolic and diastolic pressures for males of the population, arranged by age in decades. from Hamilton et al.

Reproduced from Clin. Sci., 13, 11 (1954)

entirely dependent upon the level of pressure which is chosen to divide normal from abnormal.

A similar dependence upon the level chosen is shown, indeed more strikingly shown, by the one to one ratio of affected to unaffected siblings. Weitz (1923) found such a ratio when 160 mm.Hg. was chosen as the dividing line of systolic pressure and when deaths from cardiovascular disease were added to the affected siblings. Had he chosen a lower figure, a greater number of affected siblings would have been observed: a higher figure would have led to a deficiency of affected siblings. The conclusions generally drawn from this work are that it supports the hypothesis of Mendelian dominant inheritance in essential hypertension and that since it supports it, the dividing line is scientifically acceptable.

To translate:-

If a = b, then b = a, $\therefore$ a = b.

Now let us look for a moment at the evidence on the third basis of argument, that there is a bimodal distribution of pressure in the population. Platt (1959) has shown that the distribution-of-pressure curves for the siblings (aged 45-59 years) of subjects with hypertension (also

aged 45-59 years) have dips at or near the levels 160 mm. systolic and 90 mm. diastolic. His observations are based on the data provided by ourselves (1954) and by Sobye (1948) in Denmark. We have made a further analysis of the data concerned and we find that the distribution curves from Sobye's data provide a far greater dip, that is evidence of bimodality, than do those from our own observations. Our initial work was followed by a more comprehensive study of blood pressure levels carried out in a South Wales community by Miall and Oldham (1955). A similar analysis of their data shows no such dip in systolic or diastolic pressure (Figure 3).

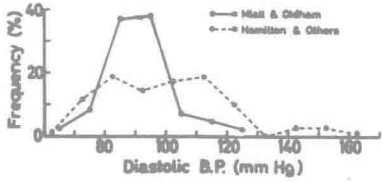

Figure 3. Frequency distribution for relatives aged 45-59 of propositi with hypertension aged 45-59. Data from Hamilton et al (1954) and from Miall and Oldham's survey in the Rhondda Fach and Vale of Glamorgan (1955, 1958). Oldham et al.

Reproduced from Lancet (1960) i, 1085

We must ask ourselves how these differences can be explained. What is it that makes these dips more striking in Sobye's than in our own original data and non-existent in those of our late co-workers, Miall and Oldham? We believe that the answer lies in the method of recording of blood pressure. In Sobye's work the artefact, for such we believe it to be, was deliberate and therefore needs no apology. In our original work, the majority of the recordings of pressures were made by Dr. Hamilton or by myself. We believe our dips to be artificial and due to an error and, with Dr. Hamilton's permission, we apologise for this. Miall and Oldham learned from our mistake and deliberately avoided our pitfall.

What is the nature of this trap? It is best set out in Sobye's own words. "Measurements were taken at intervals of five minutes until basal and stable values were obtained which generally took about five to about forty-five minutes" during which time "soothing and diverting conversation was continued". Now we originally assumed, and so did Sobye, that subjects could be divided into those with and without hypertension. But we now suggest that in our study and in Sobye's, there was conscious or unconscious discrimination against border-line pressures. That Sobye's discrimination was nearer to the level of consciousness is shown by his greater dips. Miall and Oldham, however, set out with no such preconceived assumption and hence their distribution curves show smoother outlines.

There is also a difference between the curves from our original data and those from Miall and Oldham's (Figure 3) other than the factor of bimodality. Our original curves are flatter and extend more into the realm of serious hypertension than do theirs. Now our subjects with hypertension, from whom these relatives derive, were chosen because they suffered from hypertension. Miall and Oldham chose no such group but studied a whole population. Their propositi (subjects from whom family studies stemmed) were selected from their population solely because their diastolic pressures were 100 mm.Hg. or more. It follows that a totally different distribution of pressures of hypertensive propositi will be found in Miall and Oldham's work than in our own. Figure 4 shows that

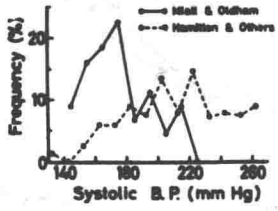

Figure 4. Frequency distribution of blood pressures in the propositi from whom the relatives shown in Figure 3. were derived. Data from Hamilton et al (1954) and from Miall and Oldham's survey in the Rhondda Fach and Vale of Glamorgan (1955, 1958). Oldham et al.

Reproduced from Lancet (1960), i, 1085

many more of their propositi have pressures in the lower range of what we chose to call hypertension, and correspondingly fewer very high pressures.

If the all or none inheritance implied in the simple Mendelian dominant hypothesis applies, this distribution of propositi within the range of hypertension should not affect the distribution of pressure amongst their siblings. But we have seen that this is not so, that the relatives from Miall and Oldham's data show a higher incidence of lower pressures than those from our series. In fact, they quantitatively reflect the distribution seen in the propositi. This fact would appear incompatible with a theory of all or none inheritance.

This quantitative concept of hypertension is strengthened by the following facts. We have shown that if the data is treated mathematically, relatives within a family can be demonstrated to show a resemblance with regard to their pressures, both systolic and diastolic, which is independent of the height of pressure. This resemblance is of modest dimensions, amounting to about one-fifth of its originator. By this is meant that for a given deviation from the general level of pressure for

a given age and sex, a relative of such an individual will statistically tend to show a deviation in the same direction, but of one-fifth the magnitude.

The mathematics of this process are highly involved and have been much criticised. They are based upon the construction of curves for expected blood pressure in the population under consideration (Figure 5).

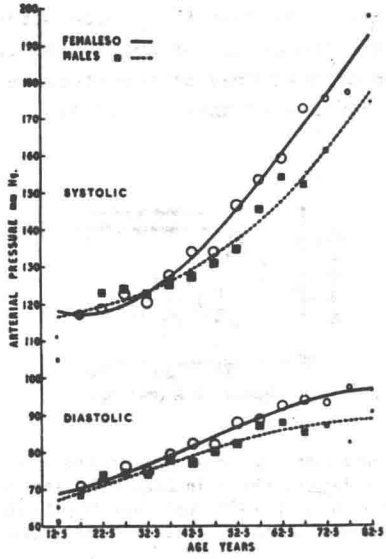

Figure 5. Systolic and diastolic pressures for females (open circles) and males (black squares) for five year age groups. The area of each circle or square is proportional to the number of subjects in that age group. Hamilton et al.

Reproduced from Clin. Sci., (1954) 13, 11

From such curves as these it is possible to calculate the deviation from the norm which any individual shows. Allowance has then to be made for the greater significance of a given deviation in younger than in older subjects. The net result is a factor, applicable to every individual, for both systolic and diastolic pressures, which we termed the Age & Sex Adjusted Score. Using such scores, we are able to compare and contrast the blood pressures of persons of differing age and sex.

From such an analysis, Miall and Oldham have shown that at any age the resemblance within families tends to apply. The offspring and younger relatives of subjects conform to this pattern as well as the older relatives, past middle age.

Furthermore, this resemblance applies where the departure from normality is towards low as well as high pressures. If you accept this

evidence, and the thesis upon which it is based, then the concept of essential hypertension as a disease inherited, all or none, is stone dead. That is unless you are going to propose another genetically inherited condition, essential hypotension. And even this would not suffice, for you must then propose some intermediate genes for rather high pressure, and some more for rather low pressure. In fact you must say that inheritance itself is multifactorial in hypertension. Which is just what we do say.

But a word about this Age and Sex Adjusted Score and the mathematical juggling behind it! It is in fact a way of showing whether an individual and, in the aggregate, groups of individuals, show pressures above or below a fixed reference point, and if so by how much above or below. The complicated formulae to construct the basic curves have been much criticised, especially in the light of the known inaccuracies of measurement of pressure. But looking at these curves again, I suggest that you or I would have drawn them very much the same if we had done it by eye. We can, then, I suggest, accept them as representing the mean readings of given populations. The facts which emerge from this are that if an individual's pressure, be it systolic or diastolic, departs from this curve, the corresponding pressure of his close relatives will tend to depart in the same direction, whatever the age of that relative. The finding that this departure of the relative's pressure is constantly one-fifth of the departure of pressure of the propositus is based upon even more complex mathematics and can for the present be set aside. What is important is that the departure is in the same direction, up or down, and occurs at all ages.

You may agree with me that this finding is incompatible with a concept of hypertension as a condition which is either inherited or not inherited and which does not manifest itself until middle life.

Instead, I put before you the concept that essential hypertension represents the upper part of the range of arterial pressure within the population where no tangible provocative factor can be found. That it is in part inherited and that, as with height and weight, this inheritance is on a quantitative basis.

It is apparent to me that other factors than inheritance are of importance but it is beyond my power to go into them in detail. Possibly the factor of renal ischaemia will be recognised as of major significance. Such a factor in no way cuts across the concept that I have presented to you, for surely there are degrees of renal ischaemia.

To conclude I would like to quote to you from Tolstoy's "War and Peace". Writing of the war of 1812, he says:-

"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.... When an apple has ripened