Hyperpiesis: High Blood-pressure without Evident Cause: Essential Hypertension*

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Benign Hypertension

The benign phase of hypertension offers a great contrast to the malignant phase. The course is long and variable, with the condition often remaining unchanged for years; thus, of Bechgaard's original 1,038 patients, 357 were alive after 20 years (Bechgaard *et al.*, 1956). Bechgaard (unpublished) has recently reported that 144 were alive after 26 to 32 years. Uraemia does not occur; bilateral neuroretinopathy does not occur; cerebral oedema does not occur, or occurs only rarely; patients tend to die of heart failure, cerebral vascular disease, or intercurrent disease. Its nature is clearly different.

The malignant phase is characterized by lesions which represent the limit of cardiovascular tolerance, fibrinoid arteriolar necrosis, retinal exudates representing focal vascular damage, hypertensive fits of similar origin, left ventricular failure in response to overloading. While each phenomenon is dependent also on other factors, thus accounting for some variation, few patients fail to exhibit at least two of these phenomena. In the benign phase the relationship between arterial pressure and the lesions that kill or cripple the patient seem to be less close; factors other than arterial pressure intrude more. Hence for a given grade of elevated arterial pressure we have a much greater variability in duration of life and course of illness; so much so that some patients live their full span¹ and die of unrelated disease.

Heart Disease

It is usual to distinguish two forms of heart disease, arteriosclerotic and hypertensive, the former with demonstrated coronary disease, the latter without. Master's (1953) figures showed that women with coronary artery disease tend to have arterial pressures much above the norm, while in men the corresponding tendency is slight. Nevertheless, the Framingham studies have displayed that both arterial pressure and plasma cholesterol are related to the future occurrence of myocardial infarction in men (Fig. 11). In both the relationship is quantitative; the correlation with arterial pressure is rather low (Dawber *et al.*, 1962).

In many patients with cardiac failure associated with elevated arterial pressure and without symptoms of ischaemic heart disease the coronary arteries are not narrowed after death (Harrison and Wood, 1949). In such patients therapeutic reduction of arterial pressure may abolish cardiac failure; the higher the arterial pressure the greater the probability that this will happen. The onset of heart failure is often not precipitated by a recent rise of arterial pressure. It would seem, therefore,

that there is a third factor not in the coronary arteries and not the arterial pressure which contributes to hypertensive heart disease. Could it possibly be related to advancing years, the disorder described by William Dock (1945) as presbycardia? As Fig. 12 shows, heart weight and arterial pressure are related quantitatively. Since, as Shirley Smith and Fowler (1955) and Hamilton (1956) have shown, heart failure can be relieved and prevented by lowering pressure, and since heart size decreases (Smirk, 1957), there is a strong case for supposing that elevation of arterial pressure is a causal factor in the cardiac changes.

Cerebral Vascular Disease

Cerebral vascular disease is still something of a morass. It is customary to divide cerebral vascular disease into embolism,

FIG. 11.—Risk of coronary heart disease according to level of diastolic blood-pressure; Framingham men 45-62, with various serum cholesterol levels. (Kagan and others, 1959. Copyright, American Heart Association.)

FIG. 12.—Relationship between systolic blood-pressure and heart weight in patients dying of hypertension and renal disease (Evans, 1921).

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As I read through this I began to wonder what I meant by a full life-span. My mind came round to a patient, age 62, who was sent to me by her doctor to reinforce his advice that she should not cycle six miles (9.6 km.) to work each day. She explained why she did. Eventually I said: "Well, at your age you should retire." The reply came: "I can't, I have to keep mum and dad." Interested in inheritance, I found from their doctor that dad, aged 90, and mum, aged 88, both had diastolics over 130 mm. Hg. This could perhaps be said to constitute a full life-span. I allowed the patient to cycle to work.

thrombosis, and haemorrhage. If we exclude embolism from the heart, which is of minor importance in essential hypertension, then it would seem that we are concerned with three quite different diseases affecting different sizes of arteries in different ways, and having different relationships with elevation of arterial pressure. All are commonly termed "atherosclerosis," which confounds the confusion.

(a) Nodular Arteriosclerosis

This disease of larger arteries essentially involves the intima, where fibro-fatty nodules appear. Thrombosis may close the vessel. This is the disease which causes coronary occlusion; it also causes stenosis and occlusion of the carotid and vertebral arteries and the circle of Willis. It has long been known that carotid artery thrombosis may first display itself by transient cerebral or retinal ischaemia. Millikan, Siekert, and Shick (1955) suggested that such attacks were embolic. Gunning *et al.* (1964) have shown that in patients presenting such attacks nodules may be found in the carotid sinus, and that these nodules may present the following layers from lumen to media: fresh platelet leucocyte fibrin thrombus, hyaline fibrin thrombus, fibrous tissue, and atheroma. The cause of the "atheroma" or nodule of grumous tissue containing cholesterol clefts is still uncertain. But there is now quite strong evidence that the nodule grows by deposits of platelet thrombi, ageing, and becoming incorporated into the wall. Such deposits may become detached as emboli friable enough to pass the retinal and cerebral arteries with no more than transient ischaemia, or as emboli stable enough to produce permanent occlusion of cerebral or retinal arteries; both kinds may occur in the same patient. Finally, the thrombus may be big enough to occlude the artery where it forms. Thus the symptomatology of this disease, so far as it affects the cerebral circulation, is much more variable than was at one time supposed.

Dr. Yates very kindly put at my disposal the notes on his patients with carotid and vertebral artery disease, and I worked out their age-and-sex-adjusted scores. These showed little deviation from zero; that is to say, the arterial pressures in these patients were not far removed from those which would have been found in a random sample of the population of similar age and sex. This disease, then, is only to a very small extent associated with raised arterial pressure. It seems, in fact, to be very much in the same relationship as its counterpart in the coronary artery. Allbut (1915) recognized this, as previously noted.

(b) Aneurysms of the Circle of Willis

These are well known. Patients presenting with cerebral haemorrhage from one of these aneurysms may tend to have higher arterial pressures than is usual for their age, but this is by no means established. There is a special association with coarctation of the aorta.

(c) Aneurysms of the Small Cerebral Arteries

Charcot and Bouchard (1868), by allowing the brain to autolyse and be washed away by running water, first demonstrated the association between cerebral haemorrhage and aneurysms of the small cerebral arteries. Recently Ross Russell (1963) has injected a barium sulphate gelatin mass into the brains of 54 subjects freshly coming to necropsy in Boston City Hospital: The diastolic pressure was over 110 mm. Hg in 16, below in 38 subjects. Small aneurysms were found in all but one of the hypertensive group and in 10 of those with lower pressures. With one exception, patients with more than 10 aneurysms all had hypertension. No aneurysms were found in patients under 50 years. These aneurysms were situated on

small arteries 100–300 microns in diameter, particularly on lateral branches of the striate arteries or on penetrating vessels from the cortex. The muscular tissue of the parent vessel terminated abruptly at the point of origin of the aneurysm, and the remnants of elastica could be seen to extend for a short distance into the aneurysm before disappearing. The wall of the aneurysm was composed of connective tissue only, an inner hyaline layer derived from intima fusing with an outer collagenous layer continuous with the adventitia of the parent vessel. Frequently the aneurysms showed evidence of leaking and thrombosis. Ross Russell's observations suggest that such aneurysms form continuously in patients with elevated pressures as they grow older. They can produce small haemorrhages and small thromboses with local softening which would resemble the miliary infarcts described by Rosenberg (1940). When the thromboses extend proximally into larger arteries, larger areas of softening may result. Finally, there may be massive rupture with massive intracerebral haemorrhage. It would seem likely that these intracerebral aneurysms are the missing link between raised arterial pressure and cerebral vascular disease.

Strokes and Hypertension

Fig. 9 has shown the relation to be expected from raised arterial pressure at insurance examination, and subsequent death from cerebral vascular disease. That these two phenomena are related as cause and effect is suggested by Marshall's (1964) observation that when arterial pressure is reduced in patients who have already had strokes further cerebrovascular episodes are reduced in frequency. Hamilton, Thompson, and Wisniewski (1964), in a controlled trial, also found a reduced incidence of stroke in symptomless hypertension treated for six years as compared with controls.

Arteriolar Lesions

The arteriolar lesions of the benign phase consist of fatty hyaline subendothelial thickening in the arterioles and elastosis in the smaller arteries. These lesions have not been produced experimentally. In man they occur in all kinds of hypertension, though most conspicuously in essential hypertension, and are generally believed to be consequences of the raised pressure. Thus they are generally less conspicuous in a kidney with renal artery stenosis than in its fellow. Their intensity is proportional to the degree to which arterial pressure is raised (Table IV). These arteriolar lesions produce minor degrees of renal impairment and may contribute to retinal or cerebral changes, but in general seem unimportant symptomatically.

TABLE IV.—*Relation Between the Severity of Hypertension, as Gauged by the Diastolic Blood-pressure, and Renal Vascular Disease (Smithwick and Castleman, 1951)*

Severity of Hypertension	Percentage having Renal Vascular Disease	
	None to Mild	Moderate to Severe
Intermittent	75	25
Persistent:		
Diastolic blood-pressure 90–109 mm.	61	39
Diastolic blood-pressure 110–139 mm.	37	63
Diastolic blood-pressure 140 + mm.	29	71

Nature of Benign Hypertension

From what we now know it would seem that the clinical manifestations of benign hypertension are due chiefly to three different pathological processes having different correlations with arterial pressure. (1) Aneurysms of the small cerebral arteries, probably the chief cause of cerebral haemorrhage. These have been so recently rediscovered that their relationship with arterial pressure has not been fully explored. Unanalysed

clinical experience would suggest a fairly high correlation with arterial pressure and age. (2) Heart failure, partly due to the increased load on the heart and partly to an unknown factor, perhaps connected with ageing of the heart; this second factor substantially reduces the correlation between heart failure and arterial pressure. (3) Nodular arteriosclerosis, displayed chiefly by coronary and cerebral artery stenosis and occlusion; this is lowly correlated with arterial pressure, and is also correlated with serum cholesterol, with age, and with the male sex.

Unlike the phenomena of the malignant phase, those of the benign phase have not been fully reproduced in animals. We are therefore unusually dependent on evidence from man. Leishman (1959, 1963) and Hodge, McQueen, and Smirk (1961) have each found falls of mortality in treated as compared with untreated patients with benign hypertension—in Leishman's series to one-third. However, these were not strictly controlled trials. Hamilton *et al.* (1964) allocated alternately to treated and control groups 22 men and 39 women who had arterial pressure of more than 110 mm. Hg over three months' observation period and no complications. Antihypertensive therapy reduced the frequency of complications in both sexes, the difference being significant to 2.5% in the males. This is the present evidence regarding the role of raised arterial pressure in the manifestations of the benign phase.

Why is the Arterial Pressure High?

Attempts to find a specific cause of the increased peripheral resistance, which is certainly present in advanced cases, have failed. It seems extremely likely that many factors are involved and in different ratios in different subjects. The situation has not materially changed since it was fully reviewed (Pickering, 1955).

Heredity and Environment

Platt and I have had a long controversy over the nature of inheritance and the extent to which it contributes to the pressures found in essential hypertension. Platt has believed that essential hypertension is inherited as a single gene and that environment plays comparatively little part. The facts have driven me to a different conclusion, which I now set out.

The evidence for single gene inheritance originally came from Weitz (1923), and was based on the assumption that a line can be drawn between normal and abnormal pressures at 160 mm.

Hg systolic. This assumption, as we have seen, is groundless. Moreover, it represented a circular argument, for the assumption was made to give a 1:1 ratio between affected and unaffected elder sibs. An analysis of our family data derived from subjects with essential hypertension (Hamilton *et al.*, 1954b) showed that children tend to resemble their parents and that the resemblance is quantitative. We determined the coefficient of resemblance in five ways; all gave a coefficient of about 0.2. Because our *propositi* had been selected for hypertension, we thought our best estimate was the resemblance between sibs of our hypertensive *propositi*, the *propositi* themselves being omitted. The coefficients for systolic pressure were 0.213 in the series of Søbye (1948), from Copenhagen, and 0.267 from our own. The coefficient of resemblance in our families derived from data from *propositi* with so-called normal pressure was not significantly different from zero on the one hand and that of our hypertensive relatives on the other. Our data were, however, not gathered with this particular purpose in mind, and were theoretically open to the objection that our *propositi* had been selected because their blood-pressures exceeded or fell below arbitrary values.

Miall and Oldham (1958, 1963) measured the blood-pressures in a 1 in 90 sample of the population of the Rhondda Fach, and over 95% of their first-degree relatives living within 25 miles (40 km.). They went on to do the same for the Vale of Glamorgan, a total of 2,245 first-degree relatives being examined. Finally, they measured the blood-pressures on a second occasion four years later. The results have shown a quantitative relationship between the arterial pressures of *propositi* and their first-degree relatives. When the deviations from the norm, adjusted for age and sex, are plotted for *propositi* against relatives, the result is a straight line. Moreover, as the number of observations increases, the scatter about the line decreases (Figs. 13 and 14). Again, the 12 regression coefficients involving the six different relationships of male *propositi* increased in value in 10 and decreased slightly in only two with the second measurement. These different coefficients showed no heterogeneity. These results suggest strongly that in the population at large blood-pressure is inherited quantitatively as a graded character, presumably due to multifactorial inheritance. This is true whether the arterial pressure is above or below the norm. The coefficient of resemblance is almost exactly the same as we had found in the hypertensive relatives.

The repeated measurements have enabled Miall and Oldham (1963) to calculate more accurately the "error-free" coefficient of resemblance, 0.399 for systolic and 0.302 for diastolic. This enables the size of the genetic and environmental factors to be estimated. To quote: "If a characteristic were entirely inherited multifactorially, 50% of its variance would be

FIG. 13

FIG. 14

FIG. 13.—Relationship between the systolic blood-pressure scores of *propositi* and the mean systolic scores of relatives. From the first Rhondda Fach survey. (Miall and Oldham, 1963.) FIG. 14.—Relationship between the systolic blood-pressure scores of *propositi* and the mean systolic scores of relatives. From the combined Rhondda and Vale initial and follow-up surveys. (Miall and Oldham, 1963.)

accounted for by a knowledge of the parental genes. The remainder reflects the fundamental uncertainty of which allele of each gene-pair of a parent was handed on. Our estimate of the systolic regression coefficient, 0.287, is also an estimate of the correlation between first-degree relatives. Its square, 0.082, estimates the proportion of variance accounted for by one parent, and an equal amount can be attributed to the other. Since at most 50% of the variance is accounted for in this way, when hereditary determination is complete, 16.4% corresponds to 32.8% hereditary determination. The complementary fraction, 67%, of the variance may be environmentally determined. The corresponding figure for diastolic pressure is 79.9%. . . . Similar calculation, using the estimated error-free regressions of 0.399 for systolic and 0.302 for diastolic pressure, would leave 36.3% of systolic variance and 63.5% of the diastolic variance attributable to non-familial environmental factors."

Since 1959, Platt has consistently taken a different point of view. In his first paper (1959) he showed that when the siblings of the middle-aged probands (aged 45–60) with essential hypertension, derived from Hamilton *et al.* (1954b) and Søybye (1948), were arranged by arterial pressure, dips in the curves were found at 150 systolic and 90 diastolic, which, as he remarked: "is exactly the figure most commonly chosen by clinicians as the dividing line between normal and high blood-pressure in middle-aged subjects." He thought this was evidence of two populations, and this meant that hypertension was inherited as a dominant gene, and he went on to calculate the gene frequency, which he estimated as 19 to 30%. We (Oldham *et al.*, 1960) therefore re-examined the data and showed that the dips were almost certainly due to digit discrimination, which was most conspicuous in Søybye's series.

More recently Platt (1963, 1964) has collected his own series of relatives and now thinks that there are three populations. I find it really quite remarkable that he continues to attach importance to the irregularity of curves with such small numbers, particularly when some of his curves, on his criteria, indicate five populations. For example, here are his consecutive numbers in a recent paper: 5, 3, 6, 8, 6, 9, 6, 4, 2, 3, 2, 3, 5, 1—total 63 for females; 1, 6, 7, 6, 7, 7, 2, 2, 1, 3—total 49 for males. These dips are supposed to be evidence for three populations—two homozygotic and one heterozygotic. For comparison, here are groups for stature taken from Galton's classical paper of 1889. For children of parents whose mean height was 69½ in. (176 cm.), the numbers of children in groups of ascending stature are: 1, 16, 4, 17, 27, 20, 33, 25, 20, 11, 4, 5—total 183. Stature is, of course, the classical example of graded inheritance. No one has paid any attention to these irregularities in Galton's curve, which are regarded as natural with such small numbers. Since measurements of arterial pressure are much less replicable than those of stature, irregularities in frequency distribution curves are even less significant.

Platt (1959) has stated: "The final proof as to whether essential hypertension exists as an entity will have to wait until a prospective survey lasting at least twenty years has been made over a large unselected population to see whether with advancing years they segregate into two groups, those whose pressures steeply rise and those whose pressures remain little affected. Until this is done I shall remain unconvinced that the work of Pickering and his colleagues has disposed of the concept of the entity of essential hypertension." Such a study has now been made by Harlan, Osborne, and Graybiel (1962), who made three measurements, in 1940, 1952, and 1958, on 785 men, being 96% of the surviving members of a group selected for naval flight training. The frequency distribution curves for the five-year age-groups as the original cohort aged are shown in Fig. 15. It is interesting to note that the systolic blood-pressure curves show what Platt would call bimodality, there being a dip at 120 mm. Hg in each age-group except the second. However, the authors attach no importance to this. Their frequency distribution curves in a group followed for 18 years are very much like those obtained by others—for example,

Hamilton *et al.* (1954a, 1954b), in different age-groups measured on a single occasion—and they confirm that arterial pressure tends to rise with age and rises more in some subjects than others. There was no evidence for segregation into two groups, those whose pressure rises steeply with age and those who remain little affected. They found rise of pressure was significantly greater in those who gained weight. It was also greater in endomorphs than in ectomorphs. Finally, there was a greater rise in those with positive family histories for vascular disease, and this was independent of weight gain. The mean rate of rise was similar to that found by Hamilton *et al.* (1954b).

FIG. 15.—Frequency distribution curves for blood-pressure in the same group plotted at five-year intervals. (Harlan, Osborne, and Graybiel, 1962.)

Morrison and Morris (1959) also found a dip in the frequency distribution curve of the blood-pressure of 90 drivers, one or both of whose parents died in middle age. They interpreted their results as meaning single gene inheritance. Lowe and McKeown (1962) carried out an analysis similar to that of Morrison and Morris on 5,239 men who attended for x-ray examination when a mass radiography unit visited an electrical engineering firm. Bimodality was not found in the curves for middle-aged men one or both of whose parents had died from cancer, from heart disease, or from stroke. Ostfeld and Paul (1963) examined 2,080 men employed at the Hawthorne Works of the Western Electric Company of Chicago. The results obtained by Morrison and Morris could not be duplicated. The division of men into those with and those without a parent dead in middle age elicited no essential difference in blood-pressure frequency distributions between the two groups.

Environment

Fig. 16 compares the regression lines of blood-pressure on age in a population sample, first-degree relatives of subjects without hypertension, and subjects with essential hypertension. The slopes of the lines for systolic and diastolic pressure are similar; the lines for the relatives of subjects with essential hypertension are at a higher level. This suggests that what is passed on by inheritance from those with high pressures is a tendency to high pressures at all ages, and not a tendency to a more rapid rise with age. It would seem, then, that the rate of rise with age is determined not by inheritance but by environment.

FIG. 16.—Regression lines of systolic and diastolic pressure on age in a population sample, the first-degree relatives of normal propositi, and first-degree relatives of propositi with essential hypertension (Hamilton *et al.*, 1954).

In producing the very highest pressures, as seen in the malignant and the severest form of the benign phase, it is probable that both the inherited and the environmental components are unusually large. In polygenic inheritance, some offspring will get a larger, some a smaller load of those genes favouring high pressures, those getting the largest share having the greatest tendency to high pressure at all ages. However, in most patients the rate of rise with age is as a rule also unusually great, as in Case 6 (see Part I), and in Evelyn's (1954) patient illustrated in Fig. 17. Whereas the mean rise of arterial pressure with age in the population and in first-degree relatives of patients with essential hypertension was approximately 1 mm. Hg per annum, Case 6 had a rise of 90 mm. and Evelyn's patient 100 mm. Hg in 10 years—that is, a rate of rise 10 times the population mean, as had Case 3 of this paper, with pyelonephritis.

FIG. 17.—Arterial pressure in a female patient with essential hypertension over a period of years. CVA=cerebrovascular accident (Evelyn, 1954).

The environmental factors known to influence rate of rise with age are three: family size, physical work, and obesity. Miall and Oldham (1958) showed that arterial pressure tended to be lower the greater the number of children for mothers, and, surprisingly, for fathers too, though to a less extent. I find it difficult to believe that this effect can be other than through the mind. The arterial pressure was also lower the harder the physical work, but this was not confirmed at re-measurement (Miall, 1959). Harlan *et al.* (1962) in their 18 years' follow-up found that the position of individuals in the frequency distribution curves tended to stay the same from year to year, but that those who put on weight tended to have a greater rise with age.

I agree with Platt that none of these factors account for the rate of rise found in severe hypertension—for example, 10 mm. Hg per annum. The evidence for salt does not in my opinion bear critical examination (see Miall, 1959). I believe factors operating through the mind may be of great importance, but the evidence concerning them is trivial. It is in fact difficult to identify such factors, much less to measure them.

Platt believes that the genetic factor is especially strong in severe hypertension. He bases this partly on three pairs of identical twins; one of each pair had come to him with severe hypertension; the other twin was almost as severely affected. Our data, however, showed that the more severely affected the patient the less his first-degree relatives resembled him, suggesting that environmental factors had been particularly important in producing the very high pressures in the patients.

Environmental factors are especially important because if they are recognizable they can be modified. Had I had the unlikely privilege, I would certainly not have chosen my parents on grounds concerned with arterial pressure, because there are others so much more important. But it would be helpful if we could prevent the higher rates of rise with age. The nature and size of the environmental factors determining the rise with age provide the most rewarding field for research in this subject. Repeated observations on individuals over 20–30 years would be particularly instructive. I would not be surprised if some of his patients gave the answers to these questions to an industrious and intelligent general practitioner.

Summary and Conclusions

It seems quite extraordinary that I have to emphasize the basic platitude that arterial pressure is a quantity, and should be treated as such. The current practice of treating it as a quality, good or bad, is responsible for a whole series of artifacts which only confuse. Raised arterial pressure seems to have, in man, a series of consequences that are related quantitatively to the degree of elevation of arterial pressure. Because arterial pressure varies so greatly in the course of 24 hours, and because the physician's estimate is so dependent on his effect on the patient, it is difficult to gauge how close this correlation is. It would seem, however, that all these consequences are dependent also on other factors, known or unknown. In some, these other factors play a relatively small part, in others a much larger part. The malignant phase seems to be an expression of a very severe hypertension, and can be reversed if the arterial pressure is reduced before the kidney is irretrievably damaged, and of this the blood urea is an imperfect guide. The benign phase is much more variable, and manifests itself through a series of events that have different, and probably rather lower, correlations with arterial pressure. The lowest correlation is probably with the process known as nodular arteriosclerosis (Allbutt's "decreased arteriosclerosis" and one of the components in contemporary "atherosclerosis"), which causes stenosis and occlusion of coronary, carotid, vertebral, femoral, and other large arteries.

The parts played by inheritance and environment are discussed. The most difficult, least explored, and potentially most fruitful field is that of environmental factors. Here there is a splendid opportunity for the family doctor to make a decisive contribution.

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