increased. No evidence has been obtained why this phenomenon is seen to such a varying degree in all clinical groups, or why there is a maximum level of tolerance for a particular patient.

Summary

A study is presented of 39 hypertensive patients on treatment with hexamethonium bromide by subcutaneous injection. The patients were drawn from the complicated-essential, malignant, or renal groups of hypertension, and uncomplicated cases were not included.

Details of treatment routine and general management are given, as it is felt that these are of great importance in the achievement of successful results.

Five patients died whilst on treatment and it was discontinued for various reasons in six others, but 28 patients received regular therapy for periods varying between three and fifteen months and were seen at least once a month in the out-patient clinic.

After the development of a very variable amount of tolerance to the drug during the first four to eight weeks, all patients were able to be stabilized on a dose which gave an average blood-pressure level much below that found in the control period. Reduction in mean systolic pressure ranged from 20 to 90 mm. Hg and in mean diastolic pressure from 8 to 40 mm. Hg, and the maximum reductions—for example, one to two hours after an injection—were often twice as great.

Hypertensive headaches (often very severe and incapacitating) were almost completely relieved in 15 out of 19 cases, and lessened in frequency and severity in the other four. Giddiness disappeared and encephalopathic attacks did not recur, except in one instance. Shortness of breath from cardiac causes was generally improved and in several cases there was striking relief from acute cardiac dyspnoea. Diminution in cardiac volume was demonstrated in five out of seven cases after three to six months' treatment, and in seven out of 16 cases electrocardiographic signs of left ventricular hypertrophy were altered towards the normal. Retinopathy was strikingly improved in all severe cases, papilloedema subsiding, and extensive exudates and haemorrhages becoming reabsorbed, with restoration of normal vision after about six months' treatment.

One instance of coronary thrombosis and two major and two minor cerebral vascular accidents occurred during treatment, but in two of the latter the blood pressure was high at the time. No evidence of increased damage was found among patients with impaired renal function.

A recent development has been the occurrence of dyspnoea and symmetrical opacities in the lung fields on *x*-ray examination in three patients after fifteen, nine, and seven months' successful treatment. The pathogenesis of this is still obscure.

Side-effects were troublesome in proportion to the size of the dose and thus most severe in the cases developing a higher degree of "tolerance." The problem of "tolerance" is discussed and some suggestions are made regarding its nature.

I should like to thank Professor J. McMichael for his help and advice in carrying out this study and in preparing the paper, also Dr. W. D. M. Paton for estimating the plasma levels, Dr. J. F. Goodwin for the E.C.G. reports, and Dr. R. E. Steiner for the cardiac volume estimations. My thanks are also due to Messrs. May and Baker Ltd. for supplies of the drug, for technical assistance, and for a grant towards the expenses of this investigation.

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EFFECTS OF HEXAMETHONIUM ON NORMAL INDIVIDUALS IN RELATION TO ITS CONCENTRATION IN THE PLASMA

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Since hexamethonium was introduced as a ganglion-blocking agent (Paton and Zaimis, 1948) a number of publications have reported upon its effectiveness in the treatment of hypertension and certain other disorders; but, apart from the original observations of Organe, Paton, and Zaimis (1949) and reports by Arnold and Rosenheim (1949), Arnold, Goetz, and Rosenheim (1949), Burt and Graham (1950), and Grob and Harvey (1950) on the production of hypotension in the recumbent subject with marked fall in blood pressure on standing up, subsequent attention has been directed mainly to the effects of the drug in disease rather than in normal individuals.

Clinical experience with a series of hypertensive patients being treated with hexamethonium at Hammersmith Hospital revealed very early that the reactions were of a most complex nature, and correspondingly difficult to interpret. We felt, therefore, that a further study of the actions of this agent in normal man was necessary.

Clinical Method

Eighteen observations were made on 16 normal young adult volunteers (4 women and 12 men). Since the best clinical results seem to be obtained from regular subcutaneous injections (Smirk and Alstad, 1951), we have given our test doses in this way. After control observations for 20 to 30 minutes, doses between 20 and 100 mg. of a 10% solution of hexamethonium bromide were given subcutaneously. In all but two this was the first dose of hexamethonium. Blood pressure, pulse rates,

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pupil changes, and subjective sensations were recorded at suitable intervals. In eight of the subjects estimates of plasma hexamethonium levels were made on venous blood. During the first one to two hours the subjects reclined on a couch or sat, and later proceeded with their ordinary occupations.

For comparison of effects the doses are recalculated as mg./kg. body weight, or as mg./litre of extracellular fluid (taken to be 20% of body weight; Gamble, 1949).

Blood pressure was recorded by the auscultatory method with a diaphragm stethoscope strapped to the

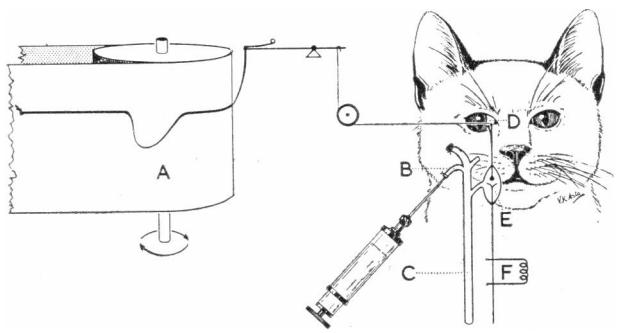

FIG. 1.—Diagram of the preparation used in the assay of hexamethonium. A=Smoked drum. B=Cannula in external carotid artery. C=Carotid trunk. D=Suture through nictitating membrane. E=Electrodes on sympathetic trunk.

arm over the brachial artery. Readings were taken in three positions—standing erect, sitting upright on the edge of the couch, and semi-recumbent on the couch with legs horizontal. Owing to the often-continued fall of blood pressure on maintaining the upright posture, an arbitrary standard time was allowed to elapse before the pressure was measured; for the first three tests (Table IV) the reading was taken in 60 seconds, but thereafter it was changed to 30 seconds, which was found to be less unpleasant for the subject. During an acute postural fall in blood pressure the sounds at times become very soft and difficult to hear; the systolic can be checked by palpation, but some of the diastolic readings must be of doubtful accuracy.

Pulse rates were counted simultaneously with or immediately following the blood-pressure measurements.

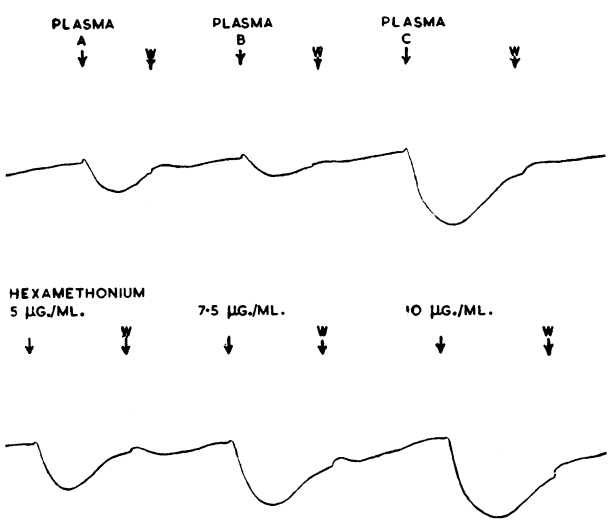

FIG. 2.—Tracings showing relaxation of the nictitating membrane when ganglionic transmission is interfered with following close arterial injection of samples of plasma containing hexamethonium (above) and of standard solutions of hexamethonium in saline (below). Estimations are made by direct comparisons of tracings. Arrows mark injections; W=saline wash-in.

Subjective effects were recorded at each point, and a note made on dryness of the mouth, blurring of near vision, and sleepiness. Objectively, pallor, conjunctival injection, and somnolence were looked for.

Pupil Changes.—Three different aspects of pupillary function were examined: resting size of pupil (so far as possible in the same lighting as the control observations), reaction to light, and contraction on accommodation.

Assay of Hexamethonium in Plasma

We have made use of a bio-assay method for estimation of plasma levels, introduced by one of us (W. D. M. P.), but it will be readily understood that this method is too difficult and too time-consuming to be used as a routine procedure in the control of therapy.

Blood samples were taken into dry all-glass syringes and heparinized immediately. The plasma was separated within an hour or two and stored in the refrigerator until assayed.

The concentration of hexamethonium in each sample was determined by comparing its effect with that of a standard concentration of hexamethonium on close-arterial injection into the continuously stimulated cat's superior cervical sympathetic ganglion. The ganglion was excited by tetanization of the pre-ganglionic cervical sympathetic trunk at rates between 15 and 50 shocks per second, and the activity of the ganglion was measured

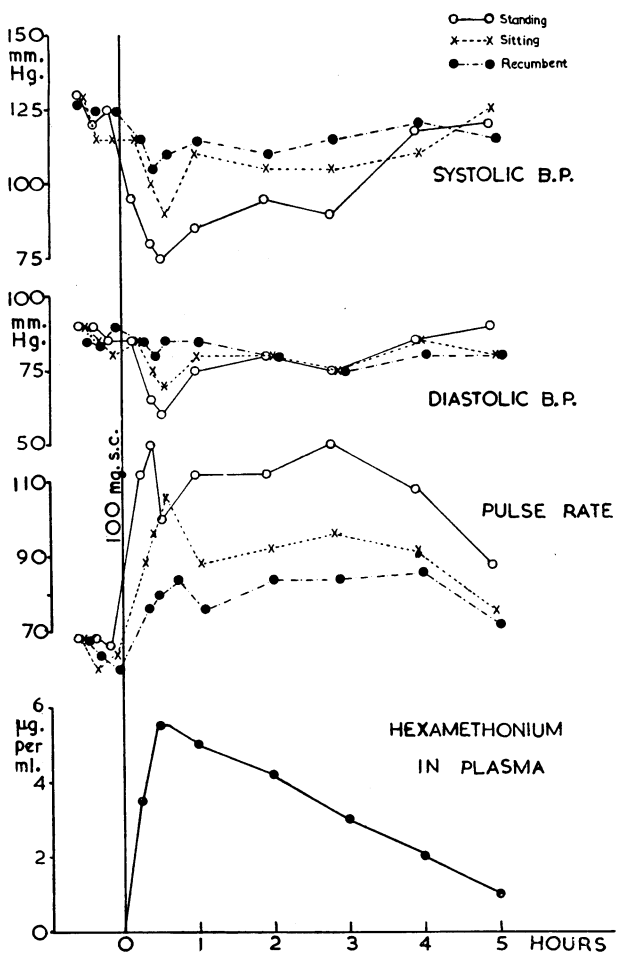

FIG. 3.—Graph of systolic and diastolic pressures and pulse rates, in standing, sitting, and recumbent postures, and levels of hexamethonium in the plasma, following a subcutaneous dose of 100 mg. in a normal individual.

TABLE I.—*Effects of 100 mg. Hexamethonium Given Subcutaneously to a Normal Individual*

Time	Blood Pressure (Pulse Rate)			Concn. of Hexameth. in plasma µg/ml.	Faintness, etc.	Other Sensations	Dry Mouth	Blurred Vision	Increase in Pupil Size		Reaction to Light		Accommodation		Other Observations
	Standing	Sitting	Recumbent						R.	L.	R.	L.	R.	L.	
− 30 min.	130/90 (68)	130/90 (68)	127/85 (68)												
− 20 ,,	120/90 (68)	115/85 (64)	125/85 (64)		—	—	−	−	−	−	+	+	+	+	
− 5 ,,	125/85 (72)	115/80 (64)	125/90 (60)												
Zero	100 mg. hexamethonium bromide (10% solution)														
+ 10 min.	95/85 (112)	115/85 (112)	115/85 (76)		Sl. faint on standing	—	−	−	−	−	+	+	+	+	Not sleepy. Pink face. Some conjunctival injection (+) Yawning. Hand cool
+ 15 ,,				3·6											
+ 25 ,,	80/65 (120)	100/75 (96)	105/80 (80)		More faint on standing	—	+	−	+	+	+	+	(+)	(+)	
+ 37 ,,	75/60 (100)	90/70 (100)	110/85	5·5	Faint + on standing	Dull posterior headache on standing	+	−	+	+	++	++	(+)	(+)	Pallor ++. Hand warmer
+1 hr. 5 ,,	85/75 (112)	110/80 (88)	115/85 (76)	5·0	Faint + on standing	—	+	−	+	+	+	+	(+)	(+)	Pallor less, but +
+1 ,, 55 ,,	95/80 (112)	105/80 (92)	115/80 (84)	4·5	—	—	−	Dazzled outside	+	+	+	+	(+)	(+)	Still pale
+2 ,, 47 ,,	90/75 (120)	105/75 (96)	110/75 (84)	3·0	—	—	+	−	+	+	+	+	+	+	,, ,,
+3 ,, 55 ,,	115/85 (108)	110/85 (92)	120/80 (86)	2·0	—	Heaviness in head	+	−	−	−	++	++	+	+	,, ,,
+4 ,, 52 ,,	120/90 (88)	125/80 (76)	115/80 (72)	1·0	—	—	−	−	−	−	+	+	+	+	—

by recording the contraction of the nictitating membrane on a smoked drum (Fig. 1). Interference with ganglionic transmission causes a relaxation of the sustained contraction (Fig. 2). The results of the assay are given as micrograms of hexamethonium bromide per millilitre of plasma.

Clinical Data

(a) Example

Fig. 3 and Table I show the typical action of a subcutaneous dose (100 mg.). The most prominent effect was on the standing systolic blood pressure; the time course is seen in the figure. The sitting and recumbent pressures showed similar but less pronounced falls. The changes in the diastolic pressures were in the same direction in each instance, but smaller. Concurrently with the pressure changes there was an acceleration of the pulse, most noticeable on standing and reaching its highest value (plus 50 beats a minute) 30 minutes after the injection. After 10 minutes the subject noticed slight faintness on standing, and this became more severe at 25 and 35 minutes; thereafter it rapidly diminished, and was not complained of after 65 minutes. Pallor of the face was noted after 30 minutes and took about three hours to disappear. At the same time he remarked on a heavy feeling in the head and became slightly sleepy. He did not notice any disturbance of vision, except for some dazzle on going out into bright sunshine. Objectively, however, the pupils were noticeably dilated between 25 minutes and three hours after the injection, and for most of this time contraction on accommodation was diminished, though the reaction to light was never much affected. Dryness of the mouth was complained of after 25 minutes, and persisted for four hours.

Simultaneously with these events, hexamethonium appeared in the plasma, having a concentration of 3.6 µg. per ml. in 15 minutes, reaching a maximum of 5.5 µg. in 37 minutes, and falling thereafter to 1 µg. after five hours.

(b) Grouped Results

1. *Systolic Blood Pressure.*—Effects similar to those just described, but with considerable variation in magnitude, were seen in all subjects. The average blood-pressure fall in the standing posture was 30%, while in the sitting posture it was 19.5% and recumbent it was 9.5%.

Fig. 4 shows the maximal falls expressed as a percentage of the control blood pressure, plotted against the dose in milligrams per litre of extracellular fluid. It will be seen that there is only a broad correlation between the dose and the effect on the blood pressure. Two subjects (A and B) appeared to be exceptionally sensitive to the drug; it may be significant that one of these—A—failed to show the usual tachycardia on standing up, her pulse rate falling to 56 a minute, with other appearances rather like a vaso-vagal attack, which were relieved by lying flat. The other—B—felt only slight giddiness with a systolic pressure of 55 mm. Hg, but he too failed to develop tachycardia. The possibility of the occurrence in some individuals of this "vagal" type of reaction would increase considerably the variability of the response; although the incidence of the reaction is low, it can be alarming enough to call for caution in the choice of test dosage.

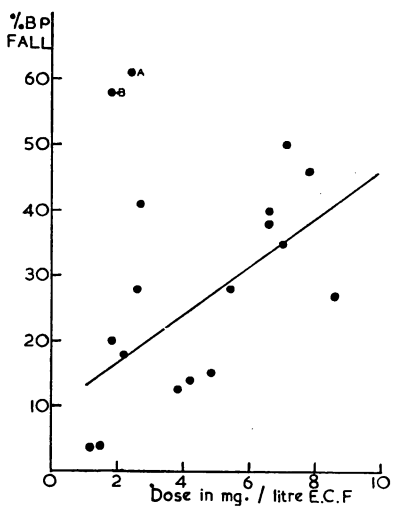

FIG. 4.—Relationship between maximal percentage fall in standing systolic blood pressure and the initial test dose of hexamethonium in 16 normal subjects (18 tests). The regression line is drawn through all points excluding A and B. $r=0.6824$. $P<0.05$.

The maximum fall in the blood pressure was reached in 30 minutes in nine subjects, in 15 minutes in seven subjects, and not until 60 minutes after injection in two; in every case a detectable fall had occurred within 15 minutes. Recovery took place with varying rapidity, being slower with large blood-pressure falls, and was usually well advanced by two hours, though often not complete for three to six hours with larger doses. The time course of the changes in sitting and recumbent pressures was parallel with the above.

2. *Diastolic Blood Pressures.*—These were recorded throughout, but, as already mentioned, their accuracy was doubtful in some cases. In 15 out of 18 cases the same order of percentage fall in diastolic pressures as in the

systolic pressures was seen in the erect position (mean 28%), but in the sitting and recumbent positions the changes were generally insignificant (less than 10 mm. Hg).

3. *Pulse Rate.*—Pulse rates were counted in the first eight subjects, and in all these the rate rose as the blood pressure fell, but the magnitude of the rise showed too great an individual variation to be of use in assessing the effects of the drug. For this reason routine counting of pulse rate was discontinued in the later tests, but tachycardia was usually obvious except in the two cases of bradycardia already referred to.

4. *Subjective Effects.*—Faintness or lightheadedness on standing, sometimes with nausea or sinking feelings in the abdomen, was complained of when the blood pressure fell below 100 mm. Hg in 10 subjects, although these symptoms were not noted in two subjects until the pressure had reached 80 and 55 mm. Hg. In the remaining subjects the blood pressure never fell below 100 mm. Hg and only very transient giddiness, or nothing at all, was noticed. The rapidity of the fall in pressure as well as the actual level reached evidently contributed to the severity of the reaction, and sometimes the faintness passed off whilst the blood pressure was still at a level at which they had previously felt faint.

Four subjects commented on a feeling of warmth in the feet, though none observed it in the hands. One said that his feet felt full, and that they squelched when he stood up. Another experienced a feeling of warmth in the abdomen "like eating a hot meal." Dryness of the mouth of slight or moderate degree was mentioned by 13 subjects.

5. *Objective Effects.*—Pallor of the face was conspicuous in eight subjects during the period of low blood pressure, and occurred mainly in those showing the greater falls. Conjunctival injection was not systematically looked for, but it was sometimes obvious, and one man complained of itching of the eyes. In about half the cases drowsiness was evident to the observer, and was usually confirmed by the subject.

Ocular Changes

Table II summarizes the pupillary changes observed in the 18 tests. The results are arranged in ascending order of dosage. Fig. 5 shows the relationship of ocular changes and plasma concentration of hexamethonium in one of the subjects.

TABLE II.—*Observed Effects of Hexamethonium on Pupillary Function in 18 Normal Individuals, Arranged in Ascending Order of Dose Given. The Figures After the Plus Signs Refer to the Times of Onset and Offset of the Change*

Dose Given (mg. per litre E.C.F.)	Increase in Pupil Size		Interference with Light Reaction		Interference with Accommodation	
	Degree	Duration (Hours)	Degree	Duration (Hours)	Degree	Duration (Hours)
1·2	−		−		−	
1·5	−		−		++	1–?
1·8	−		−		−	
1·85	−		−		−	
2·2	−		−		−	
2·35	−		+	½–?	−	
2·6	−		−		−	
2·7	+	1½ only	+,+	½–1½	+	¾–1½
3·9	+	½–1	−		−	
4·2	+	½–1½	+	½–1	−	
4·9	+	½–3	+	½–2	+	½–2
5·4	+	1–3	+	¼–3	++	¼–4
6·5	+	½–2	−		+	½–2
6·5	−		−		+	½–1
7·1	(+)	½–4	++	½–2½	+	1½ only
7·1	+	1–3	++	⅛–3	++	½–3
7·8	+	½–4	+++	½–4	++	½–4
8·6	+	⅛–4	+	¼–1	++	⅛–4

Pupil Size.—There was no increase in pupil size at doses less than 2.7 mg. per litre of E.C.F., but above this dose level the pupils always increased in size except in one test. No attempt has been made to assess differences in degree of this change, but the duration was generally longer with the higher doses. The widening of the pupil was never maximal and, moreover, the outline was sometimes irregular, suggesting the paralytic or "dead" pupil rather than the actively dilated pupil of sympathetic stimulation; this probably indicates an interference with both sympathetic and parasympathetic ganglionic transmission.

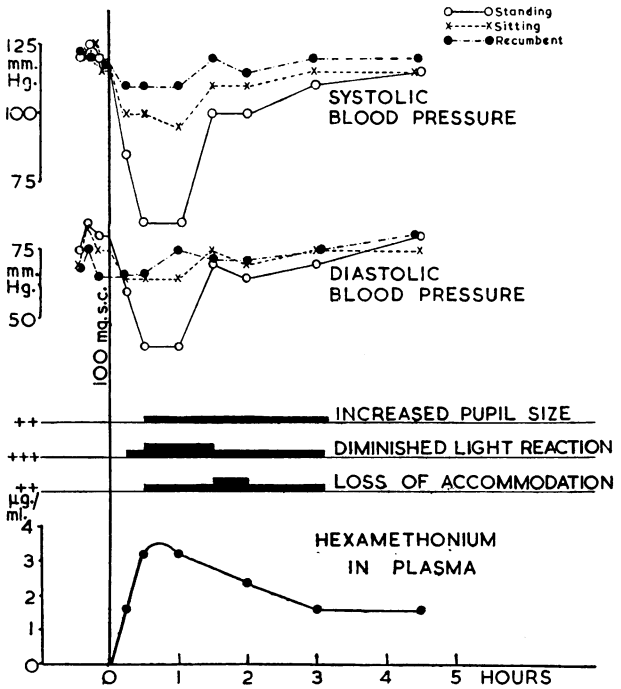

FIG. 5.—Relationship of ocular changes to blood pressure fall and plasma hexamethonium levels in a subject who received 100 mg. subcutaneously.

Interference with Light Reaction.—This was assessed in three grades according to whether the reflex was perceptibly diminished (+), very sluggish (++), or abolished (+++). No interference was seen with doses below 2.35 mg. per litre; above this level there was a rather variable effect: four cases showed no change at 2.6, 3.9, 6.5, and 6.5 mg., but one at 2.7 mg. showed complete paralysis. In the remainder there was a general increase in the degree and duration of reduction of the light reflex in proportion to the dose. When the light reaction was partially paralysed the contraction was often ill-sustained, although the pupil did not undergo the repeated fluctuations of true hippus. Poorly sustained contraction may sometimes be seen in normal pupils, but is much commoner under the influence of hexamethonium.

Interference with Accommodation Reaction.—No change in accommodation was seen below 4.9 mg. per litre, with the exceptions of an unusually late effect in a one-eyed subject at 1.5 mg., and a slight very transient effect in a second subject at 2.7 mg. With doses above 4.9 mg. per litre there was consistent interference with or loss of accommodation for periods between one and four hours. As this reaction has a considerable voluntary component it is possible that the slighter degrees of ganglion block by hexamethonium may be compensated by increased effort on the part of the subject. The convergence of the eyeballs is quite unaffected.

Concentration of Hexamethonium in the Plasma

Fig. 3 showed a typical graph of the rise and fall of concentration of hexamethonium in the plasma after a subcutaneous injection. To show the extent of variation in shape of such curves they have all been superimposed (Fig. 6). Correction for dose and body weight has not been made, since this would alter the height but not the form of the curves. Fig. 7 shows the standing blood-pressure changes and plasma-concentration curve for the subject who showed the most rapid absorption.

The three phases of the curve—that is, the rise, the peak value, and the subsequent fall—considered pharmaco-

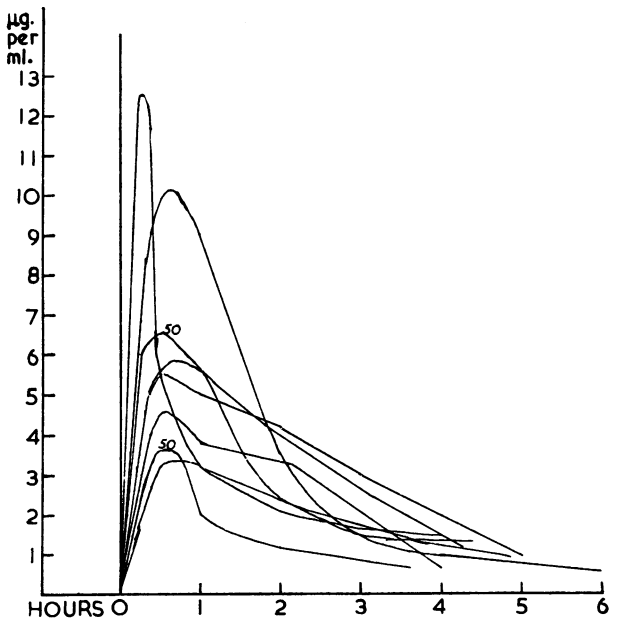

FIG. 6.—Plasma concentration curves from all eight subjects, superimposed to show differences in shape (not adjusted for body weight. Two received 50 mg. and six received 100 mg.).

logically, correspond to the three factors determining the plasma levels—that is, the rate of absorption, the volume of body fluid in which the hexamethonium is dissolved, and its rate of excretion by the kidney. These three aspects are considered in turn.

Rate of Absorption.—The rate of absorption can be estimated from the speed with which the peak concentration is approached. The highest value was attained in approximately half an hour or less in all tests. In every test at least half the peak value, and often much more, was reached in 15 minutes. If absorption is an exponential process—that is, if equal fractions of the unabsorbed residue are assimilated in equal times—then half the total dose must usually be absorbed in about 15 minutes. A few of the plasma curves have been regular enough to allow an estimate of the rate of excretion to be made, and hence an estimate of the amount left unabsorbed at various times. When this is done the absorption — that is, the fall in the amount still unabsorbed — follows the postulated exponential course. These considerations imply that absorption should be seven-eighths complete within about one hour in most individuals.

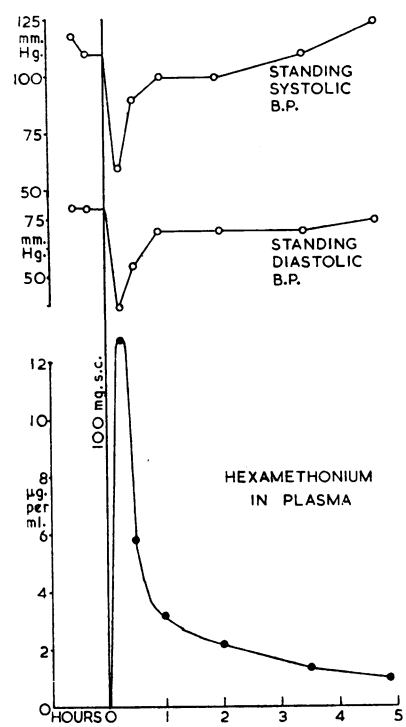

FIG. 7.—Plasma concentration curve and standing blood pressures in the subject who showed the most rapid absorption of hexamethonium after subcutaneous injection.

Distribution in the Body. — The peak plasma values in each test are given in Table III. They correspond in magnitude to a distribution of the drug in a volume equivalent to between 10 and 41% of body weight. Of these values four lie within the 15–25% range (which appear to be the extreme values for extracellular fluid given in the literature), two lie above this (28% and 41%), and two below it (10.3% and 12.2%). The range and average (23.1%) of these figures suggest that hexamethonium is in fact dissolving in extracellular water. Incomplete distribution outside the vascular compartment and a variable rate of excretion would readily account for individual discrepancies.

TABLE III.—*Peak Plasma Levels Found in Each Subject with Dose of Hexamethonium Injected and the Weight of the Subject. Columns 5 and 6 Show the Estimated Volume of Solution of the Drug at the Peak Times in Litres and as a Percentage of Body Weight Respectively*

Subject No.	Dose Given	Wt. of Subject	Peak Plasma Level	Calc. Vol.	% of Body Weight
1	100 mg.	58 kg.	10 mg./litre	10 litres	17·2
2	100 ,,	92 ,,	4·5 ,,	22 ,,	24·2
3	100 ,,	76 ,,	5·5 ,,	18·2 ,,	23·9
4	50 ,,	64 ,,	6·4 ,,	7·8 ,,	12·2
5	100 ,,	76 ,,	12·8 ,,	7·8 ,,	10·3
6	100 ,,	70 ,,	8·0 ,,	12·5 ,,	17·9
7	100 ,,	70 ,,	3·5 ,,	28·6 ,,	40·9
8	50 ,,	51 ,,	3·5 ,,	14·3 ,,	28·0

Excretion.—It is already known that about 90% of a parenterally administered dose can be recovered from the urine during the subsequent 12 hours (Zaimis, 1950; Milne and Oleesky, 1951; Wien and Mason, 1951; Harington, unpublished). We have calculated the expected clearance of hexamethonium by simple filtration in our subjects from the plasma-concentration curves, assuming that the glomerular filtration rate (G.F.R.) remains normal under the influence of the drug (Moyer and Mills, 1953) and has therefore a mean value of 125 ml. per minute (s.d.=25 ml. per minute). The periods of observation were four to six hours, by which time the plasma concentrations had sunk in five subjects to 1 µg. per ml. or less, and in the remainder were below 1.6 µg. per ml.

In Table IV the expected amounts excreted have been calculated first from the mean G.F.R. and secondly from the upper and lower limits of the G.F.R. (taking ± twice the standard deviation for this purpose). Although the dose given differs in some instances considerably from the former calculated value, in one case only does it fail to fall within the range of the expected excretion. These results are compatible with the excretion of hexamethonium by simple filtration without tubular excretion or reabsorption—that is, like inulin—and in this our findings agree with those of Young, de Wardener, and Miles (1951), who made a direct comparison of inulin and hexamethonium clearances.

TABLE IV.—*Expected Amounts of Hexamethonium Excreted Over Four to Six Hours by Simple Glomerular Filtration, as Calculated from Plasma-concentration Curves and Normal Range of Glomerular Filtration Rates*

Subject	Expected Total Excreted (mg.)		Dose Injected (mg.)
	From Mean G.F.R.	From 2×S.D. Range of G.F.R.	
1	143	86–200	100
2	66	40–93	100
3	86	52–121	100
4	100	60–140	50
5	99	59–138	100
6	150	90–210	100
7	74	44–103	100
8	44	25–61	50
Average	95		88

Correlation of Clinical Data with the Concentration of Hexamethonium in the Plasma

Blood Pressure

It has already been mentioned that the degree of reduction of blood pressure runs parallel to the rise and fall of

hexamethonium in the plasma. In Figs. 3, 5, and 7 this parallelism can be seen for three types of curve, and the same relationship was found in the remaining tests. The maximum blood-pressure fall always coincided within a few minutes with the peak plasma concentration, and the blood pressure returned to the control value when the plasma concentration fell to about 2 μg. per ml. (1–3.5 μg.). In no case was there a detectable fall in blood pressure with a plasma concentration of less than 1 μg. per ml. No observations of blood pressure were made during the first 10 minutes after injection, so that the plasma levels at the onset of the blood-pressure falls are not accurately known.

To reduce the standing systolic blood pressure below 100 mm. Hg (which was the usual level at which faintness occurred in normal subjects), plasma concentrations varying from 2.5 to 7.8 μg. per ml. were necessary in different individuals.

The variability of these responses led to a more detailed analysis of the individual tests. In Fig. 8 all the plasma concentration values obtained in each of five subjects are

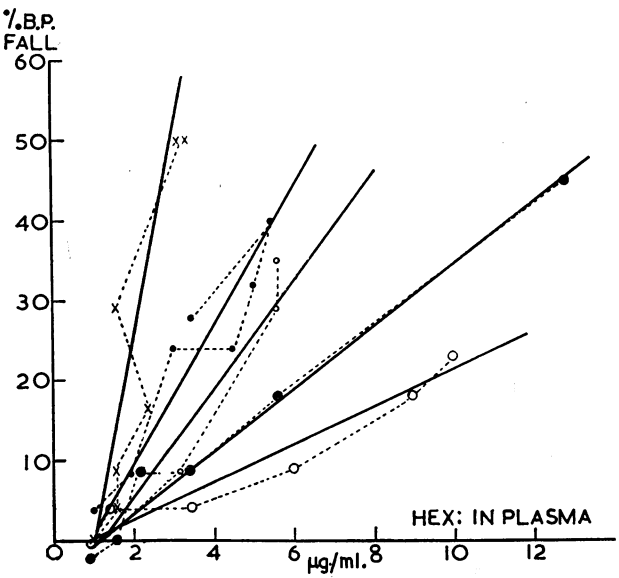

FIG. 8.—Relationship of percentage fall in standing systolic blood pressure to different plasma levels of hexamethonium in five subjects. Although the relationship is a linear one for each individual, the sensitivity of the different individuals is very variable.

plotted against the corresponding reductions in standing systolic pressure, making no distinction between the rising and falling phases of the curves. This graph illustrates the point made earlier, that a definite threshold value of hexamethonium in the plasma (about 1 μg. per ml.) is necessary before detectable changes in blood pressure occur. For each individual there is a surprisingly close relationship between the plasma concentration and the effects on the blood pressure; this relationship is unusual in that the effect of the drug varies directly with its concentration in the body rather than with the logarithm of its concentration. This regular relation for an individual subject contrasts strongly with a considerable variation in sensitivity between different subjects, and the latter accounts for the wide scatter in response to a test dose already shown for the whole group (Fig. 4).

It is possible to obtain an index of sensitivity for each individual from the slopes of lines shown in Fig. 8; this index is expressed as fall in blood pressure per unit concentration of hexamethonium in plasma. For the five subjects of Fig. 8 this index is respectively 3, 4.5, 8.5, 11, and 25% fall in standing systolic B.P. for each μg. per ml. It follows from this that there exists in normal individuals a basic variation in sensitivity to hexamethonium over at least an eightfold range, quite apart from differences in absorption, distribution, and excretion, or liability to "vagal" attacks of the kind mentioned earlier.

Dryness of the Mouth

This effect of hexamethonium was noticed by six of the subjects at minimum plasma levels of 2, 2, 3, 3.5, 4, and 8 μg. per ml. In the other two subjects it was not present, but in neither of these did the plasma concentration exceed 3.5 μg. per ml.

Ocular Changes

Table II showed the relationship between dose of hexamethonium and interference with pupillary function. In the eight subjects in whom plasma levels of hexamethonium were estimated a more direct comparison of these changes with concentration of the drug can be made.

Increased pupil size was seen with plasma levels above 1, 1, 1, 1.5, 2, 4, and 5.5 μg. per ml. In one subject no increase was seen, although the peak plasma value was 12.8 μg. per ml.

Interference with light reaction was observed in five subjects at threshold values of 1.5, 1.5, 2, 5, and 8 μg. per ml., but failed to occur in three subjects in which peak plasma levels of 5.5, 6.4, and 12.8 μg. per ml. were reached.

Interference with accommodation was observed in seven subjects at plasma levels above 1, 1, 1.5, 1.5, 3, 4, and 5.5 μg. per ml., but not in the eighth subject, whose peak value was 6.4 μg. per ml.

These results are ranked in order of magnitude, as the three pupillary functions seem to be affected independently of each other in the individual subject; on the other hand, the ranges of thresholds for interference with the three functions are similar.

Discussion

The effects of hexamethonium in normal man have been examined in some detail because this substance may be regarded as a prototype of the drugs which, by paralysing autonomic ganglia, are likely to prove useful in the treatment of hypertension and certain other disorders.

In this study no effects of hexamethonium have come to light which cannot be explained on the basis of blocking of either sympathetic or parasympathetic ganglia, with the possible exception of the drowsiness which occurs in many subjects.

Under the conditions of this study and with initial test doses of 25–100 mg., the ganglia which appear to be most prominently affected are those of the sympathetic chain, since the fall of blood pressure with postural accentuation has been the earliest and most constant finding. After these blood-pressure effects the detectable actions of next importance are on the ciliary and salivary ganglia. With the doses used there was no subjective evidence of significant interference with intestinal or bladder autonomic nerve supply.

It is interesting to find that in a particular subject the pupillary resting tone, reaction to light, and contraction on accommodation may be affected to different degrees by hexamethonium, and also that the order of onset of interference with these functions may vary with the individual. Such differences in behaviour between ganglia, and also apparently between different pathways within the same ganglion, are already known in the response to nicotine, hexamethonium, and other substances in animals. The interest of these variations lies in the hope they offer that other ganglion-blocking agents may be found which will have an action directed more specifically towards ganglion pathways subserving different functions—for example, those controlling vasomotor tone.

Postural hypotension with hexamethonium has been recognized from the earliest reports, and all our subjects showed this phenomenon. Although the maximum blood-pressure fall was always seen in the standing position, the falls in the sitting and recumbent positions ran a parallel time course in each case. When the average maximal depressions in blood pressure for the whole group are compared, the falls in the sitting positions are about half and those in the recumbent positions are about one-third of those in the

standing position. It is interesting that the hypotension in the sitting position is not greater, and, in fact, that the blood pressure rises promptly on sitting down.

A great deal of attention has been paid in these experiments to recording blood pressure in the erect posture, using a fixed time limit as described. Standing systolic readings have proved to be a convenient measure of the total effect of the drug on the blood pressure, since the changes in these readings are bigger in proportion to the errors of technique than in the sitting or recumbent positions, and, moreover, they provide an important measure of the maximum effect of the drug.

The distribution of hexamethonium in the body and its excretion at a rate comparable to that of inulin correspond to its quaternary nature. Bases in general penetrate the cell membrane only in the un-ionized form (Höber, 1945). Salts of quaternary nitrogen when in solution are completely ionized, and hence can only traverse the cell membranes very slowly. Accordingly they must lead an extracellular existence in the body, and should be unable to be either secreted or reabsorbed by the kidney tubules.

The indication from clinical data (Fig. 4) that normal subjects vary considerably in their response to hexamethonium was borne out and further elucidated by the plasma-concentration curves. Part of this variation is obviously due to the differences in absorption, distribution, and excretion already described; but the main variation, and one that cannot be eliminated by changing the route of administration, lies in the actual response of different subjects to the same concentration of the drug in the plasma (Fig. 6). The immediate practical application is that it is not safe to give initial doses of more than about 30–40 mg. subcutaneously to ambulant patients, even though this dose may produce little response in many individuals.

The somewhat unexpected finding of a linear rather than a logarithmic relationship between the plasma concentration and the effect on the blood pressure has some practical importance in addition to its theoretical interest; when treating patients for hypertension the dose should not be increased too rapidly. Increments of not more than 25–50 mg. should be used according to the individual patient's sensitivity.

The manner in which these findings in normal subjects may be applied to hypertensive patients under treatment is being studied and will be reported later.

Summary

A detailed study of the clinical effects of a subcutaneous test dose of hexamethonium in 16 normal individuals is reported, and plasma-concentration curves are described in eight of these.

No effects have been observed which could not be attributed to ganglionic block, with the possible exception of drowsiness.

Calculations from the concentration–time curves of hexamethonium in the plasma indicate that the drug is evenly distributed through the extracellular fluid, and they are compatible with its excretion by glomerular filtration.

Considerable variation in the response of different individuals to hexamethonium has been shown to occur, in relation both to the dose given per kilogram of body weight and to plasma levels. The thresholds for reduction of blood pressure, for elevation of pulse rate, and for interference with three separate pupillary functions varied from subject to subject, independently of each other.

For a given individual there was a close linear relationship between the plasma concentration and the degree of blood-pressure reduction.

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FARMER'S LUNG

BY

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A condition conveniently named "farmer's lung," readily recognized clinically and radiologically, has been reported in the medical literature in the past, but some confusion has existed about the causal mechanism and the natural history of the disease. The purpose of this paper is to review the literature, to present a small series of cases, and to advance a theory to explain its aetiology.

Review of the Literature

Campbell (1932) presented case histories of a small number of agricultural workers from North Westmorland who were referred to his clinic as possible cases of tuberculosis. All gave a history of sudden onset of intense breathlessness, cough, slight fever, and, in some, loss of weight following exposure to dust from mouldy hay.

The clinical picture in each case was of a distressed, blue, dyspnoeic patient, and clinical examination revealed widespread crepitations throughout the lungs. Radiologically the picture was of increased lung markings with superimposed soft shadows. Spontaneous recovery in one to two months occurred, but some residual fibrosis and emphysema were noted in a few cases. One patient subsequently died, but necropsy showed coincidental cystic disease of the lungs (Campbell, 1950 —personal communication). Through the kindness of Dr. Campbell it has been possible to study the *x*-ray films of one of his original cases followed up for 18 years. Some fibrosis and emphysema were the only findings.

Fawcitt (1936, 1938, 1940) studied the condition in West Cumberland and concluded from culture of similar moulds in the sputum and the hay dust that this was a fungous infection of the bronchi and lungs. He used the term "bronchomycosis feniseciorum" and advocated treatment with iodides. It should be stated that the condition described by Campbell (1932) and that of many of Fawcitt's (1938) cases were clearly not true aspergillosis, which is a distinct and well described clinical entity (Sayers and Meriwether, 1932; Smith, 1947). "Thresher's lungs," if aspergillosis is excluded, is an analogous condition in workers exposed to mouldy corn dust, and presents a picture identical to farmer's lung.

Duncan (1945), in a review of fungous diseases, stated that he had received specimens of sputum relating to this disorder from physicians in rural areas stretching from Cumberland to Devon. He cultured many varieties of