HYPERTENSION

The Coincidence of Conditions

Part II.

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The Consequences of Hypertension

Thus far the picture has been evolved of arterial pressure varying greatly throughout the population; rising generally as age advances, more rapidly in some individuals than in others; being determined in any individual by age, sex, inheritance, obesity, exertion, anxiety and other specific renal or endocrine factors; perhaps too being influenced by factors unknown but of magnitude; and being described when elevated by no defined cause as essential hypertension, and as secondary hypertension if some closely correlated disease process is identified. It is part of this picture that hypertension defies precise definition.

It is necessary now to examine this last feature of the concept from the standpoint of prognosis. If it could be shown that at some particular level of pressure there suddenly appeared an adverse trend in life expectation, the case for a separate disease entity, called essential hypertension, would be strengthened, but not proved. It could be argued that all pressures above that level constituted hypertension, all below, normality. Such arguments have been advanced, for example by Robinson and Brucer³⁴ who claim that expectation of life deteriorates when pressures above 130/80 are encountered. This fact indeed cannot be denied but inspection of their figures reveals that there is no abrupt change at those pressures. It can be seen that the prognosis begins to worsen from the modest figures of 105/75 and that this adverse trend accelerates as pressures rise. This phenomenon is widely recorded, in part from the figures derived from insurance companies and in part from the observations of clinical records. There is an unfortunate dichotomy between these two sets of data, the former being derived from subjects selected so that those with gross elevation of arterial pressure are excluded, the latter from patients with considerable hypertension only. None the less the pattern is the same throughout, that as arterial pressure rises, expectation of life falls, and at an accelerating rate. A further point emerges clearly from these studies, namely that

for any given pressure the expectation of life is better for women than for men, a fact which is within the experience of any practising physician. But it is common to all these observations that there is no point on the scale of pressures at which any sudden change in mortality appears. The curves are smooth but not linear. This is in keeping with the view that hypertension represents simply the upper end of the range of a smooth distribution of arterial pressure in the general population.

The adverse prognosis of hypertension is wrought through the ill effects that it has upon the cardiovascular system, the heart and the arteries bearing the brunt of the attack. Other organs are involved, but such involvement is secondary to the underlying cardiovascular disease.

The commonest agent to which heart failure is ascribed in this country, or in other peoples of European stock, is hypertension. The point has already been made that such a diagnosis is often recorded more for the sake of nosological simplicity than as a critical appraisal of the degree of responsibility, and is based in such cases upon the finding of a blood pressure elevated to but a modest degree. The picture is further complicated by the coincidence in many such patients of coronary artery disease. Cardiac hypertrophy is related to the height of the blood pressure both in rabbits²⁷ and in man,⁸ but in neither of these studies is the correlation at all close. It is a commonplace in clinical practice to find patients who have been known to have marked hypertension for years and yet who show little evidence of cardiac hypertrophy. On the opposite side of the picture there are seen patients whose clinical records extend over a considerable span with nothing other than mild hypertension yet who die of cardiac failure and, post mortem, show gross cardiac hypertrophy. The explanation of these anomalies sets a problem to which there is no simple answer. In the latter case it is possible that it is the failure per se that is responsible for the major portion of the hypertrophy, since Davis and

Blumgart⁵ have shown that failure, from whatever cause, and hypertrophy go hand in hand. Should this be so then the attribution of the death to the hypertension in such a patient is not as valid as it would appear.

The story is told of a post mortem demonstration where the blood pressure of the patient, a woman aged 75 at death, had been in the region of 190/100. Death was shown to have been due to left ventricular failure; the possible role of hypertension was discussed and, there being no other recognized cause for the findings, hypertensive heart disease was the final diagnosis. The comment of a physician that the patient appeared to have died of normality is full of meaning. What factor or factors in this instance led to gross cardiac hypertrophy, failure and death? In their population sample, Hamilton, Pickering, Roberts and Sowry¹¹ show pressures of this order to exist in 35 per cent. or more of females between 70 and 79 years. It would seem illogical to attribute death in this one instance to a condition present in 35 per cent. of similar individuals, in the large majority without ill effect. The cause of the cardiac failure presumably lay in a combination of coronary disease, myocardial degeneration and other agents. It is admissible that, had the pressure for years been lower, the patient might not have died. But to use this argument in reverse to claim that hypertension was the responsible agent seems incorrect.

To learn the reasons for cardiac hypertrophy in patients with little hypertension or other demonstrable cause is inseparably linked with its converse, namely to fathom why there is no hypertrophy in certain patients with considerable elevation of blood pressure of some duration. Such instances would appear to indicate that it is not the hypertension per se which causes the hypertrophy.

None the less, when all such anomalies are carefully considered, it remains a fact that hypertension is a major factor in the development of cardiac failure in this country. Such cases do not detract from the clinical importance of hypertension. They do, however, reveal the imperfect understanding of the events witnessed.

Arterial disease and its correlation with hypertension present no less of a problem than does heart failure. Of all arterial diseases, by far the most important is atheroma. That there is a causal relationship between hypertension and atheroma is proven beyond reasonable doubt, although there is evidence to show that the relationship may not be direct. Thus Davis and Klainer⁶ have shown that although atheroma of the coronary vessels is commoner in hypertensive than in normal individuals, there is within their

hypertensive group little or no correlation between the severity of the atheroma on the one hand and the severity and duration of the hypertension on the other. Their evidence is not completely conclusive, however, since their assessment of the severity and duration of the hypertension was based in part upon the weight of the heart. There is to this train of thought the objection that severe coronary atheroma may prevent the development of cardiac hypertrophy in the presence of hypertension. Since both hypertension and atheroma independently may cause cardiac hypertrophy⁵ such an argument is unlikely to be true, but it remains possible. The increased atheroma of the pulmonary arteries found in patients with mitral stenosis⁴¹ is perhaps the strongest evidence for the association between atheroma and a raised arterial pressure.

To what extent are the diseases and disasters immediately attributable to atheroma ultimately able to be laid at the door of hypertension? It is a commonplace that coronary thrombosis is commoner amongst hypertensive populations than amongst normal populations. How much commoner is indicated by the figures of Master.²¹ By statistical definition his hypertension represents 2.5 per cent. of the population; in his patients with coronary occlusion, hypertension as defined by him was found in 22 to 30 per cent. of men of varying ages and amongst 63 to 78 per cent. of women. This finding supports the clinical observation that hypertension is a more important factor in the development of coronary disease in women than in men. In accord with the thesis already advanced, that arterial pressure rises with age, Master's definition of hypertension too rises with age. It is of interest to note that despite this, the percentage incidence of hypertension amongst his patients with coronary occlusion also rises with age. Turned about, this means that the number of subjects with normal pressures and coronary thrombosis is greater at young than at old age. This observation lends support to the validity and scientific soundness of allowing for age when estimating the departure from normality of arterial pressure. For if such a procedure were not in accord with the natural process of man's development and ageing, then the fact that Master's definition of normal pressures leads to an increase in upward range of normality as age advances would be reflected in an increase in the incidence of so-called normal pressures in coronary thrombosis in older age.

It is probable that cerebral haemorrhage in particular, but also cerebral thrombosis, are more directly related to hypertension than is coronary artery disease. Although normal or near normal blood pressure is encountered amongst the victims

of 'strokes' it is uncommon. Once again, however, the fact that it can and does occur shows that hypertension is not 'the cause' of strokes but only a factor. From the closer correlation which may exist between 'strokes' and high blood pressure than between coronary disease and the same agent, it would appear that in cerebral vascular disease hypertension has a bigger slice of the aetiological cake than in coronary disease. Why this should be so is uncertain; that there is no counterpart in the heart of cerebral haemorrhage is perhaps a relevant factor, for excluding the cerebral haemorrhage associated with berry aneurysm, hypertension is far and away the leading aetiological factor in such lesions.

Other vascular lesions associated with hypertension include peripheral vascular atheroma, giving rise to intermittent claudication or to ischaemic changes in the limbs, and medial degeneration of the large arteries. The former lesion is without doubt more closely correlated with ageing than with hypertension. It is probable also that the same holds true in the latter lesions, but the absence of symptoms in life renders the lesion one often only diagnosable at post-mortem examination or shortly before it. In such circumstances, the part played by hypertension is difficult to assess.

Of all vascular lesions, none bears a closer relationship to hypertension than does fibrinoid arteriolar necrosis of the malignant phase. Atheroma is associated in a widely differing measure according to its site, from a modest association in coronary disease to an intimate one in cerebral vascular accidents; but fibrinoid necrosis appears as the sole vascular lesion directly attributable to hypertension. Pickering²⁴ has developed the theme at length and cites as the main evidence the occurrence of such a lesion in hypertension of sufficient severity due to every recognized 'cause' save one. Thus the lesion has been recorded in hypertension associated with nephritis, pyelonephritis, polycystic kidney, periarteritis nodosa, Cushing's syndrome, phaeochromocytoma²⁵ and toxæmia of pregnancy. The one exception is hypertension due to coarctation of the aorta, where a large part of the vascular bed is shielded from the high pressure. The reversibility of the lesion is now one of the encouraging features of the treatment of hypertension. That the lesion is reversed is inferred from the subsidence of clinical counterparts, namely, papilloedema, and haemorrhages and exudates within the retinae, together with lessening of albuminuria and improvement in renal function. It is part of the thesis directly attributing the fibrinoid lesion of the arteriole to the hypertension that all such methods of reversing it have one

factor in common, namely, the lowering of arterial pressure, be it by employing ganglion blockade or by removing a 'causative' lesion such as a unilateral pyelonephritis or a phaeochromocytoma.

Byrom's⁴ work on hypertensive encephalopathy in rats takes this particular story one chapter further, showing that the fibrinoid necrosis is associated with intense local spasm of the arterioles. Byrom recalls earlier work wherein Bayliss² demonstrated the inherent property of an isolated segment of artery of constricting in response to an increase of the pressure within its lumen.

Against this theory is advanced the argument that there are many subjects with diastolic pressures above the level of 140 mm. Hg often considered to be critical for the fibrinoid necrosis, who do not show the lesion nor its clinical counterpart, malignant hypertension. It is, in fact, no part of the thesis that all whose pressures exceed a certain level will develop the lesion. Coincidental conditions which play a part include the rate of development of the hypertension and, perhaps not wholly independent of this, the age of the patient. Thus in young subjects with hypertension of recent onset, there appears to be a greater liability for fibrinoid necrosis to develop, as is demonstrated by the occurrence of this lesion in toxæmia of pregnancy and in acute nephritis at comparatively low levels of diastolic pressure. The corollary of this is the elderly female, severely hypertensive for many years, whose diastolic pressure remains at 150 or 160 mm. Hg with no evidence of the malignant phase.

Although of infrequent occurrence when contrasted with the so-called benign phase, hypertension in the malignant phase assumes great importance because of its natural history. Unless arterial pressure is reduced, death occurs within one to two years in the great majority of such patients, from cardiac or renal failure or from cerebral vascular catastrophe in most. Hypertensive encephalopathy, variously ascribed to focal thrombotic lesions, to oedema or to vascular spasm, is a frequent manifestation. No treatment in medicine is more imperative, and no reward greater to the doctor than when a patient with this condition is rescued from the downward path.

Compared with the cardiac and vascular diseases associated in greater or lesser measure with hypertension, its other consequences are of lesser importance. This is not to say that to the patient they are of no annoyance, for the headache and the vertigo which may accompany a raised pressure are at times most distressing. Particularly does this apply to the headache on waking which patients with severe hypertension often experience. Its resemblance to migraine, and indeed the liability of hypertensive subjects to migrainous

attacks, make the picture somewhat confusing. It is probable, however, that a large part of all the symptoms associated with high blood pressure are of neurotic origin. For this, the blame must rest largely with the medical profession who, keen to find causes, and eager to apportion blame for every ill, have used hypertension as a scapegoat too freely. There are probably few normal people who from time to time do not experience mild headache, or slight tinnitus, or transient postural vertigo. Once the individual knows that his pressure is above what it should be such symptoms acquire for him new significance. Previously dismissed or brushed aside, now they are stored in the memory and by a process of increasing agitation become more frequent and more severe.

The consequences of hypertension are manifold; cardiac and vascular lesions (often discussed as though they were identical with hypertension) are seen to bear varying degrees of indebtedness to the condition; one lesion, arteriolar fibrinoid necrosis, responsible for the syndrome of malignant hypertension with its grave prognosis, is directly attributable; and symptoms, some severe, others annoying, are either directly or indirectly attributable. In the latter group of symptoms, one of the coincident conditions necessary for their development is the doctor who imparts to his patient the knowledge that his pressure is raised.

The Treatment of Hypertension

Ideally the treatment of any disease process should be aimed at its cause, preferably so as to eradicate it before it can take effect, that is, by prophylaxis. If the thesis elaborated here is accepted, namely, of a multifactorial basis for hypertension, then prophylaxis must likewise be of many kinds. Some suggest themselves and are within the realm of practical medicine. The marked decrease in, and the lessening severity of, severe streptococcal infections are playing their part in decreasing the incidence of glomerulonephritis. Again, the easier control (albeit still difficult) of urinary infections should see a lessening of pyelonephritis. Increased awareness and greater precision in diagnosis of phaeochromocytoma and Cushing's syndrome, with better methods of treatment, if not able to prevent hypertension, should at least favour the prevention of severe forms from such causes. But when these and a few other lesions associated with raised arterial pressure are removed, the agents left are seen still to be the major body of the enemy. Some are clearly not capable of removal. The effects of ageing may well be lessened and delayed, but can hardly be expected to be abolished. To attempt to eradicate, by eugenics,

the factor of inheritance in a disease process which does not maim nor cripple until late in life would be not only somewhat illogical but also incompatible with human nature. The greatest hope of prophylaxis in hypertension must lie in the sphere of environment. To speculate, it would appear possible that greater facilities in creative arts, pastimes and sport and a lessening of causes of frustration may be important steps in removing part of the genesis of hypertension. It is conceivable that physical exertion prolonged further into adult life by recreation in those not able to give full vent to it in their work may achieve a reduction in the incidence of this disorder. A better understanding of dietary factors involved and avoidance of obesity may come to greater prominence. These aspects, although seemingly remote from the acute manifestations of hypertension, lie in the field of preventive medicine and are of importance.

Of narrower interest, but at the present time of greater practical value, are the measures available to bring about a lowering of pressure. They are of two kinds: Firstly, the infrequent opportunity of removing a potent or specific factor from the patient, such as an adrenal tumour or a unilateral diseased kidney. Although the results are sometimes disappointing, the success in other cases is so gratifying that the search will ever continue for such lesions. Secondly, and of wider application, are the methods of lowering arterial pressure by interfering with one or more of the mechanisms by which it is maintained. This essay is not an appropriate place to dwell upon the details of such measures, and it is proposed only to refer to them in so far as they are influenced by, or influence, the central theme.

Pride of place must be accorded to the methonium compounds, made available to patients with hypertension as a result of the work of Paton and Zaimis.²³ Of these, hexamethonium bromide has now largely been replaced by penta-pyrrolidinium ('Ansolysen'), and more recently by related compounds such as 'Ecolid' and mecamlamine. Available for oral and parenteral use, their actions in autonomic blockade can result in profound lowering of arterial pressure. The side-effects, inseparable from the desired hypotensive effects, and the insecurity from over-dosage render this form of treatment laborious and unpleasant, alike for the doctor and patient. From this it follows that such treatment can only effectively be carried out in the presence of symptoms of sufficient severity or of a prognosis of sufficient gravity to warrant enduring the discomforts and dangers inherent in it. None the less, it is with this treatment that the most promising results have been obtained, and the

achievements of Smirk and his colleagues³⁸ are a source of encouragement to others. The proper control of this form of treatment requires great skill and experience, and above all much time, by both the patient and doctor. None would decry its value who has seen even one patient, once near death from malignant hypertension, attend regularly for years for control of treatment. This method of control of arterial pressure is now widely accepted as the most effective treatment for all in the malignant phase. The contraindications are few; renal disease as a cause is no bar, although results are less satisfactory and dosage requires even more careful supervision. In particular, it has come to be realized that the severe renal failure often encountered in malignant hypertension may be predominantly a failure of function, and result from cardiac failure. The author has one such patient, who at the age of 69 was admitted to hospital in extremis. His blood pressure was in the region of 280/150; he showed severe right and left heart failure, Cheyne-Stokes respiration and the picture of terminal uraemia, his blood urea being 285 mg. per 100 ml. Treatment with parenteral 'Ansolsen' resulted in a rapid recovery. Now, two years later, he remains well, about the everyday occupations of his retirement and largely symptom-free. His treatment, with 'Ansolsen' injections twice daily and reserpine, continues and is of no more bother to him than is insulin to a diabetic. He is fortunate in being tolerably free from side-effects. Those that he has, he has learnt to minimize, and he and his family are fully aware of their indebtedness to the treatment.

Age, per se, is no contraindication to such treatment but, since there are required intelligence in the patient and will-power to tolerate the side effects, it is inappropriate for the senile.

Cardiac failure is certainly no obstacle and indeed Smirk, whose experience in this field surpasses any others', regards the methonium compounds as the most important weapons in the treatment of such failure when due in large measure to hypertension. The greater the contribution of hypertension to the failure (which in general can be inferred as the higher the pressure) the better the prognosis for the patient, for the greater will be the load that can be shed.

There is considerable divergence of opinion as to whether vascular thromboses constitute indications or contraindications to such treatment. There are those, such as Smirk, who maintain that the prognosis is improved and that such lesions call more urgently for the lowering of co-existent high pressures. Others, notably McMichael,¹⁹ are impressed by the occurrence of such thromboses during the course of treatment

and believe that some at least have been occasioned by the treatment. The matter must remain in debate and empirical in nature until a carefully controlled trial has shown wherein lies the greatest risk and until the relationship of arterial pressure to vascular thrombosis, both on a long term and on an acute basis, is more clearly understood.

The most difficult decision which confronts the physician is the treatment of the patient who is relatively symptom-free yet possessed of a severe degree of hypertension. It can only be said here that often the decision will be based largely upon the temperament of the subject. Effective treatment with ganglion blocking drugs is at present such that he will not remain symptom-free whilst receiving it.

Drugs derived from *Rauwolfia serpentina*, of which reserpine is the most commonly employed, have an action in lowering arterial pressure the site and nature of which is not known. That it is not of itself potent enough materially to lower the severe forms of hypertension is now recognized. As an adjunct to treatment with methonium compounds it is of considerable value and it is now customary to employ the two types of treatment simultaneously, the combination appearing to be synergistic. The central depressant action of reserpine has resulted in suicide in a number of instances, and its use and dosage have therefore to be regulated with care.

Sympathectomy has largely been abandoned because of the unpredictable but disappointing results. Other measures include adrenalectomy, and a low sodium diet, neither of which finds much practical application.

There remain the host of non-specific measures by which the sufferers from hypertension, rather than the hypertension itself, are treated. Of these, phenobarbitone has probably the greatest number of devotees. Usually added to this is the advice to take life quietly. Whether in many patients anything is achieved other than depression by the barbiturate and demoralization by the inactivity remains in doubt. It is certain that the use of both agents is excessive, and that a more philosophical approach to the problem would often be helpful.

The subject of treatment has thus far been concerned with prophylaxis on the one hand and immediate steps to lower arterial pressure on the other. There remains for consideration the natural history of the condition. In no part of the subject is there more uncertainty, either when the problem is that of the individual or relates to groups. One feature deserves special mention, namely the possibility that oft repeated transient lowering of pressure may come to work in the reverse direction to that in which we have seen

repeated or prolonged elevation to operate. For just as elevation, of whatever origin, may result in subsequent fixed raising of pressure, so may lowering, by whatever means, eventually lead to more permanent depression of arterial pressure. There is as yet little evidence to show whether this in fact applies but the possibility should encourage the prolonged administration of hypotensive drugs in the hope that for each individual patient the time may come when withdrawal of treatment may witness return of hypertension to only a trivial degree.

This line of thought may be taken further and the possibility envisaged of a safe and simple treatment, capable of application without discomfort for prolonged periods, to be administered not to the severe, established hypertensive but to the younger patient with early and perhaps transient elevation of pressure. At the moment, this ideal seems remote but so must have insulin seemed to the diabetic of 1921.

Conclusion

Throughout this essay an attempt has been made to see hypertension in perspective. The effect at times has been to lessen the importance which is attached to it. Without question in its severe forms high blood pressure is a major hazard to health and life. It is when the elevation is modest that undue emphasis has perhaps been placed upon it in the past. The measure of the ill effects is related to the severity of the condition and appreciation of this fundamental fact is not helped by the continued search for a definition. For once hypertension is rigidly defined then a disease is defined and the doctor is tempted to say that the patient either has or has not that disease. Once conceived as an entity, the condition is presumed to have a cause. The search for this continues in a manner which suggests that many of the people engaged envisage a single responsible agent. That such an over-simplification of the true state of things is welcomed by the layman is not surprising. What is of interest is that the medical profession itself should come to think likewise.

The concept that is advocated is of arterial pressure, itself only amenable to approximate measurement, varying greatly throughout the population; being determined at any time in any individual by a multitude of factors, of which the contributions of age, sex and inheritance have within broad limits been defined; rising generally with age and markedly in certain well defined diseases, particularly of the kidneys and of the endocrine glands. When elevated by no defined cause it is described as essential hypertension, and in its upper reaches it is associated with an increased incidence of certain cardiovascular

diseases, whilst in its uppermost extremes it is responsible for a specific disease process, the necrotizing arteriolitis of malignant hypertension. Such elevations of pressure are capable of reduction in a limited number of instances by the removal of a potent aetiological factor but seldom even in these circumstances does the pressure fall to the levels most commonly found in persons of similar age and sex. Finally, high pressures are often able to be lowered by a variety of drugs and procedures which grossly disturb the normal physiological control of many bodily functions.

This picture shows hypertension, not as a specific entity, but as a departure from normality brought about by a number of agents acting together in a coincidence of conditions.

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