REVIEW ARTICLE

THE INTERRUPTION OF GANGLIONIC TRANSMISSION AND SOME OF ITS PROBLEMS

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DURING the last few years considerable attention has been paid to ganglionic blocking substances; first because they proved to be clinically useful and second because they are of great interest to physiologists and pharmacologists. Substances such as penta- and hexamethonium, tetraethylammonium, azamethonium, pentolinium and Arfonad have been frequently discussed[1–15] and detailed descriptions may be found even in textbooks[16,17]. For this reason I will restrict myself to the discussion of new information and of a few problems which are still unsolved and which are interesting both from an academic and a clinical point of view.

Structure-action Relationships

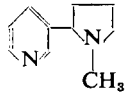
A glance at the formulæ of Tables I and II will at once suggest the difficulty of reaching conclusions about the structural features necessary for ganglionic activity. Table I gives compounds known to mimic acetylcholine at the ganglionic synapse. Such molecules might be expected to be modelled on acetylcholine or at least on parts of acetylcholine. This, however, is not always so, and the compound most difficult to account for is nicotine. In his recently published book Barlow[18] reviews in detail the literature relevant to structure-action relationships, and in discussing the requirements for acetylcholine-like activity at the ganglionic synapse concludes that "the idea that it is the electron density at various points which is important rather than the presence of some particular group or groups, would seem to be a much more realistic approach to the problem." "But," he continues, "electronic activation is not the only factor; steric effects and Van der Waal's forces may also play a part." Table II shows compounds able to compete with acetylcholine at the ganglionic synapse. Again no convincing relationships can be found among these substances. It appears that with an increasing number of active compounds the problem has become not less but more complicated, and will remain so, until more is known about the intimate properties of the different effector cells upon which drugs act.

Looking at the problem from a more general point of view, the primary difficulty is to comprehend the relation between acetylcholine itself and the effector cells. Acetylcholine is known to be active at several sites, the ganglionic synapse, the neuromuscular junction, the effector cells innervated by post-ganglionic cholinergic nerve fibres, and possibly also the central nervous system, producing what we call "different actions." It depolarises motor end-plates and ganglion cells, depresses some smooth muscles and stimulates others, stimulates glandular secretions, and so on.

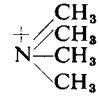
It seems almost incredible that one single molecule should produce so many different actions. One possible explanation is that its structure is such that it can fit and activate receptors with different properties. On the other hand possibly the initial stage of the trigger mechanism of all these actions is the same but our methods are still too crude to detect it. Whatever be the explanation the molecule of acetylcholine is a masterpiece and possesses to perfection the properties requisite for producing these actions. It is therefore not surprising that none of the innumerable synthetic compounds can really imitate acetylcholine in all its actions.

TABLE I

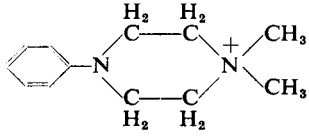
COMPOUNDS MIMICKING ACETYLCHOLINE



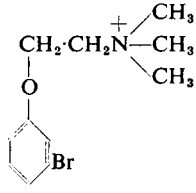
Nicotine



Tetramethylammonium (TMA)



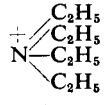
1 : 1-Dimethyl-4-phenylpiperazinium (DMPP)



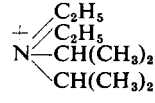
2-*m*-Bromophenoxy-trimethyl-ethylammonium (MBF)

TABLE II

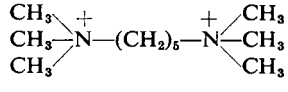
COMPOUNDS COMPETING WITH ACETYLCHOLINE



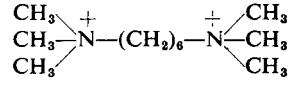
Tetraethylammonium (TEA)



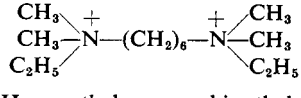
Diethyldi-*iso*propylammonium



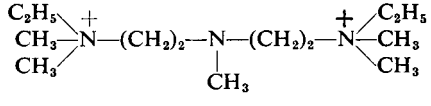
Pentamethylene-α : ω-bistrimethyl-ammonium (Pentamethonium)



Hexamethylene-α : ω-bistrimethy-ammonium (Hexamethonium)l

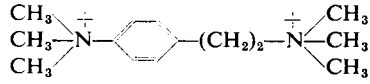


Hexamethylene-α : ω-bis-ethyl-dimethylammonium

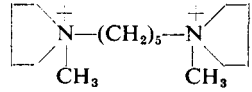


3-aza-pentane-3-methyl-α : ω-bis-ethyldimethyl-ammonium (Azamethonium)

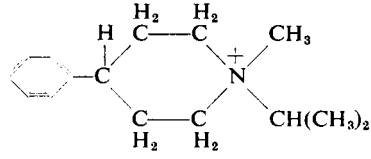
TABLE II—*continued*



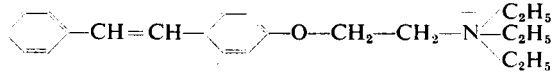
1-ω-trimethylethylammonium-4-trimethylammonium benzene



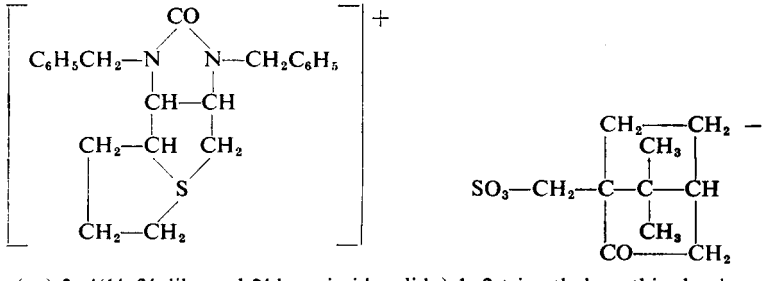
Pentamethylene-α: ω-bis (1-methylpyrrolidinium)
(Pentolinium)



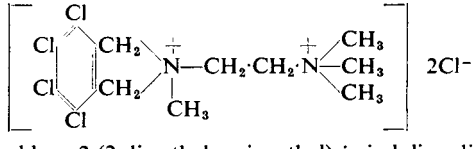
1-Methyl-1-*iso*propyl-4-phenylpiperidinium



2-Stilbenoxy-ethyl-triethylammonium
(Elvetil)



(−)-3:4(1′:3′-dibenzyl-2′-keto-imidazolido)-1:2-trimethylene thiophanium
(+)-camphor sulfonate
(Arfonad)



4:5:6:7-Tetrachloro-2-(2-dimethyl-aminoethyl)-*iso*indoline dimethochloride

The Modes of Action

The autonomic ganglia are distributing centres from which impulses from a single pre-ganglionic fibre may be relayed to one or several post-ganglionic fibres. The nerve fibres of the autonomic nervous system act

by the release of either acetylcholine or of adrenaline and noradrenaline. Dale[19] called *cholinergic* those nerve fibres which act by the release of acetylcholine and *adrenergic* those nerve fibres which act by the release of adrenaline or noradrenaline. All pre-ganglionic, sympathetic and parasympathetic nerve fibres are cholinergic—in other words the synaptic transmission across an autonomic ganlion is effected by acetylcholine. In 1953 Paton and Perry[20] obtained direct evidence that injected acetylcholine can cause depolarisation of the cells of the superior cervical ganglion, and Perry and Talesnik[21] obtained the same effect in the ciliary ganglion. These electro-physiological analyses on the two types of ganglion cells form a valuable addition to our knowledge of the mechanism by which acetylcholine mediates the transmission of the nervous impulse from the pre-ganglionic to the post-ganglionic fibre.

According to the chemical theory of ganglionic transmission the arrival of a nerve impulse at the nerve endings of the pre-ganglionic fibre is followed by the release of acetylcholine. Acetylcholine has a powerful and rapid action producing a depolarisation of the ganglion cell, in other words a stimulation of the ganglion cell, thus initiating an impulse in the post-ganglionic fibre. The release of acetylcholine is very rapid, and its destruction, by a specific enzyme, cholinesterase, is also rapid, being complete in a few milliseconds. After this the synapse is ready to transmit another impulse. However, when very large amounts of acetylcholine accumulate at the ganglionic synapse depolarisation will persist[20]. During this process electrical inexcitability develops and ganglionic blockade results. Consequently acetylcholine has two actions at the ganglionic synapse: (*a*) it may stimulate and (*b*) it may interrupt ganglionic transmission.

There are a great number of substances which interfere with the transmission at the ganglionic synapse, but their effects are produced by different modes of action. In the first instance they may be broadly divided into two categories:

1. Substances whose chemical structures bear some resemblance to acetylcholine and act by mimicking acetylcholine, competing with or allowing it to accumulate at the ganglionic synapse.

2. Substances whose chemical structures bear little or no resemblance at all to acetylcholine and which probably act on the pre-ganglionic nerve endings or on the effector cells, changing some of the properties essential for normal transmission.

The first group includes:

(*a*) Substances whose properties must be very similar to those of acetylcholine and which imitate its action at the ganglionic synapse. The depolarisation of the ganglion cells, which drugs of this kind produce, is initially associated with increased excitability, but as the depolarisation persists the phase of increased excitability passes, and transmission of excitation across the synapse no longer occurs.

(*b*) Substances competing with acetylcholine for the ganglion cell receptors, thus reducing the effectiveness of acetylcholine. In order to combine with the same receptors such molecules must obviously share

many of the properties of acetylcholine, but must also be deficient in some important quality needed to initiate depolarisation.

(*c*) The anticholinesterases, which cause an accumulation of acetylcholine by preventing its normal destruction. Thus their effects are indirect and all the phenomena following their administration are produced by acetylcholine itself.

The second group includes miscellaneous molecules which apparently act on the pre-ganglionic nerve endings or on the effector cells, and whose ganglionic blocking activity is small in comparison with their main pharmacological actions. For instance, local anæsthetics can affect ganglionic transmission by interfering with the release of the chemical transmitter and by reducing the sensitivity to acetylcholine of the ganglion cells[22–24].

Larrabee and Posternak[25] studied the ganglionic activity of some general anæsthetics. According to their results, chloroform and ether depress synaptic transmission through a sympathetic ganglion in concentrations similar to those known or assumed to exist in the blood during surgical anæsthesia. At the same time these substances depress synaptic transmission more readily than conduction along any type of axon.

Exley[26] has made a comprehensive study of the action of barbiturates at the ganglionic synapse. His results show, first, that not all barbiturates are equally active. The most active are butobarbitone and amylobarbitone; the least active are the thiobarbiturates; second, that the ganglionic and the central depressant activities show little correlation, and thirdly that the active barbiturates neither interfere with the release of acetylcholine nor depolarise the ganglion cells, but reduce the sensitivity to acetylcholine. In discussing his results Exley reaches the conclusion that the mechanism by which barbiturates diminish the excitability of the ganglion cells to acetylcholine must be different from that of the more specific quaternary ammonium compounds, and proposes to substitute the term "ganglion depressant" for "ganglion blocking."

A ganglionic blocking activity can be demonstrated also among tertiary amines known mainly as antihistamine drugs (diphenhydramine, promethazine), or as substances antagonising acetylcholine at the post-ganglionic cholinergic nerve endings (atropine, scopolamine, Trasentin)[26a]. Longo, von Berger and Bovet[27], applied the term "central ganglionic blocking substances" to a group of drugs (caramiphen, ethopropazine, benzhexol) which possess both ganglionic blocking properties and a relatively specific type of central depressant activity.

It is obvious that molecules such as those just mentioned in the second group, in whose properties there are basic differences, cannot produce a ganglionic blocking effect through the same mechanism. But to analyse such mechanisms is very difficult and little more can be achieved until our knowledge of the intimate properties of the effector cells is more complete.

Papers and reviews by various hands have recently appeared in which problems arising round different modes of action have been discussed in detail. To these I should like to add one comment. All the above

substances can produce a block at the ganglionic synapse at some stage of their action, and if we consider the problem from the point of view of the final result, all can be described as ganglionic blocking substances. On the other hand, if we apply the classical definition which requires that the substance should leave the nerve endings and the effector cells unaffected, the field is greatly narrowed. Possibly the term ganglionic blocking substances should be applied only to substances competing with acetylcholine. A conservative attitude must be preserved even towards substances blocking by depolarisation until more is known about the condition of a ganglion cell which has been submitted to a long-lasting depolarisation.

Substances Competing with Acetylcholine

Substances blocking ganglionic transmission by depolarisation start their activity with a powerful stimulation of the whole of the autonomic system, and obviously cannot be used clinically. On the other hand, the ganglionic blocking activity of the substances discussed in the second group is rather small in comparison with their main effects. Because of their high activity and specificity only substances blocking by competition with acetylcholine will be discussed.

Tetraethylammonium

Tetraethylammonium appears to be the simplest quaternary ammonium derivative which blocks ganglionic transmission by competing with acetylcholine, and it was the first substance to be used clinically[1]. However it has now been superseded and is largely used as a tool in pharmacological analysis. It has always been thought that the main pharmacological actions of tetraethylammonium are due to the paralysis of the autonomic ganglia. Zamboni[28] has, however, produced some evidence that the fall in blood pressure after tetraethylammonium administration is not due only to the ganglionic blockade, but also to a depressant action on the vasomotor centre.

The blocking action of tetraethylammonium is increased by the introduction of methyl side-chains on the alkyl carbon(s) *alpha* to the quaternary nitrogen, and it appears that diethyl-di*iso*propylammonium has a molar potency 12·6 times that of tetraethylammonium.[29]

Penta- and hexamethonium, pentolinium, azamethonium

These substances at present hold the centre of the picture as they have proved to possess great activity coupled with high specificity and their pharmacological actions both in animals and man have been studied in great detail[2,3,5,6,8,9,11–14,30–32].

The absorption of the methonium compounds and allied substances from the intestine is poor, rendering oral therapy difficult to control. This is not surprising as they are quaternary ammonium molecules. Harington[33], studying the absorption and excretion of hexamethonium, found that the rate of absorption of various hexamethonium salts differs considerably. For instance a comparison of the bromide with the chloride

salt showed that more than twice as much hexamethonium appeared in the urine after the administration of the bromide. In addition the excretion of the bitartrate and methosulphate is significantly smaller than for either the bromide or the chloride. This is a very interesting and still unexplained fact.

All studies made in connection with the fate of these drugs in the body show that their elimination depends almost entirely on the kidney. Excretion is rapid and this is one of the difficulties which occur in treating hypertension with methonium compounds. Attempts have been made to lengthen the action of the drugs. Smirk[34] has found that the effects of both hexamethonium and pentolinium are more prolonged when dissolved in 25 per cent. polyvinylpyrrolidine, and Goldsmith *et al.*[35] confirm this finding. However, excretion studies made by Harington and reported by Rosenheim[36] have shown that hexamethonium is as rapidly excreted in the urine when injected in this form as when given in aqueous solution.

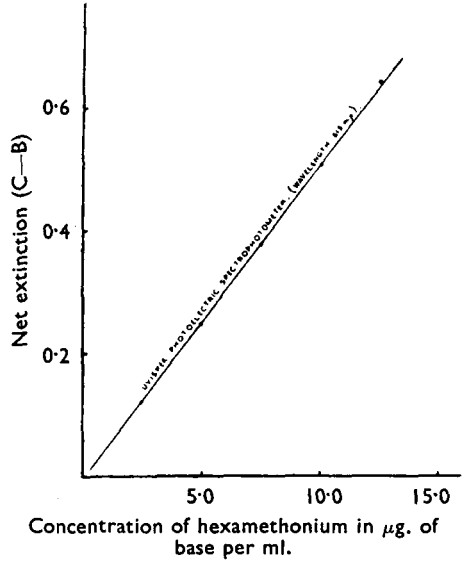


FIG. 1. Standard curve for the determination of hexamethonium using a uvispek photoelectric spectrophotometer.

For the estimation of rather high concentrations of methonium compounds (not less than 2 mg. of substance present in the fraction of biological fluid to be analysed) the method described by Zaimis[37] and that modified by Harington[33] is satisfactory. In this method the methonium ion is precipitated as the reineckate salt and measured photometrically in acetone solution. Up to the present only biological methods have been possible in detecting low concentrations of these substances. As these methods, however, are time-consuming and need skilled hands and complicated equipment, a chemical method sufficiently sensitive to detect low concentrations of the drugs in plasma and suitable for routine use in a clinical laboratory was sought. For the first attempts to estimate chemically low concentrations of hexamethonium, methods already in use for low concentrations of tetraethylammonium were tried. However, neither the method employed by Cochin and Wood[38] (personal experience) nor that employed by Mitchell and Clark[39] (Child, Ph.D. Thesis[40]) could be used for the estimation of hexamethonium. After many attempts with different dyes, Child[40] has finally succeeded in developing

a chemical method for the estimation of hexamethonium in plasma. This method is based on the extraction of the methonium ion from the plasma by the use of Amberlite IRC-50, a weak cation exchange resin, and subsequent elution with dilute acid and complex formation with bromothymol blue. The complex is extracted with chloroform and a part of the chloroform layer is then re-extracted with dilute alkali. Thirty minutes later the intensity of colour developed in the alkaline layer is determined spectrophotometrically. This method may be used for plasma levels of hexamethonium as low as 2 μg. base/ml. (Fig. 1). The method has been tried in order to estimate plasma levels in patients under hexamethonium treatment. From the results obtained it is clear that further refinement is needed before it can conveniently be used for routine purposes. Such work is at present in progress. The formation of a complex between bromothymol blue and hexamethonium has also been reported by Ballard *et al.*[41] and Gottlieb[42].

The main clinical uses of ganglionic blocking substances have been in the treatment of hypertension, in the reduction of bleeding during operations, in peripheral vascular diseases and in the treatment of peptic ulcer[30–32,34,36,43–52]. None of these substances shows any appreciable selective preference for sympathetic or parasympathetic ganglia, and unless the intention is to block the whole of the autonomic system their clinical use is always complicated by undesired effects. For instance a fall in blood pressure is inconvenient during the treatment of a peptic ulcer, while a decreased motility of the gastrointestinal tract is equally undesirable during the treatment of hypertension. These difficulties are, however, circumvented by clinicians who use appropriate counter-agents to reduce the unwanted activity. Pilocarpine, carbacol, eserine and neostigmine are successfully used to overcome paralysis of accommodation, dry mouth, paralytic ileus, urinary retention, i.e., the unwanted effects of parasympathetic blockade. Methedrine or noradrenaline infusion have been found quite satisfactory in diminishing hypotension. Considering the mode of action of these substances it was expected that anticholinesterase drugs would antagonise their effects at the ganglionic synapse. However, the evidence for such an antagonism is as yet inconclusive.

Dr. Goetzee and myself[53] are studying the influence of lowered body temperature on the effects produced by different drugs. Hexamethonium has been one of the drugs studied. Experiments have been carried out on cats, under chloralose anæsthesia. Body temperature is lowered at the rate of about 4° C. per hour by the circulation of cold water through a thin rubber bag inserted into the abdominal cavity. Figure 2 shows the result of an experiment in which contractions of the nictitating membrane were elicited by stimulation of the cervical sympathetic. The first two doses of hexamethonium were administered at an interval of one hour while the body temperature was constant at 39° C. The third dose was administered after the body temperature had fallen to 30° C. It is clear that the intensity of the block is increased at this temperature and the duration of activity prolonged. Thus body temperature must be included among the other factors that influence the intensity and duration of a

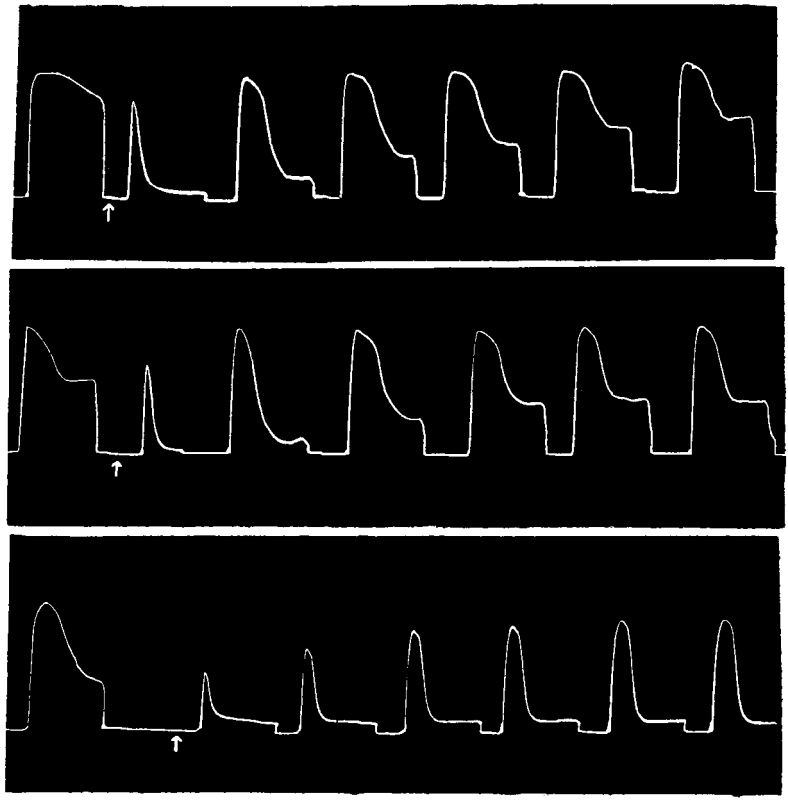


FIG. 2. Cat, 2·3 kg. The effect of three successive doses of 1·5 mg. hexamethonium dibromide. Contractions of nictitating membrane elicited every 10 minutes by pre-ganglionic stimulation at a frequency of 20 shocks per second. Period of stimulation 2 minutes. First and second doses at 39° C. body temperature, third dose at 30° C.

ganglionic blocking substance. This effect should be of particular interest to anæsthetists making use of ganglionic blocking substances during operations carried out on patients whose body temperature has been lowered.

The clinical results achieved in the treatment of hypertension by the methonium compounds vary very greatly and there is no doubt that they cannot be so used without a considerable understanding of their mode of action. Rosenheim[36], using hexamethonium for almost all his cases, feels "that hexamethonium and its homologues should be used in those patients with severe benign hypertension in whom the progress of the disease, the presence of fluffy exudates in the fundi, or the occurrence of hæmaturia suggests the approach of the malignant phase." Smirk, on the other hand[34] uses the methonium compounds and allied substances widely in the benign phase of the disease. According to him "a true basal blood pressure over 175 systolic, 100 diastolic, is probably a

sufficient indication for treatment even in a symptomless patient." Commenting on their usefulness Pickering[44] remarks that "methonium compounds offer by far the most promising therapy that has been produced for hypertension." "But," he continues, "their use makes the most exacting demands on the physician and patient. To use them successfully the physician must have faith in them, and know how to help his patient over the difficulties their use involves. The patient must be sufficiently aware of the gravity of his condition to tolerate the discomforts, have sufficient morale to persevere, and sufficient intelligence to adjust his way of life to the changes in behaviour which the use of these drugs entails."

In 1948 Brown and Gray[54] showed that a close-arterial injection of acetylcholine or nicotine into the skin or mesentery causes a discharge of impulses in the sensory nerves. Their experiments, although providing conclusive evidence that acetylcholine is not involved in the normal function of sensory endings, clearly demonstrate that the latter have properties very similar to the receptive parts of ganglion cells or motor end-plates. Douglas and Gray[55] using a similar method found that an intravenous injection of hexamethonium completely abolished the sensory discharge initiated by the close-arterial injection of acetylcholine although there was no change in the responses to potassium or to touch. The concentrations of acetylcholine used by them were of the same order of magnitude as those which Brown, Dale and Feldberg[56] used to excite a muscle twitch. This fact shows that the sensitivity of the sensory pathways in the skin is similar to that of the motor end-plate, where the sensitivity to acetylcholine is high and associated with normal function. Moreover Armstrong and Keele[57] showed that acetylcholine applied to the exposed base of a cantharidine blister, produces pain in human subjects. This cantharidine induced blister is formed by a separation of the epidermis from the underlying dermis and when the blister is opened the pain nerve terminals are directly accessible to applied solutions. The blister technique is more sensitive and also less unpleasant than other procedures. In their experiments Armstrong and Keele use a specially developed apparatus for producing a continuous and almost simultaneous graphic record of the subjects' assessment of the intensity of pain. Pain thus produced is readily antagonised by the previous application of hexamethonium.

Hexamethonium abolishes in the carotid body the respiratory stimulant actions produced by acetylcholine, nicotine and lobeline but does not interfere with those produced by oxygen lack, potassium or cyanide. Douglas[58] in discussing his results, arrives at the conclusion that: (*a*) the selective abolition by hexamethonium of the response to the nicotine-like drugs indicates that these do not act at a synapse on the chemo-sensory afferent pathway, (*b*) that the pathway from the oxygen-sensitive elements of the cat's carotid body runs to the respiratory centre uninterrupted by any ganglion-like synapse, as hexamethonium in doses much greater than those causing profound block of sympathetic and parasympathetic ganglia failed to exert any apparent action on the carotid body responses to anoxia and (*c*) that the behaviour of the carotid body is strictly analogous

to the behaviour of the skin. Since then other workers have obtained similar results[59–61]. Thus we have now experimental evidence that ganglionic blocking substances are capable of antagonising sensory responses, elicited in the skin and carotid body by a mechanism which is specific against the stimulating properties of acetylcholine, nicotine and similar substances. The use of ganglionic blocking substances in the human subject often results in striking relief of certain types of pain. The types of pain most readily relieved are hypertensive headaches, peptic ulcer pain, anginal pain, causalgia after peripheral nerve injury or pain in herpes zoster and pulmonary infarction. (For references see Moe and Freyburger[1], and Paton and Zaimis[2].) This antagonism to pain is probably associated with the release of smooth muscle spasm and improvement of blood supply which these drugs effect. But we cannot overlook the possibility that a ganglionic blocking substance might act in some instances directly on certain sensory receptors.

Tolerance to all the methonium compounds develops, possibly at slightly varying rates. Mohanty[62], trying to elucidate the mechanism by which tolerance develops, found that the ganglia of an eviscerated or dehepatised cat did not develop tolerance after an intravenous injection of hexamethonium; but when by cross-circulation experiment, the isolated liver of another animal was incorporated into the circulation, tolerance developed in the whole animal. In addition, a solution of hexamethonium treated with liver homogenate, when applied to isolated ganglia, produced resistance to the effects of further hexamethonium doses. Mohanty concludes that the action of the liver on hexamethonium gave rise to a substance which competed with hexamethonium at the ganglia without itself producing any important degree of ganglionic block. These results are interesting but it is difficult to see how they are to be correlated with certain clinical findings. First there is definite evidence[30] that as far as parasympathetic ganglia are concerned, either tolerance does not develop, or it develops much more slowly. It seems improbable that a substance produced by the action of the liver on hexamethonium would compete with hexamethonium at the sympathetic and not at the parasympathetic ganglia. Second, it is known[30] that there is a remarkable difference in the speed at which tolerance develops. Again, if the appearance of tolerance is linked with the formation of a substance in the liver the lack of uniformity in the development of tolerance can hardly be accounted for. The possibility has occurred to me that these facts about tolerance may be linked with two other phenomena. First, with the much discussed potentiation of adrenaline and noradrenaline which always occurs in the presence of ganglionic blocking substances. Experimental results clearly show that this potentiation cannot be attributed only to the abolition of the normal compensatory nervous mechanisms, as it is found both after vagotomy and after section of the spinal cord at a high level. Bartorelli *et al.*[63] discussing their own results together with those obtained by previous workers conclude that there is as yet no satisfactory explanation of this potentiation. Second, during the administration of ganglionic blocking substances for the reduction of blood pressure in operations a

very interesting phenomenon has been observed. When the first dose of a ganglionic blocking substance is administered a lowering of the blood pressure is produced, but the blood pressure returns apparently quite rapidly to its initial level, and any subsequent doses are practically without effect[64]. This very acutely developing tachyphylaxis is not in accordance with the results obtained in animal experiments, where no matter what ganglionic pathway is tested no such phenomenon occurs. The possibility of ganglionic blocking substances acting at other sites has been previously discussed. I should now like to put forward the suggestion that hexamethonium or the other ganglionic blocking substances may sensitise the receptors to adrenaline and noradrenaline, an effect more apparent under such conditions as surgical anæsthesia. If an action of this kind occurs the effect of ganglionic blocking substances will be of

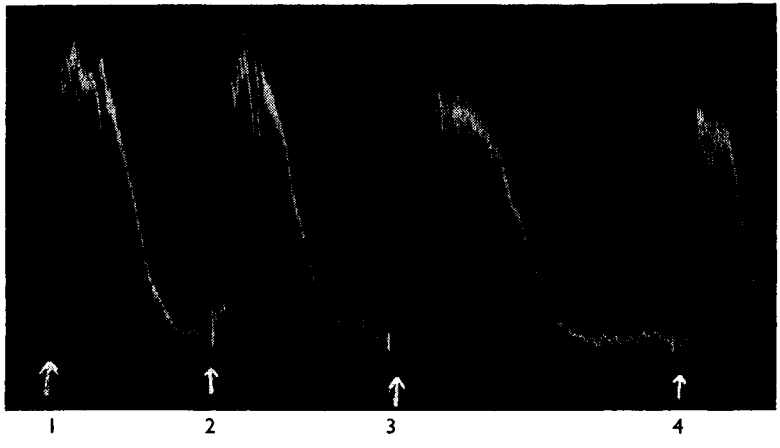


FIG. 3. Cat, 2·7 kg. Chloralose anæsthesia. Blood pressure record. At arrows 1, 2 and 4, 20 μg. adrenaline. At arrow 3, 0·5 mg. tetramethyl ammonium iodide. All doses were given intravenously.

short duration and subsequent doses will be ineffective, not because they fail to block ganglionic transmission again, but because this is masked by the peripheral sensitisation of the receptors to adrenaline and noradrenaline. This too could be a possible explanation of the potentiation of adrenaline and noradrenaline in the presence of ganglionic blocking substances and a reason for the decreasing sensitivity of the sympathetic ganglia to the action of these substances, a phenomenon usually described as tolerance development. In a series of experiments with tetramethylammonium it was observed that this substance reduces the rise of blood pressure produced by adrenaline. Figure 3 shows the result of such an experiment. Is it then possible that a ganglionic stimulant substance reduces the sensitisation of the receptors to adrenaline while a ganglionic blocking substance increases it? The answer to this question can only be found by experiment, but such a possibility is to some extent supported by the findings of Bülbring[64a] that hexamethonium has a stimulant action

and sensitizes the taenia coli of the guinea-pig to different forms of stimulation, and also those of Zauder[65] that hexamethonium potentiates the response of the isolated intestine to both acetylcholine and histamine. According to Zauder this potentiation is independent of innervation and is due to "an increase of the excitability of the muscle in a manner as yet unexplained."

Elvetil

The pharmacology of Elvetil has been described by Cavallini and his colleagues[66]. According to them the substance blocks the transmission in the autonomic ganglia and its duration of action is unusually prolonged. At the same time the substance shows a preference for the parasympathetic system. For instance, in dogs and cats, an intravenous dose of 0·5 mg./kg. reduces or abolishes for about 30 minutes the response to vagus stimulation, but to block the superior cervical ganglion a dose of 3 to 4 mg./kg. is required.

Arfonad

Arfonad[15] is a substance much used by anæsthetists for lowering blood pressure during operations[67–69]. It is popular because its effect is short-lasting so the anæsthetist feels more confident of controlling the blood pressure. Substances which possess high specificity are appreciated by pharmacologists who are inclined to regard them as ideal for clinical applications. For the pharmacologist Arfonad cannot be so classified for while it blocks the transmission of the autonomic ganglia it also liberates histamine[15,70], has a direct action[71], and it is uncertain which of these actions is the main cause of the fall in blood pressure in human beings. If I, as a pharmacologist, had to analyse the substance and give an opinion I should certainly feel very worried and doubtful about its clinical usefulness. Its successful application however, proves that the final value of a substance can only be assessed after both pharmacological and clinical tests.

SU-3088

A few months ago there appeared a short report[72] of a new drug, 4:5:6:7-tetrachloro-2-(2 dimethylaminoethyl)-*iso*indoline dimethochloride, with promising properties. The substance was described as being very potent, of long-lasting activity, easily absorbed when administered orally, and free from tolerance development. However, from the recently published first clinical report[73] it is apparent that expectations have not been fulfilled. The article ends as follows: "Results at present seem to indicate that control of blood pressure has been a little more consistent than with pentolinium; certainly effects continue longer and fewer mg. are required each day. Side actions and variations of effect are similar. It is not yet certain whether a schedule of therapy can be worked out for Su-3088 which will achieve results comparable to those we have obtained with hexamethonium, given orally, for four years. At least this new drug should be a useful addition to the agents now available for control of

hypertension and the reduced mg. requirement and decrease in number of tablets needed each day should predict a financial saving for patients." This is regrettable as an orally active ganglionic blocking substance would have great clinical advantages and is much needed.

Reading through the clinical literature it is interesting to see that every one of the ganglionic blocking substances has its supporters, possibly because the difficulty of dealing with the autonomic nervous system makes clinicians prefer to use a drug to which they are well accustomed. But for the pharmacologist and the physiologist all of them are little gold-mines of information, for through their differences physiological events can be clarified and the modes of action of different drugs studied.

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