Brit. J. Pharmacol. (1951), **6**, 155.

PARALYSIS OF AUTONOMIC GANGLIA BY METHONIUM SALTS

BY

W. D. M. PATON AND E. J. ZAIMIS

From the National Institute for Medical Research, Mill Hill, London, N.W.7

(Received December 18, 1950)

The production of ganglionic block by the lower members of the polymethylene bistrimethylammonium series was briefly described in earlier papers (Paton and Zaimis, 1948, 1949a, b). The experiments, which are now reported in full, were designed to analyse the mechanism by which these compounds paralyse autonomic function and to determine how far such ganglionic blockade accounts for the pharmacological properties of the drugs. We have found that the compounds interfere with transmission only at the synapse itself, that they cause block without any previous excitation, and that they do not interfere with the release of acetylcholine in the ganglion. Further, they are free from other pharmacological actions, in particular from curare-like, muscarine-like, or histamine-liberating activity. They constitute, indeed, the most specific ganglionic inhibitors so far described.

Certain members (the butane, pentane, and hexane derivatives) have been submitted to clinical trial, and have received the approved names of tetramethonium, pentamethonium, and hexamethonium respectively. These names will be used in this paper; the other members of the series will be referred to by the number of carbon atoms in the polymethylene chain.

METHODS

Cats anaesthetized with chloralose (80 mg./kg.) were used for most experiments. In experiments on the superior cervical ganglion, the contractions of the nictitating membrane were recorded on a smoked drum. These contractions were evoked by the application of maximal " square-wave " electrical stimuli, of 0.5 msec. duration, to the cut peripheral stump of the cervical sympathetic, divided and separated from the vagus in the neck, or to the postganglionic trunk after dissection of the ganglion. Perfusion of the ganglion was by the technique of Kibjakow (1933) and Feldberg and Gaddum (1934), the perfusion fluid being warmed to the cat's body temperature by its passage through a tube passed into the stomach of the cat and emerging from a small cut in the oesophagus, close to the ganglion (MacIntosh, 1949). The perfusion fluid was Locke's solution containing 5×10^{-6} eserine. The acetylcholine in the perfusate was assayed on the blood-pressure of an eviscerate, eserinized cat.

Cat's blood-pressure was recorded in the usual way by means of a siliconed cannula containing a little 1 per cent heparin, inserted into the carotid artery. For studying the effects of vagal stimulation, the left or right vagus nerve was divided in the neck, and the peripheral end was separated from the sympathetic and excited electrically. To record intestinal activity in the cat, a length of small intestine, about 6 cm. long, was selected and glass cannulae inserted at each end, tying them in by ligatures round the submucosa only; after the intestine

had been washed out, it was filled with saline, one cannula was occluded, and the other cannula was connected to a sensitive bellows recorder. Experiments on the peristaltic reflex of the rabbit's ileum were made by the method of Trendelenburg (1917).

Intravenous injections were made through a glass cannula tied into the jugular or femoral vein.

Vasodilatation in the rabbit's ear was recorded by means of Hatfield's (1950) heat-flow meter; this consists of a tellurium disk 1 cm. diameter, with copper gauze welded to either side. When placed on a surface losing or absorbing heat, a potential difference, easily recorded by a galvanometer, is set up between the two thermo-junctions so formed, such that for a heat loss of 100 kg. cal./sq. m./hour an electromotive force of approximately 70 microvolts is obtained. The disk is stuck to the surface of the ear by a layer of cellulose tape.

Methonium salts, tetraethylammonium, and tetramethylammonium were all given as iodides, and nicotine as tartrate. Doses are all given in terms of the salts.

RESULTS

Action on cat's superior cervical ganglion

If the cut peripheral end of the cervical sympathetic in the cat is stimulated electrically at a frequency of 10/sec., a well-sustained contraction of the nictitating membrane can be recorded. This is depressed or abolished by the injection intravenously of substances which block transmission in the superior cervical ganglion. Such a relaxation can be produced by the members of the methonium series from C3 to C10, but with various degrees of activity; pentamethonium and hexamethonium are particularly effective, and doses of 0.02 mg./kg. injected intravenously sometimes produce a detectable effect. Fig. 1 illustrates this action for hexamethonium in a dose of 0.23 mg./kg.

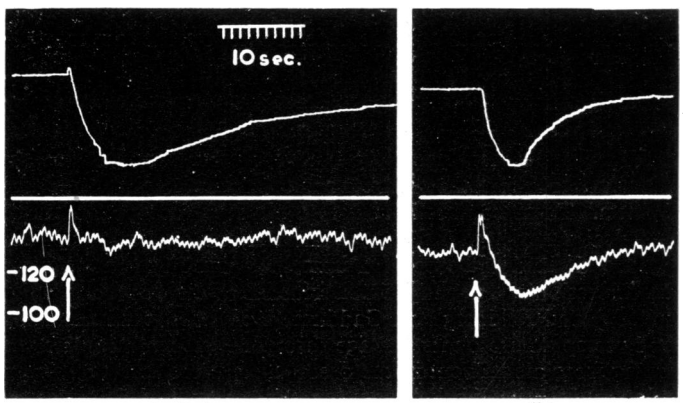

FIG. 1.—Cat, chloralose. Contraction of nictitating membrane to preganglionic excitation at 10 shocks/sec. (above) and blood-pressure (below). (*a*) At arrow, 0.23 mg. hexamethonium iodide per kg. intravenously; (*b*) at arrow, 1.5 mg. tetra ethyl ammonium iodide per kg. intravenously.

The sensitivity of the ganglion depends on the nature and duration of the preganglionic excitation. For instance, if stimulation at a rate of 10/sec. is maintained for 15–20 min., the proportionate reduction of the height of contraction of the nictitating membrane by a given dose of pentamethonium or hexamethonium may be 20–30 per cent greater at the end than at the beginning of excitation. Similarly, a ganglion which receives continous stimulation is more sensitive to these drugs than

one which receives brief periods of stimulation at intervals. The experiments of Fig. 1 and 2 exemplify this. In Fig. 1, the continuously excited ganglion was 75 per cent blocked (as measured by the response of the membrane) by 0.23 mg. hexamethonium per kg.; whereas in Fig. 2, with intermittent excitation, twice this dose of hexamethonium only reduced the tension developed after 10 sec. of stimulation by about 15 per cent. Fig. 2 also shows how the ganglion becomes more sensitive

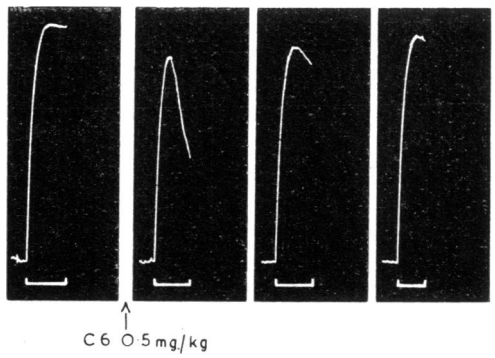

FIG. 2.—Cat, chloralose. Nictitating membrane. Preganglionic excitation at 10/sec. for 30 sec. every 2 min. At arrow, 0.5 mg. hexamethonium iodide per kg. intravenously.

to the drug even during the first 30 sec. of stimulation. Before hexamethonium, the contraction of the membrane was well sustained during the whole of the stimulation period. After the injection of hexamethonium, the contraction height is at first (as we have just seen) little short of the normal; but it soon begins to fall away, and at the end of 30 sec. is reduced to 40 per cent of the normal height. Lastly, we gained the impression that the ganglion became more sensitive if the rate of stimulation was high than with slower frequencies; thus a small dose of pentamethonium (0.02 mg./kg.) was ineffective when the ganglion was excited at 10 shocks/sec. to its preganglionic nerve, but caused a 30 per cent paralysis when excitation at 30/sec. was used.

The duration of action of pentamethonium or hexamethonium on the superior cervical ganglion varied from 3–4 minutes to 20–30 minutes or more according to the dose, and is considerably longer than that of tetraethylammonium; Fig. 1 shows a comparison of the two drugs. Even when the manifest effect of an injection had passed off, the presence of the drug could still be detected 5–15 minutes later by its augmentation of the effects of a similar injection. When precautions were taken to allow for this, it appeared that doubling a given dose of pentamethonium or hexamethonium increased the relaxation of the nictitating membrane by about 20 per cent of the initial contraction height; and that a 20- to 30-fold increase in dose covered the range from a detectable action to a maximal action.

There was never any enhancement by pentamethonium or hexamethonium of the contraction of the nictitating membrane during such an experiment; and, if either drug was injected before excitation of the preganglionic trunk had started, no contraction of the membrane was seen, even with doses as large as 10 mg./kg. This is to be contrasted with the action of such drugs as nicotine or tetramethylammonium, which both augment the contraction of the preganglionically excited nictitating membrane and elicit a contraction when it is not being stimulated.

Site of action

The action of the drug can be shown to be neither on the nictitating membrane nor on the postganglionic trunk. Adrenaline excites as strong a contraction of the membrane after an injection of hexamethonium as before it. In the experiment of Fig. 3, 100 μg. adrenaline were injected intravenously; then the cervical sympathetic was stimulated, and during this excitation, when the contraction of the membrane had reached its peak, 1 mg. hexamethonium iodide was injected, causing complete abolition of the contraction; 100 μg. adrenaline, however, still produced a normal contraction of the membrane.

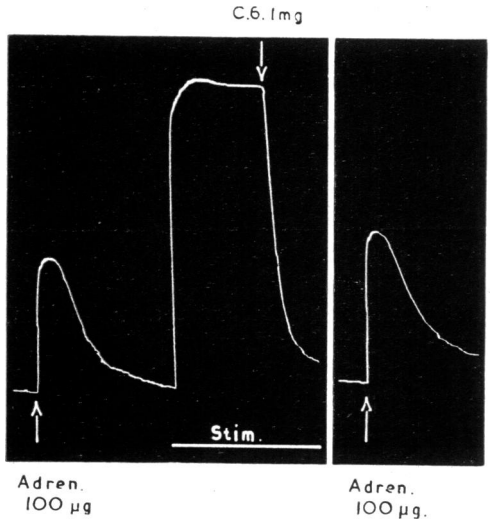

FIG. 3.—Cat, chloralose. 2.9 kg. Nictitating membrane. Contractions elicited by (*a*) 100 μg. adrenaline intravenously; (*b*) preganglionic excitation at 10/sec.; (*c*) 100 μg. adrenaline intravenously. During (*b*), at arrow, 1 mg. hexamethonium iodide intravenously.

A similar experiment was done using stimulation of the postganglionic nerve trunk (Fig. 4). First, postganglionic stimulation was applied. Then the preganglionic trunk was stimulated, and during this excitation 0.75 mg. hexamethonium per kg. was injected; this caused complete relaxation of the nictitating membrane, as shown by

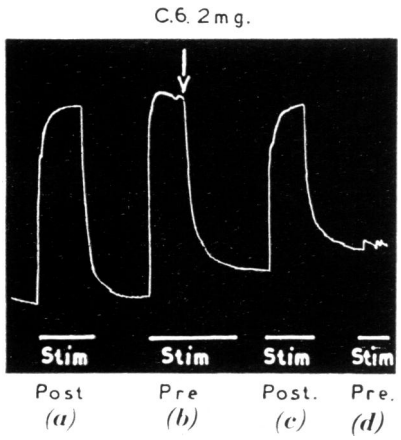

FIG. 4.—Cat, chloralose. 2.7 kg. Nictitating membrane. Contractions elicited by excitation of (*a*) and (*c*) postganglionic trunk, (*b*) and (*d*) preganglionic trunk, at 10/sec. Periods of stimulation shown by continuous line. At arrow in (*b*), 2 mg. hexamethonium iodide intravenously.

the absence of further relaxation when the stimulus ceased. Immediately after this, however, postganglionic stimulation was still able to produce a contraction which reached the same height as before, although a subsequent preganglionic stimulation was ineffectual.

Effect on release of acetylcholine

The superior cervical ganglion was perfused with eserinized Locke's solution and the effluent assayed for acetylcholine on the cat's blood-pressure. Fig. 5 shows the record from this experiment. Before stimulation of the cervical sympathetic, the effluent contained no detectable acetylcholine (certainly less than 3 mμg./c.c.). It was then stimulated for three minutes at a rate of 10/sec., producing a vigorous contraction of the nictitating membrane, and causing the appearance of 11 mμg. acetylcholine, per c.c. in the effluent, with a total output of 49.5 mμg.; inset in the record of nictitating membrane is the depressor effect of 0.5 c.c. of this effluent (Fig. 5*a*). Then 10 mg. pentamethonium iodide was injected into the arterial cannula. Excitation of the nerve was now without effect on the nictitating membrane, but acetylcholine still appeared in the effluent (Fig. 5*b*) in a concentration of 13 mμg./c.c., the total output being 47 mμg., although the dose of pentamethonium was so large that there was sufficient in the effluent to cause a subsequent gradual fall of blood-pressure in the assay cat. Two tests were used to verify that the depressor material was acetylcholine. A sample was made alkaline, stood at room temperature for 20 minutes, neutralized, and reassayed. No depressor activity remained. Another sample was tested after the injection of 0.3 mg. atropine sulphate per kg. into the assay cat. This abolished the depressor effect, without lessening the effect of a small dose of histamine. A dose of pentamethonium, therefore, more than 1,000 times that required to cause some degree of ganglionic block, leaves acetylcholine release in the ganglion entirely unimpaired.

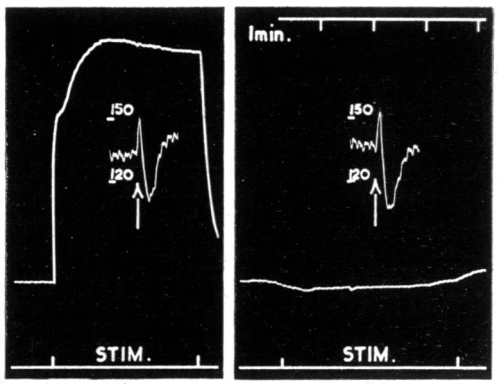

FIG. 5.—Cat, chloralose. Perfused superior cervical ganglion. Contractions of nictitating membrane to preganglionic excitation at 10/sec., and (inset) blood-pressure responses to 0.5 c.c. effluent from ganglion; (*a*) before, (*b*) after the injection of 10 mg. pentamethonium iodide into arterial perfusion cannula.

The same conclusion was reached by doing this experiment slightly differently (Fig. 6). The cervical sympathetic was stimulated continuously and the successive four-minutely volumes of effluent assayed for acetylcholine. During the stimulation, pentamethonium (10 mg.) was injected. A complete paralysis lasting about seven minutes resulted and was followed by a gradual recovery of the contraction of the nictitating membrane. The output of acetylcholine, however, reflected nothing of the paralysis, but fell steadily throughout the experiment, so that it was much less when

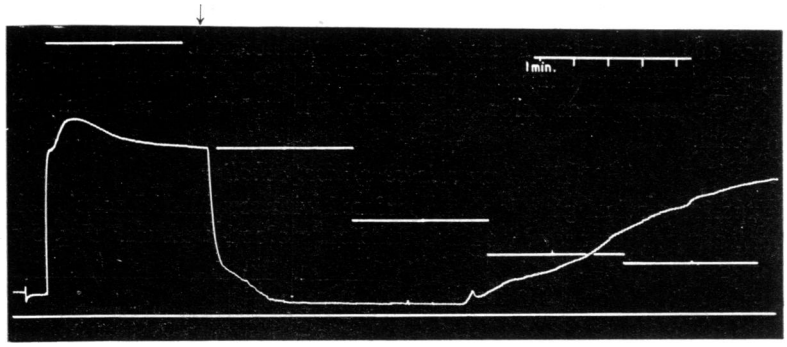

FIG. 6.—Cat, chloralose. Perfused superior cervical ganglion. Contraction of nictitating membrane, and histogram of acetylcholine output from ganglion during continuous excitation at 10/sec. At arrow, 10 mg. hexamethonium iodide into arterial perfusion cannula.

the contraction of the membrane was returning than it had been during the period of complete block. This experiment, therefore, besides showing that the drug does not prevent the release of acetylcholine, also shows that it does not interfere with the processes of acetylcholine synthesis and release which are called into play during sustained preganglionic excitation of the superior cervical ganglion.

Pentamethonium and hexamethonium, therefore, act neither on the organ receiving the postganglionic innervation nor on the nerve trunks or preganglionic nerve terminals, but must interfere, as curare does (Brown and Feldberg, 1936), with the transmission process at the ganglionic synapse itself by raising the threshold for excitation of the ganglion to the acetylcholine released. It is not easy to demonstrate this so clearly for ganglia other than the superior cervical ganglion; but, as will be clear from the experiments still to be described, these compounds have few actions which cannot be explained by this type of ganglionic block, and have many actions which cannot be explained in any other way.

Action on cat's blood-pressure

In a cat anaesthetized with chloralose, pentamethonium or hexamethonium regularly cause a fall of blood-pressure, such as that shown in Fig. 7, when injected.

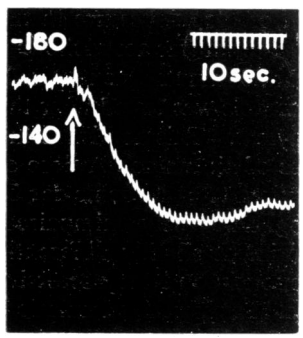

FIG. 7. — Cat, chloralose; blood-pressure. At arrow, 0.3 mg. pentamethonium iodide per kg. intravenously.

in a dose of 0.2–2 mg./kg. The fall usually starts 5–10 sec. after an intravenous injection, and proceeds (often rather gradually) to reach a maximum in 1–3 min. Just as with the superior cervical ganglia, a comparison with tetraethylammonium shows the effects of the methonium salts to be slower in onset and several times longer in duration; a depressor response due to tetraethylammonium is shown for comparison in Fig. 1.

The magnitude of this fall depends partly (but not only) on the height of the blood-pressure when the injection is made. Thus, in Fig. 7, when the blood-pressure was 160 mm. at the start, a fall of 60 mm. was obtained; but when the initial blood-pressure was at a lower level, for instance 105 mm. in Fig. 8, the fall due to hexamethonium was only 10 mm.

With still lower pressures, pentamethonium and hexamethonium have even less action, and in the pithed spinal animal they have no depressor action at all. In general, the action of these drugs is to lower the blood-pressure of the chloralosed cat to a certain point, usually about 60–80 mm., but no further, however big the dose (cf., Fig. 8*d*); the effect of increasing the dose beyond that required to produce this maximal effect is simply to prolong the hypotension. With no dose was any pressor effect seen, whether the initial blood-pressure was high or low. Atropine, neoantergan, and vagotomy had no effect on the response.

The depressor action was particularly distinct in animals in which the respiration was depressed. Thus, in one experiment, a dose of decamethonium just sufficient to begin to paralyse the respiratory muscles was given; this led to a typical, slow asphyxial rise in blood-pressure of about 30 mm. mercury during the next two minutes. Hexamethonium (10 mg./kg.), given at this point, caused a big fall of blood-pressure, from 194 mm. to 80 mm., followed by a gradual recovery in the next ten minutes. Similarly, after a dose of thiopentone, which depressed the breathing and caused a similar gradual rise in pressure to 165 mm., pentamethonium (10 mg./kg.) caused an abrupt fall in pressure to 40 mm., with recovery during the next 10–15 minutes. Later in the same experiment, the same dose of thiopentone was given, but with simultaneous artificial respiration; pentamethonium was then relatively slow in its action, and lowered the blood-pressure only to 80 mm.

This intimate relationship between the action of pentamethonium or hexamethonium and the height of the blood-pressure at the moment when one of these drugs is injected, together with their complete ineffectiveness when the blood-pressure is below a certain level, point directly to the proba-

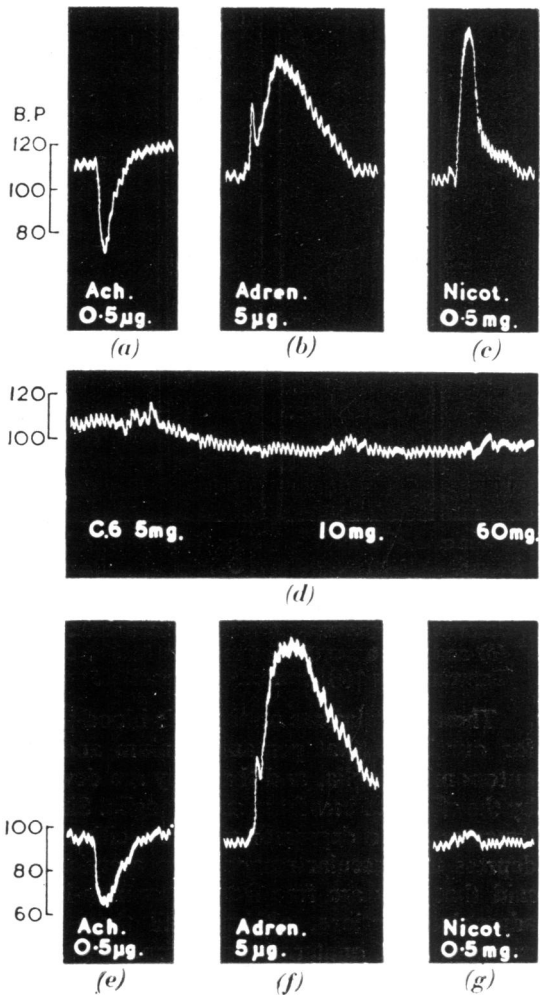

FIG. 8.—Cat, chloralose; blood-pressure. Intravenous injections: (*a*) and (*e*) acetylcholine, 0.5 µg.; (*b*) and (*f*) adrenaline, 5 µg.; (*c*) and (*g*) nicotine, 0.5 mg.; (*d*) hexamethonium iodide, 5 mg., 10 mg., 60 mg. in succession.

bility that they produce their depressor effect by releasing sympathetic vascular tone. This was confirmed by finding that they prevent the action of substances such as nicotine or tetramethylammonium which, by exciting the autonomic ganglia, increase the intensity of the vasoconstrictor discharge from ganglia controlling the blood-pressure. Fig. 8 shows the effect of 75 mg. hexamethonium in abolishing the effects of nicotine. Fig. 9 shows a smaller dose abolishing the action of a similar dose of nicotine, and greatly attenuating the vigorous pressor response to a big dose of tetramethylammonium iodide. On the other hand, in Fig. 8 it can also be seen, for instance, that a large dose of hexamethonium had but little effect on the action of 0.5 μg. acetylcholine. Such effect as is visible can be attributed simply to the lowering of the general blood-pressure; and the level to which the acetylcholine reduced the blood-pressure was even lower after hexamethonium than before. The duration of the acetylcholine action was actually somewhat prolonged. Similarly, the effect of 5 μg. adrenaline was not reduced. On the contrary, the pressor action of this dose was nearly twice as great as before the injection of hexamethonium, and its action was correspondingly longer lasting.

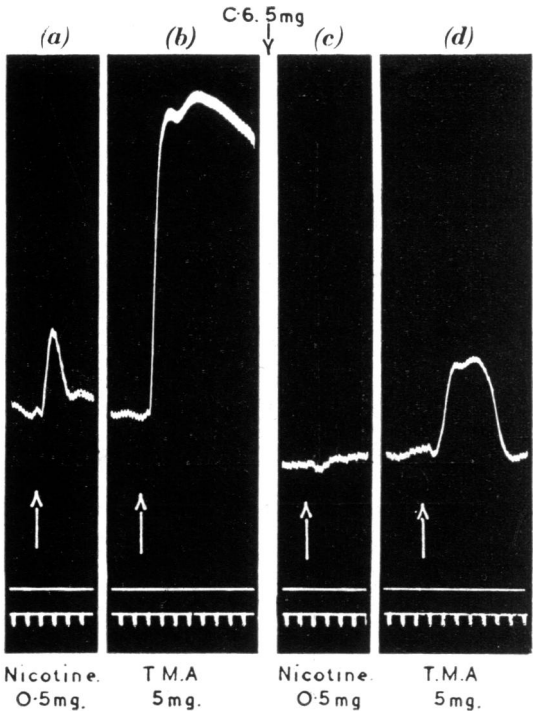

FIG. 9.—Cat, chloralose, 2.5 kg.; blood-pressure. Intravenous injections: (*a*) and (*c*) nicotine, 0.5 mg.; (*b*) and (*d*) tetramethylammonium iodide, 5 mg. Between (*b*) and (*c*) hexamethonium iodide, 5 mg.

These experiments on the cat's blood-pressure provide, therefore, further evidence for our belief that pentamethonium and hexamethonium act solely by paralysing autonomic ganglia, and that they are devoid of action on the effector cells supplied by the efferent fibres from such ganglia. Since, in the absence of autonomic tone, these drugs cause no depressor response, either prompt or delayed, and since they do not depress the vascular responses to acetylcholine and adrenaline, it can now also be said that they are free from muscarine-like, histamine-liberating, atropine-like, or adrenolytic actions, although all these properties are known to exist in other compounds of quaternary nitrogen.

Observations incidental to our main experiments have exemplified how ganglionic block by pentamethonium or hexamethonium may depress reflex cardiovascular responses. For instance, when an animal is asphyxiated, reflex mechanisms normally bring about a considerable rise in blood-pressure (60–100 mm.), with pronounced cardioacceleration; but after an injection of pentamethonium or hexamethonium

this response is reduced and may even be absent. On the other hand, these reflex mechanisms also serve to limit such changes in blood-pressure in the normal animal as those caused by the injection of acetylcholine or adrenaline; hence the injection of hexamethonium actually increases and prolongs the action of adrenaline and acetylcholine.

Action on effects of vagal stimulation

Pentamethonium and hexamethonium will also inhibit the effects of stimulation of the peripheral stump of the vagus, cut in the neck, on the heart rate and blood-pressure. In the experiment of Fig. 10, the right vagus was faradized for 10 sec.,

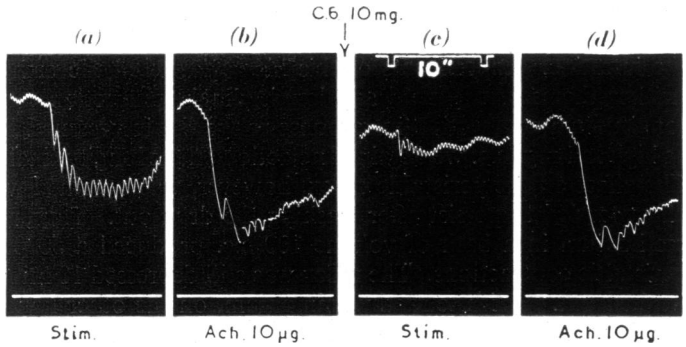

FIG. 10.—Cat, chloralose; blood-pressure. Intravenous injections: (*a*) and (*c*) right vagus stimulated at 10/sec. for 10 sec.; (*b*) and (*d*) injection of 10 µg. acetylcholine. Between (*b*) and (*c*) 10 mg. hexamethonium iodide.

causing a fall in blood-pressure and considerable slowing of the heart; 10 µg. acetylcholine caused a similar response. Then 10 mg. pentamethonium was injected intravenously. Two minutes later, faradization of the vagus was ineffective, although acetylcholine had the same action as previously. Exactly the same results were obtained when hexamethonium or tetramethonium was used. These experiments again provide evidence that the action of these drugs is restricted to ganglia, and does not extend to the effector organ.

Effect on the heat output of the rabbit's ear

The heat-flow meter, recently devised by Hatfield (1950), offered a simple means of recording an increase in blood flow through a rabbit's ear as an increase in the rate of loss of heat from the ear to the environment. Fig. 11 shows the result of injection of 10 mg. pentamethonium iodide per kg. into one ear vein of an animal to whose other ear the recording disk was fastened. After a brief latency, the heat output of the ear rose abruptly,

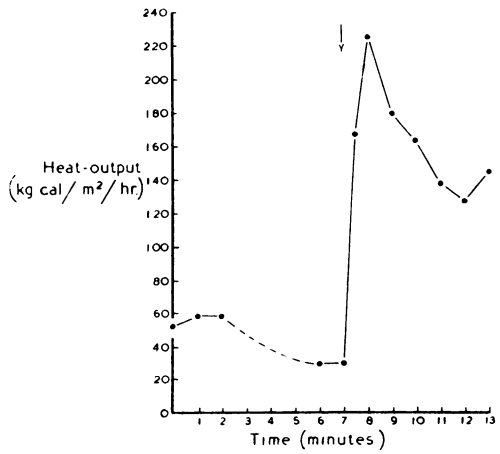

FIG. 11.—Rabbit. Heat output from the ear, recorded by Hatfield heat-flow meter. At arrow, 10 mg. pentamethonium iodide per kg. intravenously.

and then more slowly fell again, synchronously with the visible flushing of the ear. If the ear was already flushed, because, for instance, of the warmth of the surroundings, this rise in heat output was much smaller, and it became more prominent as the ear was colder and more vasoconstricted. Just as with the cat's blood-pressure, the action of pentamethonium in increasing the blood-flow in the rabbit's ear requires the presence initially of some degree of sympathetic tone.

Effects on small intestine

Rabbit ileum.—As we have previously described, pentamethonium and hexamethonium are very active in paralysing the peristaltic reflex of the rabbit's or guinea-pig's isolated ileum, which can be elicited by raising the pressure within the lumen of the intestine. Experiments of this kind showed at the same time how these drugs neither themselves caused any longitudinal contraction nor altered the myogenic, longitudinal contraction in response to the rise in pressure. Even with concentrations as high as 1 mg./c.c. we obtained no action on the longitudinal contraction of the ileum. The effect on the peristaltic reflex, however, was obtained with small doses; and the effect tended to persist after washing the drug out. Thus, a dose of 0.1 mg. pentamethonium in a bath of volume 100 c.c. produced a 50 per cent reduction of the peristaltic contractions. The reflex was still depressed 10 min. after the drug had been washed out. With tetraethylammonium, on the other hand, a dose of 0.7 mg. was required to produce the same effect, and the reflex was rapidly restored to normal after a single washout.

Cat ileum.—An attempt was made to demonstrate the same phenomenon in the ileum of the chloralosed cat, leaving the intestine *in situ*, so that the effect of a drug on the nictitating membrane and on the peristaltic reflex could be compared simultaneously. But effects of a different kind are obtained in this preparation (Fig. 12).

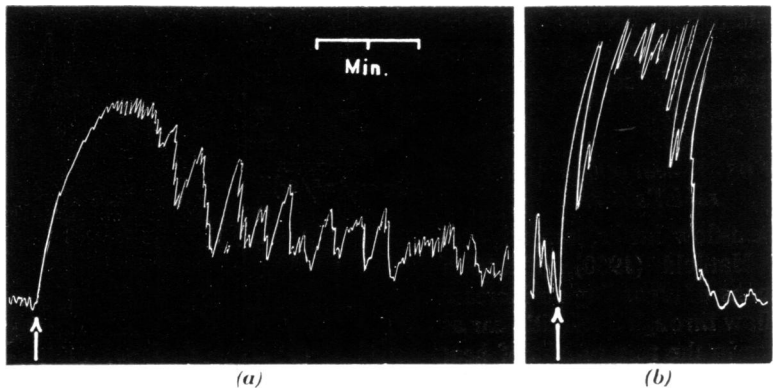

FIG. 12.—Cat, chloralose. Record of movements of small intestine. Intravenous injections. (*a*) At arrow, 0.24 mg. hexamethonium iodide per kg. (*b*) At arrow, 1.5 tetraethylammonium iodide per kg.

After the injection of 0.24 mg. hexamethonium, the rhythmic activity of the intestine is increased greatly in amplitude. During this period the gut was the site of very vigorous, circular contractions, without the progressive quality of the peristaltic

wave. Precisely the same effects (also shown in Fig. 12) were obtained with tetraethylammonium (1.5 mg.). It was impossible to say, from these experiments, what, in fact, had happened to the peristaltic reflex. Bayliss and Starling (1900) showed that, not only was the sympathetic innervation of the cat intestine inhibitory in function, but that vagal excitation might also have an inhibitory action; and that local enteric reflexes easy to display in the rabbit were, in the cat, difficult to demonstrate. There is no reason, therefore, to suppose that the effects we have observed in the cat are due to anything other than the release of a strong sympathetic and possibly vagal tone inhibitory to a predominantly myogenic, rhythmic activity of the intestine.

Other actions

All the actions we have so far described can be attributed to these drugs blocking the action of acetylcholine released at the ganglionic synapse by a preganglionic nerve volley. This is, in fact, far the most important action which they display; in addition, a similar, but much feebler, antagonism to acetylcholine, and related drugs, can be shown at the neuromuscular junction and on the frog's rectus muscle. This antagonism has already been described in our earlier paper. Occasionally, and only with very large doses, a slowing of respiration of the chloralosed cat was observed. An example may be found in Fig. 8, in which the rhythmic fluctuation of the blood-pressure due to the respiration can be seen to become slightly less frequent for a minute or two after the last large dose of hexamethonium. This slowing of respiration may be associated with some transient reduction of the respiratory minute volume. We have not analysed this effect, nor have we excluded interference with pulmonary reflexes as the cause of it.

Our previous paper reported our results on the toxicity of these compounds, and it should be referred to for details. In mice and rats pentamethonium and hexamethonium had an LD50 of 50–90 mg./kg. when the drugs were injected intravenously. Rabbits tolerated doses of more than 40 mg./kg. intravenously. Further, rabbits receiving 10 mg. hexamethonium per kg. intravenously every day for a month did not lose weight or suffer in health, and autopsy showed no abnormalities attributable to the drug.

Discussion

All the properties of these members of the methonium series can be ascribed to their power of raising the threshold of the ganglion cell, and in far less degree of the motor endplate, to acetylcholine or to drugs acting like acetylcholine. They can block the superior cervical ganglia, the ganglia maintaining sympathetic vascular tone, those mediating the effects of the vagus on the heart, and the peristaltic reflex of the intestine. Recent work (Paton and Perry, 1950) has shown that they do not depolarize the ganglion cell, as do nicotine and tetramethylammonium, but are pure blocking agents of the same kind as *d*-tubocurarine or tetraethylammonium. On the other hand, they have no direct action on smooth muscle, such as that of the intestine, nictitating membrane or blood-vessels, nor on the heart; they do not interfere with the vascular actions of adrenaline or acetylcholine; they do not affect striated muscle directly; they do not excite autonomic ganglia; they do not interfere with the release

of acetylcholine, nor with the processes of synthesis involved in prolonged stimulation of the superior ganglia.

The high potency of these compounds, and their remarkable specificity, suggests that they may provide a useful physiological tool. The absence of neuromuscular activity and of histamine liberation in particular, makes their use more convenient than that of *d*-tubocurarine, which is in other respects an efficient ganglion-blocking agent. They lack, too, the side-actions of tetraethylammonium ion, such as the intense parasthesiae which result from an intravenous injection, and its occasional pressor effect, said to be due to the release of an adrenaline-like substance (Page, 1949). Their specificity has, indeed, already been of use in the analysis of the action of compound 2688F (Ambache, 1949) and of the action of drugs stimulating the small intestine (Feldberg, 1950).

Relative potency in different tests

In our previous paper, quantitative data were given for the activity of these compounds on two test objects, the superior cervical ganglion and the peristaltic reflex of the rabbit ileum. These figures are shown again in Table I. Inspection of the potencies estimated by the two tests reveals the interesting fact that the ratio of the

TABLE I

RELATIVE POTENCY OF METHONIUM SALTS ON SUPERIOR CERVICAL GANGLION AND ON PERISTALTIC REFLEX

Relative potency (C6 = 100)	C3	C4	C5	C6	C7	T.E.A.
(*a*) On superior cervical ganglion	<1.0	2.0	80.0	100.0	10.0	5.0
(*b*) On peristaltic reflex of ileum	4.3	5.9	33.3	100.0	16.7	14.0
(*a*) ÷ (*b*)	<0.2	0.34	2.4	1.0	0.6	0.36

potencies in the two tests varies considerably from one compound to another. The extremes are pentamethonium and C3; for the ratio is 2.4 for pentamethonium, but is less than 0.2 for C3; i.e., pentamethonium is proportionally more effective on the sympathetic ganglion and C3 on the peristaltic reflex. Taking all the compounds tested, they can be arranged (in order of increasing action on the ileum relative to the superior cervical ganglion): pentamethonium—hexamethonium—tetraethylammonium—tetramethonium—C3.

The comparison just quoted is between ganglia of considerably different structure and function. But even between more closely related ganglia, such as the superior cervical ganglion and those maintaining vasomotor tone, significant differences appear; Fig. 1 shows how a dose of hexamethonium may have a considerable effect on the superior cervical ganglion and none on the blood-pressure, although a dose of tetraethylammonium with a less sustained effect on the cervical ganglion caused a substantial fall in blood-pressure. The extent of these variations in sensitivity remains to be discovered. It presents, already, an interesting parallel to the discrepancies in blocking actions at the ganglionic and neuromuscular synapses recently recorded by many workers. There may be latent in such differences the possibility of obtaining, with different ganglionic blocking agents, an action directed specifically at a particular set of ganglia within the autonomic system.

Relation of activity to chemical structure

It is still premature to attempt to relate the chemical structure of known ganglion-blocking drugs to their pharmacological activity. For instance, among salts containing methylated quaternary nitrogen are several highly effective compounds (e.g., pentamethonium, hexamethonium, *d*-tubocurarine); but ganglion-blocking activity occurs also among ethylated quaternary salts (e.g., tetraethylammonium, bistriethylammonium decane, 2512F). Again, although a five or six carbon atom methylene chain produces the highest potency in the bistrimethylammonium series, it causes almost the lowest activity in the bistriethylammonium series (Chou and de Elio, 1947). It seems likely that order will not be achieved among such flagrant inconsistencies until there has been further analysis of the details of the action of the various compounds concerned.

In a discussion (Paton and Zaimis, 1949a) of the fact that decamethonium is the most active member of the methonium series in producing neuromuscular block, it was argued that the evidence indicated that the drug acted by forming a link at each end of its molecule with receptor groups spaced the corresponding distance apart. On such a theory, the ten carbon atom chain is a measure of the inter-receptor distance. Similar arguments may be invoked here, for, as with decamethonium, there appears to be no other physical property of the molecule competent to change its activity by a factor of 40 when a single carbon atom is removed from the polymethylene chain. We suggest, then, that we are again measuring an inter-receptor distance, but it is quite different from that at the motor endplate. Despite the profound analogies between transmission processes at the myoneural and at the ganglionic synapses, there are evidently significant and fundamental differences between them.

SUMMARY

1. The shorter chain members of the polymethylene bistrimethylammonium series cause ganglionic block. The pentane and hexane derivatives, pentamethonium and hexamethonium, are particularly effective.

2. Pentamethonium and hexamethonium do not affect the response of the nictitating membrane to adrenaline or to stimulation of the postganglionic trunk of the superior cervical ganglion. Injected into the perfused ganglion, they do not affect the release of acetylcholine produced by stimulating the preganglionic trunk. They do not cause any initial excitation of the ganglion. They paralyse ganglionic transmission solely by raising the threshold of the ganglion cell to the acetylcholine released at preganglionic nerve endings.

3. Intravenous injections of pentamethonium or hexamethonium cause a fall of cat's blood-pressure which is greater the higher the initial level of pressure; they also cause vasodilatation of the rabbit's ear. They abolish or reduce the pressor action of nicotine and of tetramethylammonium, and reduce the pressor response to asphyxia. The action of acetylcholine on the blood-pressure is not reduced by large doses of hexamethonium, but is slightly prolonged; that of adrenaline is considerably enhanced and prolonged. The vascular actions of pentamethonium and hexamethonium are entirely attributable to removal by these drugs of autonomic vascular control.

4. Slowing of the heart and fall in blood-pressure produced by peripheral vagal stimulation are abolished by pentamethonium and by hexamethonium, without any reduction of the effects of an initially equiactive dose of acetylcholine.

5. Pentamethonium and hexamethonium abolish the peristaltic reflex of the isolated rabbit intestine. When they are injected intravenously into a cat anaesthetized with chloralose, they arouse vigorous localized activity of the circular muscle in the small intestine; tetraethylammonium shares this action.

6. The relative potency of the methonium salts in paralysing ganglionic transmission varies according to the nature and activity of the ganglion studied.

References

Ambache, N. (1949). *J. Physiol.*, **110**, 145.
Bayliss, W. M., and Starling, E. H. (1900–1). *J. Physiol.*, **26**, 125.
Brown, G. L., and Feldberg, W. (1936). *J. Physiol.*, **86**, 10*P*.
Chou, T. C., and de Elio, F. J. (1947). *Brit. J. Pharmacol.*, **2**, 268.
Feldberg, W. (1950). *Proc. XVIII Internat. Physiol. Cong.*, p. 197.
Feldberg, W., and Gaddum (1934). *J. Physiol.*, **81**, 305.
Hatfield, S. (1950). *J. Physiol.*, **111**, 10*P*.
Kibjakow, A. W. (1933). *Pflüg. Arch. ges. Physiol.*, **232**, 432.
MacIntosh, F. C. (1949). Unpublished.
Page, I. H. (1949). *Amer. J. Physiol.*, **158**, 403.
Paton, W. D. M., and Perry, W. L. M. (1950). *J. Physiol.*, Proc., July 14–15.
Paton, W. D. M., and Zaimis, E. J. (1948). *Nature, Lond.*, **162**, 810.
Paton, W. D. M., and Zaimis, E. J. (1949a). *Brit. J. Pharmacol.*, **4**, 381.
Paton, W. D. M., and Zaimis, E. J. (1949b). *J. Physiol.*, **108**, 55*P*.
Trendelenburg, P. (1917). *Arch. exp. Path. Pharmak.*, **81**, 55.