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THE PARALYSIS OF AUTONOMIC GANGLIA, WITH SPECIAL REFERENCE TO THE THERAPEUTIC EFFECTS OF GANGLION-BLOCKING DRUGS

BY

W. D. M. PATON, B.M., B.Ch.

(From the National Institute for Medical Research, Mill Hill, London)

All the activity of the sympathetic and parasympathetic nervous systems passes, on the efferent side, through peripheral relay-stations—the autonomic ganglia. Drugs which can interfere with transmission of excitation across the synapses in such ganglia must therefore influence autonomic activity profoundly and offer considerable opportunities for clinical exploitation. In the following review of present knowledge about such drugs four of them have been chosen, such that an account of them outlines the main characteristics of ganglionic block and of its potentialities.

For normal transmission in a ganglion at least two conditions must hold: acetylcholine must be normally released by the nerve terminals of the preganglionic nerve, and the acetylcholine so released must be able to excite the ganglion cell. Accordingly, paralysis of transmission may take place in several ways. First, there may be interference with the release of acetylcholine: procaine injections, or a deficiency of calcium in the fluid bathing the ganglion, can cause block in this way (Harvey, 1939; Harvey and MacIntosh, 1940). But, in general, this type of block is not at present of much practical importance. Secondly, the acetylcholine released may be prevented from acting on the ganglion cell by some drug which is itself otherwise inactive; this may be called "block by competition," indicating that such a drug acts by competing successfully with acetylcholine for receptor groups on or in the ganglion-cell membrane. Curare, tetraethylammonium, and hexamethonium are the most important drugs of this

kind (Brown and Feldberg, 1936; Paton and Perry, 1951). Finally, the ganglion cell may be the site of a long-lasting depolarization, so that it can no longer give a normal response to the released acetylcholine, even though this acetylcholine is normally released and has full access to the cell. Such a " block by depolarization " is produced by nicotine and by acetylcholine itself (Paton and Perry, 1951). With block of this kind a period of excitation precedes the paralysis.

There are many drugs capable of blocking ganglionic transmission in one or other of these ways; but some of them fail to be specific and have other actions either on effector organs themselves or at other synapses. Now, upon the degree of specificity of a drug depends in large measure its usefulness. With a really specific drug, precise and accurate pharmacological and clinical investigation is possible. With a drug lacking such specificity, ambiguous results and false interpretations only too easily occur, and not a few controversies owe their origin to the existence, in a given agent, of more activities than were at first suspected. Emphasis will therefore be laid on what is required of a ganglionic-blocking agent that it may be called specific.

Nicotine

The history of ganglionic block begins in earnest in the 1890's with nicotine. It was with nicotine that Langley, having shown that it paralysed the ganglionic synapse (Langley and Dickinson, 1889), proceeded to clarify many features of the constitution and function of the autonomic nervous system. As an example of the method one may instance his work with Anderson on the ciliary ganglion (Langley and Anderson, 1892). This group of cells had been variously held to be associated with the third nerve, the fifth nerve, and the ciliary branch of the cervical sympathetic " according to the predilection of the particular observer." Langley and Anderson showed that, when the ganglion had been painted with nicotine, stimulation of the third nerve central to the ganglion no longer caused any constriction of the pupil, although stimulation of the short ciliary nerves beyond the ganglion was still pupillo-constrictor. On the other hand, excitation of the ciliary branch of the sympathetic remained effective after nicotine. The ganglion was therefore identified as an autonomic ganglion functionally in the efferent path of the third nerve, but not in that of the sympathetic fibres.

To Langley's work with this technique in mapping out the autonomic ganglia we owe much, or even most, of our knowledge of the arrangement of the autonomic ganglia. The most charming if not the most serious-minded tribute to his work in Cambridge may be quoted here:

> There was a young man of East Anglia
> Whose nerves were a network of ganglia.
> As was clear to be seen,
> He abhorred nicotine,
> Which makes ganglia Langleyer and Langleyer.

Nicotine has proved to be a reliable and fairly specific agent for blocking autonomic ganglia in pharmacological research. But there is one important point about its action which removes it from clinical use. This is the fact that it blocks by depolarization, so that its paralysing action on the ganglia is preceded by a strong stimulation. In attempting, for instance, to paralyse the ganglia controlling the blood pressure, it is necessary to pass through phases in which powerful sympathetic and vagal excitation may in turn be seen, causing a large rise in blood pressure, interrupted by a slowing of the heart, and followed by a further rise due to the release of adrenaline from the suprarenals. In animal experiments one is usually able to wait for these effects to pass before giving a further dose, and can gradually obtain the desired state of complete ganglionic block. But, for clinical practice, the necessity of passing through excitation to obtain paralysis makes nicotine (or any other drug which blocks by depolarizing) unsuitable for use in man.

Curare

When we turn to curare we come to the first of the other main group of blocking agents—those which block by competition. Curare has been used in analysing ganglionic function since the time of Claude Bernard (1857). Its use in more recent years enabled Eccles (1944) to reveal and analyse the so-called "synaptic potential," which is the electrical accompaniment of the transmission process at the ganglion synapse, and corresponds to the "end-plate potential" at the motor end-plate. Other work has shown that D-tubocurarine (or preparations owing their activity largely to this alkaloid) blocks the ganglia of the small intestine (Gross and Cullen, 1945), those controlling the blood pressure (Heymans, 1947), the vagal ganglia in the heart, and

certain vascular reflexes (Burstein *et al.*, 1949). Some of these results were obtained in man, so that it seems probable that even the doses used in anaesthetic practice will have some ganglionic activity, though this should not be great.

One interesting paper describes the results of a comparison in animals of the sensitivity of different ganglia to D-tubocurarine (Guyton and Reeder, 1950); it was observed that the ciliary ganglion and the vagal ganglia were more sensitive than the ganglia supplying sympathetic fibres to the nictitating membrane, the heart, the splanchnic blood vessels, and the pupil. This is an interesting example of varying ganglionic sensitivity, which is mentioned below.

Although free from the stimulating action shown by nicotine, curare has, for purposes of ganglionic blockade, two other disadvantages. The first, of course, is that it causes neuromuscular paralysis—a feature which makes it useless clinically as a ganglionic blocking agent. Moreover, even for the pharmacologist its use presents difficulties, for it possesses a third action, that of histamine-liberation (cf., MacIntosh and Paton, 1949), which it exerts in doses not greatly different from those which block ganglia. This is a serious complication in any study of blood pressure or of blood flow, and must, of course, affect almost any analysis in which the whole animal is used.

Tetraethylammonium Ion

As long ago as 1914 Marshall described the hypotensive actions of this drug; and its mode of action, together with that of the chemically related compound tetramethylammonium, was elucidated in a classical paper by Burn and Dale in 1915. But nearly thirty years passed before Acheson and Moe (1946) and Acheson and Pereira (1946) re-examined its properties and drew attention to the possibilities of its clinical exploitation. It is chiefly to these workers and their colleagues Lyons and Hoobler that we owe the renewed interest in ganglion-blocking agents of recent years.

Tetraethylammonium is a fairly specific ganglionic inhibitor. It has not, indeed, been completely studied even now, and no one has proved, for instance, that it does not interfere with the release of acetylcholine. But there is no doubt that the bulk of its actions are those

of ganglionic blockade and that it lacks any stimulant action on ganglia. It has been shown to block the superior cervical ganglion, the ganglia supplying the nervi accelerantes of the heart, the vagal ganglia to the heart, those supporting vasomotor tone and mediating vascular reflexes, those of the pupil, the stomach, the bladder, the salivary glands, the small intestine, the sweat glands, and the splanchnic nerves to the adrenal. Studies of this kind have established that it is a valuable tool to the pharmacologist and, for diagnostic purposes, to the clinician.

The actions of tetraethylammonium, however, are relatively transient, and its potency is not very high. Further, it has other side-actions of an interesting (and puzzling) nature: (1) the paraesthesiae and metallic taste experienced by patients after intravenous injection : (2) the ability to cause repetitive firing in frog nerve and hence fibrillary twitchings in muscle (Cowan and Walter, 1937) ; (3) the ability to cause muscular paralysis in some patients (Burt and Graham, 1950) ; and (4) the ability to evoke the secretion of adrenaline (or a related substance) from the liver and adrenals so that it actually causes, under some conditions, a rise in blood pressure (Page, 1949).

Of these side-effects the fourth in particular seems to be a possible source of confusion. The other side-actions—paraesthesiae, fibrillations, and muscular paralysis—may be clinically undesirable, but these effects are at least easily distinguishable from those attributable to ganglionic paralysis. It is much harder, however, when faced with the result of an injection of tetraethylammonium, to be certain how far the total effect observed is due solely to autonomic blockade and how far it is modified by adrenaline secretion. Thus the tachycardia observed after an injection of tetraethylammonium in man, the failure of attempts to select patients for sympathectomy according to their response to tetraethylammonium (Soloff, Burnett, and Bello, 1948), the ability of tetraethylammonium to lessen the gastric secretion in response to histamine and to urecholine (MacDonald and Smith, 1949 ; Robertson *et al.*, 1950), and the reduction of renal blood flow and of urine flow during a water diuresis by tetraethylammonium (Aas and Blegen, 1949) are all observations whose interpretation needs care if there is a possibility of an increase in circulating adrenaline.

But, although tetraethylammonium has not proved entirely satisfactory for producing clinically a specific and long-lasting ganglionic block, its use has demonstrated the importance of ganglion-blocking agents, and its deficiencies must not be taken as a failure of the ganglion-blocking technique.

Hexamethonium

This compound ($N^+(CH_3)_3.(CH_2)_6.N^+(CH_3)_3.$) is one of the methonium series, in which pharmacological activity varies sharply with the number of carbon atoms in the methylene chain joining the terminal quaternary groups (Paton and Zaimis, 1949). The properties of hexamethonium (C6) are also (in general) those of pentamethonium (C5) and tetramethonium (C4), and are described in detail by Paton and Zaimis (1951): for brevity I will refer only to hexamethonium unless there is some particular distinction to be drawn.

For the analysis of effects of hexamethonium on ganglia, the cat's superior cervical ganglion is still an unrivalled test object, using as a record of its activity the contraction of the strip of smooth muscle in the orbit called the nictitating membrane (to which some of its post-ganglionic fibres run). With this preparation excitation of the preganglionic nerve at 10 shocks a second causes a sustained contraction for many minutes or as long as an hour. This contraction is temporarily weakened by agents paralysing transmission through the ganglion, and it may be used for quantitative comparisons.

Proof of Ganglionic Block by Competition

But more elaborate tests must be done to determine whether it is indeed ganglionic block that is occurring. That hexamethonium has not affected the power of the nictitating membrane to contract is shown by injecting adrenaline (which excites the membrane directly) before and during a paralysis by hexamethonium; the contraction to adrenaline is unaltered in the presence of a fully paralysing dose of hexamethonium. That the nerve trunk running from the ganglion to the membrane has not been attacked is shown by stimulating it before and during the effects of a dose of hexamethonium and comparing the result with that of pre-ganglionic excitation. Although pre-ganglionic excitation becomes ineffective, post-ganglionic excitation is still fully effective. But it might still be that the pre-ganglionic trunk, or its

delicate nerve terminals, is attacked. This is tested by perfusing the ganglion and determining whether the release of acetylcholine by excitation of the pre-ganglionic nerve persists in the presence of hexamethonium. Even with the injection of a large dose of hexamethonium exclusively into the ganglion perfusion system, acetylcholine is still normally released. Finally, it was observed that the ganglion was not depolarized during the action of hexamethonium and that the paralysis was never preceded by excitation (Paton and Perry, 1951).

Effects on the Blood Pressure

The effects of hexamethonium on the cat's blood pressure are of particular interest, with reference to its use in hypertension. A dose of 1–2 mg./kg. usually produces a moderate fall of blood pressure ; but further doses, up to 20–30 mg./kg., produce no further effect. At the same time, the effects of nicotine (a stimulant to the vasomotor ganglia) are abolished, but the effects of acetylcholine and adrenaline are not reduced. Such an experiment (which could equally well be done in man) shows: (1) that the actions of hexamethonium on the blood pressure are exerted only by the release of autonomic tone, and not by any direct vascular action ; (2) that it has no other depressor effect even in large doses ; and (3) that it has no atropine-like or " adrenolytic " action.

The actions of acetylcholine and adrenaline are, however, altered. The depressor effect of acetylcholine is prolonged (although hexamethonium is free of anticholinesterase activity) ; and the pressor effect of adrenaline is both increased and prolonged. These effects are no doubt due to the paralysis of the compensating mechanisms normally maintaining the constancy of the blood pressure. Similar observations have been made with tetraethylammonium (Page and Taylor, 1947). When using ganglion-blocking agents, therefore, it is necessary to remember that the response to drugs and procedures affecting the blood pressure will necessarily be exaggerated, as the mechanisms maintaining a normal blood pressure are weakened.

The pharmacological study of hexamethonium, in short, has shown it to be a specific ganglion-blocking agent of low toxicity, and to be free from other properties such as stimulation of nerve terminations, ganglia, striated muscle or smooth muscle, neuromuscular blocking action, atropine-like action, histamine

liberation, or anticholinesterase activity (all of which have been found in other quaternary compounds in association with the power to block autonomic ganglia). For such reasons it was proposed for clinical trial (Paton and Zaimis, 1948).

Sensitivity of Different Ganglia

Hexamethonium is not equally active on all autonomic ganglia. Of those ganglia tested in animals hitherto, it appears that the parasympathetic ganglia to the salivary gland are the most sensitive, then the superior cervical ganglion, the vasomotor ganglia and visceral ganglia, and the vagal ganglia in the heart, in turn. This "spectrum" of ganglionic sensitivity seems to vary with each ganglion-blocking agent. Thus tetramethonium has more and pentamethonium less effect on the intestine relative to their effects on the superior cervical ganglion than has hexamethonium. Tetraethylammonium, too, causes for equal hypotensive effects a much greater paralysis of ocular accommodation than does hexamethonium. The work of Guyton and Reeder (1950) with curare, already quoted, provides further examples of the same phenomenon of varying ganglionic sensitivity. The reasons for this variation are still entirely obscure, and the sensitivities of different ganglia to different drugs must each be determined individually. Nevertheless, these observations offer a hope of eventually obtaining ganglion-blocking compounds more or less adapted to particular ganglionic systems.

Potency and Ganglionic Activity

A characteristic of a muscle partially paralysed by curare is that, while a single shock to its motor nerve may yield a quite vigorous twitch, with repeated stimuli the tension rapidly falls away—that is, a curarized muscle cannot hold a tetanus. The most likely explanation for this is that the acetylcholine output at the junction falls as stimulation proceeds. Normally this does not matter, as considerably more acetylcholine than necessary is released ; but in the curarized muscle, whose threshold to acetylcholine is raised, the fall in output can reveal itself in a deepening neuromuscular block.

It is probable that a similar situation exists with pentamethonium or hexamethonium. It is known that the acetylcholine output from a perfused ganglion undergoing continuous stimulation falls with time.

Corresponding to this, after a suitable dose of hexamethonium, a pre-ganglionically excited tetanus of the nictitating membrane, which previously produced a well-sustained contraction, now produces a spiky contraction, which at first is not far in height from the control, but which cannot now be maintained. Thus, as stimulation is prolonged, the ganglion becomes more sensitive to the blocking agent. In the same way, if high rates of stimulation are used the ganglion is more sensitive to the blocking agent than with slower rates; this fact can be made use of in assaying small amounts of the drug.

These effects, by which intense or prolonged activity alters the state of the ganglion and increases the action of pentamethonium or of hexamethonium, are relevant clinically. They may explain why it has been possible to give doses relieving hypertension or ulcer pain without paralysing, say, the normal function of the small intestine and bladder. For if one makes the assumption that in hypertension the vasomotor ganglia are hyperactive (or, in ulcer, the ganglia of the stomach), then it should be possible to diminish this overactivity considerably before interfering with the quieter-paced normal function.

Further, if this is true then the proportion of side-actions to therapeutic effect will be least in the truly functional disorders. On the other hand, in those conditions in which there is no specific overactivity of this sort, in which any effect produced is due to the paralysis of some normal function, side-actions may be expected to be more severe. It may be possible, therefore, to infer from the intensity of side-effects whether the action of hexamethonium in a given disease is through the relief of an abnormal autonomic pressure, or whether it is simply that the reduction of a normal autonomic function happens to provide some palliation of the disorder.

Effects of Hexamethonium in Man

The first trials (actually carried out with pentamethonium) (Organe, Paton, and Zaimis, 1949) served to establish the primary fact that the order of activity of these drugs was roughly the same in man as in the cat (in which most of the analysis of their action was done). Since then much valuable information has been gained, chiefly in the two fields of cardiovascular and gastric function.

Effects on Normal Blood Pressure and in Hypertension

Arnold and Rosenheim (1949) and Arnold, Rosenheim, and Goetz (1949) showed that pentamethonium lowers the blood pressure to a degree comparable to, and sometimes greater than, that by sedation or by tetraethylammonium; that with this is associated a warming of the skin of the lower limbs and an increase in digital blood flow; and that adrenaline is still fully effective in the presence of pentamethonium.

Burt and Graham (1950), in a quantitative analysis of these vascular actions, confirmed and extended these findings. They found that the effects of pentamethonium and hexamethonium were associated with an increase of limb blood flow, and that this increase was greater, more regular, and longer-lasting in the lower limbs than in the upper limbs, although vigorous reflex vasodilatation of the upper limb could be obtained. The paucity of the response of the upper limb is a curious observation, about which one can only speculate. Sweating was also investigated, and was depressed by both drugs in those cases in which a rise in skin temperature was elicited. They have also observed paralysis of the bladder (by cystometrogram) and abolition of movements of the small intestine studied through an ileostomy.

Lately, several more studies of the actions of hexamethonium or pentamethonium have been initiated by Turner (1950, 1951), Saville (1950), Campbell and Robertson (1950), Mackey (1950, personal communication), Smirk (1950, 1951), Frankel (1951), Locket (1951), and others, bearing more directly on its use in hypertension and toxaemia of pregnancy. This is all recent and current work, and it is perhaps still premature to do more than outline its character. There is no doubt, however, that regular oral doses of pentamethonium and hexamethonium can in many cases cause a substantial fall in blood pressure, which may be maintained for weeks or months. With this fall there is usually relief of such symptoms as headache, dizziness, ocular disturbance, and breathlessness on exertion. Further, there have already been indications that the physical signs of hypertension, particularly in its so-called "malignant" phase, may actually regress. There may be disappearance of papilloedema, diminution of heart size, and improvement in renal function. There is tentative evidence that some of these benefits may persist after ceasing to give the drug, suggesting

that it may succeed in interrupting the " vicious circle " postulated by Byrom and Wilson (1939).

These results are promising. But it seems probable that the action of these drugs in hypertension will not be fully exploited until another property displayed by them is analysed: the ability, reported by all workers, of causing postural hypotension.

Postural Hypotension

For a substantial time after an injection, after any effects on the supine blood pressure have passed, profound falls in blood pressure may be obtained in some subjects if the subject stands quite still for a few minutes. This is indeed the only important difficulty in using hexamethonium clinically, although it is not yet clear how seriously it should be regarded. Two facts make it questionable whether this hypotension is due simply to relaxation of control of arteriolar tone: the first is that it outlasts the effect on the supine blood pressure; the second, that exercise promptly relieves it. The latter observation brings forcibly to mind the venous pump mechanism actuated by the muscles, and raises the question whether there is not rather some relaxation of venous tone involved.

A similar conclusion is suggested by Enderby's (1950) stimulating observation that a patient with a systolic blood pressure lowered by pentamethonium or hexamethonium to a level of 60–70 mm. Hg is in an excellent state for many surgical operations (particularly those of the ear, nose, and throat or of the plastic type); for under these conditions bleeding is minimal yet tissue oxygenation and nutrition are said to be fully preserved. These results have now been amplified (Enderby and Pelmore, 1951) and confirmed (Hughes, 1951). It is difficult to believe that bleeding would be lessened if such a fall in blood pressure was achieved solely by arteriolar dilatation; but hypotension due to the accommodation of blood in relaxed venous reservoirs would be quite compatible with a dry operative field. It appears, in short, that the postural hypotension and the dry surgical field caused by hexamethonium indicate that one of its actions is the relaxation of a venomotor tone. There is little physiological evidence to support the existence of a sympathetic tone of this kind; but if it does exist it must influence considerably our views of how hexamethonium acts, how it should be used in hypertension, and how postural hypotension as a side-action is to be minimized.

Effect on Gastric Activity

We owe to Kay and Smith (1950a, 1950b) the studies of the action of hexamethonium on gastric function. These workers have shown decisively that intramuscular doses of hexamethonium will inhibit spontaneous secretion of hydrochloric acid to the point of achlorhydria, will reduce the volume and acidity of spontaneous night secretion of gastric juice, and will inhibit the motor activity of the intestine and relieve ulcer pain when this is present. They also find that it reduces the gastric secretion to insulin-induced hypoglycaemia, but does not affect the response to histamine. They have continued their studies, using larger doses by oral administration, and have found a similar reduction in gastric secretion. Hexamethonium has also been shown radiographically to reduce the emptying time of the stomach considerably, and to lessen the mobility of the duodenum and jejunum (Douthwaite and Thorne, 1951). It is clear from this work that hexamethonium is potentially important for the treatment of peptic ulcer. A hopeful beginning has already been made (Scott, Kay, O'Hare, and Simpson, 1950) on the difficult task of establishing whether it does in fact accelerate healing of peptic ulcer as well as relieve pain. But it is still uncertain, for instance, whether such beneficial effect is due to depression of acid gastric secretion or to depression of gastric and intestinal motility.

" Side-actions "

Bromism and iodism can be avoided by the use of non-toxic salts of hexamethonium (Paton and Walker, 1951 ; Campbell and Robertson, 1951). The technique of diminishing undesired elements of the syndrome of ganglionic block (arbitrarily termed " side-actions " is still developing. Severe ileus should not be allowed to persist: neostigmine is effective (Bourne and Hosford, 1951). Fall in blood pressure may, in view of Enderby's results, be less hazardous than it appears. Postural control is obviously of prime importance, but control of blood pressure by sustained infusions of adrenaline has nothing to recommend it: " adrenaline shock," which may be lethal, has been known for over 30 years (Blackett, Pickering, and Wilson, 1950).

Future Work

The actions of hexamethonium in man hold therapeutic promise and, as one reviews them, are all attributable solely to ganglionic block. With this promising beginning, one turns to consider future lines

of progress. There is, of course, a great deal of work to be done in confirming the results already obtained and comparing their therapeutic uses with established procedures. It is only two and a half years since these compounds were proposed for clinical trial; and the technique of their use, like the techniques of using curare or digitalis, has still to be evolved.

One looks forward to an analysis of the haemodynamics of the circulation in man after hexamethonium; the extension of the use of the drug to other clinical conditions involving autonomic activity; the study of combinations of a ganglion-blocking agent with a drug exciting, say, that part of the autonomic nervous system whose activity it is desired to retain. Physiologically, there are many details of the blocking process to be elucidated. Further, without doubt other blocking drugs will be developed whose actions will require analysis, although it is doubtful if any of them will be so simple chemically as hexamethonium; there are, indeed, many already recorded in the literature worthy of study.

Use of Hexamethonium for Clinical Research

Perhaps the most important aspect of hexamethonium is that it provides a potent and specific tool for analysing autonomic activity. Whatever the therapeutic uses of such a drug, in the long run one of its most valuable features will be that it allows a direct experimental attack on that much abused word "functional" and such relatives as "vagotonia" and "autonomic imbalance," so often attached to a disorder "according to the predilection of the particular observer." Langley and his colleagues were able to use nicotine to analyse the structure and function of the autonomic nervous system in animals; their work was essentially that of defining the autonomic connexion between normal activity in normal organs and the central nervous system.

We can now extend this study to clarifying how far certain abnormal activities in normal or abnormal organs originate in the central nervous system and are mediated through the autonomic nervous system. In physiology, indeed, hexamethonium is already proving a useful weapon; thus Feldberg (1950) has been able to analyse satisfactorily the action—which had recently been called in question—of substances such as acetylcholine, histamine, and barium on the small intestine,

and to show that barium (so long regarded as a specific stimulant to smooth muscle) in fact has a powerful ganglionic stimulating action. Likewise, Kay and Smith (personal communication) are already finding that ulcer cases may be divided according to their response to hexamethonium ; there is no need to point out the possible importance of such a division.

As a tool, however, neither hexamethonium nor any other ganglion blocker is useful unless it is specific. It is possible, of course, that a particular side-action may be, for a particular disorder, useful rather than otherwise. One could quote the compound " banthine " (Longino *et al.*, 1950) to illustrate this. This is stated to have both a sympathetic ganglion-blocking action and a somewhat more intense atropine-like action ; such a combination might be a convenient mixture of properties. But at the same time this makes it very difficult to discover whether the drug has any action on *parasympathetic* ganglia, for the effects of block of these have already been produced by the atropinic postganglionic block. In the words of Longino *et al.*, " The amount of drug necessary to block parasympathetic synapses could not be determined by the methods employed." For all one can tell from the evidence so far, there may be no such parasympathetic block exerted in the tolerated dose range of the drug. Whatever the usefulness of such a drug in treatment, it is clear that its use can tell us little more about, say, gastric ulcer than we have gained from experience with atropine itself. For reasons of this kind, an attempt has been made to emphasize the value to be attached to the specificity of a ganglion-blocking drug.

One may end on a frankly physiological and even more frankly speculative note. The physiological interest of ganglia lies particularly in their relation to the other two synapses—the motor end-plate between nerve and muscle, and that between nerve cells—the central nervous synapse. A longer-chained member of the methonium series, decamethonium, acts only at the myoneural junction. Next to this there are pentamethonium and hexamethonium, closely related to decamethonium but acting only at the ganglionic synapse. May not this be a pointer to yet other compounds specific for the central nervous synapse ? And if there are, may there not be, as with ganglia, degrees of specificity within the central nervous system ? It is engaging to consider what sorts of action one might

expect from such drugs. One thing, at least, seems certain—that the synapse in its various forms has many problems and surprises in store for both clinician and physiologist.

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