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TREATMENT OF ARTERIAL HYPERTENSION BY PENTA- AND HEXA-METHONIUM SALTS

BASED ON 150 TESTS ON HYPERTENSIVES OF VARIED AETIOLOGY AND 53 PATIENTS
TREATED FOR PERIODS OF TWO TO FOURTEEN MONTHS

BY

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Although from the therapeutic aspect it was the curarizing effects of the higher members of the methonium series which first attracted attention (Barlow and Ing, 1948a, 1948b; Paton and Zaimis, 1948a), it soon became evident that the penta- and hexa-methonium halides, shown to be ganglion-blocking agents by Paton and Zaimis (1948b), were effective in producing reductions in blood pressure in normal and in hypertensive individuals (Arnold and Rosenheim, 1949; Arnold *et al.*, 1949; Paton and Zaimis, 1949; Burt and Graham, 1950; Hunter, 1950; and Davison, 1950). Preliminary tests carried out in this department (Restall and Smirk, 1950) indicated that good results could be obtained by the use of these substances as a mode of treatment in hypertension.

Further reports have been published on this use of penta- and hexa-methonium salts (Turner, 1950; Saville, 1950; Campbell and Robertson, 1950). No definite conclusions were reached by the first two authors, but Saville was hopeful that pentamethonium bromide would find a place in the treatment of hypertension. Both of these workers used relatively large doses to investigate effects, and neither reported the results of treatment over a long period. Campbell and Robertson (1950) report results similar to those of Restall and Smirk in respect of relief of such manifestations as headache and breathlessness. Further practical details concerning the management of cases are given by Smirk (1950a, 1950b, 1951), who claimed that effective blood-pressure reduction with subcutaneous injections of penta- or hexa-methonium bromide led to a clinical improvement in severe hypertensives which is of a higher order than that ordinarily obtained by other methods. The results obtained by oral therapy were much less reliable, though sometimes good. Turner (1951) has had similar results, and cites favourable experience in the toxæmic and other hypertension of pregnancy. Frankel (1951) prefers hexa- to penta-methonium bromide, and regards intramuscular injection as more effective than oral dosage. Locket (1951), who has apparently used mainly oral therapy with

hexamethonium bromide, regards the results as unsatisfactory. Bromism may occur. Locket thought there were patients who ceased to react to the substance.

The tests alluded to in this department convinced us of the possible usefulness of penta- and hexa-methonium salts in the long-term treatment of hypertensives, and accordingly we investigated the response to these methonium halides in 150 cases of hypertension of varied aetiology—benign essential (fixed, 72; labile, 15; following sympathectomy, 11); malignant (11); renal (nephritic, 7; surgical kidney, 3); pregnancy toxæmia (post-, 21; acute, 2); polycythaemia vera (1); and miscellaneous (7).

Fifty-three patients have been under treatment for periods of 2 to 14 months. Of these, 32 have been treated for six months or more. In selecting for treatment preference was given to those with the highest blood pressures, especially when the basal pressure was high, and to the patients with the most severe potentially reversible hypertensive manifestations. These included papilloedema, retinal haemorrhages, exudate, and oedema, cardiac asthma, hypertensive heart failure, cardiac enlargement and electrocardiographic changes, severe headache, dizzy and encephalopathic attacks, and minor strokes. Recently we have accepted patients over 65, but, at the outset, fear of cerebral and coronary complications decided us in most instances against treating patients in this age group.

Our main purpose has been threefold: (a) to investigate the effects of an adequate test dose which might give an indication of the possibility of treatment; (b) to find if these methonium salts reduce blood pressure in hypertensives irrespective of aetiology; and (c) to ascertain if hypertensive patients may be treated adequately with these methonium salts with relief of signs as well as symptoms. Our experience has indicated that, if postural effects were taken into account, a true index of potential reduction of blood pressure under treatment might be achieved by small subcutaneous test doses without adverse effects on the patient.

We record many instances of the relief of papilloedema, retinal oedema, and left ventricular failure, as well as of symptoms such as headache, dyspnoea, and vertigo. Turner (1950) seemed inclined to be diffident about symptomatic relief, and his experience with three cases urged him to caution in the use of these salts. Using smaller test doses, and being fully aware of the development of tolerance to the methonium salts, as well as utilizing postural effects in the treatment, we have experienced no complications in those patients we have treated, all of whom have shown symptomatic relief and objective improvement of one kind or another when signs were present.

It is not proposed to discuss the pharmacology of these methonium salts, so carefully worked out by various authors (Barlow and Ing, 1948a, 1948b; Paton and Zaimis, 1948a, 1948b, 1949; Balaban, Levy, and Wilde, 1949), and the pharmacodynamics of these salts in man is the subject of another paper in preparation (Restall and Smirk), but attention will be drawn to the development of tolerance which occurs in the course of treatment.

Relation of Treatment to Pathogenesis

Many writers express the view that reduction of the blood pressure in arterial hypertension by sympathectomy or by drug action is a treatment of symptoms and a stopgap form of therapy to be employed only until some attempt can be made to correct the fundamental cause. In terms of other views on pathogenesis, the evidence for which is presented elsewhere (Smirk, 1949), the maintenance of the blood pressure as near to normal as practicable is much more than symptomatic treatment; on the contrary, effective blood-pressure reduction by suitable means is likely to arrest or retard pathological processes responsible for the development of the disorder.

According to this latter hypothesis there is no single or simple primary cause of essential hypertension. The disorder is thought to arise in some cases as the result of the simple overactivity of physiological processes, whereas in other cases pathological processes such as renal arteriolosclerosis may be primary. The fundamental concept is that, while initial blood-pressure increases may be, and commonly are, of composite origin, such pressure increases, if frequent, large, or prolonged, lead to a number of pathological and functional changes which tend further to maintain or elevate the blood pressure. Once this self-perpetuating cycle of changes has been set up the condition may be described as essential hypertension.

There is strong circumstantial evidence that many factors which raise the level of the blood pressure enhance strongly the liability to the subsequent development of essential hypertension. These include certain geographical environments, race, heredity, emotional lability or disposition to over-alertness and tenseness, occupation or domestic environment involving a tendency to stress and strain, over-average liability of the vasomotor system to respond by vasoconstriction to tenseness and emotion, physical activity or metabolic stimuli, over-average body weight or sthenic habitus. It is thought that such factors predispose to essential hypertension in so far as they are factors which tend of themselves to elevate somewhat the level of the blood pressure. When sufficient of these factors are present, or when they are present in a degree which may be regarded

as pathological, the higher level of the blood pressure so engendered tends to set up pathological changes which of themselves perpetuate or increase further the initial blood-pressure rises.

The various pathological and functional changes induced as the result of primary blood-pressure rises (or excessive vasoconstriction), which, when they are developed, may lead to secondary blood-pressure rises, are thought to include such factors as the following: (a) inelasticity of large arteries; (b) exaggerated contraction of hypertrophied arterioles; (c) the release of pressor agents from ischaemic kidneys; (d) to a very minor degree, increased passive resistance of hypertrophied arterioles; and (e) an unknown non-renal factor or factors capable of perpetuating certain blood-pressure increases after the primary exciting causes of these increases have ceased to operate.

In terms of the above hypothesis the fundamental unity of the clinical picture in essential hypertension is not dependent upon the blood-pressure elevation being regarded as the result of a single or simple pathological process, it is due to the fact that the clinical manifestations and complications are caused almost entirely by events which are secondary to a single characteristic of the disorder—namely, high blood pressure—brought about mainly by vasoconstriction. It would follow that any condition associated with high blood pressure from any cause would be likely to lead, if the high pressure persisted for long enough, to the various pathological changes which, it is suggested, may be responsible for maintenance of existing increases or for further increases of the blood pressure in essential hypertension.

Essential hypertension is both a syndrome and a disease. It is a syndrome in that its characteristic clinical and pathological features form part of all protracted high-blood-pressure cases, whatever the primary cause. It is a disease in that in the clinical entity we call essential hypertension the syndrome is the whole disorder. In nephritis, cortical hyperadrenalism, and many other conditions associated with blood-pressure elevation, the syndrome of essential hypertension is only part of the disease.

Evidence that our present knowledge of hypertension is consistent with the views expressed has been given elsewhere (Smirk, 1949). Holding provisionally such views, the authors prefer to regard effective blood-pressure reduction as a fundamental and not as a secondary objective in treatment. If it were found that effective reduction of the blood pressure would not retard the disorder, then the hypothesis would need revision. On the basis of this hypothesis the present paper is concerned with two matters: (1) can one obtain substantial control over the level of the blood pressure in various types of arterial hypertension, and (2) are there classes of patients in which blood-pressure reduction is beneficial?

Effects of Various Methods of Administration

We have administered penta- or hexa-methonium salts orally and by subcutaneous, intramuscular, and intravenous injection. Most of the results to be described here have been obtained with subcutaneous injection, and most of the formal tests have been made with hexamethonium bromide. In treatment, however, the effects of which have been closely observed, we have used almost as much penta- as hexa-methonium

bromide. In the course of treatment we have often gone from the one to the other without important subjective changes being apparent to the patient. A comparison of the hypotensive effects of penta- and hexa-methonium bromides is set out in Table III. It suggests that the hypotensive action of hexamethonium is usually the stronger. Patient 52, however, has always stated that pentamethonium has the stronger effect on her as judged by the occurrence of postural hypotension, and formal tests indicate that the pentamethonium has in her case a more powerful hypotensive action.

To prolong the effect we have tried intramuscular injection of a fine suspension in almond oil. Admixture with 1 in 400,000 to 1 in 100,000 adrenaline hydrochloride has been employed to slow absorption, and a number of investigations have been made with continuous subcutaneous injection over a 12-hour to 12-day period, using a device which empties the contents of a syringe (1-100 ml.) at a uniform rate over a selected period of time (2-32 hours). While the level of the blood pressure may be controlled in some cases by oral administration, the dose used is much larger even when it is administered with water before meals.

TABLE I.—Comparison of the Effects of the Subcutaneous and Oral Administration of Hexamethonium Bromide

Case	Subcutaneous Administration			Oral Administration		
	Dose (mg.)	Maximum B.P. Fall (Syst./Diast)	Duration of Effect (Hours)	Dose (mg.)	Maximum B.P. Fall (Syst./Diast)	Duration of Effect (Hours)
40	160	80/26	6	1,500	96/52	9
127	170	66/36	5	2,250	50/30	5
59	100	60/22	4	1,500	100/35	6
49	225	62/58	4	1,500	25/6	5½
14	120	25/4	4	1,500	25/6	4½
126	75	50/28	2½	1,500	20/20	2
124	20	46/16	4½	1,250	40/32	9
50	110	88/47	4	2,500	60/10	5
135	30	30/7	3	500	20/12	5
131	15	40/15	3	500	15/4	3
Average	102.5	55/26	4	1,450	45.21	5½

It should be emphasized that the larger doses set out in Table I, both oral and subcutaneous, are not to be administered until the patient has developed the requisite degree of tolerance to the action of the drug, otherwise there may be dangerous sequelae. In the initial stages of our work it seemed preferable to avoid the uncertainties of alimentary absorption and to use the drug by an economical route so that more patients could be treated.

Subcutaneous administration has proved very satisfactory in that the levels of the blood pressures are largely predictable, the average duration of effect from a single injection being about three hours, though it has been longer, especially with larger doses. The disadvantage of subcutaneous injection is that with the smaller doses a maximal effect is ordinarily obtained within the first hour, and in some cases a dose large enough for effective lowering over a three-hour or four-hour period may cause giddiness when patients have been standing for a few minutes between the 15th and 60th minutes after injection.

In 30 patients doses of 15-25 mg. subcutaneously exercised their maximum hypotensive effect at the following times (in minutes) after the injection: 45, 36, 14, 27, 10, 40, 25, 30, 45, 30, 35, 50, 40, 45, 30, 25, 30, 40, 10, 45, 30, 45, 30, 20, 20, 30, 40, 20, 75, 35. When doses of 100-250 mg. are injected subcutaneously the

maximum hypotensive effect often comes later, and in 16 patients the times (in minutes) were: 20, 55, 120, 120, 110, 60, 150, 55, 35, 150, 130, 75, 120, 17, 30, 25. The therapeutic regime should be adjusted to the individual response of the patient.

To overcome initial giddiness we gave intramuscular injections of a suspension in almond oil. These were effective in lessening the incidence of dizzy attacks on standing and they prolonged the action of the drug to eight hours. But it was felt that the preparation would be unsuitable for continual use. In a number of patients the addition of 1 in 100,000 adrenaline has prevented

FIG. 1.—Effects of 15 mg. of hexamethonium bromide subcutaneously on the course of the blood pressure with and without the addition of 1/100,000 adrenaline hydrochloride. The additional fall of blood pressure after a meal is shown.

postural faintness shortly after administration without interfering much with the subsequent lowering of blood pressure.

When penta- or hexa-methonium salts are administered by means of an electrically operated syringe (Smirk, unpublished), it is possible to reduce the level of the blood pressure to a selected level and maintain this under quiet conditions with little alteration. Conversations with the patient involving emotional topics still raise the blood pressure considerably (Table II). Meals commonly cause a temporary

TABLE II.—Effect of Emotion on the Blood Pressure in Patients While Under the Action of Hexamethonium Bromide

Case No.	Original Blood Pressure	Basal Blood Pressure	After Hexa-methonium Bromide	Emotional Topic	Blood Pressure Rise
29	272/150	224/140	162/114	Physician enters; talks of illness	28/22
40	240/140	234/136	157/105	Visitors arrive	27/25
41	240/120	160/80	158/108	Business worries	32/12
				Mental illness of mother	42/22
49	258/141	196/106	176/104	Disagreement with nursing staff	28/18
54	220/160	172/110	118/86	Her loss of memory	24/12
				Separation from husband	45/24
57	235/141	213/118	170/108	Visitor arrives	51/32
58	248/150	178/124	178/120	Husband's war service, pilot in Battle of Britain	62/20

rise followed by a more substantial pressure fall (Fig. 1). In some patients smoking raises the pressure. Many patients tolerate this automatic method of administration with few symptoms beyond dryness of the mouth, and the blood pressure may be maintained at the normal or near to normal level, day and night, for sessions of 12 days or more. There must be especial care during the hours of sleep, when the blood pressure will fall further. In anticipation of this the rate of injection of the drug should be reduced at about 5 p.m. There is a somewhat greater tendency to digestive upsets with this method of administration, perhaps because of the larger doses employed.

Influence of Posture on Falls of Blood Pressure Induced by Penta- and Hexa-methonium Salts

A large majority of patients show blood-pressure falls after injection of penta- and hexa-methonium salts. Ordinarily the blood pressure falls progressively as the patient rises from the horizontal posture successively to semi-recumbency, sitting up in bed, sitting with the legs dangling, and finally to standing upright. This is of some importance from the point of view of initial investigation and treatment of patients, for if a large dose be administered to a patient recumbent a fall of blood pressure may be obtained, but should he sit or stand up at this time the dose may be sufficient to lower the pressure still further and syncope may occur. For example, some patients after injection of these methonium salts may exhibit falls of only 15 or 20 mm. of mercury in the systolic pressure when in the

FIG. 2.—Effect of posture on the systolic blood-pressure level in 33 hypertensive patients following initial doses of 15 to 20 mg. of hexamethonium bromide subcutaneously. When patients are maintained in the horizontal posture the falls are rather less than those shown here. The diastolic-pressure falls are about one-third of the systolic falls.

horizontal posture, but the systolic pressure may on occasion fall by 100 mm. of mercury when the vertical posture is assumed (Fig. 2 and Tables III, IV, and V).

We would point out that the knowledge of this occurrence prompted us to test patients in the sitting posture initially, for if the dose (15 mg.) produced a large fall (in some cases 150 mm. systolic and 90 mm. diastolic) the resulting low pressure might be accompanied by signs of faintness, which could quickly be remedied by placing the patient in a horizontal position. Indeed, by controlling posture we have been able to control the blood-pressure level as

TABLE III.—Comparison of the Hypotensive Effects of Penta- and Hexa-methonium Bromides

Case No.	Effect of Pentamethonium						Effect of Hexamethonium						Doses	
	Standing		Sitting		Lying		Standing		Sitting		Lying			
	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.		
52	{ Before	280/160	76	290/170	72	290/168	68	280/140	76	294/140	76	300/142	80	190 mg. C5
	{ After	140/98	76	204/120	72	220/122	68	160/100	80	214/126	72	270/142	76	190 mg. C6
58	{ Before	160/100	80	164/100	72	184/108	64	160/98	80	164/100	72	168/102	60	75 mg. C5
	{ After	108/68	100	124/88	84	150/100	72	84/58	88	112/78	88	145/90	72	75 mg. C6
59	{ Before	190/120	88	200/128	80	208/128	68	194/130	80	190/130	72	174/114	64	100 mg. C5
	{ After	112/80	120	134/98	112	170/110	92	104/78	124	138/94	100	190/124	80	100 mg. C6
133	{ Before	168/112	88	166/110	94	170/110	88	166/116	86	166/112	86	168/106	84	55 mg. C5
	{ After	102/80	98	122/88	90	138/74	78	50/?	100	94/76	92	146/100	76	55 mg. C6
134	{ Before	166/132	86	164/130	82	168/126	78	168/132	82	178/132	84	168/122	88	35 mg. C5
	{ After	138/110	84	146/116	76	168/118	72	134/110	92	144/108	82	154/110	72	35 mg. C6
123	{ Before	188/104	72	200/110	68	190/102	64	190/104	64	200/110	64	220/120	60	120 mg. C5
	{ After	120/72	80	194/116	68	200/120	64	110/78	84	156/98	60	196/112	56	120 mg. C6

TABLE IV.—Effect of Posture on the Blood Pressure and Pulse Rate Before and After Hexamethonium Bromide

Case No.	Before Hexamethonium						After Hexamethonium					
	Standing		Sitting		Lying		Standing		Sitting		Lying	
	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.
67	240/100	112	238/96	108	256/98	100	108/65	115	140/76	113		
68	245/103	78	247/108	72	230/99	80	140/82	84	160/88	80	182/92	73
20	172/110	88	188/110	82			130/108	104	148/98	88	210/130	
135	160/90	100	174/102	96	168/98	96	No reading		110/66	100	122/78	96
4	204/116	64	214/122	64	196/112	60	123/90	80	140/90	70	170/100	62
7	184/140	90	178/144	76	184/136	76	116/108	96	136/124	90	156/124	82
52	240/180	98	220/170	85	210/160	80	110/88	96	162/124	90	180/130	80
127	198/120	96	212/128	92	204/128	84	132/88	100	142/98	96	148/102	88
125	226/134	94	220/138	100	220/136	96	174/112	104	184/110	100	186/108	92
21	210/144	84	204/139	76	200/136	74	102/82	88	122/90	88	146/110	76
54	168/102	100	176/104	96	178/108	84	104/76	92	140/96	90	155/104	84
115	196/110	78	200/118	78	194/104	72	144/106	80	162/112	62	178/106	70
59	190/128	80	210/140	76	200/130	64	148/120	124	170/128	104	180/130	80
126	160/110	76	160/106	72	170/102	76	92/66	96	130/92	92	148/98	76
124	182/116	118	188/128	90	200/122	80	144/102	112	176/122	84	192/122	78
61	220/152	88	230/147	80	230/140	80	136/100	132	180/128	92	200/134	92
18	198/136	65	208/140	72	205/140	68	164/124	84	184/120	80	198/130	68
14	168/99	66	165/104	60	155/100	62	137/97	91	143/93	80	147/95	74
11	190/128	116	182/122	118	184/130	92	144/114	118	148/108	114	154/120	100

Doses have ranged from 15 to 150 mg. according to the state of tolerance which had developed at the time.

TABLE V.—*Effect of Posture on the Blood Pressure and Pulse Rate Before and After Hexamethonium Bromide in Patients who have had a Sympathectomy*

Case No.	Before Hexamethonium						After Hexamethonium					
	Standing		Sitting		Lying		Standing		Sitting		Lying	
	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.	B.P.	P.R.
31	138/96	90	160/100	82	170/100	64	96/78	110	126/92	82	132/88	66
32	218/130	80	220/130	80			124/92	128	150/102	108	170/110	100
33	226/150	100	230/150	110			130/114	108	160/130	100		
34	250/144	74	252/154	72	250/144	74	146/102	124	180/122	96	210/128	72
26	170/124	75	158/124	84	170/124	75	102/72	138	134/108	90	150/120	72
28			206/134				142/110	116	188/134	112	238/92	84
104	172/114	92	178/110	84			100/74	100	128/98	64		
30	148/102	76	178/120	84	182/118	76	110/70	90	138/106	88	142/100	80
27	190/124	76	216/132	72	220/126	68	110/74	112	162/102	100	202/114	80
25	190/126	69	216/132	60	220/122	57	132/106	94	158/110	81	163/107	63

Doses have ranged from 15 to 150 mg. according to the state of tolerance which had developed at the time.

desired. In this connexion it is of practical importance to remember that most patients are ambulant, and it is in this way that dosage can be adjusted suitably so that blood pressures in the standing and sitting postures are sufficiently but not excessively reduced, thus allowing of out-patient control of treatment.

Influence of Blood-pressure Level on the Magnitude of Falls Induced by Hexamethonium Bromide

The hypotensive effect of a 15-mg. dose of hexamethonium bromide administered in the sitting posture is compared in 20 patients with mild and in 25 with severe degrees of arterial hypertension (Table VI).

TABLE VI.—*Influence of Blood Pressure Level on the Magnitude of Falls Induced by 15 mg. of Hexamethonium Bromide With Corresponding Pulse Rate Changes*

Case No.	Diagnosis	Basal Blood Pressure	Before Hexamethonium		After Hexamethonium	
			Casual B.P.	Pulse Rate	Fall of B.P.	Change of Pulse Rate
113	E.H.		278/138	68	40/14	-4
34	E.H.	198/134	255/150	72	51/16	+32
115	E.H.	204/116	248/125	70	16/+7	0
68	E.H.	176/92	246/110	68	104/26	+12
127	E.H.	210/148	240/160	100	70/40	-20
49	M.H.	196/106	240/140	99	108/42	+9
130	E.H.	208/112	238/116	92	50/14	-8
67	E.H.		238/96	108	136/28	+16
56	P.T.	198/140	238/154	96	78/34	-4
101	E.H.	162/118	234/118	64	52/6	+8
55	M.H.		235/175	90	55/45	+20
100	P.T.	216/148	230/150	80	28/10	+4
105	E.H.	156/128	228/134	72	64/16	+8
112	E.H.	162/98	228/112	88	82/24	+16
131	E.H.	206/108	224/110	72	36/8	
125	E.H.	188/124	222/134	88	42/14	+16
110	E.H.		218/120	88	56/10	0
57	P.T.	213/118	220/120	96	46/+4	+20
72	P.T.	168/116	218/136	84	38/10	+12
38	E.H.		216/102	102	84/28	-2
16	E.H.	214/124	215/112	84	117/40	+28
121	P.T.	206/134	214/138	100	10/+4	-22
58	P.T.	178/124	212/136		12/0	
63	E.H.	210/119	210/106	76	30/16	+4
112	E.H.	162/98	210/116	72	40/14	+4
82	E.H.	140/92	180/110	102	30/0	+2
92	E.H.	134/100	180/98	50	46/6	+2
20	E.H.	149/98	178/120	80	50/30	+4
11	R.H.		178/132	114	38/20	+6
90	P.T.		178/112	84	28/12	+6
1	E.H.	160/102	176/104		74/28	0
95	E.H.		176/130		38/24	
86	E.H.	136/88	174/120		24/14	
135	E.H.	172/100	172/102	96	64/40	-16
89	P.T.	148/106	170/114	78	16/4	+9
80	E.H.	142/88	170/104	66	18/8	+10
75	E.H.	124/86	170/98	72	38/2	+6
44	R.H.		170/126	82	22/10	+36
91	E.H.		170/108	88	22/14	0
8	E.H.	118/78	160/100	78	76/34	+8
81	E.H.	128/86	162/118	58	42/28	+14
92	E.H.	134/100	162/110	93	26/6	+9
93	P.T.	124/88	162/96	70	28/0	+2
108	P.	130/102	162/114	86	20/10	+12
84	E.H.	146/90	160/90	72	22/2	

E.H.=Essential hypertension. M.H.=Malignant hypertension. P.T.=Post-toxaemic hypertension. R.H.=Renal hypertension. P.=Polycythaemia.

The degree of blood-pressure lowering induced by 15 mg. of hexamethonium bromide seems, on an average, to be greater when the initial casual systolic blood pressure is high. This is by no means an invariable relationship, and the statement is the expression only of a general tendency. In general the blood-pressure fall is also greater in cases selected for a high basal systolic pressure as contrasted with those exhibiting a low basal systolic pressure. There is no pronounced relationship between the initial diastolic pressure and the extent of the fall in diastolic pressure after 15 mg. of hexamethonium bromide.

Basal-blood-pressure Lowering by Penta- and Hexamethonium Salts

In the absence of drug action blood-pressure lowering takes place under conditions of physical, metabolic, and emotional rest, and the resulting level is called the basal pressure (Addis, 1922; Alam and Smirk, 1943; Smirk, 1944). Kilpatrick (1948) has shown that in health the basal pressure is a physiological constant and in hypertension it varies much less than does the casual pressure.

Administration of adequate doses of penta- or hexamethonium bromide leads to decrease in the blood pressure to well below the basal level even with the patient in the horizontal posture (Fig. 3). Much smaller doses cause falls of pressure to below the basal level if the patient is in the semi-recumbent or the sitting posture. Small initial doses of 15 mg. of hexamethonium bromide, given subcutaneously in the sitting posture, decreased the blood pressure below the basal level in 29 out of 57 patients. Some of these results are seen in Table VI. In all of 10 patients whose blood pressure falls had not been to as low a level as the basal, the administration in the sitting posture of a larger dose brought the blood pressure below the basal level without difficulty.

It would appear that in the standing and sitting postures, and probably in the lying posture, the reduction of the blood pressure to below the basal level can be effected in almost all patients provided an appropriate dose is given. As will be shown later, the magnitude of the dose required depends upon the degree to which a state of toleration has developed; it might be anything from 15 to 300 mg. It is evident from the above statements that the substances cause reduction in the basal as well as in the supplemental (that is, casual minus basal) pressure, and that the casual blood pressure may be reduced below the original basal.

FIG. 3.—Effect of continuous subcutaneous injection of hexamethonium bromide on the blood pressure. Injection rates shown on the chart. In the sitting and lying postures the systolic and diastolic blood pressures are reduced to well below the level of the patient's basal blood pressure (B.B.P.).

Effect of Penta- and Hexa-methonium Salts on the Pulse Rate

It has been remarked by Arnold and Rosenheim (1949) and Burt and Graham (1950) that the falls in blood pressure after administration of these methonium halides are accompanied by acceleration of the pulse. Certainly, sharp falls in blood pressure are usually associated with pulse acceleration, which may be as much as 20 or 30 beats a minute. Acceleration of the heart occurs with both penta- and hexa-methonium salts (Table III).

There is, however, no invariable relationship between the blood pressure and the pulse rate (Table VI). Blood-pressure falls are occasionally associated with slowing of the pulse. In some patients the fall of blood pressure ordinarily is accompanied by acceleration of the pulse, but if the blood-pressure fall is excessive, to low levels which cause faintness, then the pulse slows as it usually does in a fainting attack.

After months of treatment a proportion of patients exhibit less acceleration when the blood pressure falls, perhaps because of habituation to the lower blood-pressure level, possibly from improved heart action. In fact, cardiac acceleration and palpitation, which in some patients may be prominent in the early stages of investigation or treatment, are little cause for trouble later. For example, one patient's palpitation after hexamethonium bromide made us consider abandoning the treatment. The heart rate, however, was controlled by digitalis though no failure was present. After some months the digitalis was omitted and there was no recurrence of palpitation following the hexamethonium injections. In most patients palpitation has subsided without recourse to other drugs.

Ordinarily the change of pulse rate is more closely related to fall in blood pressure than to the amount of drug in the body; for example, there is often little change in the pulse rate when the patient remains in the horizontal posture, but when the patient assumes the vertical posture and the blood pressure falls the heart rate usually accelerates (Tables III and IV). This is evident in most hypertensives whether they have had a thoraco-lumbar sympathectomy or not. There is this difference: that, even though the pulse rates in these two groups have been comparable before a methonium

salt was given, there is more pulse acceleration on standing in the sympathectomized hypertensive (Table V) than in the others.

Response of Various Types of Arterial Hypertension to Hexamethonium Salts

Observations have been made on 150 patients with hypertension. Of these patients 88 have been investigated in a way which gives a rough idea of the magnitudes of the effects obtained injecting these methonium salts. Because factors such as the initial blood-pressure level influence the magnitude of the falls of blood pressure, the following figures should not be taken to indicate important differences in the responses of the different types of hypertension. All these tests were of three

to four hours' duration, with blood-pressure measurements at intervals of about 10 minutes. They were carried out by trained technicians. Their presence throughout the tests has been an important factor in avoiding any reactions more unpleasant than transient faintness. The following results were obtained in the various groups of patients tested with a 15-mg. test dose of hexamethonium bromide given subcutaneously.

- Essential benign hypertension (46):
Average reduction, 48/19 mm.; Range 152/92—7/+4 mm.
- Malignant hypertension (7):
Average reduction, 39/24 mm.; Range 78/44—15/7 mm.
- Renal hypertension (11):
Average reduction, 31/12 mm.; Range 98/60—0/+14 mm.
- Toxaemic hypertension (14):
Average reduction, 37/13 mm.; Range 103/35—4/3 mm.
- Hypertensives with sympathectomy (10):
Average reduction, 61/25 mm.; Range 138/64—24/10 mm.

Emphasis is placed on the fact that these results are from a small test dose (15 mg.) in the sitting position and that, with the exception of one or two nephritic patients, much greater falls in blood pressure were easily produced by larger doses of the drug.

Our experience is that when a good fall is produced by a 15-mg. test dose given subcutaneously in the sitting posture there is seldom any difficulty in maintaining a reasonably low blood pressure in the course of treatment with suitable doses of methonium salts. In those cases where there is a poor response to the test dose of 15-mg. it is nearly always found that a larger dose produces a useful fall of blood pressure and that continued treatment is practicable.

It is not surprising that almost all cases show some fall in the level of the blood pressure irrespective of aetiology, because, even if the pressure rise in some instances is partly the result of a humoral mechanism, it would seem probable that those processes which normally maintain the tone of blood vessels still continue to operate. If this be so, decrease of nerve impulses by the blocking of sympathetic ganglia will still lead to a fall in the blood pressure as the result of the removal of normal sympathetic tone, and this would still be expected to happen even though the

elevation of the blood pressure were the result of a humoral mechanism which, it might be supposed, could not be overcome by the action of ganglion-blocking drugs.

Tolerance to Penta- and Hexa-methonium Salts following Repeated Administration

Repeated administration of penta- or hexa-methonium salts in 53 cases under treatment indicates that some tolerance is acquired within a few days and the dosage needed to produce a given effect continues to increase for some weeks. After a time, however, the dose required does not need further increase. When tolerance has been acquired to one of the drugs

as 120/80. An occasional patient already feels faint at 170/105. More usually faintness first appears between 150 and 135 systolic. Most of our patients who have exhibited symptoms even when the pressure was above normal became habituated to lower pressures in the course of regular administration of penta- or hexa-methonium salts in doses large enough to bring the blood pressure down to just a little above the symptom level. This, of course, requires increase of the dose as tolerance develops. Table VII sets out the

TABLE VII.—Improved Tolerance to Low Blood-pressure Levels Following Repeated Administration of Penta- or Hexa-methonium Salts

Case No.	Initial Blood Pressure	Symptoms Produced	Initial Blood-pressure Level at which Symptoms were Produced	Later Blood-pressure Level Tolerated Without Symptoms
9	204/124	Angina	186/120	176/126
10	224/148	Faintness	72/56	120/90
14	248/136	"	104/78	104/78
16	266/155	"	128/96	100/76
17	210/130	Dizziness	180/145	118/85
29	242/140	Faintness and vomiting	138/90	104/76
30	178/120	Lightheadedness	110/70	112/98
52	226/152	Faintness	135/100	120/90
53	200/124	"	155/110	110/60
58	248/150	Faintness and vomiting	145/115	120/95
61	220/137	Faintness	164/130	148/102
13	204/158	"	110/70	128/88

FIG. 4.—Comparison of the doses of hexamethonium bromide required to produce approximately equivalent effects before and after tolerance to the drug has been acquired as the result of repeated administration.

it is found that there is a corresponding increase of tolerance to the other. Fig. 4 indicates that five or ten times the original amount of drug may be required to produce the same effect after tolerance has developed. However, in a few instances, after several months of treatment, the dosage required to produce a given effect has actually diminished to slightly below the highest level.

Improved Tolerance of Low Blood-pressure Levels following Repeated Administration of Penta- or Hexa-methonium Salts

There have been hypertensive patients who surprised us by showing no symptoms with blood-pressure falls of over 100 mm. Hg, even on the first clinical trial. Patients accustomed to blood-pressure levels of 220/130 or more have dropped to levels such as 110/80 and experienced no symptoms or only mild lightheadedness. Other hypertensives show symptoms before the pressure falls to classical normal levels such

blood-pressure levels which caused symptoms at the outset of treatment and contrasts them with the lower pressure levels which were well tolerated at a later stage of treatment. Hypertensives remain susceptible to the symptoms associated with lowered blood pressure, which, however, make their appearance at a lower level of the blood pressure than they did before the vascular system became habituated to a more normal level. The symptoms encountered are referred to in more detail later.

Potentiation of Hexamethonium Salts by a Salt-poor Diet

At an early stage of this investigation one or two patients who had been taken off hexamethonium bromide because of a temporary shortage were placed on a Kempner salt-free diet. When supplies of the drug became available dosage at about the original level was resumed. One of our patients who had taken earlier doses without notable symptoms became unconscious, and another had an excessive fall of blood pressure to 95 systolic while lying flat and with the foot of the bed raised. This last patient experienced at rest a strong precordial pain which appeared to be anginal. Subsequent investigation showed that the Kempner diet and also a salt-poor diet without protein-deprivation (0.2 g. of sodium in 24 hours) enhanced the response to hexamethonium bromide.

Fig. 5 illustrates responses to 15 mg. of hexamethonium bromide before and during the administration of a salt-free diet. Observations on six other patients gave similar results and on one other an ambiguous result. There is therefore a definite indication that the blood-pressure-lowering effect of hexamethonium salts is enhanced by salt deprivation, an observation which is of clinical importance in the treatment of hypertensives, particularly those with congestive heart failure.

FIG. 5.—Effect of a salt-poor diet on the response to hexamethonium bromide.

Effect of Penta- or Hexa-methonium Salts on Headache

One of the most striking symptomatic effects of the treatment of hypertension by penta- or hexamethonium salts is the relief of headache, which may be prompt and which may date from the inception of therapy. In 27 out of 29 consecutive cases with severe headache, relief was considerable or, more usually, substantially complete. By "substantially complete" it is meant that the headache was removed or if it remained it was considered by the patient to be infrequent and of inconsiderable magnitude. In most patients the headaches were relieved almost as soon as there was effective reduction of the blood-pressure level during the day and part of the night. In some patients the headaches were relieved only in the course of months. Avoidance of the horizontal posture during both day and night is an important factor in the relief of headache. In some instances sleeping in the sitting posture may by itself be sufficient to relieve a morning headache. *Recurrences of headache can nearly always be traced to a break in the therapeutic regime such as failure to raise the dose of hexamethonium bromide as tolerance develops.* Patients have also stated spontaneously that, in addition to relief of headaches, the head feels clearer and they themselves feel brighter in the morning. This statement has been volunteered so many times that it would appear that the lack of brightness and general feeling of sluggishness common in the morning in hypertensives is often relieved in this way. Table VIII sets out a summary of these results. The relief is not confined to any particular type of hypertension and is not dependent on rest in bed. A few observations have been made with other types of headache, as, for example, those due to migraine—so far without relief.

Although hypertensive headache is relieved by penta- or hexa-methonium injections, these may on occasion induce a headache, which, however, is

TABLE VIII.—Effect of Penta- and Hexa-methonium Salts on Headache

Case No.	Previous Duration of Headaches	Severity of Headaches	Duration of Treatment	Degree of Relief
55	Mainly 5-6 months. Some for 2 years	Severe	6 months	Almost complete
53	16 months	"	10 "	Substantially complete
51	Several years	Troublesome	11 "	"Complete"
47	Occasional headaches for 12 months	Troublesome in morning	11 "	"Complete"
52	Headaches for as long as she can remember	Very severe	14 "	Substantially complete
41	3 months	Mild	7 "	Complete
40	Every night for several years	Severe	8 "	Almost complete—about one per month
17	Morning headaches about 8 years	"	8 "	Complete relief
61	9 years—since 2nd pregnancy	"	7 "	Much less
60	2 years	Severe—sometimes lasting a week	11 "	Considerable
14	Many years	Very severe	14 "	Complete
16	Headache	Severe	9 "	Considerable
21	Since discharge from Navy in 1946	"	8 "	Complete
59	3 years	Moderate	9 "	Substantially complete
56	1 year	Severe	6 "	Almost complete
42	1 "	Moderate	7 "	Complete
49	Dull headaches almost every a.m. for 4 years	"	7 "	"
57	Increasing generalized headaches for last 2 or 3 years	Severe	7 "	"
76	Headache	"	6 "	"
100	6 months	"	4 "	Much improved
105	8 years	"	3 "	Improved
115	5 "	Very severe	1 month	Substantially complete
122	8 "	Severe	2½ months	Almost complete
123	1 year	Moderate	5 weeks	Complete
125	Mornings for some time	Severe	2 months	"
142	"Years"	Difficult to evaluate	1 month	Little difference
134	2 years	Mild occipital	1 "	Complete
107	1 year	Moderate	1 "	Substantially complete
136	1 "	Very severe	1 "	Little difference

ordinarily of a different character and less severe than the hypertensive headache. This occurs especially when the blood pressure falls precipitously, and sometimes may be avoided by adding 1 in 200,000 adrenaline hydrochloride to the drug, so as to lessen the rate of absorption.

Effect of Penta- and Hexa-methonium Salts on the Incidence of Encephalopathy and Dizzy Attacks

Of the patients treated, six had experienced definite attacks of encephalopathy in the sense of having attacks either of unconsciousness or of paralytic phenomena with rapid recovery. The number of attacks of encephalopathy before treatment was comparatively few and there have been three recurrences of short duration since treatment started. It seems that encephalopathic attacks are not prevented. Spontaneous dizzy attacks, however, were frequent in seven patients, and were stated to be completely relieved by treatment. While this is purely subjective, there is a case for further study of the probability that treatment with these methonium halides may lessen the tendency to spontaneous dizzy attacks, and it is proposed to give further attention to the question of whether the incidence of encephalopathic attacks is influenced by them.

It should be borne in mind that most patients on adequate dosage of penta- or hexa-methonium salts experience slight or moderate faintness occasionally on

standing quietly. Intelligent patients distinguish spontaneous dizzy attacks from the faintness induced by hypotension. Until a specific inquiry is made into the character of the sensation, they tend to describe both sensations as "dizzy turns." The sensations induced by the drug are relieved promptly by the sitting or lying posture.

Effect of Penta- and Hexa-methonium Salts on Hypertensive Changes in the Retinae

In this department stress has always been laid on the observation of the retinae in hypertension, and we have had the advantage of the opinion of Mr. Rowland Wilson in many instances. In this series our own observations were augmented by his and those of senior members of the Neurosurgical Department. When differences of opinion arose this will be indicated in the text. In all of 25 patients under treatment who had such reversible retinal changes as haemorrhages, soft exudates, or retinal oedema we observed distinctive improvement, and in many instances disappearance of the abnormality. This was particularly evident in the case of haemorrhages and of retinal oedema which was not located in the immediate vicinity of the disk, when complete disappearance could be anticipated. Soft exudate sometimes disappears, but we have not had many examples of soft exudates in this series.

Cases with papilloedema were sought out especially for treatment, and 12 were available for study and have been examined at frequent intervals. Eleven of these were examples of malignant hypertension. One patient, though papilloedema was present, appeared on other grounds to be an example of advanced essential hypertension. *It has been clear to all observers that in all patients with papilloedema treated for two months or more there has been either disappearance or a substantial diminution of the abnormality.* Ordinarily, improvement was evident in a month or less. It will be realized that, although there is no difficulty in detecting the presence of appreciable papilloedema or retinal oedema, it is often particularly difficult to decide whether these have entirely disappeared, leaving behind only those permanent changes which sometimes remain when papilloedema has disappeared—as, for example, a hazy edge to part of the disk and some loss of translucency of the disk and immediately surrounding structures.

It will be clear that the distinction between residual circumpapillary oedema and papilloedema, and the permanent changes which follow these, is not always a matter which can be decided with finality. Such differences of interpretation as have arisen have always been on this point. The opinion here expressed is, so far as we can make it, a conservative one compounded of our own and of the views of several observers who have been kind enough to help us. That there has been diminution in the extent of these retinal changes is agreed by all observers. All cases have improved to a stage where the presence of a physiological cup was generally accepted. In almost all cases one eye, and sometimes both eyes, improved to a stage where it was generally accepted that all papilloedema had disappeared from that eye. Not infrequently, however, the other eye, though exhibiting a physiological cup, would retain a fuzzy edge to a part or sometimes to the whole of the disk circumference.

In three instances, after several months, we observed return of papilloedema while the patient was still under

treatment. In one case this occurred in hospital in the course of intercurrent pneumonia; it subsequently disappeared completely from both eyes, and several months later recurred to a slight extent in one eye at a time when the patient was making further clinical improvement subjectively. In another case it recurred in both eyes in an out-patient case during an attack of glandular fever; it disappeared completely in one eye and was greatly diminished in degree in the other eye coincidentally with intensified treatment. The third case, seen recently, exhibited a slight oedema of the disk edge without loss of the physiological cup at a time when treatment seemed effective in other respects. In three patients treated by continuous injection of hexamethonium bromide, securing day and night blood-pressure reductions of the order of 80–100 mm. systolic and 30–40 mm. diastolic, the papilloedema had disappeared from one eye in each patient within 12 days of treatment and had decreased to a considerable extent in the other eye.

Effect of Penta- and Hexa-methonium Salts on Circulatory Manifestations in Arterial Hypertension

We have directed attention to the effect of penta- and hexa-methonium salts on breathlessness, gallop rhythm, alternation of the pulse, heart size, nose-bleeds, and the presence or absence of angina pectoris.

Breathlessness was complained of in varying degrees by 21 patients who were treated with penta- or hexamethonium salts. There was an appreciable measure of improvement in all (Table IX). These patients, in addition to treatment with penta- or hexa-methonium salts, had the advantage of rest in hospital. Six of these patients were given a salt-poor diet in order to economize in the amount of drug employed. The degree of improvement even in these cases appeared to be considerably greater than we have ordinarily experienced on salt restriction without the use of these methonium halides. Of the 21 patients who originally had breathlessness 19 have been maintained on treatment and improvements have been sustained. Eighteen of these are now out-patients and 17 have climbed 32 or more steps without discomfort. At the present time only one of these patients is on digitalis and none are on mersalyl. One of the two remaining patients, whose breathlessness had improved, disliked injections and declined further treatment. The blood pressure rose again and she had a further cerebral haemorrhage about 14 days after injections ceased. The other of the two maintained a blood-pressure fall without injections, so these were terminated.

Two other patients with arterial hypertension and congestive heart failure, not included in the series of 21, received a few injections of hexamethonium bromide without either favourable or unfavourable response. Treatment was not continued in the one case because of a local haemorrhagic reaction to injections, and in the other because, apart from injections, the presence of polyfocal ventricular premature systoles, with occasional R waves interrupting the antecedent T waves, suggested the probability of added risk to life.

Improvement was particularly dramatic in two patients with malignant hypertension and cardiac asthma treated day and night by continuous blood-pressure reduction to approximately normal levels for periods of 12 days. In both cases rest had failed to

TABLE IX.—*Effect of Penta- and Hexa-methonium Salts on Breathlessness*

Case		Diagnosis	Before Treatment	During Treatment	Other Treatment
No.	Age				
55	44	Malignant hypertension	Breathless getting out of bed	Walks slowly on flat without breathlessness	None
51	58	" "	Breathless in bed	Does very light jobs on farm; not breathless on flat. Slightly breathless on slopes	Mersalyl and salt-poor diet
52	47	" "	" "	Walks up 62 steps without difficulty	Salt-poor diet
76	43	" "	Repeated cardiac asthma. Breathless on walking a few steps	No nocturnal breathlessness. Walks up 31 steps without breathlessness	None
49	52	" "	Repeated cardiac asthma, almost every night for 1 month. Bed 2 years	" " "	"
99	70	Essential hypertension	Cardiac asthma. Breathless on slight exertion when up	No nocturnal breathlessness. Less breathless on exertion	Digitalis
73	69	" "	Cardiac asthma frequent. In bed 2 years	No nocturnal breathlessness. Now beginning to get up. Able to walk 200 yards on flat without breathlessness	None
41	48	" "	Breathless on stairs	Climbs stairs and hills slowly	"
40	58	" "	Breathless in bed	Walks up stairs holding conversation	Salt-poor diet
13	54	" "	Breathless on stairs and hill	Much less breathless; tested in same places	" "
17	53	" "	" " "	Tried same situations: definitely less breathless	None
58	36	Post-toxaemic hypertension	Slightly breathless only	No breathlessness in same circumstances	"
14	48	Essential hypertension	Breathless when gardening	Not breathless gardening	Salt-poor diet
60	41	Post-toxaemic hypertension	Breathless with housework	Definitely less breathless	" "
59	42	" "	Breathless on stairs	Not breathless on stairs	" "
100	43	" "	Moderately breathless at rest	Not breathless at rest or with moderate housework	None
125	52	Essential hypertension. Aortic regurgitation	Cardiac asthma severe. Very breathless on effort	Cardiac asthma mild. Still breathless on exertion	None, but will require digitalis
127	56	Essential hypertension	Congestive heart failure. Breathless at rest	Walks up 32 steps without discomfort	Digitalis. Improved without alteration of dose
134	50	" "	Cardiac asthma. Congestive heart failure. Breathless at rest	" " "	Failed while on moderate salt restriction—regime unaltered. No digitalis. No mersalyl
133	50	" "	" " "	Unrelieved by hexamethonium alone; relief on adding digitalis	Digitalis
56	40	Post-toxaemic hypertension	Congestive heart failure. Breathless at rest; gross leg oedema; basal rales	Improved, but recurred when off treatment. Improved when treatment restored. Now climbs 32 steps	None

bring relief. No attack occurred after the starting of treatment. Both patients noted that, apart from lessened breathlessness, they could breathe more deeply. The vital capacity in one of the patients increased in the 12 days from 0.9 to 2.1 litres.

Other circulatory changes were not observed in a sufficient number of instances. Of five patients who had over two months' treatment a gallop rhythm disappeared in four and was barely audible in the other. However, we do not attach great prognostic importance to gallop rhythm in hypertension. Alternation of the pulse was noted before treatment in two patients and was absent after treatment.

Nose-bleeds were complained of by five patients. There has been very little nose-bleeding since treatment started.

Angina was present in seven patients. Attacks were induced by over-lowering of the blood pressure in two patients and with slight lowering in one patient. Four patients who received treatment for two months or more appeared to have fewer attacks. This result was unanticipated, and the relief of symptoms may well be coincidental, though theoretically it is possible that the lowering of the blood pressure reduced the work to be done by the heart to a degree which is out of proportion to the decrease in the coronary flow that results from a lower arterial pressure. If there are indeed cases which receive genuine benefit it seems probable that others will be made worse. In any case, the administration of methonium salts to anginal patients is a matter which we have regarded as an indication for extreme caution.

Radiographic observations were made on 15 patients treated with penta- or hexa-methonium salts over periods of 2 to 14 months. Reduction in the degree

of pulmonary congestion was noted in all of the four patients in whom congestion was present at the inception of treatment. Certain changes in the frontal silhouette of the heart occurred; some of these were well within the limits of experimental error, the differences being so small that no conclusion could be drawn concerning change in the size of the individual patient's heart. Taking all the results together, however, there is an indication that slight reduction in the size of the heart is not unusual whether judged by the whole silhouette or the transverse diameter (Table X).

TABLE X.—*Change in the Transverse Diameter of the Heart During Treatment With Penta- or Hexa-methonium Bromides*

Case No.	Initial Transverse Diameter (cm.)	Change in Transverse Diameter (cm.)	Time Interval (Weeks)
52	17.0	-3.0	56
127	15.8	-1.7	9
134	20.4	0	2
47	13.4	-0.8	11
55	14.6	-0.2	9
13	14.2	-0.9	40
14	12.5	-0.5	36
41	15.3	-0.4	13
54	14.1	-0.4	16
57	16.0	-0.5	6
51	14.3	+1.2	38
53	14.1	-0.5	34
76	17.0	-2.1	46
63	13.7	-0.4	9
49	17.4	0	12
Average	15.3	-0.6	22.5

The algebraical average of the changes is a decrease of 0.61 cm. in transverse diameter. Eleven of the above-mentioned patients had shown impairment in exercise tolerance, and all of these were improved during methonium treatment.

Electrocardiographic changes due to arterial hypertension were present in eight of the cases in which our

observations extended over several months. In all instances changes were observed in the direction of return towards a more normal trace. In cases of moderate severity inverted T waves became positive; in severe cases the T wave inversions remained, but ST segment deviations decreased or disappeared. Such changes were most evident in the first limb lead and in the fifth and sixth (V) chest leads. Unipolar limb leads sometimes showed similar changes.

Effect of Penta- and Hexa-methonium Salts on Renal Excretion in Hypertensive Patients with Impairment of Renal Function

Our observations here are confined to four patients whose high blood pressure was associated with renal insufficiency. In no case was effective blood-pressure reduction associated with rise in the non-protein nitrogen, or with symptomatic indication of impairment in the excretory functions of the kidneys. It is clear that any patient with impairment in the excretory functions of the kidneys requires careful study in regard to the effect of blood-pressure lowering before such treatment is adopted as potentially of therapeutic value. Such results as have been obtained indicate that there are at least some patients whose excretory capacity is not reduced when the blood pressure is lowered by methonium halides.

Case 47.—Male aged 27. Chronic nephritis. Urea concentration, 1.16%. When off hexamethonium bromide the casual blood pressure was in the region of 220/125 and the T.N.P.N. was 43 and 50 mg./100 ml. When under treatment the blood pressure was in the region of 148/90 and the T.N.P.N. was 42 mg./100 ml.

Case 42.—Male aged 40. Advanced renal tuberculosis. Urea concentration, 1.1%. When off hexamethonium bromide the casual blood pressure was in the region of 190/100 and the T.N.P.N. was 62, 93, 42, and 76 mg./100 ml. When under treatment with hexamethonium bromide the blood pressure was in the region of 135/87 and the T.N.P.N. was 78, 74, 62, 57, 58, 72, 64, and 75 mg./100 ml.

Case 55.—Female aged 45. Malignant hypertension. Urea concentration, 0.98%. When off treatment the casual blood pressure was in the region of 265/170 and the T.N.P.N. was 66 mg./100 ml. When under treatment with hexamethonium bromide the blood pressure was commonly in the region of 180/110 and the T.N.P.N. was 30 and 41 mg./100 ml.

Case 49.—Female aged 53. Malignant hypertension. Urea concentration, 1.24%. When off treatment the casual blood pressure was in the region of 250/132 and the T.N.P.N. was 52 mg./100 ml. When on treatment with hexamethonium bromide the blood pressure was about 150/100 and the T.N.P.N. was 54, 48, 46, 50, 46, and 40 mg./100 ml.

In a number of instances, microscopical haematuria, albuminuria, and cast excretion have diminished or disappeared coincidentally with blood-pressure lowering, but not to a greater extent than may occur ordinarily with rest.

Dosage of Penta- and Hexa-methonium Salts

In the course of treatment we have not experienced any difficulty in substituting pentamethonium bromide for hexamethonium bromide in the same dose. Actually formal tests indicate that the hypotensive effect of hexamethonium bromide is usually slightly stronger (Table III). In all instances we have found that when tolerance is acquired to pentamethonium

bromide an equivalent degree of tolerance develops for hexamethonium bromide.

In patients who have not had the drug previously, and who are given their preliminary injection in the sitting posture, we find an initial dose of 15 mg. subcutaneously is usually sufficient to cause a considerable fall in the blood pressure when that is high, and about a third of the patients so tested, especially women, have to lie down for a short time corresponding to the trough of the blood-pressure fall. The response to later doses shows the effect of habituation to the action of the drug, so that 250 mg. per injection may have no greater effect than was initially produced by 15 mg.

We wish to stress the great importance, with these drugs, of starting with small doses, as even 15 mg. may have a large effect; but, administered in the sitting posture, there is an added factor of safety, because if the blood pressure falls excessively a change to the horizontal posture will restore the pressure towards normal. In a patient on a salt-free diet 15 mg. may be rather a substantial initial dose, though there will be little trouble if the patient lies flat. Patients with congestive heart failure may get an excessive response, and orthopnoea contraindicates use of the horizontal posture. We have had substantial blood-pressure falls from 5 mg. subcutaneously in a patient with congestive heart failure on a restricted intake of salt. Advantage of a salt-poor diet may be taken in treatment. It economizes in the use of the drug, makes oral administration more effective, and may further supplement the blood-pressure fall in a small proportion of cases by inducing a fall due to the salt-free diet itself. In the case of oral therapy the risk of bromism must be kept in mind.

Conclusions

When a suitable technique of administration is employed penta- and hexa-methonium salts appear to be most effective and generally applicable hypotensive agents.

We hold most strongly to the view that the extent of the benefits to be derived from penta- and hexamethonium bromides has not been explored unless the method of administration of these substances is one which leads to and maintains a substantial blood-pressure reduction in many classes of case to near normal levels, and for an appreciable proportion of the day and night. With oral dosage this is not always possible after tolerance has developed.

Blood-pressure reduction by penta- and hexamethonium salts has been associated with unmistakable clinical improvement as witnessed by the relief of dyspnoea, pulmonary congestion, headache, papilloedema, and retinal exudates, in the course of treating 53 severe hypertensive patients (including 11 with malignant hypertension) for periods of 1 to 14 months, with one death from cerebral haemorrhage.

Great blood-pressure reductions may be inadvisable in patients with much cerebral or coronary sclerosis. The selection of cases, and the decision on how much blood-pressure reduction should be effected, therefore requires care. For these reasons, and for others set out in the text, treatment must be individualized and controlled by measurements of the blood pressure before administration of the drugs and during the trough of the blood-pressure fall which they induce.

Attempts at treatment which do not take account of individual responsiveness to the drugs, postural

hypotension, the effect of salt intake, the acquisition of tolerance, and numerous other factors will flounder between the dangerous and the ineffectual.

Summary

There is a close similarity in the hypotensive effects of penta- and hexa-methonium bromides, though formal tests show that hexamethonium bromide is usually slightly stronger in action. We have experienced no difficulty in interchanging these substances at approximately the same level of subcutaneous dosage.

Falls in blood pressure following penta- or hexa-methonium injections are influenced by posture, being greater as the patient approaches the vertical.

Under comparable conditions patients with the higher pressures tend to have the greater blood-pressure falls after hexamethonium bromide injections.

Following sufficiently large injections of these methonium halides, the casual blood pressure falls below the original level of the basal blood pressure, and may be well below this level even in the horizontal posture.

The effects of penta- and hexa-methonium injections on the pulse rate are not constant, but usually as the blood pressure falls the pulse rate increases. This statement applies to the blood-pressure changes induced by changes in posture.

Sensitivity tests to hexamethonium bromide have been carried out in 150 cases of high blood pressure, including 72 cases of fixed and 15 labile types of essential hypertension; 11 following sympathectomy; 11 patients with malignant hypertension; 21 with hypertension following pregnancy toxæmia; two with acute pregnancy toxæmia; 10 with impairment of renal function following surgical disorders of the kidney or nephritis; one case of hypertension associated with polycythaemia; and seven cases of miscellaneous aetiology. Poor response to penta- or hexa-methonium salts has so far been restricted to certain cases of renal damage; other cases with renal damage showed good blood-pressure falls. Fifty-three of the more severe cases were treated, and we have been able to maintain a substantial measure of control over the blood-pressure level.

On the basis of 150 test doses and treatment of 53 cases we would judge that, apart from some of the cases with impairment of renal function, almost all hypertensives can have their blood pressure controlled by these drugs. Among those with impaired renal function the four selected for treatment were readily brought under control without deterioration in their renal excretory capacity as judged by the T.N.P.N. estimations.

Repeated administration gives rise to considerable tolerance, such that 5 or 10 times the original dose may be required to produce the same effect. The acquisition of tolerance to hexamethonium bromide conveys an equivalent degree of tolerance to pentamethonium bromide, and vice versa.

Following repeated administration of penta- or hexa-methonium salts, patients who at the outset exhibit symptoms such as faintness on blood-pressure reduction usually become more tolerant of the lower blood-pressure levels.

The hypotensive actions of penta- and hexa-methonium salts are enhanced on a salt-poor diet (0.2 g. of sodium in 24 hours) to such a degree that dangerous reactions may occur if the effects of this potentiation are not allowed for in determining dosage.

Hypertensive headaches can be relieved in most patients.

The relief of signs and symptoms, when present, in cases treated over a period of months was prompt and striking. Particular reference has been made to the marked improvement of dyspnoea under treatment, and to the disappearance of papilloedema and retinal exudates. Pulmonary congestion disappeared, and there are indications of reduction in heart size and electrocardiographic improvement.

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BLOOD-GROUP FACTORS AND PHYSIOLOGICAL ICTERUS

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Ever since the pioneering work of Yllpö (1913) and Hirsch (1913) it has been recognized that the icterus index of the serum of newborn infants is higher than the values considered normal for adults. Moreover, in most infants the icterus index rises during the first few days of life, not infrequently with resulting noticeable jaundice of the skin and mucous membranes. Most workers (Weech, 1947) consider that physiological jaundice is due to functional immaturity of the liver at birth. However, the course of the syndrome resembles so closely the course of erythroblastosis caused by mild sensitization to the Rh factor that the possibility has to be considered that physiological icterus may have a similar pathogenesis. For example, sensitization to the A and B agglutinogens has been shown (Halbrecht, 1944; Polayes and McNally, 1948; Wiener *et al.*, 1949) to be a not uncommon cause of a relatively benign form of icterus occurring in the newborn infant which has been designated as icterus praecox by Halbrecht (1944). Similarly it is possible that the benign syndrome of physiological icterus may be the result of some antigen-antibody reaction. Although