REVIEW ARTICLE

QUATERNARY AMMONIUM COMPOUNDS IN MEDICINAL CHEMISTRY. I*

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Interest in the biological activity of quaternary ammonium salts stems from the elegant work of Crum Brown and Fraser (1868–9), who were the first to record the curariform activity of methiodides of alkaloids such as strychnine, brucine, and atropine. Apart from a few scattered papers, the pharmacological activity of quaternary ammonium salts received little attention for many years. Hunt, Renshaw and their associates, working over a period of some 35 years from 1904 to 1939, published a very large number of papers dealing with the effects of these compounds on the autonomic nervous system; they established three basic types of activity, muscarinic, nicotinic and curariform. References to this work are listed in full in Craig's excellent review, "Curariform activity and chemical structure" (1948).

Concurrently with these studies, quaternary ammonium compounds were emerging into greater prominence by virtue of their activity against micro-organisms. Their germicidal activity was first recognised in 1916, when Jacobs and his colleagues (Jacobs, 1916; Jacobs, Heidelberger and Amoss, 1916; Jacobs, Heidelberger and Bull, 1916) investigated the relation between chemical structure and bactericidal activity of quaternary salts of the hexamethylenetetramine series. The synthesis of the sapamines (acylaminoethyltrialkylammonium salts) by Hartmann and Kägi (1928) is representative of the work that led to the recognition of the exceptional virtues of this class of high molecular weight quaternary ammonium salts (the so called "invert soaps"); the development of these compounds as germicides paralleled the study of their properties as surface-active agents and as textile chemicals.

Nevertheless the potentiality of quaternary agents was not fully realised, and their widespread use was not established, until Domagk (1935) examined certain compounds and only found notable germicidal activity when at least one of the four radicals had a carbon chain of length C_8 to C_{18}. The most important compound to emerge from this work was Zephirol (Zephiran, benzalkonium chloride), which has the structure $RN^+.(Me_2).CH_2.Ph\ Cl^-$ where R is a saturated straight alkyl chain containing from 12 to 18 carbon atoms.

Initially quaternary ammonium germicides were considered to be primarily suited for surgical and medical usage, but later an increasing application to public health and sanitation became a major factor in their commercial development and exploitation. An important stage in the

* The second part of this review, together with all the references, will appear in the April issue of the Journal.

use of quaternaries in chemotherapy followed the investigations of Browning, Cohen, Ellingworth and Gulbransen (1929) on some quaternary derivatives of anil and styrylquinoline, some of which were found to possess high activity against trypanosome infections. Later investigations by Browning, Morgan, Robb andWalls (1938)on certain phenanthridinium compounds synthesised by Morgan and Walls (1938), showed some of these substances to possess a curative action on *Trypanosoma brucei* infections in mice. Subsequent work in this field led to the development of Dimidium, homidium (Ethidium) and finally quinapyramine (Antrycide), which is still one of the most effective compounds used in the treatment of trypanosomiasis.

During the years of the Second World War, and in the immediate post-war period, much fresh light was thrown on the pharmacological properties of the quaternaries. For many years King at the National Institute for Medical Research, London, had been interested in curare, and from tube curare he had isolated a pure crystalline alkaloid, (+)-tubocurarine chloride (King, 1935). Although the complete structure was not elucidated until some years later (King, 1948), it was soon realised that this alkaloid was a bisquaternary ammonium compound. The extensive clinical investigations of West (1932, 1935a, b, c), Griffith and Johnson (1942) and Gray and Halton (1946), on curare have been the major stimulus for a vast amount of subsequent chemical, pharmacological, and clinical study. However, perhaps the most important contribution in this field was the epoch-making discovery, announced simultaneously by Barlow and Ing (1948) at Oxford, and by Paton and Zaimis (1948) at the N.I.M.R., of the neuromuscular and ganglionic blocking activity of the polymethylenebistrimethylammonium salts (the "methonium salts"). This work has provided the stepping stone from which has sprung the majority of the synthetic neuromuscular and ganglionic blocking agents to receive clinical application. Some of these drugs are choline derivatives, and it should be remembered that acetylcholine, the parasympathetic transmitter, is the only quaternary ammonium salt with a physiological rôle in the body.

Investigations into the properties of acetylcholine really began with the work of Hunt and Taveau (1906), and later it was established that this activity could be divided into two principal classes, muscarine-like and nicotine-like. The specificity of the acyl group was investigated by Chang and Gaddum (1933) and others (see Bergel, 1951), who described the biological activities of a series of different acylcholines. Other workers, notably Ing and his colleagues (Ing, 1949; Holton and Ing, 1949; and Ing, Kordik, and Tudor Williams, 1952), investigated the importance of the size of the quaternary grouping in choline derivatives and demonstrated that, while the replacement of one methyl group by another grouping decreased activity, the major decline occurred when a second methyl group was replaced. In addition, the effects of other alterations in the chemical structure of choline have been studied, especially in relation to the relative muscarinic and nicotinic activity of these compounds (see Barlow, 1955).

Quaternary ammonium salts have also found clinical value as antispasmodic and antisecretory agents in the treatment of various irritant gastric conditions. In general this type of activity is related to an atropine-like effect, as for example in lachesine (Ing, Dawes and Wajda, 1945), although there are notable exceptions such as amprotropine phosphate (Syntropan) (Fromherz, 1933, 1934, 1937). Furthermore some quaternaries such as choline theophyllinate (Choledyl) and related compounds have been used for the relief of bronchospasm. Potent anticholinesterase activity is present in certain synthetic quaternary compounds, modelled upon the non-quaternary alkaloid physostigmine, such as neostigmine and others of related structure (Blaschko, Bülbring and Chou, 1949). This type of compound has been applied to the treatment of myasthenia gravis (Walker, 1934, 1935; Schwab, 1960) and also as an antagonist to the neuromuscular blocking action of tubocurarine and curare-like compounds (Riker, 1953). Anticholinesterase activity, to a varying extent, is shown by other quaternaries, for example the heterocyclic polymethylenebisquaternary ammonium salts (Riker, 1953; Barlow and Himms, 1955; Cavallito and Sandy, 1959).

Although the antibacterial application of quaternaries has been known for some time, it is only within the last 10 years or so that their potential as antifungal agents has become apparent. Compounds such as cetrimide, dequalinium, domiphen, and hedaquinium have provided highly successful local antifungal agents. Another development of quaternaries is their use in the formulation of cosmetics (Lincoln, 1954), which is mainly due to the fortunate combination of surface-activity and germicidal action found in these salts.

From this brief introduction, it must be apparent that quaternary ammonium salts have retained the interest of chemist and biologist alike for almost a century. In our opinion, this subject has hitherto not been adequately reviewed, and the present article has therefore been written in an attempt to summarise the more important features of the research carried out during this period. We would however, like to draw attention to the article by Lesser (1949), which reviewed the current knowledge of quaternaries at that time.

It is not possible to discuss the vast number of naturally occurring quaternary salts (such as the alkaloids), and it is therefore proposed to deal only with the more important synthetic compounds that have activity or potential activity in the treatment of human or animal disease. For brevity, the term "onium" will be used throughout to represent quaternary ammonium compounds.

Pharmacodynamic Activity

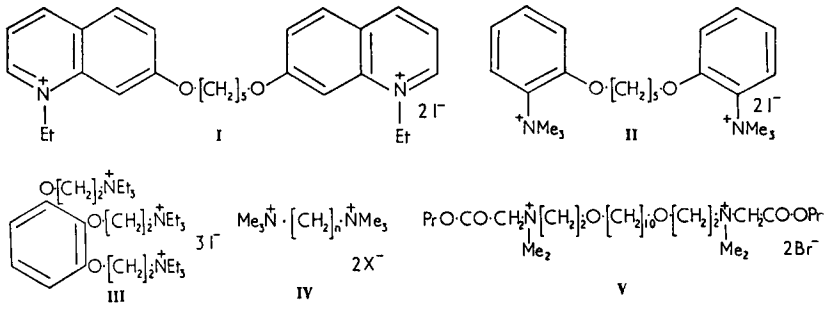
Neuromuscular Blocking Agents

The use of muscle relaxants as an aid to anaesthesia is nowadays accepted procedure; however, it is actually little more than 15 years old. The oldest known relaxant is, of course, curare; reports of its use by South American Indians reached Europe as early as the sixteenth century,

but little was known of its source or mode of action for nearly 300 years. The first clear accounts of the preparation, use and action of this poison were given by travellers such as Humboldt, Schomburgk and Waterton in the early nineteenth century; these are reported by McIntyre (1947) in his fascinating book *Curare*.

Experimental studies with neuromuscular blocking drugs started in 1850, when Pelouze and Bernard showed that the paralysis caused by crude extracts of curare was in fact due to a block at the neuromuscular junction; this work was repeated and extended by Crum Brown and Fraser (1868–69), since when it has been recognised that neuromuscular blocking properties are characteristic of onium salts as a class. However, it was not until much later that the development of satisfactory methods for the biological evaluation of neuromuscular blocking agents enabled further progress to be made. The first reliable estimations were made by Ing and Wright (1931, 1933), who measured the time taken for equimolar solutions of different neuromuscular blocking drugs to produce complete paralysis of the frog sartorius preparation.

Before King's final elucidation of the structure of (+)-tubocurarine in 1948, it was established that the drug was a bis-onium salt and sufficient of the general structure was known to provide a lead for the synthesis of simpler substitutes. In 1946 and subsequently, Bovet and his colleagues (Bovet, Courvoisier, Ducrot and Horclois, 1946; Bovet, Depierre and de Lestrange, 1947) produced a series of quaternaries with marked muscle-relaxing properties; these included 3381.R.P.[I], 3565.R.P.[II], and 3697.R.P.[III], the latter being appropriately named gallamine triethiodide (Flaxedil).



Although gallamine was the first synthetic neuromuscular blocking agent to be accorded widespread clinical use, it is still extensively employed and is included in the British Pharmacopoeia 1958. Many attempts have been made (Riker and Wescoe, 1951; Roberts, Riker and Wescoe, 1951; Pelikan and Unna, 1952) to modify the structure of gallamine to improve its neuromuscular blocking activity and to reduce the incidence of side effects; but none of these related compounds has replaced the parent substance.

A major advance in the development of synthetic neuromuscular blocking agents was the simultaneous, but independent, publication in 1948 of

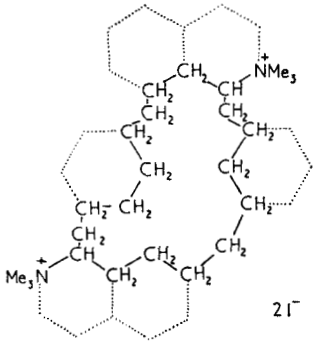
the activity of the "methonium" compounds by Barlow and Ing of Oxford, and Paton and Zaimis working at the National Institute for Medical Research. These two groups of workers investigated the pharmacology of the polymethylenebistrimethylammonium salts and found the decamethylene member, decamethonium, (C_{10}, Eulissin, Syncurine) [IV, n = 10], to be an extremely potent neuromuscular blocking agent, approximately five times more active than tubocurarine in man; but, as with all other such agents, there is considerable difference in the relative potency between various animal species. The methonium compounds also possess ganglionic blocking activity, which is optimal with the hexamethylene analogue, hexamethonium or C_6 [IV, n = 6]; this proved to be the stepping stone from which the bulk of the numerous synthetic hypotensive agents now available have been developed.

Decamethonium differs from tubocurarine in its method of action, since it produces neuromuscular blockade by depolarisation of the muscle end plate, whereas tubocurarine acts by competing with acetylcholine for the end plate receptor. Robson and Keele (1956) have given an excellent summary of the three main mechanisms of neuromuscular blockade (Competitive, Depolarising and mixed Competitive and Depolarising); they have also reviewed the experimental criteria used to differentiate these three mechanisms. It does not fall within the scope of this review article to expand upon this subject.

Decamethonium, like all depolarising agents, is not antagonised by anticholinesterases (for example, neostigmine), which may indeed enhance its action. This lack of a satisfactory antagonist has been a serious disadvantage in its clinical use, and although some successful antagonists were later developed (Phillips and Castillo, 1951; Phillips, 1952; Dallemagne and Phillippot, 1953; Vandam, Safar and Dumke, 1953), decamethonium has never really fulfilled its early promise as an adjuvant to anaesthesia; nevertheless some anaesthetists still favour its use (Hale Enderby, 1959; Fisk, 1961). Decamethonium was omitted from the British Pharmacopoeia, 1958. As with gallamine, numerous efforts have been made to improve the biological properties of decamethonium by modification of its structure, but probably the only compound of this type worthy of mention is diohexadecanium (Prestonal) [V], which has achieved some success abroad, although it is apparently not used to any great extent in this country (Griffith, Cullen and Welt, 1956; Jolly, 1957; Rendell-Baker, Foldes, Birch and D'Souza, 1957). Interest in this type of structure has not, however, entirely flagged since currently Lewis and Stenlake and their associates in Glasgow (Edwards, Lewis, McPhail, Muir and Stenlake, 1960; Edwards, Stenlake, Lewis and Stothers, 1961, and earlier papers) are preparing and studying the properties of numerous poly-onium compounds. While their results are not yet complete, certain trends of considerable interest have developed.

A most interesting compound developed recently is cyclo-octadecane-1,10-bis(trimethylammonium iodide) or cyclomethone (VI); it will be apparent that while this compound is related to decamethonium, the ring is the same size as the central ring of tubocurarine [VII]. Lüttringhaus,

Kerp and Preugschas (1957) in Germany have found that this compound acts like tubocurarine in chicks and equals its potency in producing neuromuscular blockade. The Czechs, Votava and Metysová (1959), however, describe it as a short-acting muscle relaxant, only partially antagonised by neostigmine, and consider it to be of the "mixed" type of relaxant, although more closely related in mechanism of action to decamethonium than to tubocurarine, as evaluated by the different sensitivity of different species of animals.



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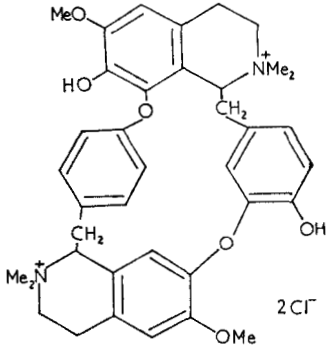

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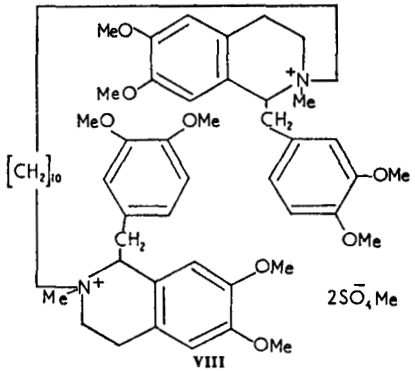


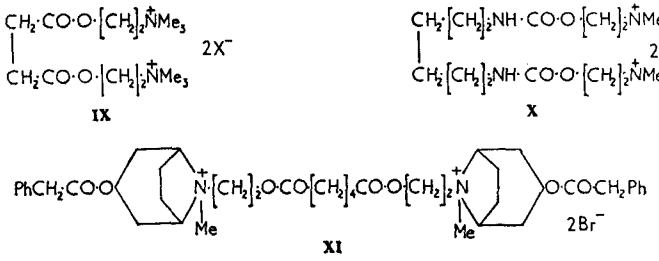
VIII

The replacement of the trimethylammonium groups in decamethonium by heterocyclic quaternary groups was studied by Collier and Taylor (Collier and Taylor, 1949; Taylor and Collier, 1950, 1951), whose results supported the criteria postulated by Craig (1948), particularly in that, ". . . in general all of the really effective curare-like compounds have the nitrogen present in a saturated ring", and " . . . the methoxyl group enhances curare-like activity". Laudexium methylsulphate (Laudolissin), [VIII] emerged from this work. This produces a curare-like paralysis of voluntary muscle, which is somewhat slower in development but of similar duration to tubocurarine itself. Although laudexium achieved a measure of clinical success (see for example Bodman, Morton and

Wylie, 1952; Dundee, Gray and Riding, 1954) it has now been largely superceded by the shorter acting muscle relaxants.

Undoubtedly, the most important development in the use of synthetic neuromuscular blocking agents was the introduction of the short-acting depolarising agent, suxamethonium, B.P. (Scoline, Anectine, Brevedil M.), [IX]. Although suxamethonium had been known for many years, its application to anaesthesia, as a very short-acting muscle relaxant, was not reported until 1949 (Bovet and Bovet-Nitti, 1949). Its very brief duration of action is due to rapid enzymatic destruction, one of the metabolic products being the comparatively inactive monocholine ester of succinic acid (Lehmann and Silk, 1953), and in view of this no antagonist is normally necessary. In addition to its use in minor operations of short duration, the introduction of suxamethonium led to the development of a new technique in the use of relaxants in anaesthesia. Thus suxamethonium is now very widely employed as a relaxant in major surgery in the form of continuous intravenous infusion, using the "drip" technique; the relaxant effect may be halted at any time by merely discontinuing the supply. The use of suxamethonium has been the subject of many excellent reviews (de Beer, Castillo, Phillips, Fanelli, Wnuck and Norton, 1951; Thesleff, 1952; Collier, 1953; Paton, 1953; Randall and Jampolsky, 1953; and Bovet and Bovet-Nitti, 1955).

Practically every conceivable modification of the suxamethonium molecule has been made (see for example Brücke, 1956) but as so often occurs in this field, optimal activity still remains with the parent compound. However, one of these modifications, hexamethylenebiscarbaminoylcholine (Imbretil), [X], which is one of the most potent relaxants known, has achieved some clinical success abroad. (Delaby, Chabrier and Najer, 1953; Brücke and Reis, 1954; Kobinger and Kraupp, 1955; Foldes, Wolfson, Torres-Kay and Monte, 1959; Wiemers and Overbeck, 1960).



Although suxamethonium is probably the most widely used of all the relaxants, nothing is perfect in this imperfect world and suxamethonium is no exception. Not only is there no satisfactory antagonist for those rare occasions on which an antagonist may be required, but, more important, there have been several reports of severe post-operative muscle pains and stiffness after the use of this drug (Churchill-Davidson, 1954; Konow, 1959; Leatherdale, Mayhew and Hayton-Williams, 1959; Foster, 1960; Burtles, 1961; Burtles and Tunstall, 1961; Bush and Roth,

1961). Because of this, various workers have attempted to produce a short-acting neuromuscular blocking agent of the curariform type, devoid of these inherent disadvantages. Thus in our laboratories (Collier, Gladych, Macauley and Taylor, 1958, 1959; Brittain, Collier and D'Arcy, 1961), a series of bis-onium salts combining the chemical properties of laudexium and suxamethonium has been prepared and their pharmacology investigated. Although some of these compounds possess curare-like activity none was suitable for clinical use.

Haining and his co-workers in Edinburgh (Haining, Johnston and Smith, 1959) have described a series of bisquaternary tropeines, one of which, *NN'*-4,9-dioxo-3,10-dioxadodecamethylenebis(3-phenylacetoxytropanium bromide), [XI], combines the short duration of action of suxamethonium with the approximate potency of tubocurarine chloride; this compound is antagonised by neostigmine. It is not yet commercially available, and no indications as to its clinical value were given in the paper on its pharmacological properties (Haining, Johnston and Smith, 1960).

Amongst other onium compounds described by various workers as potential neuromuscular blocking agents are benzoquinonium (Mytolon), (Hoppe, 1950, 1951) and hexafluorenium (Mylaxen), (Cordaro and Arrowood, 1955; Foldes, Molloy, Zsigmond and Zwartz, 1960); however, neither of these drugs has fulfilled its earlier promise.

While it was not intended to include natural compounds in this review, the Erythrina alkaloids are especially worthy of exemption. Although these contain a tertiary nitrogen atom, they possess marked curare-like action (Hanna, Macmillan and McHugo, 1960), which is abolished by quaternisation. This is the only known class of compound that loses curare-like activity on conversion of a tertiary to a quaternary nitrogen. Another natural compound important enough to warrant mention is C-toxiferine I, one of the calabash curare alkaloids. As early as 1953, Waser first suggested that, in view of its extremely high potency and lack of secondary effects, this alkaloid should be investigated in clinical anaesthesia, and two papers have now appeared on this use (Waser and Harbeck, 1959; Foldes, Wolfson and Sorkoll, 1961).

Before concluding the subject of muscle relaxants, their application to the treatment of tetanus should be briefly considered. Curare, in various forms, has been widely used for this purpose since the early 1940's. Woolmer and Cates (1952), and Shackleton (1954) have reported on the treatment of tetanus with suxamethonium; although regarded as a valuable contribution to recovery, the use of this drug presented problems owing to its very short action and the fact that the continuous administration required practically constant medical supervision. Gallamine triethiodide has also been successfully used in the treatment of tetanus (Van Bergen and Buckley, 1952; Parkes, 1954). Honey, Dwyer, Smith and Spalding (1954) have pointed out that a long-acting relaxant is desirable, and tubocurarine has been successfully used by various workers in a number of cases. In addition, Garland (1959) has reported the efficacy of intramuscular injections of laudexium, another long-acting muscle relaxant, in the treatment of this condition.

In spite of the vast amount of work done in the field of neuromuscular blockade, saturation point has not yet been reached and in many research groups there is still enthusiasm for the synthesis and investigation of new neuromuscular blocking agents. This is well exemplified by the various International Symposia held within the last few years, for example in New York 1951, Rio de Janeiro in 1957, and Venice in 1958, and by the numerous books and review articles that have been published (for example Foldes, 1957; Bovet, Bovet-Nitti and Marini-Bettòlo, 1959; Lewis and Muir, 1959; Adriani, 1960; Davis, 1960; Foldes, 1960). In addition, a whole issue of *Anesthesiology* (**20**, (4), 1959) and a complete issue of *Studii si Cercetari de Biochimie* (**3**, (4), 1960) have been devoted to the study of muscle relaxants.

Ganglionic Blocking Agents

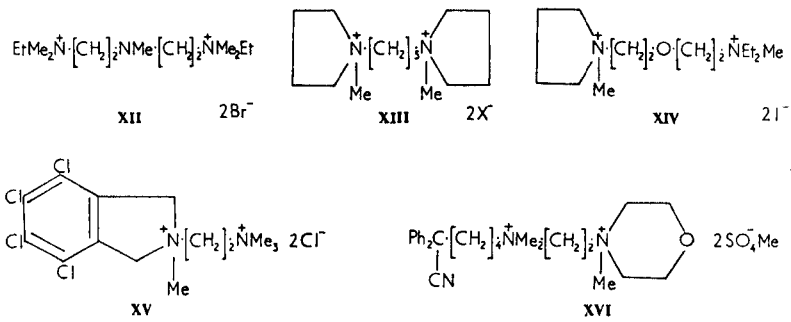
Quaternary ammonium compounds have achieved success as ganglionic blocking agents and since this class of drug still continues to be of importance in the treatment of hypertension, it is inevitable that much of this section must review the use of onium salts as hypotensive agents.

In a classical paper, Burn and Dale (1914) compared the effects of tetramethyl- and tetraethylammonium salts on blood pressure, drawing attention to the almost specific ganglionic blocking action of the tetraethylammonium salt (TEA). Some 30 years later Acheson and Moe (1946) and Acheson and Pereira (1946) re-examined the properties of TEA and showed that it produced ganglionic blockade without the preliminary stimulation normally produced by nicotine, and occasionally by the curare alkaloids. Although this compound has been used in man for the treatment of peripheral vascular disease (Berry, Campbell, Lyons, Moe and Sutler, 1946; Boyd, Crawshaw, Ratcliffe and Jepson, 1948) and of hypertension (Berry and others, 1946; Lyons, Moe, Neligh, Hoobler, Campbell, Berry and Rennick, 1947), it has never achieved wide clinical recognition. None of the numerous congeners of TEA has been found to be better than the parent compound (Moe and Freyburger, 1950).

The introduction of the methonium salts by Barlow and Ing (1948) and by Paton and Zaimis (1948) renewed interest in the ganglionic blocking agents, and initiated a vast new field of research. Paton and Zaimis (1949) showed that the activities of the methonium series varied with the number of methylene groups in the chain. The decamethylene member is a potent neuromuscular blocking agent, while those compounds with a shorter chain, particularly the tetra-, penta-, and hexamethylene compounds, have a marked ganglionic blocking effect. An excellent review on the methonium salts has been published by Paton and Zaimis (1952). The hexamethylene member (hexamethonium, C_6) achieved an initial success in the treatment of hypertension and is still official in the British Pharmacopoeia, although in recent years its use has diminished. A very interesting paper was published by Gill and Ing (1958), in which they discussed the mode of action of hexamethonium on the ganglia. Much work has been undertaken on modifications of the methonium molecules, both in altering the alkyl groups in the quaternary structure, and in replacing one

or more of the methylene groups in the chain by various hetero atoms or groups. Generally little appreciable improvement in activity over that of the parent substances has been achieved by these changes. However, there is one exception, namely when the central methylene group in the pentamethonium series is replaced by an *N*-methyl group, one of the products, 3-methyl-3-azapentamethylene-1,5-bis(ethyldimethylammonium bromide) (azamethonium, Pendiomide) [XII] shows potent ganglionic blocking activity (Bein and Meier, 1950, 1951; Haley, Leitch, McCormick and McCulloh, 1954), although Smirk (1952) has found it to be less effective than hexamethonium. Azemethonium is not commercially available in this country.

An important step in the development of clinically useful ganglionic blocking agents was made by Libman, Pain, and Slack (1952), who replaced the trialkylammonium groups of the methonium salts by heterocyclic nuclei. The activity of one of these compounds, pentamethylenebis-(1-methylpyrrolidinium halide), [XIII] is about five times that of hexamethonium on the nictitating membrane of the cat (Wien and Mason, 1953; Mason and Wien, 1955). This compound, pentolinium (Ansolysen) has largely replaced hexamethonium in the treatment of hypertension; although pentolinium shows some side effects these are less severe than those exhibited by some other hypotensive agents, for example the non-quaternary drug, mecamylamine (Sears, Snow and Houston, 1959).



XII XIII XIV XV XVI

An interesting unsymmetrical compound related to both pentolinium and the methonium salts was described by Frommel and his associates (Frommel, Vincent, Gold, Melkonian, Radouco-Thomas, Meyer, de Quay and Vallette, 1955; Frommel, Vincent, Radouco-Thomas, von Allmen and Vallette, 1955) although this compound, 3-oxapentamethylene-1-1(1-methylpyrrolidinium-5-(methyldiethylammonium) di-iodide, [XIV], has not achieved any notable clinical success. A more important unsymmetrical compound is 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl) isoindoline dimethochloride (chlorisondamine, Ecolid), [XV]. In animal experiments, this compound has been shown to be a long-acting, orally effective ganglionic blocking agent (Plummer, Trapold, Schneider, Maxwell and Earl, 1955; Maxwell, Plummer and Osborne, 1956). In clinical practice this compound has been shown to be a powerful hypotensive agent with consistent activity when given by mouth, and, moreover,

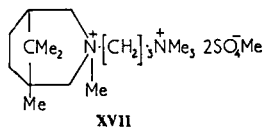
parenteral administration is some fifteen times more effective than oral. Chlorisondamine is more potent than pentolinium and has a longer duration of action, although it may give rise to more severe side effects. (Grimson, Tarazi and Frazer, 1955a, 1955b; Maxwell and Howie, 1955; Winsor, 1955; Smirk and Hamilton, 1956).

Adamson, Billinghurst, Green and Locket (1956) have described another interesting group of unsymmetrical bis-onium salts containing a benzhydrylalkyl structure, and satisfactory clinical trials of two members of this group in the treatment of hypertension were described by Locket (1956). More recently, McKendrick and Jones (1958) have reported a clinical study on the most active member of this series, *N'*-(5-cyano-5,5-diphenylpentyl)-*N'N'N''*-trimethylethylene-1-ammonium-2-morpholinium bismethylsulphate (pentacynium, Presidal), [XVI], in the management of hypertension and have found this agent to be of value; its side effects however, are similar to those of other ganglionic blocking agents. In a later publication, Locket (1958) has evaluated the hypotensive efficacy of compound 189c56, the 4,4-dichlorophenyl analogue of pentacynium, and has reported very favourably on this agent; it is invariably effective when given by mouth, and in a single daily dose it consistently produces the expected degree of hypotension. However, the dosage of this drug would seem to be highly critical since a slight alteration in the controlling dosage leads to a marked effect on the extent and duration of the hypotension.

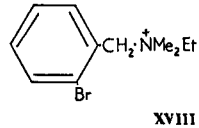
In recent years there has been a tendency to drift away from the use of quaternaries for treatment of hypertension, notable and successful examples of this being the development of mecamylamine and more recently pempidine (Lee, Wragg, Corne, Edge and Reading, 1958; Spinks and Young, 1958). Indeed, the quaternisation of pempidine (Bretherick, Lee, Lunt, Wragg and Edge, 1959) while increasing the ganglionic blocking activity, greatly diminished the duration of action and increased the oral toxicity. In spite of this trend, however, new quaternaries still emerge. For example, γ-trimethylammoniumpropyl-*N*-methylcamphidonium dimethylsulphate, (trimethidinium, Camphidonium, Ostensin) [XVII], which bears a superficial resemblance to the potent secondary amine, mecamylamine, has been recently clinically evaluated (Dunsmore, Dunsmore, Goldman, Elias and Warner, 1958; Borhani, 1959). Houston and Sears (1960) have shown that while the prolonged action of this drug was a great help, its main drawback, especially in high dosage, was its irregular absorption. This was not a major source of difficulty but it occurred sufficiently often to be a potential hazard to patients. Moreover, trimethidium sometimes gave irregular severe postural hypotension.

A recent development has been the introduction of bretylium tosylate (Darenthin) [XVIII], which is a hypotensive onium salt with a new type of action. It is one of a series of benzyl quaternary ammonium compounds described by Boura and his associates (Boura, Copp and Green, 1959; Boura, Green, McCoubrey, Laurence, Moulton and Rosenheim, 1959); the pharmacology of this compound was investigated by Boura and Green (1959) and others (Boura, Copp, Duncombe, Green and McCoubrey, 1960; Duncombe and McCoubrey, 1960). In animal experiments,

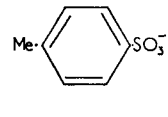
bretylium selectively blocks the peripheral sympathetic nervous system by an action on the adrenergic nerves, in which it selectively accumulates; it does not inhibit the effects of circulating or injected adrenaline or noradrenaline. Bretylium has no apparent effect on the parasympathetic or central nervous systems. Boura, Green, and others (1959) found this drug to be orally effective in man, and recommended its extensive trial in the treatment of hypertension. However, later reports by other workers were not so favourable (Dollery, Emslie-Smith and McMichaels, 1960; Evanson and Sears, 1960; Hurley, Page and Dustan, 1960; Lowther and Turner, 1960). Although by the elimination of parasympathetic blockade, the development of bretylium marked a "break through" in hypotensive therapy, it must be accepted in the face of this evidence that in its present form the drug is unsuitable for long-term treatment of hypertensive patients (Leishman, 1961), despite the fact that some patients who have been submitted to unremitting ganglionic blockade for years are almost lyrical in their enthusiasm for bretylium (Dollery, 1960). Even now there is still interest in the clinical possibilities of bretylium, and recent notes have discussed the mechanism of the acquired tolerance that develops in hypertensive patients who initially respond to the drug (Green, 1961; Laurence and Nagle, 1961; Lowe, 1961; Montuschi, 1961; Zaimis, 1961).

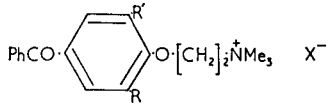


XVII

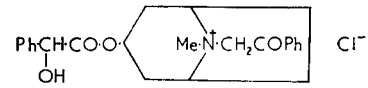


XVIII





XIX



XX

Boura and his co-workers (Boura, Coker, Copp, Duncombe, Elphick, Green and McCoubrey, 1960) have continued to investigate the hypotensive activity of monoquaternaries, and have recently described the compound 172C58 [XIX, R = R′ = Me], which is a less active hypotensive agent than bretylium; its main value would seem to be as a pharmacological tool, its advantages over bretylium being its more rapid and readily reversible action and its freedom from sympathomimetic properties. The same workers have also investigated the related compound 225C59 [XIX, R = H; R′ = Br], which although possessing similar adrenergic neurone-blocking properties, produces muscarine-like effects at high dosage. Many chemical variations on the compound 172C58, which included branching or lengthening the chain, additional substitution or hydrogenation of the 4-benzoyl group and several variations of the groups in the 2- and 6-positions and in the cationic head, have led to lower activities.

The plethora of commercially available antihypertensive agents reflects both the difficulties encountered in the treatment of hypertension and the absence of the ideal drug. A further onium salt now available is phenacyl homatropinium chloride (phenactropinium, Trophenium) [XX], a quaternary derivative of homatropine; this is a powerful ganglionic blocking agent which was recommended by Robertson, Gillies and Spencer (1957) for use in the production of controlled hypotension during surgery. Eyre-Walker (1961) has reported favourably on its use in gynaecological cases. In addition to its ganglionic blocking and antihypertensive actions, phenactropinium is a powerful inhibitor of cholinesterase and pseudocholinesterase (Lehmann and Patston, 1958), which suggests that it may, under certain circumstances, potentiate the neuromuscular blocking action of suxamethonium.

Nádor and Gyermek (1958) have reported on the activities of a series of quaternary derivatives of atropine, structurally related, to some extent, to phenactropinium. Of these compounds the one most worthy of note is Gastropin, the 4-diphenylmethyl quaternary derivative of atropine, which combines marked ganglionic blocking activity with only slight parasympathetic paralysing action.

It is evident that the number of onium compounds with ganglionic blocking and hypotensive activity is large and continually increasing. Moreover, except in certain limited examples, there is no well defined structure-activity relationship, and it is therefore unlikely that activity in compounds of widely different structure can be interpreted in terms of a single mechanism of action. However, in the case of bisquaternary compounds, the relationship between ganglionic blocking activity and inter-quaternary distance has been discussed by Gill (1959).

The laboratory evaluation of ganglionic blocking agents (Lewis and Muir, 1960) and their clinical use in the treatment of hypertension (Birchall, Weber and Batson, 1956; Liertzer, 1957; Page, 1957; Turner, 1959; Mackinnon and Hammond, 1960; Leishman, 1961; Smirk, 1961; Turner and Lowther, 1961; Wien, 1961) have formed the subject of several excellent reviews within the last 5 years. In addition, the proceedings of a symposium on hypotensive drugs and the control of vascular tone in hypertension has been published (Harington, 1956).

Anti-acetylcholine Agents and Anticholinesterases

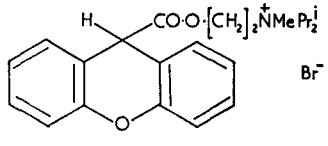
The effects of anti-acetylcholine agents on the body resemble the effects produced by cutting the parasympathetic nerve supply to the various tissues and organs. This anti-acetylcholine effect does not arise from a suppression of acetylcholine formation but from a failure of the liberated acetylcholine to stimulate the effector cell. Drugs of the atropine-alkaloid series are classic members of this group. The anti-acetylcholine action of atropine cannot be fully utilised in clinical practice because of the numerous side-effects of the drug. Attempts have been made to synthesise compounds in which spasmolytic properties predominate specifically over undesirable effects on the cardiovascular system; the resulting group of compounds form the so called "spasmolytic" drugs,

which have wide application in the treatment of gastrointestinal disorders and of certain spastic disorders of the biliary and genito-urinary tracts. It is important at this stage to draw a distinction between the two types of spasmolytic drug, the atropine-like drug (neurotropic), and the papaverine-like (musculotropic); it is in the former class that onium compounds occur.

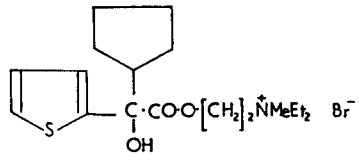
It was amongst tropic esters of amino alcohols that useful synthetic spasmolytics were first discovered, for example the γ-dimethyl-amino-neopentyl ester (amprotropine phosphate, Syntropan) (Fromherz, 1933, 1934, 1937). Compounds based upon atropine such as methylatropinium nitrate (Eumydrine) and mandelyltropine methobromide (Novatropine) followed, but did not achieve any notable success. More successful compounds were the simple quaternary derivatives of hyoscine, for example the methobromide (methscopolamine, Pamine) and the butobromide (Buscopan).

Methanthelinium bromide (Banthine), while once widely used in the treatment of peptic ulcers, has now been largely replaced by the analogue, β-di-isopropylaminoethyl xanthen-9-carboxylate methobromide (propantheline, Pro-Banthine) [XXI], which is more potent, and exhibits less severe, although not less frequent, side effects. Scott and Sutherland (1956) have reported that the pain relieving properties of propantheline rendered it a valuable addition to current methods of treatment of duodenal ulceration.

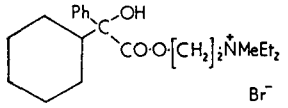
Another potent gastric antisecretory and spasmolytic agent in man (Kirsner and Palmer, 1953) is penthienate bromide (Monodral) [XXII], the pharmacology of which has been described by Luduena and Lands (1954). A further effective onium salt is oxyphenonium bromide (Antrenyl), [XXIII], which after satisfactory pharmacological investiga-



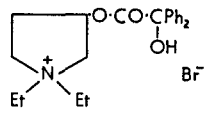
XXI



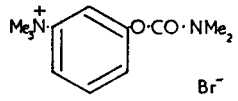
XXII



XXIII



XXIV



XXV

tions (Plummer, Barrett, Rutledge and Yonkman, 1953; Barrett, Rutledge, Plummer and Yonkman, 1953), was shown to have spasmolytic properties comparable to atropine, and to give good results in the treatment of peptic ulcer in man, its freedom from bitterness being a distinct advantage in its use (Rowen, Bachrach, Halsted and Schapiro, 1953).

This compound has also been recommended for pre-anaesthetic medication to reduce salivary secretion and to prevent laryngospasm or bronchospasm (Stephen, Bowers, Nowill and Martin, 1956).

Several other onium salts are to be found in this class of drug, but most of these have achieved only partial or moderate success in their clinical use. Specific examples are, 3-diethylamino-1-phenyl-1-cyclohexyl propan-1-ol ethochloride (tridihexethyl, Pathilon); 3-pyrrolidino-1-phenyl-1-cyclohexyl propan-1-ol methochloride (tricyclamol, Elorine); 4-diphenylmethylene-1,1-dimethylpiperidinium methosulphate (diphemanil, Prantal); 1-(3-hydroxy-5-methyl-4-phenylhexyl) piperidine methobromide (Darstine); and 1-ethyl-3-piperidyl benzilate methobromide (pipenzolate, Piptal). Recently, Sterkel, Brucker and Knight (1958) have described the benzilate of 1,1-diethyl-3-hydroxypyrrolidinium bromide (benzilonium bromide, Portyn) [XXIV] as a potent anti-acetylcholine agent, useful in the treatment of duodenal ulcer; this drug became commercially available only last year.

As with hypotensive agents, there is a very large number of drugs, both quaternary and non-quaternary, available for use in the treatment of the various ulcerous conditions which specifically respond to anti-acetylcholine drugs. It would seem that the ideal drug for the treatment of peptic and duodenal ulcers has yet to be found, which is not surprising since, in spite of the high incidence of this complaint and in spite of much intensive research, the cause is still uncertain. The use of anti-acetylcholine drugs in the treatment of these ulcers has been the subject of several reviews (Cayer, 1956; Roth, Wechsler and Bockus, 1956; Texter and Ruffin, 1956; Texter, Smith and Barborka, 1956; Bachrach, 1958), although Hadley (1961) in discussing the medical treatment of peptic ulcer, has stated that "drugs are relatively unimportant".

It would seem that quaternary ammonium anti-acetylcholine drugs have been mainly used in the treatment of gastrointestinal ulcers, and have played little part in the wider spectrum of application common to many of the non-quaternary anticholinergic drugs. For example, anti-acetylcholine drugs have an accepted rôle in relieving the rigidity and tremor of postencephalitic Parkinson's disease (paralysis agitans), and other basal ganglion disorders; in addition these drugs have been found to be successful in controlling or mitigating the Parkinson-like syndrome that may occur with continued high dosage of the phenothiazine tranquillisers. While many successful drugs in the treatment of Parkinsonism have been acid addition salts of tertiary amines, there seems to be little or no evidence that quaternisation of these bases produces agents of any therapeutic value.

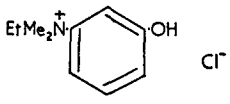
An interesting example of the diversity of action of onium salts is the fact that, although some show potent anti-acetylcholine action, others potentiate the action of acetylcholine by their anticholinesterase activity. The most important natural anticholinesterase is physostigmine (eserine), one of six alkaloids isolated from the seeds of *Physostigma venenosum*, a perennial vine found in West Africa. This alkaloid achieved early notoriety from the use of the seed—the Calabar bean—as an ordeal poison

in native witchcraft trials. As early as 1863, Robertson recorded strong miosis when treating himself with an extract of the bean, and as a consequence suggested its use in ophthalmology. Stedman (1926), and Stedman and Stedman (1929), attempted to discover the part of the molecule which was responsible for activity and found esters of *N*-methylcarbamic acid to be the most effective of the compounds studied. Further investigations on dialkylcarbamic esters were carried out by Aeschlimann and Reinert (1931) who found the most active anticholinesterase to be the quaternary, neostigmine (Prostigmine) [XXV]. This drug was originally introduced into therapeutics for its stimulant action on the intestinal tract; some 4 years later it was found to be markedly effective in restoring muscle strength in myasthenia gravis (Walker, 1935), and superior in its action to physostigmine. Its use has continued in the diagnosis and treatment of this condition. With the introduction of the curare-like neuromuscular blocking drugs into clinical practice, this very versatile onium salt has fulfilled a further rôle as an antagonist to these agents. Much work has since been done on the development of other synthetic anticurare agents; edrophonium (Tensilon) [XXVI] was discovered as a curare antagonist following a systematic analysis of the pharmacological activity of phenolic onium salts closely related to neostigmine (Randall, 1950), and has since been introduced as a therapeutic agent with a selective action on the skeletal myoneural junction. Osserman and Teng (1956) have described the successful use of edrophonium as a diagnostic agent for myasthenia gravis in over 300 patients, and also reported on its value in the differential diagnosis of myasthenic from cholinergic crisis. Recent experimental studies have been made by Nastuk and Alving (1958–59), who investigated the properties of edrophonium and some closely related analogues on activity at the neuromuscular junction, particularly in augmenting muscle tension output, the time course of this augmentation effect, and the anticurare activity.

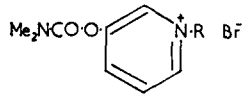
Various heterocyclic analogues of neostigmine have been studied and some have achieved clinical success. Thus benzpyrinium bromide (Stigmonene) [XXVII, R = CH_2-Ph] has been used in the United States as an anticholinesterase drug for the treatment of post-operative abdominal distention and urine retention (Anon, 1951); however, it does not appear to have been used in this country. One of the main disadvantages of neostigmine is its short duration of action, and pyridostigmine (Mestinon) [XXVII, R = Me] was introduced by Tether (1954), who found it to have a rather longer action and to be less apt to cause side-effects on the alimentary canal. Later reports have confirmed that pyridostigmine offers definite advantages over neostigmine in the treatment of myasthenia gravis (Churchill-Davidson and Richardson, 1955; Lange, 1955; Tether, 1956).

Ambenonium chloride (Mytelase) [XXVIII], introduced for the management of myasthenia gravis by Schwab, Marshall and Timberlake (1955), resembles pyridostigmine in that it also is a cholinesterase inhibitor having activity similar to that of neostigmine. As with pyridostigmine, the somewhat more sustained action and lower incidence of gastrointestinal

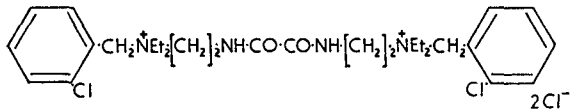
side-effects of ambenonium offer distinct advantages when compared with neostigmine. The pharmacology of ambenonium has been described by Lands, Karczmar and their associates (Lands, Karczmar, Howard and Arnold, 1955; Karczmar, 1957; Lands, Hoppe, Karczmar and Arnold, 1957; Lands, Hoppe, Arnold and Kirchner, 1958). More recently Blaber (1960) has investigated the antagonism of muscle relaxants by ambenonium and its methoxy analogue in the cat, and found that although both compounds possessed anticholinesterase activity, there was no correlation between their relative abilities to antagonise tubocurarine paralysis and their abilities to inhibit muscle cholinesterase *in vitro*.



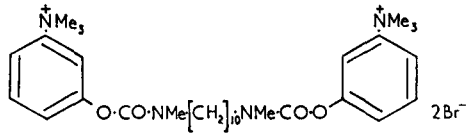
XXVI



XXVII



XXVIII



XXIX

It is evident, therefore, that of the drugs used in the treatment of myasthenia gravis, onium salts derived initially from physostigmine seem to be the only really successful agents; although organophosphorus cholinesterase inhibitors have been investigated in this context, they have been found to be uncertain in their action and liable to frequent and uncontrollable toxic effects. The status of drugs currently used in the treatment of myasthenia gravis has been summarised by Turner (1959), and a most important review on synthetic analogues of physostigmine has been made by Stempel and Aeschlimann (1956). A general review by Holmstedt (1959), although dealing primarily with the pharmacology of organophosphorus cholinesterase inhibitors, does contain a section on quaternary ammonium anticholinesterases.

So far, we have dealt primarily with the use of anticholinesterase onium salts in the management of myasthenia gravis, and as antagonists to curare-like agents. Anticholinesterases are however, of value in the treatment of glaucoma, and both physostigmine and neostigmine have been used for this purpose. Whereas both of these have a short duration of action, decamethylenebis(*m*-dimethylaminophenyl-*N*-methylcarbamate)

dimethobromide (Demecarium bromide) [XXIX], a potent and long-acting anticholinesterase, has recently been found by Krishna and Leopold (1960) to be an effective agent in the control of glaucoma, confirming reports by earlier workers. This drug offers distinct advantages over the established agents, although it does possess certain disadvantages which necessitate caution in its use.

A novel and recent development in the design of synthetic quaternary ammonium anticholinesterases has been described by Thomas (1961a, b), who has reported on the activities of a series of heterocyclic spiran quaternary ammonium salts, in which the two rings are linked together by a common nitrogen atom, thus providing a rigid molecule. Although as yet there is no evidence that compounds of this general type may eventually prove to be of therapeutic value, this structure does offer new and interesting stereochemical possibilities.