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HYPERTENSION AND ITS CONTROL BY HEXAMETHONIUM

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High blood pressure, with its cardiovascular and renal consequences, is perhaps the greatest barrier to survival after middle-age. As in other chronic progressive and so far incurable maladies, the multiplicity of vaunted remedies serves only to emphasize their failure to bring lasting benefit. In fact, for milder degrees of essential hypertension no medicament or specific treatment has yet been shown to rival the benefit produced by adjustments of regime, diet, habits, and weight. For the more severe grades of essential hypertension the past decade has brought methods of attacking the neural mechanisms which, though they may not cause hypertension, are part of the means by which it is maintained. These forms of treatment are surgical (lumbo-dorsal sympathectomy) and medical (by various ganglion-blocking substances, notably hexamethonium compounds). For a treatment of hypertension to be acceptable it must be available for use by general practitioners for patients living at home and pursuing their daily work; no treatment that depends upon continuous intricate control in a clinic or through an institution is of real value in a disease which is so common and widespread and which often covers one or two or more decades of a patient's life.

In this paper we report the treatment and follow-up of 83 patients who have received hexamethonium bromide for hypertension. The criteria upon which the results of such treatment must be based are discussed, a special distinction being drawn between lowering of blood pressure and prolonging life. The indications and methods for the use of hexamethonium, and the significance and control of side-effects, are considered. Finally, recommendations are made concerning the safeguards needed for induction of this treatment and the manner in which it may be maintained at home and in work.

Ever since a raised blood pressure became recognized as a frequent primary anomaly and was named essential hypertension it has been presumed that the pressure should be reduced if possible. It was recognized that removal of the cause would be the ideal aim, but as the cause remained unknown lowering of the blood pressure would be the means of delaying the many disasters of which hypertension seemed to be the immediate precursor. In those days there was no sure means of diminishing a high blood pressure, although rest in bed

and sedatives would help. Sometimes pressure fell spontaneously (owing usually to heart failure or to cardiac infarction), and it was noticed in these cases that the patient's condition at the same time deteriorated. By analogy, it was sometimes explained to hypertensive individuals that even if their pressure could be lowered they would not feel any better for it, the implication being that if the pressure was raised it was a compensation of some sort that was inevitable and necessary, although harmful in the long run.

Teleological and often contradictory notions such as these were but examples of the many arguments prevailing up to the time of the second world war. Now that there are means of lowering high blood pressure in a fairly controlled manner the opportunity arises to test many of these unfounded assumptions. Over several decades writers on the treatment of hypertension have agreed upon certain basic requirements, mainly the need for readjusting the patient's mode of life and the advisability of moderation in diet. Also they have all suspected that the intake of salt should be restricted. Although it has only comparatively recently been decided which element of sodium chloride is the undesirable one, the restriction of salt (and sodium in any combination) remains to-day an integral and important part of treatment.

The effects of any new form of treatment have always had to bear comparison with the well-known results of "conservative" measures comprising essentially avoidance of physical and mental stress, an increase in the hours of rest, the use of sedatives, the reduction of obesity if it existed, and the moral support of a medical attendant. This is still the treatment adopted by physicians when the newer medicinal, dietetic, and surgical measures have been judged inadvisable or ineffective. It is capable of bringing substantial subjective improvement and some reduction in the pressure in about two-thirds of those who conscientiously follow such a regime.

The advantageous effects of a diet consisting only of rice have been described by Kempner (1949). Such a diet, which is very low in protein and contains less than 0.5 g. of sodium in the 24 hours, is capable of lowering the blood pressure and bringing other objective benefits such as improvement in the state of the retinae and

regression of the electrocardiogram towards a more normal form. In general, patients have not been able to tolerate this monotonous diet for long periods, and it has been found that a more liberal diet, provided it contains less than 0.5 g. of sodium daily, may give results nearly as good. Emphasis is placed upon this prevailing notion, which later became a proved fact, that salt was in some way linked with the existence of essential hypertension, as it is an important part of the hexamethonium treatment.

About the time that the results of Kempner were being made known Smithwick (1948) published his results of dorso-lumbar sympathectomy for hypertension. Hailed at the time as a fairly sure and reasonably safe method of bringing down the blood pressure, it was widely practised until, with the passage of years, it became clear that even with the most extensive sections of the sympathetic a lasting reduction of pressure was conferred on only a minority of patients (Evelyn *et al.*, 1949). This did not necessarily mean that the tenure of life was not on the whole increased, and it is believed by those who used the surgical method in properly selected patients that it has often materially improved the prognosis (Hammarström and Bechgaard, 1950; Smithwick, 1951; Morrissey *et al.*, 1953).

Ganglion-blocking Agents

Soon after the popularity of sympathectomy was reaching its height came the first observations on ganglion-blocking agents. Arnold and Rosenheim (1949) employed pentamethonium iodide intravenously and intramuscularly, and found that it produced transient lowering of pressure in hypertensive patients and sometimes even excessive reduction needing correction by adrenaline injection. In the following year were published the papers of Restall and Smirk (1950) and Turner (1950) on the use of hexamethonium bromide. There followed the series of Smirk and Alstad (1951) based on the treatment of 53 patients. These writers selected for treatment the more severe grade of hypertension, including patients showing papilloedema and other vascular retinopathies, cardiac asthma, hypertensive heart failure, and encephalopathy; they concluded that, apart from some of the cases with impairment of renal function, almost all hypertensives can have their blood pressure controlled by these drugs. McMichael (1952) has given qualified approval of parenteral hexamethonium treatment based on a series of 27 cases, and more recently Moyer *et al.* (1953) have, among 58 patients, found hexamethonium chloride to be an effective hypotensive agent, the action of which was sometimes augmented by hydralazine hydrochloride ("apresoline"). Work on the control of malignant hypertension has also been published by Page (1951).

Adverse views on the oral value of administration of methonium compounds have been given by Locket *et al.* (1951), whereas in the hands of Mackey and Shaw (1951) and Campbell *et al.* (1952) this method was effective. Kilpatrick and Smirk (1952) have found the oral route a useful substitute for injections, although the results were less predictable; oral therapy was more likely to be successful when the patient was sensitive to small subcutaneous dosage. Provided the adjuvant effect of a salt-free diet was remembered, and provided close and continued clinical observations were used to adjust dosage, they believed that the oral route could be valuable, especially when excretion was delayed, as in some cases of chronic nephritis.

Material and Results

The material for this survey comprised a group of 83 patients derived from hospital and private practice who have been treated with hexamethonium for hypertension in one hospital over a period of three years. The majority of these

patients have been followed by us in a clinic reserved solely for patients with hypertension, and have been admitted from the clinic for 24-hour blood-pressure observations in the ward.

In the clinic, the blood pressure, in the lying and standing positions, has been taken independently by two observers. Routine sensitivity tests with hexamethonium showed that there was a definite postural hypotensive effect in all cases, whatever the sensitivity of the blood pressure to hexamethonium in the horizontal position. This postural effect persisted on exercise (Fowler and Guz, 1954) and was found to be an important factor in controlling the blood pressure. It was shown that hexamethonium could be used successfully irrespective of the original sensitivity test made in the lying position.

Severity of the disease was assessed on retinal and renal changes as well as on the height of the blood pressure, but details of the former have not been included. The blood-pressure figures presented below indicate that treatment for the main part was reserved for the most severe cases.

In Table I is shown the route by which hexamethonium was administered in 83 patients treated for hypertension. In addition, it shows that treatment had been abandoned

TABLE I.—Treatment of 83 Hypertensive Patients with Hexamethonium

Route	Treatment Continued	Treatment Abandoned	Total
Parenteral ..	35	16	51
Oral ..	25	7	32
Total ..	60	23	83

in a higher proportion (31%) of those treated parenterally as compared with those treated orally (22%). There were two reasons for this difference. First, there were more severe cases of hypertension in the parenterally treated group and more of these patients had died; secondly, it was unjustifiable to continue a remedy parenterally if it proved to be ineffective. Oral therapy was often continued with good symptomatic results in cases in which it was having little or no influence on the blood pressure.

Parenteral treatment was far more effective in controlling the blood pressure than oral therapy (Table II). In the cases with an initial diastolic blood pressure of 120 mm. Hg or

TABLE II.—Comparison of Parenteral and Oral Treatment in Controlling the Blood Pressure in 60 Subjects with Different Initial Blood-pressure Levels, Still Under Treatment

Range of Initial Diastolic B.P.	Control of Blood Pressure in										Total of All Cases
	Parenterally Treated Cases					Orally Treated Cases					
	Good	Fair	Poor	Nil	Total	Good	Fair	Poor	Nil	Total	
120 or less	0	1	0	0	1	2	2	1	4	9	10
121--140	9	8	9	1	27	1	2	3	4	10	37
Over 140	2	3	1	1	7	0	1	1	4	6	13
Total ..	11	12	10	2	35	3	5	5	12	25	60

less, oral therapy was effective in controlling it in half the cases treated. For the 13 cases with an initial diastolic blood pressure over 140 mm. Hg, control was fair or good in five out of seven treated parenterally, while for the orally treated cases in this group there was no effect on the blood pressure in four patients out of six. In this group of six orally treated patients with very high diastolic pressures the side-effects produced by effective therapy given parenterally were not tolerated by the patient or rigid control of the blood pressure was found to be contraindicated. Despite the poor blood-pressure control in this group of six cases with a high initial blood pressure treated orally, the symptomatic result was good in four cases, fair in one, and recorded as nil in a patient (Case 9) who presented with a monoplegia (Table V). The effect of leaving the blood

pressure uncontrolled in this group of cases cannot yet be assessed, as the patients have been under surveillance for too short a period for this purpose, the average duration of treatment for the group being a little over seven months.

It will be seen in Tables III, IV, and V that the symptomatic result of treatment bore no relation to the degree of blood-pressure control. When the patients presented with symptoms rather than complications of hypertension, there was uniformly satisfactory relief of these symptoms. Headache was the most distressing presenting symptom in 21 (25%) of the 83 cases (Table III). This Table included only those in whom headache was the most important presenting symptom, and by omitting those cases in which headache was an incidental or even a joint presenting symptom a

TABLE III.—Control of the Blood Pressure and Relief of Headache in 21 Cases of Hypertension Presenting with Headache

Control of Blood Pressure	Relief of Headache				
	Good	Fair	Poor	Nil	Total
Good	5	1	—	—	6
Fair	4	2	—	—	6
Poor	3	—	—	—	3
Nil	4	2	—	—	6
Total	16	5	—	—	21

more certain assessment of the relationship of headache to the level of blood pressure was made possible. As shown in Table III no relationship exists between the control of blood pressure and the relief of headache.

In numerous papers on the subject of the treatment of hypertension with hexamethonium, full details are given about a few patients; it may not always have followed that these illustrative cases were the average response to treatment, although this is often the impression which the paper conveys. In our series there was an extraordinarily wide range of response to treatment. For this reason a précis of each case in our series which is still continuing treatment is given in Tables IV and V.

In 12 patients one injection only in the 24 hours was given, on retiring at night. These were patients in whom side-effects were marked and the prevention of heart failure, the most common termination of hypertension, was the dominant consideration in treatment. It is well recognized that the blood pressure in normal persons and in hypertension falls during sleep, and, if it were not for the practical consideration of avoiding unpleasant side-effects, a single injection given in the morning would be of more value in maintaining an even lowering of blood pressure. It appeared, however, that by using hexamethonium to lower the blood pressure during the night below the level reached by sleep alone the cardiac reserve was increased. The dose given in these cases caused no symptoms, as the injections were given just before retiring. The same dose given in the morning was found to be intolerable to the majority of these patients.

Duration of Treatment

As experience with hexamethonium therapy was gained, the oral route was used less often, and in all severe cases the attempt to control the blood pressure was made by using hexamethonium parenterally. Table VI shows that 32% of the patients still under treatment had been given hexamethonium for less than six months.

Those cases which had been treated parenterally for two years or more showed far more satisfactory control of the blood pressure than the group treated for less than six months. Clearly, as time went on, the less satisfactorily controlled patients would be taken off parenteral treatment, but failure to control the blood pressure was usually evident in the first six months of treatment. All 16 patients for whom parenteral therapy was abandoned were treated for under six months. Details of these patients are given in Table VII.

Side-Effects of Hexamethonium

Most of the side-effects are directly attributable to the ganglion-blocking action of this drug or to the fall in blood pressure.

TABLE IV.—Parenteral Treatment with Hexamethonium Bromide in 35 Patients Continuing Treatment

Case No.	Age First Seen and Sex	Presenting		Dose in mg.	Symptomatic Result	Control of Blood Pressure			
		Symptom or Condition	B.P.			Duration Treatment (Months)	B.P. Recording	Hours after Injection	Assessment of Control
1	49 M	Angina pectoris ..	210/130	100 b.d.	Good	24	175/100	7½	Good
2	59 M	Epistaxis	240/125	60 ..	"	8	225/140	8½	Nil
3	40 F	Headache	230/130	100 ..	"	24	180/110	7	Fair
4	39 F	"	230/120	120 nocte	"	6	180/100	16	"
5	53 M	Nil (life) later A.P. ..	285/125	100 ..	"	12	220/115	16½	Poor
6	34 M	Headache	210/130	200 ..	"	24	140/90	17	Good
7	53 M	"	220/140	60 ..	"	6	170/120	17	Poor
12	52 M	"	220/130	60 b.d.	"	4	200/120	5	"
25	55 M	Hemiplegia	200/125	60 ..	"	4	160/110	7½	Fair
26	53 M	Angina pectoris ..	220/140	100 ..	"	24	155/110	4	"
							175/110	7	Good
27	50 F	Headache	240/160	250 ..	"	12	175/100	7½	"
31	60 M	Blurred vision ..	300/180	80 ..	Fair	3	300/170	6	Nil
37	35 M	Lassitude	240/130	50 ..	"	11	200/140	8	Poor
41	53 M	Congestive failure ..	200/140	50 nocte	"	10	130/90	6½	"
							200/120	19	Fair
45	48 F	Precordial pain ..	250/140	100 ..	Good	12	245/135	13½	Poor
49	34 M	Headache	280/180	150 b.d.	"	12	140/100	7	Good
50	55 F	Dyspnoea	260/145	60 nocte	"	4	130/110	1½	Fair
54	55 F	"	230/130	60 ..	"	9	200/120	17½	Poor
59	36 M	Epistaxis	210/140	80 b.d.	"	10	175/115	7½	Fair
60	40 F	Angina pectoris ..	220/140	50 ..	"	2	170/120	7½	Good
61	58 M	Dyspnoea	230/140	80 ..	"	3	180/130	4½	Poor
62	46 F	Bilious attacks ..	250/140	100 ..	"	1	200/130	5	"
63	56 M	Cerebral thrombosis ..	250/130	50 nocte	"	10	230/150	19	"
65	59 F	Headache	245/140	60 ..	"	3	170/100	17	Good
66	58 F	Epistaxis	300/160	50 t.d.s.	"	10	200/130	3	Fair
68	48 M	Headache	220/125	60 mane	"	2	170/125	9	"
				70 nocte					
69	48 F	Dyspnoea	250/150	60 ..	Fair	3	225/115	16½	"
70	61 F	"	250/130	60 b.d.	Good	1	200/115	7	"
71	37 F	Nil	235/130	80 ..	N.A.	1	210/125	8½	"
72	66 M	Nearly blind	290/145	80 ..	Nil	5	225/110	4½	Poor
76	60 M	Paroxysmal dyspnoea ..	210/130	70 ..	Good	6	140/90	2	Good
77	36 M	Hypertensive encephalopathy ..	215/130	160 ..	"	3	160/100	4	"
78	45 M	Severe dyspnoea ..	170/130	120 ..	"	5	110/80	3	"
80	44 F	Congestive heart failure ..	210/130	100 ..	Fair	6	150/100	3½	"
81	58 M	Dyspnoea	245/130	120 ..	Good	1	170/100	4	Fair

TABLE V.—*Oral Treatment with Hexamethonium in 25 Patients Continuing Treatment*

Case No.	Age First Seen and Sex	Presenting		Dose in Tabs. of H.M.B. or H.M.T.	Symptomatic Result	Blood Pressure Control		
		Symptom or Condition	B.P.			Months after Treatment	B.P.	Assessment of Control
9	55 F	Monoplegia	250/150	H.M.T. 4 t.d.s.	Nil	8	220/120	Nil
10	41 M	Headache	200/125	H.M.B. 4 ..	Fair	15	150/95	Good
				H.M.T. 4 ..				
				alt. weeks				
11	44 F	Dyspnoea	230/110	H.M.T. 4 t.d.s.	Good	12	240/110	Nil
16	45 F	Headache	260/170	H.M.B. 4 ..	Fair	6	250/140	"
18	51 F	Anxiety neurosis ..	240/135	H.M.B. 1 b.d. (placebo)	Good	15	215/100	Poor
19	59 F	Cerebral thrombosis ..	250/130	H.M.B. 2 t.d.s.	"	4	200/120	(weight reduction) Fair
				H.M.T. 2 ..				
				2 wks. altly.				
22	51 F	Headache	245/120	H.M.T. 3 t.d.s.	"	12	230/120	Nil
24	48 F	Angina pectoris ..	235/125	H.M.B. 2 q.d.s.	"	1	220/120	"
29	57 M	Headache	220/150	H.M.B. 2 ..	"	10	230/140	"
30	52 F	Giddiness	230/130	H.M.T. 5 t.d.s.	"	24	240/115	Poor
34	54 F	Headache	210/130	H.M.B. 4 ..	"	12	210/130	Nil
35	46 M	Retinal haemorrhage ..	190/120	H.M.B. 2 ..	"	30	150/90	Good
40	62 F	"	200/120	H.M.T. 2 ..	Nil	10	170/115	Poor
42	40 M	Headache	250/150	H.M.T. 2 ..	Good	6	210/125	Fair
44	62 M	"	200/115	H.M.B. 2 ..	Fair	15	150/110	"
46	52 M	"	210/150	H.M.B. 2 ..	Good	12	210/140	Nil
				H.M.T. 2 ..				
				3 wks. altly.				
51	44 M	"	200/120	H.M.B. 1 t.d.s.	"	6	150/80	Good
52	43 F	Dyspnoea	190/120	H.M.B. 2 ..	Fair	8	185/130	Nil
				H.M.T. 2 ..				
				3 wks. altly.				
53	57 M	Headache	240/140	4 H.M.B. 1 t.d.s.	"	12	220/130	"
55	43 F	Dyspnoea	195/130	H.M.B. 6 b.d.	Good	20	190/120	"
57	55 F	Lassitude	220/130	H.M.B. 2 t.d.s.	"	12	160/100	Fair
58	55 M	Visual disturbance ..	220/120	H.M.T. 2 ..	Fair	24	220/130	Nil
73	35 F	Headache	200/120	H.M.T. 3 q.d.s.	Fair	18	175/100	Fair
74	45 F	"	245/150	H.M.B. 2 t.d.s.	Good	1	200/115	Poor
				H.M.T. 2 ..				
				2 wks. altly.				
75	60 M	Left ventricular failure ..	180/130	H.M.B. 5 b.d.	Good	12	170/120	"

H.M.B. = Hexamethonium bromide. H.M.T. = Hexamethonium bitartrate.

TABLE VI.—*Correlation of Blood-pressure Control with Duration of Treatment in 60 Patients Still under Treatment*

Duration of Treatment	Control of Blood Pressure in									
	Parenterally Treated Group					Orally Treated Group				
	Good	Fair	Poor	Nil	Total	Good	Fair	Poor	Nil	Total
Under 6 months ..	4	7	4	1	16	0	1	1	1	3
6 months to under 1 year ..	2	4	4	1	11	1	1	1	4	7
1 year to under 2 years ..	2	0	2	0	4	1	3	2	6	12
2 years and over ..	3	1	0	0	4	1	0	1	1	3
Total ..	11	12	10	2	35	3	5	5	12	25

TABLE VII.—*Details of 16 Patients Treated Parenterally who Died or for Whom Treatment was Abandoned*

No. of Cases	Details	Result
5	Advanced cases of malignant hypertension, uraemia	All five died
3	Cardiac infarction: 2 developed after treatment was abandoned during treatment	Both died Recovered
4	Cerebral vascular accidents: 1 thrombosis during treatment 1 " after treatment abandoned 1 haemorrhage (presumed) during treatment (post mortem) ..	Recovered Died "
4	Treatment abandoned because of side-effects	3 alive, 1 unknown

Effects Due to Fall in Blood Pressure

Postural Hypotension.—This has been regarded by some as an undesirable side-effect, but we have utilized it in treatment. Conway (1953) has shown that the fall of blood pressure in the horizontal position is unpredictable in hypertensive subjects and there is no fall of diastolic blood pressure in normal persons when lying horizontally. Work done at the Hammersmith Hospital on normal persons

(Morrison and Paton, 1953) differs from Conway's findings only where the blood pressure was taken in the semi-recumbent instead of the lying position. The postural hypotensive effect is, however, constant. When treatment is started, postural faintness can be unpleasant, and, unless the patient is told to lie flat on recognizing this symptom, the natural reaction is to "walk it off." This may be ineffective and the patient lose consciousness. Later mild symptoms can and should be walked off.

Muscle Weakness.—True weakness of muscles is a common symptom when the blood pressure falls to a low figure in severe cases of hypertension. This effect is probably due to a temporary deficiency in the blood supply.

Angina pectoris and intermittent claudication are in some cases clearly related to the fall in blood pressure.

Lassitude and increased susceptibility to cold may occur in severe cases of hypertension rigidly controlled by hexamethonium bromide; these symptoms are often worse when the blood pressure is lowest. Raynaud's phenomenon developed in a patient with pre-malignant hypertension after the blood pressure had been adequately controlled for six months.

Effects Due Directly to Ganglion-blocking Action

Gastro-intestinal Disturbance.—Dryness of the mouth is a constant symptom at the start of treatment, but after a few months it distresses only the less stable patients. Alteration of bowel habit is more common with oral than with parenteral therapy. Constipation is rather more common than diarrhoea but easier to treat. In one case treatment was discontinued when the patient strangulated his hernia straining at stool.

Bladder Disturbance.—Slight difficulty in starting micturition was often experienced during parenteral therapy. One patient had relief of stress incontinence by the hexamethonium. Another patient, who received 250 mg. of hexamethonium bromide twice daily, developed complete retention after each injection for about ten hours and then suffered sudden urinary incontinence.

Paralysis of Accommodation.—This was met by prescribing spectacles to correct the visual disturbance for close work when under the influence of hexamethonium. This remedy was found to be effective.

Impotence.—This could be overcome by giving the evening injection at a later hour when necessary.

Discussion

The value of a remedy used for the treatment of hypertension might be gauged by the effect upon symptoms, by the control of the blood pressure, or by prevention of the complications of hypertension, and the consequent improvement in the expectation of life. These criteria are reviewed in turn.

1. Relief of Symptoms

Many symptoms are attributed to hypertension, of which only headache occurs with any consistency. It is common experience for the headache and other symptoms to develop for the first time after the patient knows that the blood pressure is raised. The symptoms of hypertension are relieved by any treatment if it is given with sufficient confidence and enthusiasm. There is no evidence that at the same time the expectation of life is increased or that the patient will be allowed to escape the complications of hypertension. Ayman (1930) clearly showed the effect of suggestion on the symptoms of hypertension by treating hypertensive patients with dilute hydrochloric acid by mouth, obtaining by this means excellent relief of symptoms and, with the lessening of anxiety, even some reduction in blood pressure. These findings were later confirmed by someone who misinterpreted his results to such an extent that by a peculiar process of rationalization he believed that hydrochloric acid was of intrinsic value, lowering the blood pressure by some chemical effect.

Stewart (1953) has made a careful study of headache in hypertension and produced convincing evidence to show that the headache is usually due to anxiety in subjects who know that their blood pressure is raised. He assessed the significance of headache in hypertension by comparing a group who knew they had hypertension with a group unaware that their blood pressure was raised. With the present material the relationship of headache to the raised blood pressure has been studied by comparing the relief of symptoms in patients grouped according to the degree by which the blood pressure is controlled with hexamethonium bromide. Using this technique to evaluate the significance of headache in hypertension, we agree substantially with Stewart's conclusions. Relief of anxiety when it was thought that the blood pressure was controlled caused disappearance of headaches and other symptoms. As Stewart observed, there are a few cases in which headache does appear to be a direct effect of the increased blood pressure, as in the following instance.

Case 37.—A man aged 36 presented with headaches, a feeling of tightness, and throbbing in the head. He was found to have severe essential hypertension with a blood pressure of 240/130. There were grade II changes in the fundi oculi and the left ventricle was moderately enlarged. The cardiogram showed left ventricular strain. The blood pressure was well controlled in hospital by hexamethonium bromide dissolved in polyvinylpyrrolidone 50 mg. subcutaneously, morning and night. When seen one month later in the out-patient department, he stated that for two hours after each injection he felt very weak, the eyes were blurred, and the mouth dry. The next two to three hours he felt very well, but then developed a headache which was "tight" and throbbing in character. When seen nine hours after an injection, at a time when the headache was becoming very severe, the blood pressure was 280/160.

It was thought useless to assess the value of hexamethonium bromide by the relief of those symptoms of which the hypertensive patients complain. However, if this criterion is used the results will appear to be very satisfactory. Relief of symptoms appeared to be greatest in those attending a clinic for hypertensive patients as compared with the remainder attending the general medical out-patient depart-

ment. Although the relief of symptoms could not be correlated with the control of blood pressure, it was intimately related to the reassurance they obtained from the treatment. It would be surprising if any operation, confidently performed, for the relief of the symptoms of hypertension failed to succeed in this aim in the vast majority of cases.

2. The Value of Blood-pressure Control

It has often been stated in the past that artificial lowering of the blood pressure was an unwarranted interference with a necessary adaptation by which the tissues obtain a sufficient blood supply against an increased peripheral resistance. This was an assumption incapable of proof before an effective means of controlled blood-pressure reduction was introduced. In any large series of cases treated with methonium compounds there will now be examples that vividly illustrate the truth of this assumption under certain circumstances. A study of such material will also put this valid contention into its proper perspective.

In the present series 3 out of 83 patients suffered from the reduction of blood pressure; none died, and in each of them treatment with hexamethonium was abandoned.

In one instance (Case 32) a left hemiplegia occurred one hour after a subcutaneous injection of hexamethonium dissolved in water. The paralysed limbs made a slow but complete recovery. Later all cases were treated with hexamethonium dissolved in polyvinylpyrrolidone. In this way absorption from the subcutaneous depot is slowed and not only prolongs the action of hexamethonium but renders the fall in blood pressure less precipitous. Despite this modification of treatment a patient (Case 56) suffered a cardiac infarction one and a half hours after injection.

The third example clearly illustrates the need for a high head of pressure in some cases of hypertension. This patient (Case 13) was admitted to hospital with essential hypertension. Her blood pressure was satisfactorily controlled by two injections a day of hexamethonium bromide in polyvinylpyrrolidone subcutaneously. When followed up in the out-patient department she later complained of failing memory and mentioned that her speech became slurred two hours after an injection. It was now clear that she was suffering from the effects of progressive cerebral ischaemia, and treatment with hexamethonium bromide was therefore discontinued. Patients who show progressive cerebral ischaemia should not be treated with agents to reduce the blood pressure, but occasionally it may not be obvious that this process is taking place before treatment is instituted.

Despite the danger of precipitating thrombosis by lowering the blood pressure, the danger of a high blood pressure *per se*, regardless of aetiology, is a consideration of the greatest importance. We have found that, by the careful choice of patients, fluctuations in the blood pressure are not attended by a much-increased risk of thrombosis even when the blood pressure falls to a very low level, sufficient sometimes to cause loss of consciousness.

3. Prevention of the Complications of High Blood Pressure

While the reduction of blood pressure in hypertension is not without danger under certain circumstances, the changes that a marked elevation of blood pressure produces in the cardiovascular system inevitably threaten life.

Heart Failure.—The most common cause of death in hypertension is heart failure, followed by cerebral haemorrhage and thrombosis and then coronary artery disease (Bell and Clawson, 1928). Unless essential hypertension has entered the malignant phase renal failure is a very rare cause of death, in Christian's (1926) series making up only 4.5%. Although the development of heart failure may not be exactly related to the height of the blood pressure, the association is intimate. Since heart failure may for years be the only manifest complication of hypertension, and since it is the commonest cause of death, the effect of hexamethonium in preventing this complication is of major importance. In the treatment of incipient heart failure it

has already been shown to be of value, although in no way replacing treatment with digitalis and mercurial diuretics when these drugs are indicated. Kelley and his co-workers (1953) have claimed that congestive heart failure due to causes other than hypertension can be relieved by hexamethonium, and they have discussed the mechanisms by which this relief may occur. Further clinical studies on the cardiac reserve of our hypertensive patients treated with hexamethonium are in progress.

Cerebral Haemorrhage.—It is hoped that lowering of the blood pressure may lessen the chances of a cerebral haemorrhage occurring. Normal arteries can withstand enormous pressures without breaking—far beyond any levels obtaining in life (Lampert and Müller, 1926). It has been suggested that the danger of cerebral haemorrhage is related to a fluctuating high blood pressure (Westphal and Bär, 1926). If this is the case, it may be argued that hexamethonium bromide, even with its absorption delayed by polyvinylpyrrolidone, would cause the fluctuation in blood pressure which might precipitate a cerebral haemorrhage. On the other hand, it has been shown that the rise of blood pressure on exercise in the hypertensive person is lessened under the influence of hexamethonium bromide (Fowler and Guz, 1954).

4. Expectation of Life

At least ten years must elapse before any definite pronouncement could be made on the effect of blood-pressure control in prolonging life in benign essential hypertension. Final assessment of the value of hypotensive drugs in preventing the complications of hypertension must also await the passage of time in benign cases of the disease. In so-called malignant and pre-malignant hypertension, when the expectation of life is so short without treatment, a clear-cut assessment of the value of blood-pressure control should easily be made. In practice there are certain difficulties, of which the most important is the recognition of pre-malignant hypertension. Many of the so-called pre-malignant cases of hypertension which have done well on hexamethonium may have been misdiagnosed. Once renal failure has developed, lowering of the glomerular filtration pressure resultant on blood-pressure reduction may precipitate a terminal uraemia; but unless there is evidence of severe renal damage it is difficult to be certain that the prognosis without treatment is immediately grave.

Practical Aspects of Selection and Management

Experience gained while using hexamethonium in a clinic for hypertension has convinced us that this drug has a definite part to play in the control of a selected group of hypertensive patients.

As a method of controlling the blood pressure hexamethonium compares favourably with sympathectomy. A drawback in severe cases of hypertension is the necessity for repeated subcutaneous injections, for even in patients who are obviously benefiting from their treatment it may be difficult to persuade them to continue injecting themselves for more than a few months. When it is judged that continued treatment is of value it may be useful and fair to liken the patient's state to that of the diabetic patient with his insulin. Many practitioners have believed that hexamethonium therapy is too complicated and hazardous for them to undertake, and one of the purposes of the present paper is to try to show how the medical attendant can continue the management of these patients.

Indications

The indications for treatment with hexamethonium bromide are for the relief of symptoms either in the presence of high blood pressure or in those cases where the blood pressure in itself is constituting a definite peril to the patient. In the former category may be placed the acute episodes of left ventricular failure, eclampsia, and hypertensive encephalopathy, together with the chronic disorders of benign and malignant essential hypertension and certain

cases of renal hypertension in which renal function is still adequate. In the latter category it is difficult to stipulate what degree of sustained hypertension constitutes a more than average menace to life; the level of the blood pressure must be taken in conjunction with retinal, urinary, cardiographic, and radiosopic findings, but in this series it has been felt that the administration of hexamethonium should be seriously considered in all cases with a diastolic blood pressure of 130 mm. Hg or more.

On the whole hexamethonium treatment has been reserved for the younger hypertensive patients in this series and certainly those under 60 years of age, when there is less chance of gross arterial disease being present. A previous cerebral or coronary thrombosis is not a contraindication, but special caution is needed in lowering the blood pressure in such cases. Similar reserve should be shown in the use of hypotensive agents in the presence of anginal symptoms or when there is cardiographic evidence of myocardial ischaemia. Renal failure with a rising blood urea is an absolute contraindication to hypotensive therapy, which only aggravates the situation by impairing renal function still further.

Route

In common with most other workers we have found that the only reliable route for administration of hexamethonium compounds is the subcutaneous one. This does not preclude the use of oral preparations in milder hypertensive patients or in individuals intolerant to other routes. Absorption is variable, however, and Harington (1953) has found that this amounts to no more than between 1% and 6% (depending on the preparation) when taken after food, though if administered when fasting the percentage may be as high as 40. The bitartrate compound introduced in order to obviate the danger of bromism is particularly unsatisfactory in this respect. The variable absorption of oral preparations may lead to sudden severe side-effects such as paralytic ileus and irreversible hypotension. Nevertheless, satisfactory symptomatic results were obtained using oral therapy. It might be argued that an inert tablet would be equally successful and less unpleasant from side-effects, but it would seem that in a certain group of patients oral hexamethonium bromide is controlling the blood pressure when a fall in the level is more than can be accounted for by the relief of anxiety. In the main, however, oral therapy was reserved for the milder cases or even as a placebo measure, severe hypertensive patients, and in particular those in a malignant or pre-malignant phase, being treated, with rare exceptions, by the parenteral route. Oral and parenteral routes may be combined as a nightly injection with tablets during the day.

Routine

The routine treatment adopted in the present series consisted of two or three subcutaneous injections of hexamethonium bromide daily; the watery solution was used in the earlier cases, but later all patients were treated with a delaying preparation (hexamethonium bromide in polyvinylpyrrolidone). In addition further delay was attained by including a small dose of ephedrine (0.5 mg. in 0.1 ml.) added to the dose in the syringe, but the retardation was found to be only slight, and its addition was reserved for the more intelligent patients. Every patient under treatment had the head of the bed raised on 9-in. (23-cm.) blocks.

A nightly injection technique was reserved for two groups of cases. (1) Those in whom side-effects were so marked after an injection that their daily life was made miserable. With one injection on retiring, the side-effects were lost in sleep and had disappeared on rising in the morning. (2) Less severe cases of hypertension, in which the clinical picture clearly indicated that cardiac failure rather than any other complication of hypertension was imminent.

In practice, treatment with a single daily injection has in some cases appeared to be beneficial, and over the months the exercise tolerance has improved even in patients who had in the past been in cardiac failure. In one patient,

however, receiving injections twice daily, left ventricular failure supervened as the fluctuating blood pressure started to rise.

Case 78.—A 48-year-old man with previous symptoms of left ventricular failure which had been adequately controlled by digitalis, diuretics, and salt restriction was started on hexamethonium treatment by subcutaneous injection twice daily. While still under in-patient observation he began to experience the early symptoms of pulmonary congestion nine hours after each injection, with greatly increased dyspnoea and dry cough. These symptoms would subside rapidly after the subsequent injection.

After admission to hospital and the usual routine clinical examination with investigations to exclude underlying causes for the hypertension, a decision was made regarding the need to control the blood pressure with hexamethonium bromide. Although the indications for blood-pressure control have been broadly stated, more emphasis has been laid on signs rather than symptoms in assessing the need for treatment.

It was felt that too much emphasis has been placed on the resting blood pressure. There can be little relation between the artificially low blood pressure reached by weeks of bed rest with sedation and the blood pressure during the activities which the patient with hypertension is normally allowed to carry out. When the patient is seen later in the medical out-patient department there can be no comparison between the blood pressures recorded there and the figure reached after prolonged bed rest in hospital.

The majority of patients in this series have been followed up after discharge in a clinic for hypertension. Once stabilized they attend the clinic at two- to three-monthly intervals, bringing their night apparel, so that they can, if necessary, be admitted for 24-hour blood-pressure observation.

Changing Sensitivity to Hexamethonium

As treatment is continued, both the blood-pressure response to hexamethonium bromide and the side-effects of the drug undergo changes. Patients often develop an increasing tolerance for the first ten days of treatment, but this is by no means invariable. During this time side-effects abate in parallel with the rising blood pressure. Later the sensitivity to hexamethonium bromide varies in an inconsistent way and sensitivity to the drug may increase; this is especially common during the first six months. It is therefore not only necessary to see these patients at frequent intervals but also to admit them for 24-hour blood-pressure observation. Side-effects at this stage of treatment tend to become less severe even when the blood pressure continues to be satisfactorily controlled, but new symptoms due to the ganglion-blocking action of the drug may arise *de novo* at any time. No way of predicting the response to treatment with hexamethonium bromide could be found, and even the hexamethonium sensitivity test done before the start of treatment was of little value in forecasting the effect of therapy.

Continuation Treatment

Although the use of hexamethonium bromide is indicated for the control of an appreciably raised blood pressure in the presence of symptoms, if the blood pressure remains uncontrolled with adequate treatment and side-effects are present no attempt to persist with the drug should be made.

Successful treatment of pre-malignant hypertension in favourable cases does not depend on specialist knowledge of the drug, but follows painstaking observations and repeated blood-pressure recordings while the patient is under treatment. Observation of renal function at the onset of treatment necessitates hospital supervision, but later the patient's doctor, if he has the time, is the best fitted to carry out the treatment. Initially hexamethonium bromide may be given eight-hourly or even more often to ensure adequate and smooth control of the blood pressure. On discharge from hospital the patient should be stabilized on injections given every 12 hours. The dose should be increased

cautiously by not more than 10 mg. at a time. It is best done by increasing the evening injection alone for a few days, so that any unpleasant effects from the increased dosage may be lost in sleep, before increasing the morning dose.

Hexamethonium bromide is not the ideal treatment for hypertension, but is at present the most effective means of controlling the blood pressure. Despite reports of new allied compounds which are supposed to possess advantages because of their more selective sympathetic-blocking action, these claims have, for the most part, been based on rather crude experiments. It seems unlikely that this series of ganglion-blocking agents will possess appreciable differences in regard to their site of action, although their potency may vary. It also seems that changes in the structure of the methonium compounds to make them more easily absorbed from the bowel render them less effective ganglion-blocking agents. Since these compounds are excreted by simple glomerular filtration there is no way by which renal excretion can be delayed.

A more effective treatment for hypertension is needed. At the present time, however, the methonium compounds afford the only effective method of blood-pressure control in a proportion of hypertensive patients.

Patients with significant grades of hypertension should not be deprived of the benefit which can be conferred by hexamethonium treatment, a therapy which at best may transform the health of the patient, and at worst may only have to be discontinued.

Summary

Hexamethonium bromide has been used in the treatment of 83 hypertensive patients who have been followed up over periods varying from six months to three years.

In all instances treatment was initiated in hospital. It was found that hexamethonium bromide might be used successfully even when a sensitivity test is unfavourable. Patients continued this treatment at home with self-administered twice-daily injections, using the delayed-action hexamethonium bromide. After several weeks most were readmitted for a 24-hour blood-pressure survey. In some cases oral treatment by hexamethonium bitartrate was substituted for one or both injections.

Parenteral treatment was far more successful in controlling blood pressure than oral therapy, especially in those patients with the highest initial diastolic pressure. The blood-pressure control was good or fair in 66% of all those continuing parenteral treatment, as compared with 36% of those on oral therapy.

The effect of hexamethonium treatment in relieving symptoms bore no relation to the degree of blood-pressure control. When patients presented with symptoms rather than the complications of hypertension relief of symptoms was uniformly satisfactory. Headache was the presenting symptom in 25% of the 83 cases.

In 12 patients only one injection was given in the 24 hours, on retiring at night. These were patients threatened with left ventricular failure. They benefited by the several hours of lowered pressure through the night and at the same time were spared the side-effects often experienced soon after an injection.

During the course of parenteral treatment nine patients died and in six others treatment had to be abandoned for various reasons.

The side-effects from this treatment have been classified as those due to the fall in blood pressure and those directly due to ganglion-blocking action. Means of relieving such side-effects have been described.

The value of a remedy for hypertension has to be judged by (1) its control of the blood pressure, (2) the relief from symptoms, (3) the prevention of complications, and (4) the consequent improvement in survival time. These criteria have been discussed in the light of the results obtained.

The indications for treatment by hexamethonium bromide are as follows: sustained essential hypertension with a diastolic pressure at 130 mm. Hg or more; patients aged up to 55 or 60; progressive increase in blood pressure; threatening left ventricular failure due to hypertension; severe symptoms, notably headache and incapacity for work; threatened change from benign to malignant hypertension.

Contraindications were: blood pressure lower than the critical diastolic level mentioned above; age of 60 or over; evidence of more than slight impairment of renal function; evidence of more than slight cerebral or coronary disorder. While a reduction of pressure might be undesirable in these two groups, it must be remembered that continuing high pressure may equally, and perhaps earlier, bring serious hazards.

The practical application of these methods of selection and of treatment have been described with particular reference to treatment at home and at work.

For a substance to be accepted as a useful remedy for a disease so widespread and protracted as hypertension it must be available for use and control by the general practitioner. After the initiation of treatment the most important share in the control and management must be in his hands.

The possibilities, methods, and effects of oral therapy have been discussed.

While hexamethonium is not an ideal treatment for hypertension it is at present the most effective means of controlling high blood pressure. The risks of continuing high pressure far outweigh the possible danger from sudden fall of pressure.

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THE MEDICAL TREATMENT OF HYPERTENSION*

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The survey by Master *et al.* in 1943 showed that 30 to 40% of subjects over 40 years of age, and 65 to 75% of those over 70, have hypertension. It is well recognized that the prognosis is good in the majority of cases, but in many instances hypertension is followed by an increasing degree of disability which merits active therapy. The fact that hypertension, in itself, is often compatible with a normal life expectation tends to obscure its high mortality in those who develop symptoms. In his study of one thousand patients, Bechgaard (1946) found that 41% of males and 22.4% of females died within five to ten years of the onset of symptoms.

It is essential to have an acceptable definition of hypertension. Wood (1950) has defined the limits of normal blood pressure as 145/90 mm. of mercury, stating the precautions necessary in recording this. Systolic hypertension in the young is usually a response to emotion and exercise; in older subjects it is an indication of loss of elasticity of major arteries, and there are other causes. In essential hypertension it is the increase in the diastolic blood pressure which is significant, and this is the pressure to which reference is made subsequently in this review. In our survey we have examined patients presenting with a diastolic pressure of 100 mm. and over. Four years ago a new drug, hexamethonium, was placed at our disposal, and for the first time we had a reasonably certain method of reducing the level of the diastolic pressure to an extent greater than with general methods of treatment. It is therefore opportune to review our experience with hypertension over these four years, having particular regard to its treatment.

It is of interest to attempt to correlate the manifestations of hypertension in man with experimentally induced hypertension. Page (1949) has comprehensively reviewed the methods of production of hypertension in animals. The types of greatest interest in relation to the pathogenesis of hypertension in man are the hypertension which follows renal ischaemia and that resulting from administration of D.C.A. (deoxycortone acetate). The renal ischaemia experiments are based upon the work of Goldblatt *et al.* (1934), and implicate a humoral pressor mechanism. Wilson (1953) has examined the renal factors. It is possible that the mechanism of renal ischaemia, with its vicious circle of hypertension and further renal damage, operates in malignant hypertension.

In studying the basophil adenomata of the pituitary. Cushing (1932) recorded observations which have been followed by the implication of pituitary and adrenal factors. Merrill (1952) has been concerned with the adrenal mechanism, suggesting a psychic origin of stress

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