BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 3 1956

TREATMENT OF HYPERTENSION*

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In the treatment of hypertensive vascular disease, a great variety of effective remedies are now available—so many, indeed, that considerable discrimination is required in the selection of the therapeutic procedures best adapted to a particular patient. Some are powerful remedies, not easy to administer or regulate, and call for the fullest co-operation between doctor and patient. Others, simple in themselves, demand skill in application to get the best results. Occasionally the justification for recommending a surgical procedure, remedial or palliative, will require careful consideration. With a multiplicity of aetiological factors, and with great variations in the pattern, course, and intensity of the disease, it is natural that treatment must vary widely from patient to patient and be adapted to the requirements of the particular individual. No single remedy is uniformly successful.

I. General Measures

Management

Of the general measures widely applicable, consideration must be given to the judicious and tactful management of the hypertensive patient. By their manner, attitude, and personality, some doctors are able to accomplish more than others for hypertensive patients. They owe their skill to the confidence they inspire. The first step in successful treatment is therefore the employment of conscious or unconscious psychotherapy. By this means the doctor establishes a relationship of mutual trust of particular advantage to the patient, who is thereby steadied in his outlook, reassured, and encouraged. The relief of emotional tension promotes a sense of tranquillity, which in itself can set a blood pressure at lower levels.

As a general rule, the fears of high blood pressure should be countered at the earliest opportunity, with the explanation that such a condition may persist for years without disagreeable happenings. It may even subside spontaneously, without serious embarrassment or permanent crippling. Doubts and fears can usually be set aside by explaining that the condition is comparatively benign, that suitable treatment is available when it is required, and that frequently no particular specific remedies are necessary. Such an attitude can do much for the patient, simplify his care and supervision, and permit the judicious use of appropriate remedies as and when these appear necessary.

Most people, and hypertensive patients in particular, feel better, make more headway, and have a lower pressure when under the protective and understanding care of a sympathetic and encouraging adviser. Relief from emotional stresses with the resolution of conscious or subconscious conflicts is of importance, particularly in

the earlier stages of the hypertensive process—that is, before irremediable damage has been done to vital organs. Conversely, it is bad practice to inform a patient bluntly that his blood pressure is worse and his drug treatment proving valueless. Such an attitude is never justified. It betrays a lack of appreciation by the doctor of the part he ought to play in the management of the hypertensive patient, whose confidence is readily undermined by injudicious comments and whose progress may thereby be affected adversely.

Neither doctor nor patient should be misled by blood-pressure readings. There is nothing to be gained by commenting on isolated readings, whether real or fictitious. The level of the mercury seldom correlates with well-being. Simple facts such as these can profitably be explained to the intelligent patient at the outset of treatment.

Advice on the better adjustment of the individual to real-life problems comes most appropriately from the patient's own practitioner. Expert psychiatric treatment aimed at the correction of personality and other defects is sometimes helpful and even occasionally curative in the earliest stages, but in the presence of established vascular disease, advancing at an increasing tempo, time should not be wasted on this particular aspect of treatment. For the great majority, simple measures, combining firm reassurance and steady encouragement, form the background of successful therapy.

Way of Life

The personal habits and way of life deserve consideration. It is often true that a routine which includes long hours of sleep, a short rest at midday, the quiet week-end, and a peaceful annual holiday, along with the cultivation of a placid and philosophical temperament, can counteract much of the nervous tension, irritation, and fatigue associated with long hours of exacting work, with all its present-day distractions and frustrations. Most hypertensive patients require advice on adapting their way of life to their blood pressure. Even in the severest grades of hypertension, blood pressure commonly falls temporarily to normal limits in deep sleep, whether physiological or induced by barbiturates or other sedatives. Hence the importance of adequate rest and sound sleep in relieving, even for a few hours at a time, the burden thrown on the vascular system. Amylobarbitone sodium, 3 gr. (195 mg.) at bedtime, repeated in an hour if necessary, is a valuable remedy in all stages of hypertensive disease.

Diet

Many hypertensive patients tend to overeat, and, if this be associated with corpulence, then a clear indication for dietetic treatment exists. The prescription of an exact diet of 1,500, 1,200, or 1,000 calories, with the cultivation of the habit of restricted indulgence, will do much to ease symptoms and increase a sense of well-being. Weight should be recorded at weekly intervals, and the figures are usually worthy of more attention on the part of the patient and

*A paper read in the Section of Cardiology at the Annual Meeting of the British Medical Association, Brighton, in July.

the doctor than casual blood-pressure readings. Begin by correcting obesity is a good rule widely applicable.

In the severer forms of hypertension, as exemplified by Grade 3 or Grade 4 retinæ, a reduction in sodium intake is known to be of definite value. For instance, in malignant hypertension (Grade 4) nearly half the patients will show a regression in papilloedema with restoration of vision when the sodium content of the diet is reduced to 200 mg. a day. Unfortunately, few patients will tolerate such restrictions for long, and indeed experience indicates that equally good results can be obtained in hypertensive heart failure, and in hypertension of Grade 3 or 4 severity, with a diet in which the sodium content is maintained at 500 mg. a day. This diet involves much less hardship. All food, including bread, should be cooked without salt and no salt be served with meals.

Patients vary in their tolerance to salt restriction. Many become habituated and make little complaint. Others react badly after a few days. Anorexia is a danger signal. It should at once suggest the salt-depletion syndrome characterized by weakness, nausea, vomiting, and collapse. For this reason it is seldom wise to continue the strictest diets (with a sodium content of 500 mg. or less) for more than two or three consecutive weeks. The dangers of uræmia are so real that the addition of small quantities of salt to the diet for a few days at a time are therefore justified every two or three weeks. Strict salt restriction is necessary only in the severest grades of hypertension. A reduction in sodium intake is not only of value in itself but it appears to potentiate the ganglion-blocking drugs.

LOW-SODIUM DIET

Approx. 0.5 g. Na; 1,400 calories; NaCl 1.6 g.

Breakfast: 1 egg—poached, boiled, or scrambled—or small helping of white fish. 1 slice of salt-free bread. Salt-free margarine or butter. Jelly marmalade if desired.

Mid-morning: Glass of fruit juice.

Dinner: Small helping of lean meat, fish, tripe, chicken, or rabbit. Avoid ketchups and sauces. Small helping of sieved vegetables. Small helping of mashed potato. Stewed fruit, fresh fruit jelly, fruit whip or snow with sugar *ad lib.*

Tea: 1 slice of salt-free bread. Very small helping of meat or chicken or fish, or an egg. Salt-free margarine. Jelly if desired.

Supper: 1 slice of salt-free bread. Jelly if desired. Salt-free margarine.

Bedtime: Glass of fruit juice.

Allowance for Day: $\frac{1}{2}$ pint (568 ml.) of milk. $\frac{3}{4}$ oz. (21 g.) of salt-free margarine or butter.

Provided the patient is not obese, as much sugar or glucose as desired may be added to the diet.

All food should be cooked without salt, and no salt served with meals.

Meat, Fish:—Avoid all tinned and preserved meat, including ham, bacon, sausages; kippers, finnan haddock; meat extracts as oxo and bovril, also marmite, because of their high salt content.

Fruit:—All fresh fruit is suitable, but dried fruit often contains too much salt.

To be successful the low-sodium diet requires detailed care, and note should be taken of the following considerations.

Special Instructions

(1) In the preparation of the food no salt to be added during cooking or served with the meal at table.

(2) All tinned foods which have salt already added, such as tinned meats and vegetables, tinned soups and tomato juice, are to be avoided.

(3) Smoked, brine-cured, and salty foods such as bacon, ham, sausages, smoked fish, kippers, and pickles are not permitted. This applies also to meat extracts and sauces such as bovril, oxo, marmite, ketchup, and relishes.

(4) Shellfish such as oysters and lobsters are not permitted.

(5) Only breads prepared with yeast and made without salt are allowed. Cheese is not permitted.

(6) Foods to which baking powder or baking soda has been added in their preparation are not permitted. This includes biscuits, wafers, scones, "cookies," and cakes.

(7) Only unsalted or "washed" butter is allowed.

(8) Dried fruits such as figs, dates, raisins, apricots, and prunes are to be avoided.

(9) It is particularly important that no sodium-containing medicines be taken while the diet is in use. This includes sodium bromide, sodium bicarbonate, soda-mints and most of the so-called "indigestion" tablets and powders. Similarly, "soda-water" must not be added to drinks. Salt gargles and toothpastes containing sodium are likewise forbidden.

Recipe for Salt-free Bread:—If salt-free bread cannot readily be obtained, it can be made according to the following recipe:

6½ lb. (2.95 kg.) bread flour	10 oz. (284 g.) sugar
8 oz. (227 g.) shortening	4 oz. (113 g.) yeast
2 quarts (2.27 l.) of water	

This makes six loaves. This bread takes a little longer to rise than ordinary bread.

Foods Permitted:

- (1) Meat, boiled fish, or poultry, prepared and served without added salt.
- (2) Eggs—not more than one daily.
- (3) Milk—limited to two glasses (one pint (568 ml.) as a maximum).

(4) Vegetables—any fresh or green vegetables prepared and served without salt.

(5) Fruits—all fresh and tinned or stewed fruits.

(6) Bread—only yeast bread prepared without salt.

(7) Cereals—the only dry prepared cereals permitted are puffed wheat, shredded wheat, and puffed rice.

(8) Potatoes and rice prepared without salt.

(9) Butter—only unsalted or "washed."

(10) Puddings and sweets—custards, junket and plain puddings made with the milk allowance and with no added salt. Pies with no salt added to the pastry and limited to a filling prepared with fresh or tinned fruit. Jellies, jams, marmalade, white or brown sugar, and honey.

(11) Drinks—tea, coffee, fruit juices, and carbonated drinks.

(12) Flavoursings—chocolate, cocoa, caramel, peppermint, lemon, orange, vanilla, cherries, cloves, cinnamon, nutmeg, ginger, and coffee.

(13) Seasonings—pepper, curry, mustard, mint, vinegar, sage and onion.

II. Aetiological Considerations

The next step is to clarify the diagnosis. A remedial cause must be sought, as an elevation of the diastolic pressure is a sign common to a number of different disorders. In the absence of a demonstrable cause, the hypertension is spoken of as essential or primary hypertension. Known aetiological entities associated with the production of hypertension may be arranged in four main groups: (a) *Renal diseases*: acute and chronic glomerular nephritis, chronic pyelonephritis, polycystic kidneys, hydronephrosis; (b) *Endocrine disorders*: Cushing's syndrome, pregnancy toxæmias, phaeochromocytoma; (c) *vascular disorders* (affecting renal blood flow): congestive heart failure, periarteritis nodosa, coarctation of the aorta; (d) *Neurological diseases*: certain brain tumours, bulbar poliomyelitis.

This classification is not intended to be exhaustive, nor does it account for more than 30% of all cases of hypertension. It is put forward to illustrate how the discovery of an aetiological factor may influence therapy. For instance, unilateral pyelonephritis may justify nephrectomy before hypertension has led to damage of the vascular supply of the opposite kidney. Similarly, effective treatment for the hypertension of Cushing's syndrome, if not due to a localized and removable tumour, consists of total or subtotal adrenalectomy. In younger people excision of a coarctation with reconstitution of the aorta can promptly cure this particular variety of hypertension. A less common example of a remediable cause is a phaeochromocytoma arising from the chromaffin cells of the adrenal medulla or extrarenal chromaffin tissue. The symptoms, which depend upon excessive production of adrenaline or noradrenaline, and the hypertension which occurs in either a paroxysmal or sustained form, can be completely relieved by the early operative removal of these tumours.

III. Selection of Patients for Treatment

A further principle in the medical care of these hypertensive people is to assess as accurately as possible the severity of the disability and adapt treatment accordingly. It is as important not to over-treat, when symptoms are absent or trivial, as it is to employ an intensive routine when serious dangers threaten. The patient's safety depends upon the integrity of his arteriolar walls. To gauge his vascular state as a whole and thereby arrange treatment appropriate to the individual, information of the greatest importance is obtained by direct inspection of the retinæ. Simple studies of renal concentrating power, heart size, and lability of the blood pressure are valuable aids in the assessment of the extent and severity of the arterial disease, but are subsidiary to ophthalmoscopic examination.

Retinal Grading

On the basis of the retinal appearances one of four grades of hypertensive vascular damage can be determined for each patient. The Table given below, constructed from the prognostic studies of Wagener and Keith (1939) on the course of essential hypertension, provides a basis for the adaptation of treatment to the severity of the vascular disease. This is a more satisfactory approach to therapy than the two alternatives customarily offered by dividing essential hypertension into its benign and malignant forms—both terms being misleading. Grades 1, 2, and 3 are often included in the term benign, Grade 4, being known as malignant hypertension.

TABLE

	Grade 1	Grade 2	Grade 3	Grade 4
Symptoms	None to slight	Slight Morning head- ache Vertigo	Moderate Frequent head- aches Fatigue Dyspnoea Nocturia	Severe Intense head- aches Weakness Loss of weight Dyspnoea Confusion
Blood pressure	150/100- 200/120	180/100- 270/130	180/110- 280/140	240/130- 300/180
Retinae	Minimal arterial narrowing	Definite sclerosis	As in Grade 2 with either exudates, star figures, cotton-wool patches, or haemorrhages. Definite retinitis	Papilloedema, with or without Grade 3 changes. Advanced retinitis usual
Renal function	Normal	Satisfactory: faint trace of albumin occasionally present	Impaired: albumin with casts and R.B.C.	Impaired, as in Grade 3, but progressively deteriorating
3-year mortality rates	20%	35%	75%	95%

To show the four grades of hypertension, increasing in severity from 1 to 4. Grades 1, 2, and 3 are commonly included in the term benign essential hypertension, and Grade 4 is also known as malignant hypertension. Broadly speaking, Grades 1 and 2 may be classified as mild, Grade 3 as moderately severe, Grade 4 as very severe.

Broadly speaking, Grades 1 and 2 may be regarded as comparatively mild, Grade 3 as moderately severe, and Grade 4 as very severe or malignant.

The retinal appearances provide a measure of the intensity of the hypertensive process as a whole, but in addition consideration must be given to the efficiency of the heart and kidneys, either of which, after taking the brunt of the elevated pressure for many years, may begin gradually to show signs of failure, or even suddenly fail, without an advance in retinal appearances beyond Grade 2. Left ventricular failure, particularly in an acute form, is an urgent indication for relief of hypertension. Occasionally, uraemia, beginning insidiously, continues remorselessly to a fatal issue, without the development of retinitis. The efficiency of the heart and kidneys, as well as the retinal grade, are therefore the basic factors in determining suitable treatment. Account must also be taken of the age of the patient, more vigorous methods being justified in younger people than in the elderly, whose arteries are less resilient.

Degenerative changes in vital organs may be so advanced as to debar any hope of successful therapy. This applies particularly to the state of the kidneys. If renal function is impaired there is little or no hope of reversing the process. Hypotensive drugs aggravate uraemia. Furthermore, a prompt reduction of the blood pressure in elderly people may prove harmful, if not occasionally fatal.

These considerations lead to the conclusion that patients are best selected for treatment on the basis of their vascular state as it affects certain organs and on the intensity of the hypertensive process rather than on casual or even basal blood-pressure readings. The experienced motorist setting out on a long run is less concerned about the tyre pressures, which must vary with every bump on the road, than about the wear and tear of the tyre covers. So also to the hypertensive patient—the state of the walls of his arteries and their arterioles is more important than his blood pressure at any given instant in the course of a protracted disease. In general, treatment should be determined more by vascular state than by blood-pressure readings.

It will be generally conceded that the following groups of patients should be selected for energetic treatment: (a) all showing hypertensive retinopathy—that is, Grades 3 and 4; (b) those without retinopathy but who have or have had transient cerebrovascular episodes, attacks of left ventricular failure, or angina; (c) those disabled by severe hypertensive symptoms—for example, headaches associated with a persistently high diastolic pressure—120 mm. or more.

There remains a large group of hypertensive patients who may have no symptoms, or only minor ones, and who have no serious retinal, cerebral, or cardiac changes. These patients should be kept under observation at intervals of a few months and are better under-treated than over-treated; certainly the more powerful hypotensive drugs (ganglion-blocking agents and hydralazine) should not be used in view of their attendant discomforts and dangers. Mild hypotensive agents may be employed, but whether they prevent the development of serious vascular damage is not yet known. It is unlikely that they do any harm even when used continuously for many years.

In summary—treatment with the more powerful drugs should be reserved for patients presenting with symptoms or signs of retinal, cerebral, or cardiac impairment of hypertensive origin. Milder hypotensive agents and sedatives can be employed on a prophylactic basis when symptoms and signs are less severe.

IV. Drug Therapy

Rauwolfia serpentina

This drug has proved useful by itself in the treatment of the milder varieties of hypertension (for example, retinal grades 1 and 2) and in combination with other drugs when the response to it alone is incomplete or unsatisfactory. It has many advantages, as toxic symptoms are relatively uncommon and postural hypotension seldom occurs. It has a central action, producing a feeling of tranquillity without somnolence, which may result in a fall of 10 or 20 mm. in diastolic pressure. The object is to pacify without depressing.

Many preparations are available. The refined whole root (for example, "rauwiloid," 2–4 mg. thrice daily), the mixed alkaloids (for example, "raudixin" in 50-mg. tablets, 3 to 8 daily), or the single alkaloid (for example, reserpine, 0.25 mg. thrice daily) may apparently be employed with advantage for long periods and without ill effects. Full benefit is not obtained from this drug until it has been in use for two or three weeks. A fall of 10 to 20 mm. in diastolic pressure is then commonly observed.

Few disagreeable "side-effects" have been recorded from its use. If daytime sedation is excessive on the usual therapeutic routine, the entire daily quantity may be taken as a single dose at night. Mental depression is seldom observed when raudixin is in use, but the drug should be used with caution in the emotionally unstable and in those who have passed through phases of mental depression, lest exacerbations recur. A minor sense of stuffiness of the nose and a tendency to diarrhoea are occasionally encountered. Vague pains in the back and thighs are sometimes noted, and in younger women lactation may occur. Administration of two 50-mg. tablets of raudixin three or four times a day, the first dose on rising in the morning and the last 12 hours later, makes a useful routine and may be supplemented by a phenobarbitone tablet, 30–60 mg. at bedtime, if necessary.

Veratrum

If after a fair trial *rauwolfia* fails to maintain the diastolic pressure below 100 or 110 mm., extracts of *veratrum viride*, or hellebore, may be added to the patient's treatment. "Veriloid" is a useful proprietary preparation of the active principles. It is available in 1- and 2-mg. tablets. Treatment may be started with 2 mg. four times a day, the dose being taken along with the quantity of raudixin already prescribed. With this drug a maximum hypotensive effect is usually obtained with a daily quantity 2 to 4 mg. less than that required to induce toxic symptoms. The margin between optimum benefit and early toxicity is narrow, and may amount to no more than 2 mg. in a 24-hour period. Accordingly, the dose of veriloid should be increased cautiously by adding a 2-mg. tablet to the daily dose every third or fourth day until the earliest symptoms of intolerance develop. Heartburn, increased salivation, nausea, and vomiting are the usual indications that the optimum daily dose has been exceeded. Veriloid intoxication subsides rapidly when the daily quantity is reduced by 2 to 4 mg. It is not

necessary to discontinue completely the use of this drug when toxic symptoms are induced.

Significant hypotensive effects can be induced in about half the patients taking this drug, more particularly if the maximum dose tolerated is taken steadily and in conjunction with raudixin. Most patients feel better, are less tired, and are free from headaches when full doses of veriloid are in use. Tolerance varies from patient to patient, and the daily quantity ranges from 18 to 24 mg. as a general rule. Minor toxic symptoms such as a peppermint-like flavour in the mouth or slight salivation are common. They tend to come and go, and conscientious patients ultimately learn to disregard them in the knowledge that thereby the drug is exerting a full effect. If no corresponding reduction is observed in the diastolic readings when full doses are in use, there is no justification for urging the patient to continue with this drug.

Ganglion-blocking Compounds

When signs of retinitis are present, or when the heart or kidneys are showing early signs of impairment, more energetic measures are required, firstly for the relief of symptoms, which tend to be more severe in this group, and secondly in an attempt to arrest or reverse the obliterative vascular disease. In recent years new ganglionic blocking-agents, consisting of the halogen salts of hexamethonium and pentamethonium, have proved increasingly useful. They act on both sympathetic and parasympathetic ganglia, and therefore produce a wide range of effects such as pupillary paralysis, gastric hyposecretion, and intestinal ileus as well as hypotension. At the present time, pentolinium tartrate ("ansolysen") is the methonium compound of choice. It closely resembles hexamethonium in its action, except that its effects last longer and it is about five times as strong. Its great advantage is that it can be given successfully by mouth in the majority of patients.

The ideal method of regulating pentolinium tartrate to the patient's particular requirements is by measurement of the blood pressure, taken lying and standing, at frequent intervals through the day. This can best be done in hospital by trained technicians or nurses. Where such facilities are not available a single timed reading of blood pressure each day in the erect posture between two and three hours after the morning dose of pentolinium tartrate may prove a useful guide, but fairly accurate control of dosage can be regulated by the production of hypotensive symptoms, the quantity of the drug being gradually increased by small increments, say 20 mg., until such symptoms occur. At, or a little above, the optimum dose the patient, on standing quietly at the time of maximum action of the drug, will notice slight dizziness, promptly relieved by sitting or lying down. If faintness occurs the dose should be reduced, while if no dizziness is noted the dose should be increased. The intelligent and co-operative patient can soon learn to regulate his pentolinium tartrate dosage. The dose requirements vary from patient to patient. The correct dose has to be determined by the individual's response.

The initial dose is 20 mg. twice daily, the first dose of the day being taken at 7 a.m. and the last at 10 or 10.30 p.m. The tablets should be taken crushed in a constant amount of water, preferably at least an hour before meals to ensure reasonable constancy of absorption. Doses at 12 noon and 5 p.m. suit most people. Blood-pressure readings can be recorded with advantage about 10 a.m., two hours after breakfast, and records kept of the response, with the patient lying and standing, from day to day until the dose is finally stabilized. The aim should be to obtain a systolic pressure of 120-140 in the erect posture when the drug action is maximum two to three hours after its oral administration.

If no symptoms are induced in the erect posture by 20 mg., then the following day 40 mg. is taken at 7 a.m. and 10 p.m. Assuming negative reactions, additional doses of 20 mg. each may be taken at noon and at 5 p.m. next day. The aim should be to obtain an adequate hypotensive effect throughout the 24 hours. Of the four doses, the evening one can with advantage be the largest in the hope of prolonging the effect overnight, the midday dose the smallest, and the

morning dose intermediate. When adjustments have been made and some tolerance has been developed, a day's routine after two or three weeks of cautiously increasing the dose might work out at 140 mg. at 7 a.m., 80 mg. at noon, 100 mg. at 5 p.m., 240 mg. at 10 p.m. The hypotensive effect of the evening dose can be augmented by having the patient sleep with the head of the bed raised on blocks 12 to 18 in. (30-45 cm.). If difficulties arise in adjusting the dose on the basis of hypotensive symptoms, it is usually necessary to have the patient in hospital in order to observe the blood-pressure response to a test dose over several hours.

There are two difficulties in pentolinium tartrate treatment worthy of particular consideration. Tolerance to the drug develops rapidly at first, and may in fact continue to develop to a slight extent for some months. The daily dose must therefore be raised day after day for two to three weeks, and later less frequently, if the desired postural effects are to be maintained, for without them the patient is not obtaining full benefit.

On effective methonium therapy most patients have some "side-effects." Constipation is a source of danger, as, following its relief, excessive absorption of methonium may occur with profound falls in pressure. Pentolinium tartrate is less likely to cause constipation than other hexamethonium compounds, but nevertheless the patient should be warned of its dangers and have a suitable remedy. A cascara pill or mixture may be necessary in generous doses. The bowel must be made to act at least once daily. Parasympathetic-stimulating drugs can also be used to combat constipation and also the dryness of the mouth. For this purpose oral neostigmine, 15 mg., carbachol, 0.25 mg., or pilocarpine, 1 mg. in water perhaps, thrice daily, may be used. If complaint is made of blurring of vision, physostigmine drops in a strength of 1/32% to 1/16% may help, but sometimes it may be necessary to provide an extra pair of glasses, refraction being adjusted to the change in the eye brought about by the action of the methonium compound.

Raudixin has proved very effective in counteracting the "side-effects" of the methonium compounds. When it is added to the methonium routine the response to pentolinium tartrate is enhanced, so that smaller doses prove equally effective. "Side-effects" of methonium are consequently diminished.

Mecamylamine

On account of its complete absorption and more protracted action, the powerful ganglion-blocking agent, mecamylamine, appears to be more predictable and constant in its hypotensive effects than the oral methonium compounds (Moyer *et al.*, 1956). Its "side-effects" are similar and tolerance is readily established, so that dosage must be adjusted to the individual's requirements. It is usually wise to begin with a small dose, say 2.5 mg. at 7 a.m. and 5 p.m. After two or three days these quantities may be doubled and, later, additional doses added at 12 noon and 10 p.m. As with pentolinium, the aim is to produce mild hypotensive symptoms in the erect posture two to three hours after taking the drug. A few weeks of careful study, during which the dose of the drug is titrated against the postural response, are usually required before a steady routine can be advised. The dose of all ganglion-blocking drugs can only be determined by trial and error. Preliminary experience with mecamylamine is so encouraging that it may yet prove to be the drug of choice in the severest grades of hypertension.

Malignant Hypertension

Patients in this category are gravely ill and commonly die within a few months in a confusional state, with or without evidence of left ventricular failure, and with varying degrees of renal inadequacy. Any success in treatment of this, the most serious form of hypertension, depends upon the early recognition of papilloedema, when symptoms may be comparatively slight, and on the employment of energetic measures to restore normal pressure levels. As a complication of malignant hypertension, left ventricular failure is more readily corrected than nitrogen retention. Uraemic

signs are of ill omen and usually betoken an unfavourable response to treatment.

If renal function is reasonably good, the blood non-protein nitrogen less than 50 mg. per 100 ml., and congestive failure absent or controlled, the prospects of lowering pressure and of arresting the progress of the vascular disease are reasonably good. Smirk (1953) considers that in these ill people the urgency of the situation demands that pentolinium should be used first as the "retard" preparation by subcutaneous injection in an initial dose of 3 mg. twice or thrice daily, increasing by 1 mg. per dose until suitable hypotensive levels are obtained. As much as 140 mg. daily may be required, but in our experience oral doses are equally effective, particularly when raudixin is also in use. The justification for the parenteral route is the necessity for rapid control of the blood pressure, as when hypertensive heart failure complicates the situation. Similarly, recurrent bouts of vomiting may preclude the effective use of the oral preparations. Parenteral administration is then the only alternative. With twice-daily subcutaneous injections at 12-hour intervals, a small supplementary oral dose may be given about midday, and, later, oral doses can sometimes be substituted for the two injections. As improvement is made, four oral doses of pentolinium tartrate may conveniently replace the subcutaneous injections.

Contraindications to Ganglion-blocking Compounds

A word of caution is necessary regarding the indiscriminate use of ganglion-blocking compounds. Unless the doctor is prepared personally to supervise their use, and succeeds in enlisting the intelligent co-operation of his patient, methonium or mecamlamine may do more harm than good. The patient must be taught to adjust and regulate his own treatment, and for this purpose he may be handed a leaflet giving him precise instructions. If he is uncooperative the attempt at home treatment should be abandoned.

Experience indicates that these compounds aggravate established uraemia. They should not be used in the presence of advanced cerebral arteriosclerosis, and only be commenced two to three months after either a cerebral or a coronary thrombosis. Prostatic symptoms call for considerable caution in the employment of these remedies.

Hydrallazine ("apresoline")

When renal function is moderately impaired, with a blood non-protein nitrogen in excess of 40–50 mg. per 100 ml., the response to treatment becomes less and less satisfactory. With a reduction in arterial pressure, renal function may in fact decline further. In these circumstances some success has been obtained by the oral use of hydrallazine in doses of 25 to 100 mg. It is a synthetic preparation which has the peculiar quality of considerably increasing renal blood flow while decreasing diastolic pressure. Cardiac rate and output are said to be increased. An improvement in renal function may warrant the cautious addition of pentolinium tartrate to the hydrallazine routine. When uraemia is in progress no drugs are of any avail.

Hydrallazine has distinct limitations, as "side-effects" and toxic reactions are frequent. Headache, flushings, and palpitations are common. Oedema of the skin observed about the hands and feet and drowsiness and dryness of the mouth also occur, but fortunately tend to disappear of their own accord after a few days when tolerance is gained. More serious signs of intoxication are the development of conditions resembling rheumatoid arthritis on the one hand and disseminated lupus on the other. Anaemia, hepatomegaly, and splenomegaly also occur. Intolerance for the drug usually subsides satisfactorily on its withdrawal.

V. Surgical Procedures

Lumbo-dorsal Sympathectomy

On the hypothesis that high blood pressure is the result of overactivity of the sympathetic system, bilateral excision of the paravertebral ganglia has been employed extensively during the past 20 years. Smithwick's procedure, which includes resection of the splanchnic nerves, together with excision of the sympathetic trunks from the level of the ninth

thoracic root to at least as low as the first lumbar, has yielded in expert hands striking benefit in the severest grades of hypertension. In younger people, provided renal function is reasonably good and congestive failure has not occurred, sympathectomy may produce a regression of the papilloedema, a fall in pressure, a restoration of a sense of well-being, and a prolongation of life which compares favourably with any other method of treatment at present available. It is, however, a major operation, commonly followed by a protracted convalescence and occasionally complicated by intractable root pains of a girdle type. Accidental wounding of the pleura can cause much respiratory embarrassment in the immediate post-operative period.

Sympathectomy has a limited use in the treatment of hypertension, as experience shows that a satisfactory result is most unlikely in the presence of impaired renal function, and, contrary to the use of the methonium compounds, patients who have suffered or are suffering from left ventricular failure never tolerate this surgical procedure. A poor response to methonium in combination with rauwolfia or hydrallazine, provided renal and cardiac functions are reasonably good, is a strong indication for sympathectomy, particularly in the severest grades of hypertension. For unintelligent and uncooperative patients, incapable of regulating their pentolinium or mecamlamine routine, sympathectomy is a justifiable alternative.

Bilateral Adrenalectomy

From the observation that the low blood pressure of Addison's disease could be corrected, and, indeed, overcorrected by the subcutaneous insertion of pellets of D.C.A. arose the suggestion that bilateral adrenalectomy might be justified in the severest forms of hypertension. Even with the help which cortisone and other substitution products provide, the post-operative findings indicate that subtotal or total adrenalectomy is a major undertaking, yielding uncertain results and imposing formidable risks among those surviving even a few months (Pickering, 1955). The immediate benefits resulting from the employment of the potent medical remedies now available, coupled with the substantial reduction in the mortality rate even in malignant hypertension, emphasize as nothing else can that there is no future for the employment of such a drastic upheaval as adrenalectomy in the treatment of hypertension other than in those instances where the suprarenal gland is primarily involved.

VI. Multiple Therapy

As already described, reassurance combined with light sedation in the form of small doses of barbiturates or rauwolfia are all that are required in the milder non-progressive cases of hypertension, with no more than Grade 1 or at most Grade 2 retinæ. The more powerful drugs—methonium and hydrallazine—are dangerous, but in combination have proved very effective when used cautiously in the severer forms of the disease.

Rauwolfia has the great advantage that it apparently potentiates other hypotensive agents, and when in use reduces the effective quantity of pentolinium, thus lessening the disagreeable "side-effects" of the latter preparation. In the opinion of Wilkins rauwolfia is the first hypotensive drug to try and the last to omit. Its stimulating action on the bowel may overcome to some extent the constipating action of the methonium compounds, its enhancement of vagal tone may restrain the cardiac acceleration of hydrallazine, and its central soothing action may augment the effects of veriloid by reducing that drug's tendency to gastric upset.

In the presence of hypertensive cerebral vascular disease, the combination of a low-sodium diet with rauwolfia, and later if necessary with veriloid in addition, is probably safer than intensive methonium therapy, at least in the first instance, whereas hypertensive heart failure calls for pentolinium or mecamlamine and a greater or less degree of salt restriction. Sodium retention is common when rauwolfia is in use, but seldom gives rise to difficulty if the diet is suitably adjusted and mercurial diuretics used from time to time.

For uncomplicated hypertension of Grade 3 or 4 severity, the combination of rauwolfia with a ganglion-blocking agent is the treatment of choice. This may be supplemented by salt restriction, and, if the response is incomplete or delayed, lumbo-dorsal sympathectomy may then be considered. It is said that a previous sympathectomy enhances the effects of hypotensive drugs.

VII. Conclusions

Hypertensive vascular disease presents in such a great variety of patterns, and runs such an unpredictable course, that the effects of treatment are difficult to assess.

Nevertheless, the remedies at present available, if selected judiciously, applied conscientiously, and adjusted carefully to the particular needs of the individual, offer more for hypertensive patients than ever before.

The maintenance of the blood pressure within the normal range permits a reversion of the vascular damage in the retinae, heart, and brain, provided renal function is not grossly impaired and massive tissue destruction has not occurred. Early treatment, even in the severe forms of hypertensive disease, should reduce the risk of serious complications and be the means of prolonging life.

In general, appropriate therapy, which is most often a combination of different remedies, should be determined more by the patient's vascular state than by blood-pressure readings. For the most part the retinal picture, taken with the state of the heart and kidneys, determines treatment.

Summary

A great variety of remedies are available for treatment of hypertensive vascular disease. General measures include: (a) simple psychotherapy; (b) advice regarding a physiological way of life; and (c) instructions regarding weight reduction and restricted Na intake.

The detection of a precise aetiological cause, and its prompt surgical removal, can lead to permanent cure.

In most cases treatment must be determined by the degree of vascular impairment rather than by blood-pressure readings.

All patients showing hypertensive retinopathy should have intensive therapy, also those without serious retinal changes but who have had transient cerebrovascular episodes, attacks of left ventricular failure, or angina. Most patients disabled by severe hypertensive symptoms will also require the more potent hypotensive remedies.

Patients who have no symptoms, or only minor ones, and who present no evidence of serious retinal, cerebral, or cardiac damage require advice about their mode of life, and only mild hypotensive agents such as rauwolfia.

Rauwolfia potentiates other hypotensive agents. Rauwolfia, with or without "veriloid," and a low-salt diet may keep hypertensive heart failure in check, but more commonly pentolinium and Na restriction will be required. Rauwolfia alone or with veriloid often helps the anginal patient with hypertensive coronary disease.

Low-sodium diet combined with veriloid is probably safer than intensive methonium therapy for cerebrovascular lesions. For uncomplicated Grade 3 or 4 hypertension rauwolfia with pentolinium is the treatment of choice.

Preliminary experience suggests that the effective dose of mecamlamine is more readily determined and more constant than that of the methonium compounds. It may therefore ultimately replace pentolinium, but the long-term results are not yet known.

In the presence of uraemia all hypotensive drugs are valueless, though in the milder grades of renal impairment hydrallazine ("apresoline") may prove helpful.

For patients incapable of regulating their pentolinium routine, or if the response to the drug is poor, lumbo-dorsal sympathectomy is indicated, provided renal and cardiac functions are reasonably good.

The accompanying Table and Diet Instructions are reproduced from a *Textbook of Medical Treatment* by permission of the publishers, Messrs. E. and S. Livingstone, Edinburgh.

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DURATION OF ANTICOAGULANT EFFECT IN RELATION TO URINARY EXCRETION OF DEXTRAN SULPHATE

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It has already been reported that when the effect of single equipotent intravenous doses of heparin and dextran sulphate are compared the latter compound shows a slightly greater duration of effect. Comparison of repeated equipotent doses makes this disparity in duration of effect more pronounced (Ricketts *et al.*, 1953). This observation was confirmed by Donzelot *et al.* (1955), who reported that after three to five days' treatment with dextran sulphate the increase in duration of effect of successive doses was such that adequate control of the coagulation time and satisfactory clinical responses in cases of thrombo-embolic disease could be obtained by intravenous dosage at daily intervals or even on alternate days.

One factor which it was thought might be responsible for a cumulative effect of this kind, as compared with the absence of a similar effect with heparin, was a difference between the patterns of urinary excretion of the two drugs. Estimates of the urinary excretion of dextran sulphate in patients treated with dextran sulphate for periods varying from 10 to 23 days, and similar estimates in experimental animals given repeated injections for 10-day periods, were carried out and were related to measurements of the clotting-time of blood and the one-stage "prothrombin" time, in order to investigate this hypothesis. Certain further observations on the clinical effects of dextran sulphate were made incidentally in the course of this investigation.

Materials and Methods

Dextran sulphate ("dexulate," Batch No. 52DS041) was available as a 9% sterile solution, including 0.2% sodium bicarbonate and 0.7% sodium chloride. The dextran sulphate