

PENTAMETHONIUM AND HEXAMETHONIUM IODIDE IN INVESTIGATION OF PERIPHERAL VASCULAR DISEASE AND HYPERTENSION*

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The clinical potentialities of hexamethonium iodide (C6) in producing ganglionic block were first reported by Paton and Zaimis (1948a, 1948b), who stated that it possessed greater potency and longer duration of action than tetraethylammonium bromide (T.E.A.B.). Preliminary observations of the effect of pentamethonium iodide (C5) in man were made by Organe, Paton, and Zaimis (1949). Clinical effects of C5 as a vasodilator were reported by Arnold and Rosenheim (1949) and by Arnold, Goetz, and Rosenheim (1949).

At the request of the Medical Research Council we undertook an investigation of the clinical effects of C5 and C6 with a view to assessing their value in the routine investigation of peripheral vascular disease and hypertension, and to comparing these with reflex vasodilatation and with T.E.A.B.

Methods

Investigations were made on three groups of subjects: (a) 5 normal controls; (b) 15 patients with vasomotor disorders, including acrocyanosis, erythrocyanosis, hyperhidrosis, and Raynaud's phenomenon without evidence of occlusive arterial disease; and (c) 7 patients with essential hypertension.

Whenever practicable the subjects were given each of the drugs under trial on consecutive days, but the order in which these were given was varied; a few patients were investigated before and after operations on the sympathetic nervous system. The drugs were administered intravenously—C5 and C6 in doses of 30–40 mg. during one to two minutes, and T.E.A.B. in doses of 250–500 mg. in two to four minutes. Reflex vasodilatation tests were carried out by immersing one hand and one foot in a water-bath at 43.5° C.

The subject, covered with two blankets, lay supine on a couch, with the trunk between 30 and 45 degrees above the horizontal and the lower limbs horizontal. The hands were 3 in. (7.6 cm.) above the sternal angle and the feet 9 in. (22.8 cm.) below. Room temperature varied between 17 and 22.5° C., but on any one day extremes did not exceed 1.5° C.

The skin temperature in upper and lower limbs was recorded by means of copper-constantan thermocouples attached to the nail-folds. Blood flow to hands or feet and to forearms or legs was measured by venous occlusion plethysmography, using air displacement (Barcroft and Walker, 1949). Skin colour, calibre of conjunctival and retinal vessels, and changes in nail-fold and digital-pad capillaries were noted before and after administration of the drugs. Sweating was measured by recording changes

in skin resistance on the pads of fingers and toes. Recordings were made at intervals of five minutes for 30 minutes before administration of the drug. After administration, recordings were made every one to two minutes for 10 minutes and then at five-minute intervals for periods of 60 to 90 minutes. Subjective sensations were also noted. In reflex vasodilatation tests, either skin temperature or blood flow recordings were made, because only two limbs were available for recording purposes.

Results

Blood Pressure

1. *In Controls and Vasospastic Cases.*—(a) *Systolic pressure*:—Following administration of 30–40 mg. of C5 or C6, in all except one of the patients tested there occurred a slight fall in systolic pressure, which was of a similar extent in the case of both drugs. The average fall in this group was between 15 and 24 mm. Hg (Table I). (b) *Diastolic*

TABLE I.—Average Blood-pressure Changes

Subject	Drug	Average Time of Fall (in Minutes) After Injection						Average Maximum Fall (mm. Hg)	
		Initial		Maximum		Duration		S.	D.
		S.	D.	S.	D.	S.	D.		
Normal	C5	1	1	2	2	12	60	15	15
	C6	3	12	29	22	45	42	19	11
	C5	2	4	5	6	47	49	22	11
Vasospastic	C5	3	13	10	16	41	33	24	13
	C6	3	3	23	38	62	95	41	12
	C5	2	2	20	4	60	13	29	10
Hypertensive	C5	3	3	6	3	95	95	65	41
	C6	2	2	20	4	60	13	29	10
Hypertensive post-operative	C5	3	3	6	3	95	95	65	41

S. = Systolic. D. = Diastolic.

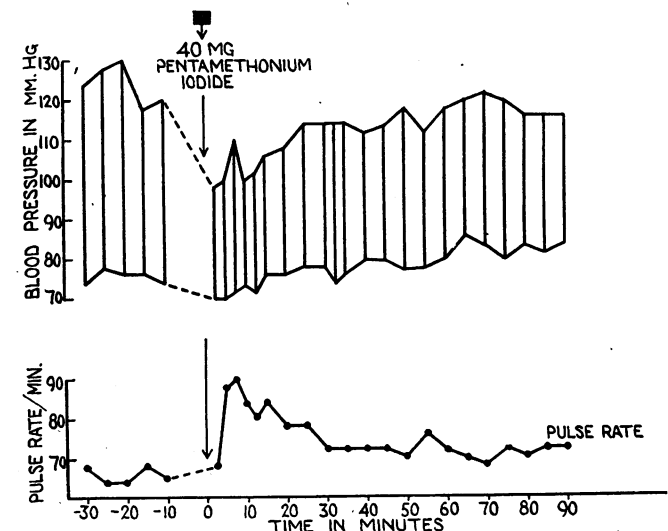


FIG. 1.—Effect of 40 mg. of C5 on blood pressure and pulse rate in a vasospastic patient.

pressure:—The range of average fall was 11–15 mm. Hg with both drugs, and as a rule began between one and five minutes after injection (Fig. 1). However, in the case of an otherwise healthy male patient suffering from Raynaud's phenomenon of hands and feet, a second severe fall in blood pressure to unrecordable levels occurred 35 minutes after injection (Fig. 2).

2. *In Hypertensive Cases.*—(a) *Systolic pressure*:—The fall in systolic pressure which occurred in every patient in this group was considerably greater than that in the previous group, and was between 29 and 41 mm. Hg. (b) *Diastolic pressure*:—The average fall with both drugs was similar to that in the control group. In no case was the fall after

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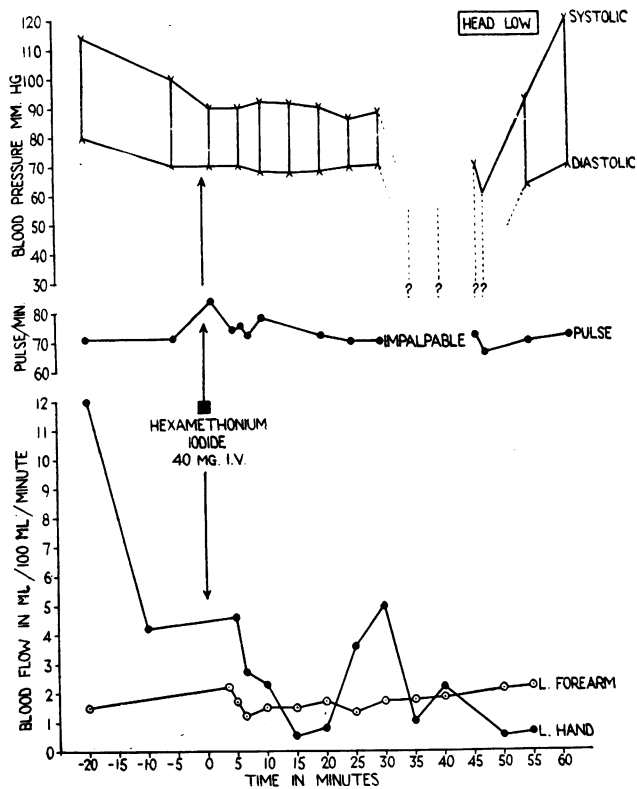


FIG. 2.—Delayed fall of blood pressure 35 minutes after administration of 40 mg. of C6 to a patient suffering from Raynaud's phenomenon. Room temperature, 19° C.

TABLE II.—Comparison of Effect of Sodium Amytal, 3 gr. (0.2 g.) Hourly for 3 Hours, with C5, 30–40 mg.

Average Blood Pressure in mm. Hg			
Sodium Amytal		C5	
Before	After	Before	After
219/126	132/87	212/110	163/97

administration of C5 as great as that after sodium amytal (Table II).

3. *In Post-operative Cases.*—In two patients tested after bilateral removal of the splanchnic nerves and the sympathetic chain from the seventh thoracic to third lumbar ganglion a further fall of 65 mm. Hg systolic and 50 mm. Hg diastolic occurred from the already low post-operative level (Table III, Fig. 3).

4. *Effect of Change of Posture.*—(a) *Passive:*—At a blood pressure of between 88/54 and 60/50 symptoms of faintness developed in six cases after administration of the drugs. Rapid relief was obtained by raising the foot of the bed on 6–9-in. (15.2–22.8-cm.) blocks, and was accompanied by rises in blood pressure from 10 to 33 mm. Hg systolic and 4 to 20 mm. Hg diastolic. The blood pressure remained unaltered when the head-down position was maintained throughout in three patients to whom C6 was given.

TABLE III.—Effect of C5 on Blood Pressure after Splanchnicectomy

Patient	Blood Pressure in mm. Hg		
	Before Operation	After Operation	
		Resting	After C5
A	230/110	144/104	70/50
B	276/116	160/88	98/60

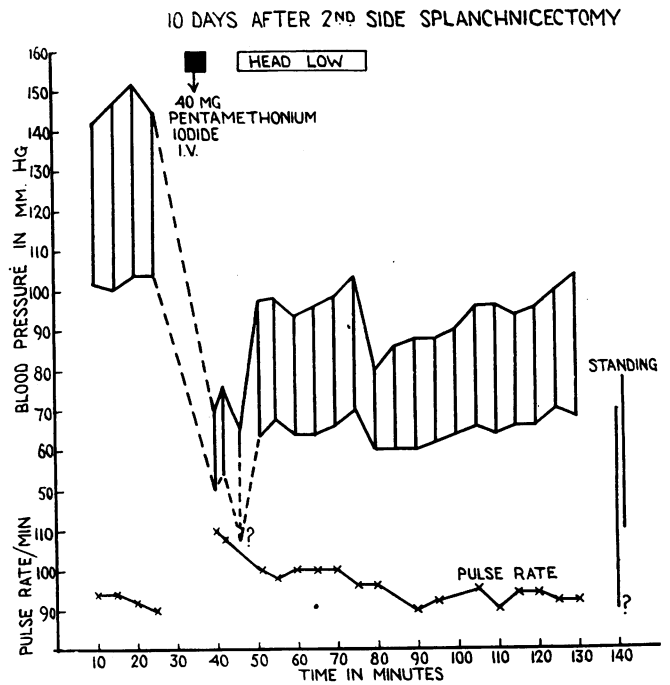


FIG. 3.—Effect of intravenous injection of 40 mg. of C5 on the blood pressure of a patient in whom bilateral splanchnicectomy had been completed 10 days before. The marked fall of diastolic pressure and the favourable response to the head-down position will be noted.

In the patient who became pulseless 35 minutes after injection of 40 mg. of C6, blood pressure became recordable at 70/— after four minutes in the head-down position, and after 13 minutes had risen to 92/62 (Fig. 2). Fig. 4 illustrates the ease and rapidity with which blood pressure can be altered by passive postural changes in a patient under the influence of C6. (b) *Active:*—One hour after the injection of C5 and C6, patients rose and stood motionless for two minutes and blood pressure was recorded at intervals

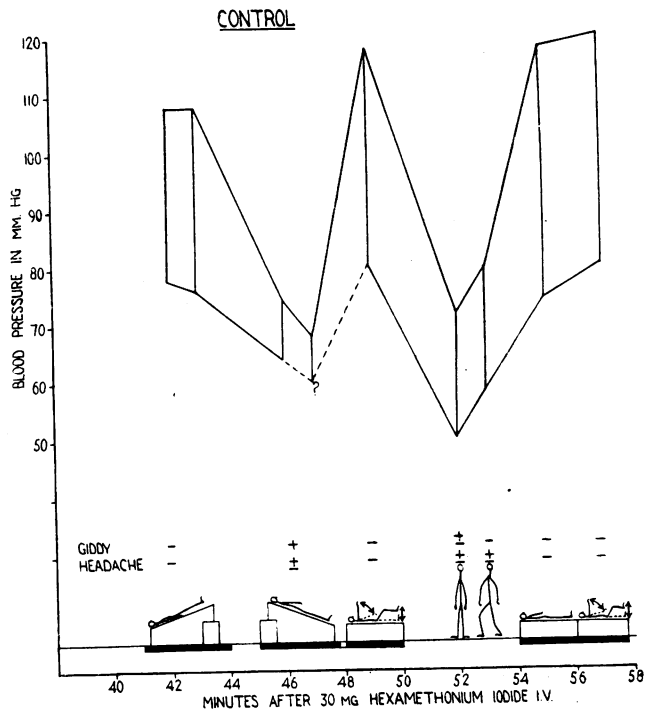


FIG. 4.—Effect of postural changes and exercise on blood pressure after 30 mg. of C6.

of a minute. In the majority of control and vasospastic subjects there was either no change or a rise of 2-20 mm. Hg in systolic and diastolic pressure, whereas falls occurred in the majority of hypertensive patients (Tables IV and V). Postural hypotension was most pronounced in the

TABLE IV.—Effects of C6 in Dosage of 30-40 mg.

	Subjects								
	Controls			Vasospastic			Hypertensive		
	↑	↔	↓	↑	↔	↓	↑	↔	↓
Blood flow:									
(a) Skin U.L.	2	1	2	4	4	1	1	0	0
" L.L.	3	0	0	2	0	0	0	1	0
(b) Muscle U.L.	1	2	1	2	5	2	0	1	0
" L.L.									
Skin temperature:									
U.L.	2	1	3	4	3	3	0	1	1
L.L.	5	1	0	13	3	0	1	0	1
Blood pressure:									
(a) Supine systolic	0	2	4	0	5	9	0	0	3
" diastolic	0	3	3	0	8	6	0	0	3
(b) Erect systolic	2	3	1*	4	4	4	0	1	2
" diastolic	2	3	1*	6	3	3	0	1	2
Pulse rate	6	0	0	13	2	0	3	0	0
Sweating:									
Toes	0	0	5	2	1	8			
Fingers	0	0	3	1	5	5			

Skin temperature ↑ = Rise of 5° C. or more or to over 30° C.
 Blood flow = Doubled or more.
 Pulse = Increase of 10 a minute or more.
 Blood pressure = Rise of 10 mm. Hg or more.
 Blood pressure ↓ = Fall of 10 mm. Hg or more.
 * Passive head-high position.

TABLE V.—Effects of C5 in Dosage of 30-40 mg.

	Subjects								
	Controls			Vasospastic			Hypertensive		
	↑	↔	↓	↑	↔	↓	↑	↔	↓
Blood flow:									
(a) Skin U.L.	3	0	1	5	3	1	3	2	0
" L.L.	1	1	0	6	0	0	0	0	0
(b) Muscle U.L.	1	2	0	1	4	0	3	1	0
" L.L.				2	0	0			
Skin temperature:									
U.L.	1	0	1	3	3	4	2	0	0
L.L.	3	0	1	8	5	0	4	0	0
Blood pressure:									
(a) Supine systolic	0	1	3	1	1	12	0	0	5
" diastolic	0	1	3	1	8	5	0	3	2
(b) Erect systolic	1	2	1	3	5	2	0	1	2*
" diastolic	1	2	1	4	4	2	1	0	2*
Pulse rate	4	0	0	13	1	0	3	2	0
Sweating:									
Toes	1	1	1	1	0	9			
Fingers	1	0	2	1	1	9			

Skin temperature ↑ = Rise of 5° C. or more or to over 30° C.
 Blood flow = Doubled or more.
 Pulse = Increase of 10 a minute or more.
 Blood pressure = Rise of 10 mm. Hg or more.
 Blood pressure ↓ = Fall of 10 mm. Hg or more.
 * After splanchnicectomy.

two post-splanchnicectomy hypertensives, in whom drops occurred of 34 mm. and 64 mm. Hg in systolic and 48 mm. and 26 mm. Hg in diastolic pressures, accompanied by giddiness (Fig. 3). These patients recovered rapidly on lying down or on walking about.

Pulse Rate

With the subjects at rest both drugs caused a moderate tachycardia, which occurred on an average two minutes after injection of the drugs, reached a maximum in one

to seven minutes, and persisted for 20 to 90 minutes (Table VI).

TABLE VI.—Effect of 30-40 mg. of C5 and C6 on the Pulse Rate

Subjects	Average Pulse Rate Before and After Injection			
	C5		C6	
	Before	After	Before	After
Normal	71	96	73	92
Vasospastic	71	99	75	93
Hypertensive	76	97	81	102

Skin Blood Flow and Digital Temperatures

(a) Effect of C5 and C6.—Early in the investigation it became obvious with both drugs that in control and vasospastic subjects greater vasodilatation occurred in the lower than in the upper limbs (Table VII and Fig. 5). In 9

TABLE VII.—Skin Temperature and Blood Flow: Average Values Before and Average Maximum After Tests

Subjects	Test	Temperature in °C.				Blood Flow in ml./100 ml./min.			
		Thumb		Toe		Hand		Foot	
		Before	After	Before	After	Before	After	Before	After
Normal	C5	27.9	28.8	26.7	32.3	1.9	4.8	1.7	7.2
	C6	27.4	27.8	24.4	32.9	3.0	10.0	3.4	11.6
	R.V.D.	28.4	34.1	22.8	33.1				
	T.E.A.B.	27.3	28.6	23.7	25.5	6.2	10.6†	3.1	8.4
Vasospastic	C5	28.9	29.2	22.9	28.1	3.0	4.8	1.0	11.8
	C6	26.3	28.0	23.9	31.8	2.2	6.1	0.7	10.1
	R.V.D.					2.5	15.5	6.4	25.6*
	C.D.B.					1.4	16.0*		
Hypertensive	C5			25.1	30.9	2.5	6.9		
	C6			25.5	32.5	2.6	10.0		
	R.V.D.					11.6	28.4*		

R.V.D. = Reflex vasodilatation test. C.D.B. = Cervico-dorsal sympathetic block. * One case. † Transient rises only.

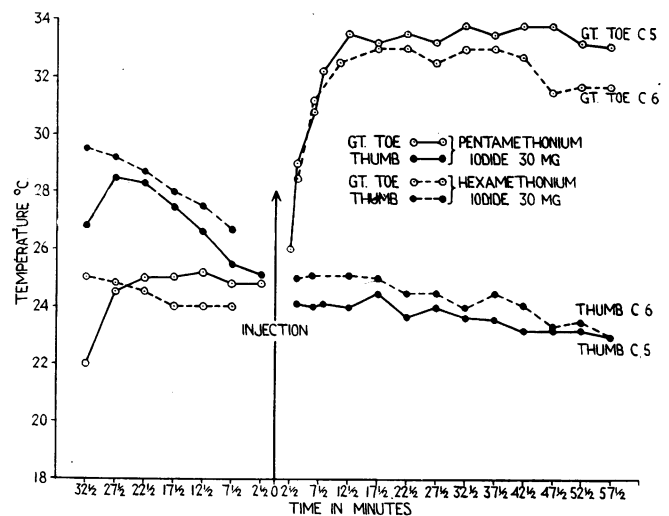


FIG. 5.—Changes in skin temperature of thumb and great toe following the administration of C5 and C6 to the same patient on different days.

tests with C5 and in 10 with C6, hand blood flow or digital temperature fell while it rose in the foot. In both hand and foot, rises in blood flow began one to two minutes after injection of C5 or C6; but whereas in the hand the rise lasted only for from 2 to 12 minutes, in the foot it persisted for 35 to 60 minutes. Digital temperature rises were slower in onset, occurring between two and nine minutes; in the upper limb they lasted for 16 to 65 minutes, but in the lower were prolonged to 35 to 120 minutes. In control and vasospastic subjects, following C5 and C6

the slight increases in digital temperature which occurred in the upper limb were similar, the average maximum temperatures being 28.8° C. (C5) and 27.8° C. (C6) in the controls, and 29.2° C. (C5) and 28.0° C. (C6) in vasospastic patients (Table VII). In the controls the degree and duration of rise in toe temperature following C5 and C6 were also similar (Fig. 5). In the vasospastic group, however, C6 had a greater and more prolonged vasodilator effect than C5 (Table VII). In six patients who had received C6, toe temperature was 30° C. for over one hour after administration of the drug, whereas after C5 this high level was maintained for the same period in only two patients.

Warmth in the feet was reported by the majority of subjects for three to four hours after administration of both drugs, and in one patient with Raynaud's phenomenon, in spite of a cold bus journey, after 30 mg. of C6 the feet remained subjectively warm for six hours. The initial resting temperature did not appear to influence the degree of rise in skin temperature. In another patient with Raynaud's phenomenon the toe temperature rose from 20.7° to 32.5° C., whereas in one of the controls it rose from 24.7° to 33.7° C.

(b) *Reflex Vasodilatation and Cervico-dorsal Block.*—In reflex vasodilatation tests the average thumb and toe temperatures reached in the control group are shown in Fig. 6. It will be noted that, in contrast to the tests with

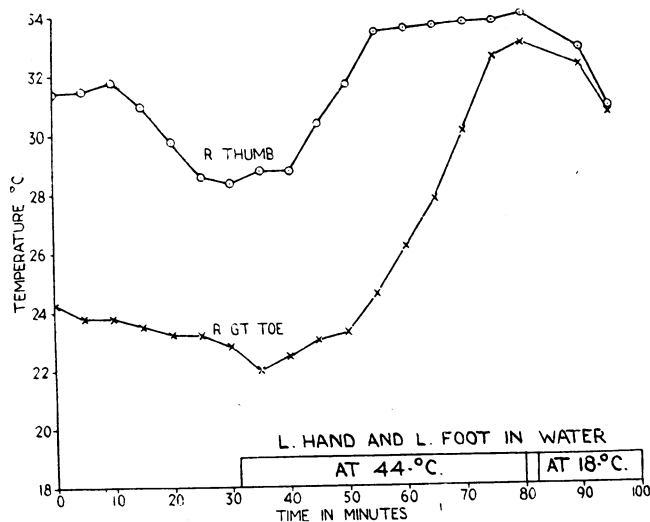


FIG. 6.—Average skin temperatures of thumb and great toe in five normal subjects during vasodilatation test. Room temperature, 18° C.

C5 and C6, the thumb temperature rose rapidly to the high level of 34.1° C., whereas the toe temperature rose more slowly to 33.1° C. (Fig. 6). In the vasospastic group, reflex vasodilatation resulted in an average increase of blood flow in the hand from 2.5 to 15.5 ml./100 ml./min. and in the foot from 6.4 to 25.6 ml./100 ml./min. In the same subject a cervico-dorsal block also produced a higher final hand blood flow than either C5 or C6.

Muscle Blood Flow

In eight cases forearm blood flow showed moderate rises which were prolonged up to one hour after injection (Tables IV and V). In 14 cases a rise of 0.5 to 3 ml./100 ml./min. occurred immediately after injection, but fell to pre-injection levels or lower within three minutes. This transitory rise was probably due to the excitement or pain of the injection, but it also occurred in subjects whose hand

blood flow and temperature showed simultaneous but more prolonged rises. In four cases forearm blood flow was unaltered or fell steadily throughout.

Leg blood flow (estimated in only two cases) showed an increase from resting levels of 7 and 1 ml./100 ml./min. to 16 and 5.6 ml./100 ml./min. respectively; in both the increase persisted for 60 to 70 minutes. Simultaneous foot blood flow recordings in the other limb showed marked and equally prolonged rises.

Effect of Posture on Blood Flow and Digital Temperature

In order to determine whether in the recumbent subject the difference in level of feet and hands was responsible for the greater response in the feet, three subjects were given 30–40 mg. of C6 while the hands were just below heart level and the feet 9 in. (22.8 cm.) above this.

Thumb temperature, which in the resting period in two subjects was between 31 and 32° C. and was 24° C. in the third, showed transitory rises of only 1–2° C. for 10 to 15 minutes and thereafter a steady fall for the remainder of the test. In contrast, toe temperatures rose 4, 9, and 11° C. respectively, and were still high at the end of 60 minutes. Similar trends were observed in blood flow; these points are at present under further investigation.

Sweating (Measured by Skin Resistance and Quinizarin Powder)

Diminution in sweating was more pronounced in feet than in hands (Tables IV and V), and was parallel to the rise in skin temperature in all cases. It was more marked in the vasospastic group than in the controls. In four subjects, three with C6 and one with C5, increases in sweating in hands lasting for one to two minutes after injection were noted, but thereafter the digits rapidly became dry. The number of patients in whom prolonged dryness occurred is shown in Tables IV and V.

In one patient with hyperhidrosis of hands and feet 40 mg. of C5 almost abolished this sweating within two to three minutes (Figs. 7 and 8); after the first injection the feet remained comfortably dry for 36 hours, the hands for seven to eight hours. He was then given a daily injection of 40 mg. for three days and thereafter two injections a week for a fortnight; but, although the immediate effect was always good, the duration of comfortable dryness fell to six hours for the feet and less for the hands, and thereupon treatment was discontinued. One dose of 60 mg. of C5 given to him by mouth had no effect on sweating or on blood pressure.



FIG. 7.—Quinizarin sweating test on a patient with hyperhidrosis before injection of C5.

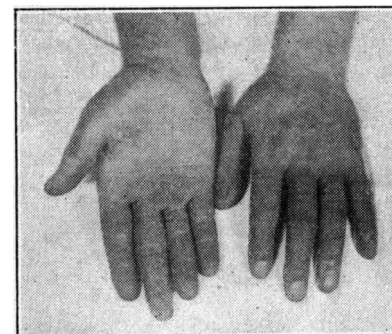


FIG. 8.—The same test as in Fig. 7, but after injection of C5.

Sweating of hands, occurring five days after cervico-dorsal sympathectomy, was abolished by an injection of C5.

Skin Colour; Capillary Changes

In all patients increased rubor was noted in the toes three to five minutes after injection of C5 or C6. The face also showed slight or moderate flushing. Injection of the conjunctival vessels was marked and persisted for up to two hours after administration of the drugs. When the subjects were under the maximum influence of the drugs the face colour and conjunctival vessels were greatly influenced by changes in posture. In the head-high position the face became pallid and conjunctival vessels emptied at once, whereas in the head-low position the face and conjunctival vessels became congested. The rubor of the feet was not diminished by elevation of the foot of the couch on 9-in. blocks.

Capillary pulsation was visible in the pads of the toes in those subjects in whom vasodilatation occurred.

Eyes

After administration of either C5 or C6 the pupils became slightly dilated in all cases, but the light reflexes remained brisk. After C5, two subjects had transient loss of accommodation. In cases of hypertension, after the administration of both drugs, the peripheral vessels of the retina beyond the second division appeared to be dilated and there was dilatation of the choroidal vessels.

Subjective Sensations

These were essentially similar with C5 and C6. A pleasant generalized feeling of warmth unaccompanied by any paraesthesiae was reported by all subjects in whom vasodilatation occurred. This was particularly noticeable in the feet, and to a much less extent in the hands. Several correctly predicted where the rise in temperature occurred. Isolated instances of tiredness, slight nausea, and dull headache were noticed for a few hours after the injection. After administration of both C5 and C6 four patients stated that the mouth and one that the nose felt dry. In one instance a marked sensation of faintness was experienced when the patient ascended in an elevator one hour after injection of C6. Apart from these, no symptoms or signs of a toxic nature were noted.

Effects of T.E.A.B.

Seven subjects (six normal and one vasospastic), of whom three were normal controls also tested with C5 and C6, were given T.E.A.B. In two cases an increase in toe temperature occurred 10 minutes after administration; one of these and one other patient showed a slight increase in temperature in the thumb. The rises in toe temperature averaged 1.8° C. and were of shorter duration than those obtained with either C5 or C6 (Table VII). In two cases increases in foot blood flow occurred within two minutes after the administration of the drug and persisted for 20 minutes, while increases in hand blood flow in the same subjects persisted for less than five minutes (Table VII).

A metallic taste, sensations of coldness and prickling in the hands and feet, and loss of visual accommodation were experienced by six out of the seven subjects. The remaining subject, who had previously had C6 and was subsequently given C5 without any side-effects, developed paralysis of a curariform type affecting the intercostal muscles, levator palpebrae, and neck and upper-limb muscles. The respiratory rate rose from 18 to 30 a minute, and respiration became abdominal in type. Drowsiness, inability to talk, and a rise in blood pressure from 126/86 to 136/94 persisted for 1½ hours. During this time

the blood flow to the hand increased from 1.6 ml. to 8 ml./100 ml./min. and a slight transient increase occurred in foot blood flow.

Discussion

Blood Pressure.—It was established that there was little difference between the effects of C5 and C6 on the blood pressure in normal subjects and in vasospastic and hypertensive conditions, the greatest falls being found in hypertensive patients; responses to both drugs showed variability in both time of onset and duration of maximum effect. The delayed fall in one vasospastic case is of interest, and indicates that it is important to observe patients for at least an hour after injection. The falls of blood pressure in post-splanchnicectomy cases after administration of C5 could be explained by abolition of the vasoconstrictor tone in those regions not deprived of their sympathetic nerve supply.

The effects of change of posture were what were to be expected in view of the action of C5 and C6 in abolishing the vasomotor compensatory mechanism. With the patient horizontal, any hypotensive effect was rarely of serious consequence. However, hypotension on standing is the greatest drawback to the use of these substances in treatment. They might be of use in hypertensive crises, as the hypotensive effects of the drugs might be controlled by adjusting the angle of the bed.

Sweating.—Though C5 and C6 are rapidly effective in abolishing hyperhidrosis over periods of several hours, the postural hypotension and the necessity for frequent injection limit their use in treatment.

Skin Blood Flow and Temperature.—The effects of C5 and C6 in increasing skin blood flow and digital skin temperature were greater in the lower limbs. These rises occurred more rapidly and were only slightly less than those induced by reflex vasodilatation, while they were considerably greater and more prolonged than those after T.E.A.B. In the upper limb the effects of C5, C6, and T.E.A.B. were slight and at best resulted in transient vasodilatation. This variation in response did not appear to be connected with relative differences in position of upper and lower limbs, but might be due to the greater inherent vasoconstrictor tone in the lower limbs as previously suggested by Pickering and Hess (1933). If this is so, however, one would have expected a better response in the vasospastic than in the normal group, which is not apparent in the results. In the vasospastic group C6 caused a greater and more prolonged increase in toe temperature than was obtained with similar doses of C5; otherwise the effects of C5 and C6 were similar.

Subjective Sensations.—The pleasant feeling of warmth which followed administration of C5 and C6 was noticeable as compared with the unpleasant paraesthesiae and feeling of coldness which occurred immediately after T.E.A.B.

Summary

The effect of intravenous administration of C5 and C6 in doses of 30–40 mg. has been studied on blood pressure, peripheral circulation, and sweating in 5 normal, 15 vasospastic, and 7 hypertensive subjects, and compared with the effect of 250–500 mg. of T.E.A.B. given intravenously to 6 normal subjects and 1 vasospastic patient.

Responses to C5 and C6 occurred within one to five minutes of administration and lasted for periods of 30 to 120 minutes.

Systolic and diastolic blood pressure fell, but in the hypertensive group the fall produced by these two substances was not as great as that resulting from sedation with sodium amylal. Postural hypotension, present one hour after administration of the drugs, was more pronounced in the hypertensive group.

It was relieved in two to four minutes by lying down or walking about, but its presence limits the therapeutic value of these drugs.

It was established that a different response was obtained in upper and lower limbs with the drugs in the doses used in this study. In the lower limbs a rapid and prolonged increase in blood flow and skin temperature occurred after C5 and C6. This approximated closely to that obtained by reflex vasodilatation, and these drugs may therefore be of value in the investigation of peripheral vascular disease in the legs. However, in the upper limbs no significant increases in skin temperature or blood flow occurred in 18 out of 31 tests with C5, and in 16 out of 31 tests with C6; in the remainder the increase in blood flow or skin temperature was slight and in no way comparable to that obtained by reflex vasodilatation. These drugs are therefore unlikely to be useful in the investigation of vasospastic conditions in the upper limb. In the dosage used the vasodilator effect of both C5 and C6 on the lower limb was much greater and more constant than that of T.E.A.B., and the side-effects of C5 and C6 were more pleasant for the patient.

Blood flow to muscle, measured by estimation of forearm blood flow, was not greatly altered.

Sweating was diminished in those digits in which temperature rose.

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An account of medical education in Turkey is given in an official publication (*Medico-Social Activity and Organization in Turkey*: Istanbul, 1946) which has just been received in this country. In Istanbul there are residential colleges with accommodation for one thousand students of medicine and related subjects. Board and tuition are given free of charge, and on qualification the graduates are expected to work for the Government for a fixed (but unrevealed) period. Since the establishment of the medical college in 1929 over 1,300 doctors have graduated from it. Turkey previously suffered from a shortage of nurses, as the only organization under which they could receive their training, the Turkish Red Crescent Society, did not produce enough trained women to supply the whole country. The number of nurses' training schools has now been raised to eight, there is a school for midwives in Istanbul, and residential training schools have been set up for village midwives. The report shows that the Turkish Government intends to build health centres in their largest cities. These centres are expected to improve environmental conditions, combat venereal and infectious diseases, and to work for improved infant and maternity hygiene. Apart from their public health activities, the centres will provide facilities for treatment. Each family in the district will have a file of its own, which will be open to Government inspection. The Turkish Ministry of Health has decided that the success of these centres will depend on the quality of their personnel, and has therefore planned that a hundred graduates a year from the School of Hygiene, Ankara, shall be trained for public health work and the best among them sent for further education in the United States. Special training schools will be set up to provide suitable nursing staff. Finally, each health centre is to be equipped with a number of "jeeps" to bring patients in from the outlying countryside.

EFFECT OF HEXAMETHONIUM IODIDE ON GASTRIC SECRETION AND MOTILITY

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Two principles underlie most of the established methods of treating peptic ulcer—namely, to reduce the acidity of the gastric juice and to relieve spasm. Of the drugs available for these purposes atropine is the most potent, but often it cannot be used owing to its side-effects. Recently tetraethylammonium bromide has been investigated, but its use also is not practicable because of the drug's short-lived action and the unpleasant effects to which it gives rise. In the present paper we report observations on the action of a new compound, hexamethonium iodide (C6), which seems to be more effective and relatively innocuous.

Hexamethonium iodide is a member of the homologous series of polymethylene-bis(trimethyl-ammonium) compounds. Three members of this series have recently been investigated clinically. They all seem to act by impeding the transmission of nerve impulses, but there are striking differences in their point of action and consequently in their effects. Thus the deca-compound (C10) blocks the neuromuscular junction of striated muscle and consequently has a curare-like effect, while the penta-compound (C5) exerts its main action at the preganglionic sympathetic synapses and is effective as a vasodilator.

The hexa-compound (C6), as we shall show, has a profound effect on the gastric secretion and motility, while, at any rate in therapeutic doses, it appears to have no curare-like action and no marked effect on the blood pressure.

Effect of C6 on Gastric Secretion

Ten patients were selected for study, their ages ranging from 22 to 52 years. They were all males with clinical and radiological evidence of duodenal ulcer, and were experiencing severe dyspepsia. While in hospital they were all ambulant save when undergoing investigation. Hexamethonium iodide was the only drug prescribed during their stay in hospital, and they were given the general ward diet.

Secretion tests were begun at 9 a.m. following a 12-hour fast. The fasting juice was aspirated and specimens were removed every fifteen minutes thereafter until the end of the experiment. Special precautions were taken to empty the stomach at each aspiration: alteration in the position of the tube, alteration in the position of the subject (forward and lateral flexion of the trunk), and the application of manual pressure to the abdomen were found to be useful adjuncts towards this end. Using this technique we have been able at all times to secure a specimen of gastric juice when required, even during the studies on spontaneous secretion. All saliva was expectorated during the tests. The volume and bile-staining of each specimen has been noted and the titratable hydrochloric acid estimated in clinical units.

1. *Spontaneous Secretion of Hydrochloric Acid.*—In each subject control observations were made, specimens of gastric juice being aspirated every 15 minutes for a period of three hours. On the following day the same procedure was adopted, but in addition 100 mg. of C6 was given by intramuscular injection immediately after the withdrawal of the fasting juice.