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THE MANAGEMENT OF HYPERTENSION*

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With the conquest of infections and resulting prolongation of life, hypertension and arteriosclerosis have become the major causes of illness, disablement, and death, especially in the second half of life. The confusion and difficulty which used to arise in differentiating hypertension from chronic nephritis has largely been cleared up, and we owe a great deal of our new understanding of the relationship between these conditions to the work of Ellis (1942) and Wilson and Byrom (1939), of the London Hospital School.

Factors in Pathogenesis of Hypertension

Over a century has elapsed since Ludwig invented the kymograph in 1847, since when the regulation of arterial pressure and the related topic of distribution of blood flow have been subjected to more close and critical study than perhaps any other subject in physiology. Vasomotor centres, carotid sinus reflexes, aortic reflexes, adrenaline (now known to be secreted with *noradrenaline*), and a host of other factors—nervous, humoral, and metabolic—have been thought, in turn, to provide possible keys to the practical mastery of blood-pressure regulation. The stupendous efforts of several generations of scientists have produced an ever-growing halo of light which merely illumines an ever-increasing sphere of darkness. Richard Bright recognized the association of nephritis and hypertension, and in the last two decades great efforts have been made to comprehend this relationship. It seems well established that a kidney with its blood flow reduced produces a substance—renin—which induces vasoconstriction (Goldblatt, 1947). Other investigators (Shorr, 1948) think, however, that renin is not the only substance concerned, and that another vaso-excitor material (V.E.M.) is formed by the ischaemic kidney. Another school believes that the kidney normally eliminates or neutralizes some pressor substance formed elsewhere in the body, as hypertension can develop in nephrectomized animals kept alive by various means (Muirhead *et al.*, 1949).

Recently a good deal of attention has been given to the possible role of the suprarenal cortex in the production of hypertension. Fisher and Hewer (1947) have shown the frequency of suprarenal cortical hyperplasia and increased cortical lipoids in patients dying of hypertension. An excess of deoxycortone acetate in the treatment of Addison's disease can induce hypertension, while a salt-free diet—for example, the rice diet—will bring the pressure down (Cameron *et al.*, 1950). In a recent lecture

Professor Rosenheim (1951) emphasized the possible role of sodium in hypertension. Reports from the London Hospital show that some forms of experimental hypertension depend on the presence of intact suprarenal glands, and throw up the possibility that altered sodium balance may be important in disturbing vascular tone (Floyer, 1951; Ledingham, 1951). Attractive though this view may be, efforts to demonstrate increased excretion of suprarenal cortical substances in the urine of hypertensives have not yet succeeded.

Less tangible factors have been sought in race, heredity, and relation to obesity and the menopause. From the follow-up of pre-eclampsics it has been shown that many of these patients who have had transient hypertension in pregnancy become cases of essential hypertension some years later (Browne and Dodds, 1939). We all recognize the association between hypertension, arteriosclerosis, and diabetes, but in such patients high pressure *per se* seldom becomes severe, though the associated arteriosclerotic lesions are often severe and contribute to the final breakdown. The part played by stress, strain, and worry in the production of hypertension is very difficult to evaluate, but it is of interest to notice that Smirk (1949) and his associates claim to have produced hypertension in rats following exposure (in a sound-proof room) to the continually recurring blast of a klaxon horn.

Hypertension and Arteriosclerosis

It is generally held now that the anatomical thickening of the arteries and arterioles which is an almost universal accompaniment of the terminal stages of hypertension does not in itself produce hypertension but rather the converse: the raised pressure within the arteries leads to reactive thickening of their walls. Volhard (1948), whose contribution to the subject deserves our highest praise, had the following hypothesis of hypertension. Emotion, worry, and similar strains raise the cardiac output. This rise in cardiac output does not normally raise the blood pressure, because the arterioles dilate automatically from reflexes arising in the aorta and carotid sinuses. Volhard thought that as a result of continued stimulation these reflexes became exhausted, reflex vasodilatation failed, and so the blood pressure became high. In later stages anatomical thickening of the arterioles caused persistent resistance to arteriolar flow with permanent hypertension. Nowadays we realize that the latter part of this hypothesis is wrong. We have powerful vasodilator drugs, and, so far as I

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can see, there is practically no hypertension which cannot be reduced to normal levels by the use of these substances. Blood vessels right through to the very last stages of hypertension are still capable of dilatation, and anatomical thickening and narrowing therefore play little part in the production of high blood pressure. Reduction of blood pressure by various sympathetic "blocking" agents, moreover, does keep open the question of a neurogenic component in hypertension. In the early stages of hypertension there are certainly many instances in which excitement and emotion seem to be the major factors precipitating a rise in arterial pressure.

Recognition and Causal Analysis of Hypertension

Let us now leave hypothesis and turn to the practical problem of the recognition of hypertension and practical decisions with which we are faced in consequence of our diagnosis. Hypertension in an adult must be diagnosed when the diastolic pressure is over 90 mm. Hg. Systolic hypertension—for example, B.P. 180/80—may be due to causes like rigidity of the aorta, and is excluded from this discussion. It is possible that in the near future we may have to alter slightly our criteria for the auscultatory measurement of diastolic pressure, for recent work in the United States suggests that the point at which the Korotkoff sounds disappear may be more accurate than the point of muffling which has usually been accepted in the past. It is quite certain that when pressure is low in an artery the auscultatory method may be quite inaccurate, especially for the diastolic pressure. In measuring blood pressure the cuff should be applied firmly round the arm so that bulging of the bag does not occur. If the expanding bag escapes from under the cuff, or if its inflated volume is entirely used in displacing soft tissues, especially in fat arms, inaccurately high readings may sometimes be obtained. The expanding rubber bag must compress the artery before the elastic limits of the bag are reached.

Having decided that a subject is hypertensive, our next problem is to decide whether or not the condition is secondary to some cause which may possibly be amenable to direct treatment. Such causes are coarctation of the aorta, unilateral pyelonephritis and congenital hypoplastic kidney, and phaeochromocytoma; while in other instances there are recognizable pathological associations which it may, however, be impossible to treat at the moment. Such are nephritis, acute and chronic, congenital cystic kidney, and Cushing's syndrome. Sometimes one may see obese, plethoric, hypertensive young subjects with livid striae on the abdomen who might be called cases of "pseudo-Cushing's syndrome" (Davies and Clark, 1950). Professor Platt (1948) has with good reason emphasized the rarity of essential hypertension under the age of 40 and the high frequency of causal conditions in the kidney in such young hypertensive subjects.

Hypertension Due to Unilateral Renal Disease

When a unilateral kidney lesion is detected it is always worthwhile to have that kidney removed, especially in the younger age group. In my own experience I have encountered four such cases: in three, removal of the unilaterally diseased kidney led to great improvement; in one (Case 1), pressures were kept almost at normal levels for eight years.

Case 1.—A bricklayer aged 39 (in 1942) complained of headache and was found to have a blood pressure of 248/160. There was severe retinitis with papilloedema. Radiologically, multiple calculi were seen in the right kidney and uroselectan showed no evidence of excretory function. Right nephrectomy was performed on February 11, 1942, by Mr. R. T. Payne. Blood pressure fell to 100/75, and the fundal changes regressed until six weeks after the operation the disks were quite clear and only a few exudates could be seen. The heart, which had been moderately enlarged, diminished

in size, and the patient has continued to be well, and working, over the last 10 years. B.P. in the first eight years after operation fluctuated between 130/90 and 160/100, but when last seen on January 3, 1952, it had risen to 175/120.

Case 2.—A 14-year-old girl was admitted on April 29, 1941, on account of blurring of vision. She had had nocturnal frequency in 1938 and was observed in Clacton Hospital as " ? abdominal emergency " in 1939, since when she had severe headaches and recently vision had become blurred. B.P. 270/160. Severe papilloedema with extensive exudates, and macular star figures with much hard white exudate between the disk and the macula, were noted. Cerebrospinal fluid pressure 240 mm. Blood urea 33 mg. Pyelography showed a small shrunken left kidney. Urine contained albumin; urea clearance was 65% of normal. The left kidney was removed on January 28, 1942, by Professor Grey Turner. It was grossly shrunken, and microscopically showed chronic pyelitis and chronic pyelonephritis. There was some endarteritis obliterans in the areas of active inflammation, but no evidence of arteriolonecrosis. After the operation her B.P. subsided to 140/90, but climbed again in the post-operative weeks to 180/120. The retinitis slowly subsided in succeeding years, and in 1948 the disk margins were clear and a few peripheral pigment deposits with pigment "peppering" at the maculae were all that could be seen. B.P. on yearly visits to hospital ranged from 160/105 to 180/115. She was last seen on December 20, 1951: B.P. 180/110; feeling well; now married and working as a secretary; the left macula was practically normal, while the right macula still showed a few pigmentary patches.

Case 3.—A 17-year-old dressmaker was admitted on March 22, 1942, under Dr. Sharpey-Schafer with headache and general tiredness. She had been recognized as hypertensive for at least three years. Albuminuria was present. B.P. 220/145. The fundi, however, showed no retinitis. Intravenous pyelography showed that the left renal outline was small, and a left nephrectomy was done by Mr. R. T. Payne on March 25. Histologically the kidney showed evidence of old pyelonephritis. The B.P. settled slowly after the operation and the most recent reading was 160/105 on December 20, 1951. She is in good health and rather obese.

Case 4.—A schoolgirl aged 12 (1942) had an epileptic fit and complained of headache with mistiness of vision. On examination the B.P. was 260/180. There was papilloedema with severe retinitis. The urine contained albumin, with red cells and hyaline casts. Uroselectan showed impaired excretion from a small left kidney. The kidney was excised on December 22, 1942, by Professor Grey Turner. After the operation the B.P. fell over two months to 170/110 and the retinitis regressed. Within a year, however, the B.P. had risen to 250/160. She again began to have fits, but the papilloedema did not recur. She continued to have very severe headaches and developed progressive cardiac enlargement. She died on May 31, 1945, two and a half years after operation.

Comment.—Case 1 gave the best result, with restoration of pressure to nearly normal levels for eight years, but he is now definitely hypertensive again. Cases 2 and 3 were partial successes, with restoration of severe hypertension to more benign levels, while Case 4 showed only a short remission. Successful treatment of hypertension by nephrectomy is thus a rare event. More often one encounters bilateral kidney disease for which nothing can be done. Generally speaking, the search for causal renal disorder is worth while in hypertensives under the age of 45, but after this age renal causes amenable to treatment are highly improbable.

Essential Hypertension

Once we have decided that hypertension is not secondary to any of these causal conditions the diagnosis will be essential hypertension. There are various categories of clinical severity. In ascending order of gravity, we may list these as follows:

1. *Intermittent hypertension.* Casual readings of elevated pressure are found which subside to normal with rest and

reassurance. The rises of pressure are sometimes ascribed to nervousness and emotion. Considering the state of anxiety in which most patients must come to see a hospital consultant, we cannot ascribe these high readings to nervousness alone. A follow-up of American soldiers with occasional hypertension showed that a majority of them became more persistently hypertensive in later years (Levy *et al.*, 1944).

2. *Remittent* labile hypertension, which subsides to a lower but not quite normal level with rest in bed and with sleep, but which remains benign and often symptom-free for many years.

3. Hypertension which is *sustained* although it continues to show some fluctuations. (a) This sustained hypertension may be *uncomplicated* for many years. (b) Sooner or later important organs become involved—brain, eye, heart—and it is a matter of chance which of these is involved first. Severe and disabling headaches should be included among the meningo-vascular cerebral complications. This stage can be called *sustained complicated* hypertension.

4. Hypertension with severe active retinal involvement but without papilloedema. In such cases there is usually evidence of cardiac strain and/or cerebral vascular complications: the diastolic pressure has by then risen to above 120 mm. Hg, and in this group the course is usually rapid, terminating in two to three years. This is often called the *pre-malignant* phase.

5. *Malignant* hypertension with retinitis and papilloedema (hypertensive neuroretinopathy). In this condition rapid cerebral, cardiac, and renal involvement takes place and patients nearly always die within a year.

Assessment of Prognosis

The course of the disease is usually benign for many years, especially in the first two of the above groups. In the third group the course is also benign for long periods, until visceral complications alter the outlook. In the fourth and fifth groups the eye grounds are a remarkably useful guide to prognosis. The more severe and active (fresh haemorrhages and soft cotton-wool exudates) the retinitis the worse the outlook, and in the presence of oedema of the optic disk patients seldom survive more than a few months. The prognostic value of eye-ground changes was clearly demonstrated by Keith, Wagener, and Barker (1939) (see Table).

Fundus Changes in Hypertension and Corresponding Prognosis
(From Keith, Wagener, and Barker, 1939)

Grade	Fundus Oculi	Prognosis
1	Only mild narrowing or sclerosis of retinal arterioles	70% alive after 7 years
2	Moderate to marked sclerosis of retinal arterioles. May be some hard white patches	
3	Cotton-wool exudate, haemorrhages, and oedema of retina superadded to above	50% " " 5 "
4	As in grade 3, but with oedema of the optic disks	75% dead in 3 years
		90% " " 1½ "

In so far as higher diastolic pressures are associated with retinal lesions of increasing severity and greater chances of cardiac strain, the prognosis becomes worse, and the condition will always cause anxiety when the diastolic pressure has exceeded 120 mm. Hg.

There are, however, many exceptions to all these rules. When the blood pressure has risen *very slowly* over a long period of years quite high pressures may be well tolerated, and women seem to stand them much better than men. Particularly after the age of 60, very high pressures may be encountered with a good prognosis and little retinitis (Burgess, 1948). This contrasts with *rapid* rises of pressure to high levels in primary malignant hypertension with consequential arteriolar necrosis. Blood and Perera (1948) have reported a series of 50 patients who survived ten years or more: in 21 of these there were high diastolic pressures

reaching 120 mm. Hg or over and even retinitis at the beginning of this long survival period. On rare occasions even malignant hypertensive neuroretinopathy may regress spontaneously. I have seen this happen only twice in the last 12 years, with the unexpected survival of the patients for two and three years respectively.

Treatment

In the symptom-complex of hypertension there is enough evidence that the hypertension itself is harmful, and that anatomical changes in the arteries on which thrombosis may occur are a long-term consequence of the elevated pressure. Reduction of pressure is therefore desirable. It should be remembered, however, that there are two vascular areas in which blood flow is mainly dependent on the level of the aortic pressure. These are the coronary and cerebral vascular beds. Reduction of blood pressure will almost certainly reduce blood flow in these situations, and in the presence of atheromatous changes in the coronary and cerebral vessels a reduced rate of flow may favour local thrombosis. Blood-pressure reduction should therefore not be lightly undertaken in patients who have shown any gross evidence of cerebral and coronary vascular occlusion.

The measures available for reduction of blood pressure are at present somewhat unsatisfactory, because we know of nothing that will neutralize the causal agencies, which still remain unknown in hypertension. Our remedies are complicated in use and only partially successful, the effects are difficult to maintain over long periods, and there are often unpleasant side-effects or even risks of harm from their indiscriminate application. The approach which I shall outline is purely a personal one, from which no doubt other experienced physicians would differ.

In our present state of knowledge we do not attempt drastic blood-pressure reduction in the benign uncomplicated hypertensives of the first three groups outlined above. Often the diagnosis need not be revealed: otherwise great personal skill and a persuasive authoritative manner may be required to reassure the patient that his hypertension is a benign condition, and likely to remain so for many years. We must not complicate a benign and often practically symptomless condition by an anxiety neurosis. Mild sedation with phenobarbitone or "theominal" may be helpful, especially in tense subjects, and weight reduction should be prescribed in the obese.

As already emphasized, patients with extensive thrombotic, cerebral, or coronary lesions should also be handled with care, as blood-pressure reduction may be risky. In elderly subjects who have had hypertension for many years, complicating vascular anatomical change may be assumed to be present, with the attendant possibility of thrombosis when pressure is reduced. Systematic efforts at pressure reduction are therefore limited to pre-malignant and malignant hypertension (groups 4 and 5 of our suggested classification) and where complications are present or impending in patients with sustained hypertension (group 3b).

Methods of Blood-pressure Reduction: 1. Sympathectomy

Extensive removal of the sympathetic chain from the mid-thoracic or lower thoracic region to the upper lumbar ganglia on both sides has had its vogue. Putting together the cases reported in this country by Chris (1951) (33 cases), Platt and Stanbury (1950) (80 cases), and Northfield (1948) (29 cases), significant reduction of blood pressure was apparently achieved in 26 out of the total 142 cases, or 18%. For the most part these were early results judged within two years or so of the operation. A most careful study by Evelyn and his associates (1949) showed that early reduction of blood pressure after sympathectomy was not sustained and that at the end of five years only 21% of the patients operated on had any significant reduction of arterial pressure. Practically 80% of the operations therefore give poor results so far as blood-pressure reduction is concerned. Furthermore, the operation has a mortality, and it is certainly not

a universal treatment for hypertension. These disappointing results may find a partial explanation in certain recent investigations.

Boyd and Monro (1949) have shown the existence of "intermediate" sympathetic ganglia outside the sympathetic chain, making *total* sympathectomy impossible even regionally. Furthermore, Barcroft and Hamilton (1948), in a complete study of sympathectomized upper limbs, have shown recovery of tone and reactivity in the small vessels after a few months, and the work of Wilkins *et al.* (1949) suggests that similar recovery takes place in the splanchnic area. Evelyn and his colleagues (1949) have noted good results (B.P. down to normal or nearly normal) in only 8% of operated cases.

If we could only select with certainty those few cases which do respond we should be very pleased to continue recommending sympathectomy, but unfortunately all the pre-operative tests to improve selection which have been tried seem to have failed utterly. We must reluctantly admit that a large number of quite useless operations have been performed and that there is very little prospect of any satisfactory improvement in surgical technique or selection in the near future.

2. Adrenalectomy

Total extirpation of the suprarenals has been tried (Green *et al.*, 1950), with maintenance of life by subsequent administration of suprarenal cortical hormones. More information on the long-term results is needed before we can pass judgment.

3. Medical Measures

(a) *Salt Depletion*.—Restriction of sodium intake will often bring down the blood pressure, and this is the basis of Kempner's (1948) rice diet. The diet consists of rice, fruit juices, and sugar, supplemented by vitamins and iron. It contains a low protein content of 20 g. a day, and the daily sodium intake is 200 mg. It is generally agreed now that the blood-pressure reduction achieved on this diet is due to sodium depletion, and any other kind of diet in which the daily sodium content is down to 200 mg. or less would be equally effective (Cameron *et al.*, 1950). Patients usually are unable to continue taking tasteless and insipid food over long periods. Recently, ion exchange resins, which prevent the absorption of sodium from the gut, have been used to permit the ingestion of a palatable diet, but there are still considerable practical difficulties about their administration (Page, 1951). Salt depletion, if pushed too far, may be dangerous by inducing uraemia, and this is particularly to be remembered in the malignant and pre-malignant phases of hypertension.

(b) *Thiocyanates* have had some vogue in the treatment of hypertension. They have a narrow margin of safety, blood levels have to be controlled at 8–12 mg./100 ml., and there are various unpleasant side-effects. They are said to relieve headaches, though in most cases the blood pressure does not fall. Page (1951) reports the use of sodium nitroprusside (30 mg. four times a day in capsules), which is probably converted into thiocyanate in the body. If these substances are used biochemical control of the blood thiocyanate level is necessary, and this makes them laborious and difficult to use with any prospect of satisfaction.

(c) *Soluble bacterial pyrogens* ("pyromen") have been used by Page and Taylor (1949). They are infused continuously to give a temperature of 101 to 102° F. (38.3 to 38.9° C.) each day. These pyrogens have been shown to dilate the kidney blood vessels, and a few successes have been achieved in cases of malignant hypertension. Reporting on this, Page (1951) said: "This is a harsh treatment, but malignant hypertension is more than harsh; it is lethal."

(d) *Veratrum Alkaloids*.—"Veratrone," "vertavis," and veratridine have been used to reduce the blood pressure. They have long had a place in the treatment of acute blood-pressure rises in eclampsia. They act by inducing a reflex vasodilatation, the afferent fibres of the reflex arc arising in

the coronary vascular bed. With Dr. M. E. Etheridge, of Melbourne, we have tried these preparations, but the margin between an effective dose and one which induces vomiting, sweating, and other unpleasant side-effects was too small. One patient took his dose about 6 a.m. in order to get the vomiting over before breakfast at 7.30. Even this enthusiast failed to achieve any real benefit from the drug, and finally gave it up. Kauntze and Trounce (1951), using "veriloid" (*veratrum viride*), think that useful results may be achieved in about 20% of cases; Page (1951) puts the percentage at 15. The hopes raised by an early report of Freis and Stanton (1948) have not been confirmed.

(e) *Dihydrogenated alkaloids of ergot* have been used in hypertension. These substances have a sympathicolytic action. Dihydroergocornine is one of these substances which lower blood pressure and reduce heart rate. Not all hypertensive patients respond to its administration, and the reductions of diastolic pressure which are achieved are modest—10–20 mm. Hg at most (Wilkins *et al.*, 1949). "Hydergine," a mixture of three alkaloids of ergot, has also been tried with some symptomatic benefit, but again the pressure reductions are quite small. These drugs can be given orally in solution (Gibbs, 1952).

(f) *Hexamethonium and related compounds* were introduced into medicine mainly by the work of Paton and Zaimis (1949) at the National Institute for Medical Research. They showed that pentamethonium and hexamethonium compounds suppressed transmission in autonomic ganglia. The therapeutic possibilities of these compounds in hypertension were realized almost simultaneously by Restall and Smirk (1950) in New Zealand and by Turner (1950) in Edinburgh. Controversial claims have followed, some writers condemning the drug as valueless—for example, Lockett *et al.* (1951)—and others, particularly Smirk, claiming excellent and striking results. There is not the slightest doubt that the drug is difficult to use, and when continued in effective doses will quite often be accompanied by very unpleasant side-effects. The same could of course be said of the indiscriminate use of digitalis, and we must not overlook valuable therapeutic possibilities because of difficulties in selection of cases and because of problems created by individual dosage regulation. The dosage required to produce effects is very variable in different individuals, and a certain amount of tolerance usually develops, which requires a great deal of patience to overcome.

Absorption of the orally administered drug is irregular and difficult to control (Kilpatrick and Smirk, 1952). It is difficult to obtain satisfactory therapeutic results by this route, and local gastro-intestinal troubles, like vomiting and paralytic ileus, seem to be more likely to occur when the drug is given by mouth. For this reason we have adopted the subcutaneous injection method recommended by Smirk and Alstad (1951), the patients treating themselves like diabetics with their injections of insulin. We have restricted our choice of patients for treatment to severe and complicated cases (groups 3b, 4, and 5).

Our results have been as follows. In all, 27 cases have been treated by subcutaneous injection. A single effective dose will bring pressures well down towards normal levels for two to three hours, after which they will climb slowly towards the control level in about six to eight hours. The malignant and pre-malignant groups have totalled seven, of whom four have undergone dramatic improvement, while three, who were in a very advanced stage when treatment was begun, died of uraemia, cerebral haemorrhage, and heart failure. (Two of the three who died showed temporary improvement of vision and regression of their retinopathy before their final deterioration.) In the others we have not only had visual improvement, objective and subjective, but disappearance of headaches and restoration of working capacity, diminution of heart size, and regression of electrocardiographic changes, which are very gratifying.

In patients with sustained hypertension with complications, good reductions of pressure are being achieved by twice- or

thrice-daily injections, and in those able to continue treatment headaches are controlled and working capacity is restored. Five patients out of 27 have been unable to continue to co-operate on account of severe side-effects or inability to carry out a rather exacting regime. (These results will shortly be communicated in more detail by Dr. Brenda Morrison.) One great advantage of the subcutaneous route is that untoward side-effects like meteorism, sickness, diarrhoea, etc., subside in a matter of hours on omission of one or two doses. We have not yet failed to reduce blood pressure, though dosage has had to reach high levels, as high as 750 mg. subcutaneously in one subject, given as 2.5 ml. of 30% solution deeply under the skin with a little procaine to avoid the pain which would otherwise result from such a hypertonic solution.

The greatest reduction of blood pressure is achieved by taking advantage of the postural drop, as recommended by Smirk and Alstad (1951). When a normal individual stands up or is quickly turned to a feet-down slope while relaxed on a comfortable couch his cardiac output falls by about 30 to 40% owing to pooling of blood in the lower half of the body. The blood pressure does not fall, however, because of reflex vasoconstriction. Under the influence of hexamethonium, this reflex is blocked and the blood pressure drops in parallel with the cardiac output (see Chart). It is an excellent thing, therefore, to keep patients on hexamethonium treatment on their feet as much as possible and doing their work. When resting, they should sit in a high chair in order to take as much advantage as possible of gravity effects on the circulation. Treatment in bed is much less effective. Even patients with malignant hypertension are encouraged to be up out of bed or sitting in a high chair for the greater part of the day. With the use of these measures treatment has usually been satisfactory.

The presence of some degree of nephritis with a raised blood urea is no contraindication to treatment. Young and others (1951) have shown that the excretion of hexamethonium into the urine parallels the glomerular filtration. The amount of fluid filtered at the glomeruli is low in nephritis, and therefore we would expect the effect of a single injection to last longer in nephritic subjects. This, in fact, seems to be the case. Nephritics with a moderate degree of kidney impairment respond, for a time at least, particularly well to hexamethonium. We have noticed no special tendency for the blood urea to rise while on treatment. Various vasodilatory influences or other measures which tend to reduce blood pressure seem to enhance the effect of hexamethonium. Among these we may list the taking of a meal (which presumably dilates the splanchnic vascular bed), restriction of salt intake, and intercurrent febrile illnesses. Perhaps the addition of some other mild vasodilatory drug to hexamethonium may in future be found to be better than hexamethonium alone.

(g) *1-hydrazino-phthalazine*.—Page (1951) has reported recently that this drug has a moderate influence in reducing the diastolic pressures, possibly through some central action. It has apparently no effect on the blood pressure in the spinal animal, which suggests that its action lies in the vaso-

motor centres higher up in the nervous system. It may be given by mouth in doses of 25 to 75 mg. Tolerance, however, quickly develops, and some unpleasant actions, like flushing of the face, palpitations, sweating, and a feeling of breathlessness, have been noted. Page (1951) reports that 33 of 70 patients had a fall of diastolic pressure of 20 mm. Hg or more while on the drug. The average total daily dose used varied from 100 mg. to 1.4 g. Good responses were reported to occur eventually in patients who had no lowering of pressure in the first ten days of treatment.

The effect of posture on blood pressure in a hypertensive subject before and after hexamethonium bromide. Before administration of the drug a fall in cardiac output induced by tilting feet down is compensated by vasoconstriction, and the diastolic pressure remains unchanged. A similar fall in cardiac output takes place under the influence of hexamethonium, but the reflex inducing vasoconstriction is blocked—pressure falling in proportion to the cardiac output.

So far, we have tried this substance on only a very small number of patients, and we only recently became aware of the suggestion that effects might not occur until one to two weeks had elapsed. The drug may well be worthy of further trial along these lines.

Conclusion

I have written enough to indicate that we have passed the stage when we were powerless to help the severe hypertensive except by taking a chance on surgical sympathectomy. Drugs of possible use are now reaching us in abundance, almost beyond our capacity for reasonable trial. Streptomycin won its place in the therapy of tuberculosis by its success in tuberculous meningitis, otherwise universally fatal. Drugs which have a place in hypertension will first prove themselves in the most severe forms, malignant and pre-malignant. Thereafter their influence on the more chronic and less severe cases will be shown only by prolonged and carefully planned statistical trials. We should not rush too soon to a combination of remedies, but rather study and record the effects of individual drugs so that we may know exactly what we are doing. Effective hypotensive agents are complicated in use, and should be reserved

for cases judged to have a bad prognosis. If a very high and sustained pressure is made to fluctuate at a lower level the whole course of the illness may possibly be more benign. Too great a reduction of pressure may be associated with some risks, especially in those who have had raised pressures for years. The powerful remedies now at our disposal must be used with caution, and their effects, good and ill, must be carefully documented. The desire to find benefit for our patients and enthusiasm for "the latest" must be tempered with critical insight. The present mood, however, is one of quiet optimism.

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The tenth session of the W.H.O. Expert Committee on the International Pharmacopoeia met on April 23–30 in Geneva. For the tenth time Dr. C. H. Hampshire, of London, was elected chairman of the committee as a tribute to his outstanding contribution to the recently published *International Pharmacopoeia* (Vol. I). In the course of this session the Expert Committee have completed the preparation of Vol. II of the *International Pharmacopoeia*, which will include about 200 monographs, many of them describing new drugs, injections, etc., as well as a dozen important appendices indicating biological assays, tables of doses for children, and tables of usual and maximal doses for adults. When completed, this volume will be published simultaneously in English and French. A Spanish edition is to follow soon thereafter. This will complete the first edition of the *Pharmacopoeia*, which will be extended and kept up to date by an *Addendum* to be issued the following year, and a second edition in 1955, again in English, French, and Spanish. A meeting of the Subcommittee on Non-proprietary Names followed on May 1 and 2. This selects internationally approved non-proprietary names for drugs, to prevent the confusion which arises from the use in different countries of different names for the same drugs. So far 600 international names for drugs have been selected, and the subcommittee is to consider 200 other new names.

THE PERIOD OF GESTATION

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In a recent communication 17,145 Birmingham births delivered during 1947 were distributed by duration of gestation, which was estimated from the first day of the last menstrual period preceding pregnancy to birth (Gibson and McKeown, 1950). We were asked whether the distribution could be used for medico-legal purposes to indicate the probable upper limit of the period of gestation. But although we had no reason to doubt the reliability of the material for the purposes for which it was collected, it was not possible to rely on individual observations, particularly in the later weeks, without a closer inspection than was then provided. We have therefore collected information on Birmingham births delivered in 1950 in order to examine more carefully the upper limits of the period of gestation.

For medico-legal purposes it would of course be desirable to record the period of gestation from the date of coitus or, alternatively, from the date of ovulation, since the interval between coitus and ovulation is shorter and less variable than between coitus and the preceding menstrual period. But in practice neither of these dates can be given for the large series of births needed (at least several thousands) to establish the range of the highly variable period of gestation. It is therefore necessary to estimate the period of amenorrhoea from the onset of the menstrual period preceding pregnancy to birth, and to make an adjustment for the probable interval between the onset of the menstrual period and coitus.

The Period of Amenorrhoea

The period of amenorrhoea was recorded in this way from health visitors' cards for 15,659 of the 18,819 births delivered in Birmingham during 1950. (Birmingham health visitors obtain the date of onset of the last menstrual period from antenatal documents and are asked to record the date only if it is definite.) The distribution is given in Table I. As we are here interested only in the longer intervals, births delivered before the 41st week are grouped. There were 247 births after the end of the 44th week, of which seven were born later than 48 weeks. The two longest periods were 356 and 359 days.

We cannot, of course, accept these estimates as reliable without consideration of certain obvious sources of error.

(a) *Uncertainty Regarding which Bleeding has been Followed by Coitus and Fertilization.*—Bleeding in the early months of pregnancy is not uncommon and may be confused with the preceding cycle. Thus the estimate may be too short if dated from bleeding during pregnancy, or too long if dated from the penultimate cycle, the last cycle being mistaken for post-ovulatory bleeding. These difficulties could of course be overcome by use of pregnancy diagnosis tests at the appropriate time (after the first missed cycle and before further bleeding), but such tests are not at present in general use.

(b) *Misleading Information from the Mother.*—It is well known that premarital conception, particularly of first births, is not uncommon, and provides the mother with a motive for post-dating the last menstrual cycle. Alternatively, in