REVIEW ARTICLE

QUATERNARY AMMONIUM COMPOUNDS IN MEDICINAL CHEMISTRY. II*

By P. F. D'Arcy, B.Pharm., Ph.D., M.P.S., and E. P. Taylor, B.Pharm., B.Sc., Ph.D., F.R.I.C.

The Research Division, Allen & Hanburys Limited, Ware, Hertfordshire

Chemotherapeutic Activity

Antimicrobial Agents

The field of antimicrobial chemotherapy has grown enormously over the past quarter of a century, and shows every sign of increasing at an even greater rate. The chemotherapeutic application of onium compounds has received a tremendous impetus since the end of the Second World War. Many members of this family have been shown to possess marked *in vitro* antibacterial activity, while others, as has been described, possess useful pharmacological and pharmacodynamic actions; in addition, recent studies have disclosed potent antifungal activity in many onium salts. Whilst the antibiotics and the sulphonamides have been responsible for the major advances in the oral and systemic treatment of bacterial infections, the onium compounds are largely restricted to topical use for local infective conditions because of their poor and unpredictable absorption from the gut, and their toxicity when injected parenterally. At the present time much concern is felt over the increasing development of strains of bacteria resistant to the antibiotics, particularly in hospital wards. The development of bacterial resistance to onium salts is rare, and our own repeated attempts to produce strains of such resistant bacteria have been uniformly unsuccessful. This absence of onium resistant bacterial strains is a definite stimulus to research aimed at the discovery of new, less toxic onium salts possessing more predictable absorption.

In the general field of asepsis, one of the most useful properties of onium salts is their surface activity. Cationic surface-active agents dissociate in aqueous solution into a relatively large and complex cation, which is responsible for the detergent action, and a smaller, usually inactive, anion. The cationic onium group may consist of a comparatively simple aliphatic ammonium, a pyridinium or piperidinium or other heterocyclic group, and usually contains a long chain alkyl group with 8 to 18 carbon atoms. In addition to the emulsifying and detergent properties usually connected with surface-active agents, these cationic compounds often have a marked antimicrobial activity associated with low toxicity and freedom from irritant effects when applied topically. In general, such onium salts are more effective in neutral solution; although reasonably stable to acids, the antibacterial activity of onium salts is appreciably diminished in acid

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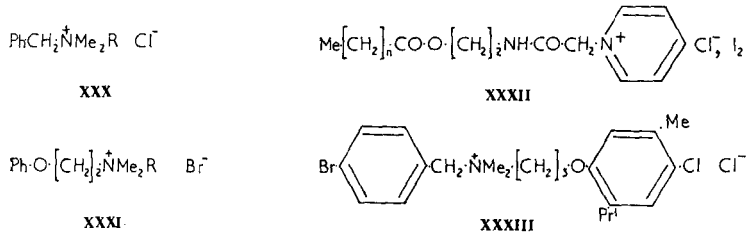
conditions. Normally, the antimicrobial properties of cationic onium salts are diminished or abolished in the presence of anionic substances such as soaps. However, a new development has been reported by Rebold and his colleagues (Rebold, Monte Bovi and Medici, 1958) who described the activity of a number of onium compounds, particularly lauryldimethyl-3,4-dichlorobenzylammonium 2-mercaptobenzothiazolate, which are unusual in that they apparently retain full bacteriostatic activity even in the presence of soaps.

One of the earliest successful quaternary ammonium antimicrobials is cetrimide (CTAB), a mixture of dodecyl-, tetradecyl-, and hexadecyltrimethylammonium bromide. The spectrum of antibacterial activity of this agent embraces both Gram-positive and Gram-negative organisms. Although primarily a general purpose and skin sterilising agent, the use of cetrimide has been recently suggested as an antifungal agent in swimming baths, since *in vitro* studies have shown it to be active against the growth of *Trichophyton* species and *Epidermophyton floccosum* (Garland, 1959). Some related compounds showing similar antimicrobial activity include cetylpyridinium chloride, laurylpyridinium chloride, benzethonium chloride, and more important, benzalkonium chloride [XXX, R = alkyl from octyl to octadecyl]. This latter compound, which like cetrimide is not a single chemical entity, is the active constituent of Roccal, and is a general purpose and skin sterilising agent; it has found specific use against urea-splitting organisms in alleviating and preventing napkin rash and the associated secondary infective conditions. A further useful member of this class is domiphen bromide (Bradosol) [XXXI, R = mainly dodecyl]. Solutions of this salt are non-toxic and non-irritant to skin, and have been used for application to wounds and burns, in obstetrics and urology, and for rapid antibacterial and antifungal disinfection of the patients' skin before operation. In addition, it has a general application, for example the disinfection of linen and utensils. Domiphen has been incorporated into antiseptic throat lozenges, and has shown success in the treatment and prophylaxis of infection of the mouth and throat.



XXX XXXII

XXXI XXXIII

Two other cationic surface-active agents have rather confusingly been marketed under the same name, although having entirely different chemical structures. Thus Desogen is a 10 per cent solution of a mixture of trimethyl-1-*p*-tolylalkylammonium methanesulphonates, which when diluted, is used as a non-irritant antiseptic for the treatment of infected wounds, and in gynaecology and midwifery; the solution may also be used for storing sterilised surgical instruments. Desogen lozenges are throat lozenges

containing dimethyl-2-*N*-methyldodecanamidoethyl (phenylcarbamoylmethyl) ammonium chloride, used in the treatment of bacterial and monilial infections of the mouth and throat. This salt was originally introduced as a topical and general household disinfectant and detergent.

A new and most interesting development in the application of quaternary ammonium salts has been the formation of a complex of iodine with an onium salt, acylcholaminoformylmethylpyridinium chloride [XXXII, n = 6 to 12]. This complex has been found to be effective as a vaginal douche in monilial infections, and is also used for the local treatment of fungal infections of the scalp and feet. It differs from other surface-active quaternaries in that the antimicrobial activity of the complex is derived almost wholly from the elemental iodine, which is slowly released on contact with skin and mucous membranes. The quaternary constituent of this complex merely provides a wetting action, which facilitates contact of the iodine with the surface areas. Unlike tincture of iodine, this complex does not cause stinging or irritation, and in addition does not stain the skin or clothing (Anon, 1959).

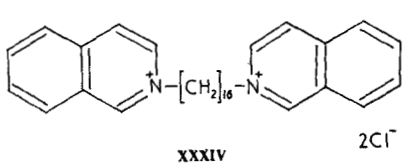
Halopenium [XXXIII] is yet another antimicrobial onium salt, and although originally prepared in 1942, it has only recently been marketed, formulated into a lozenge, for the treatment of *Candida* infections of the mouth and throat.

So far, all the onium compounds mentioned in this section of the review have been monoquaternary salts. Many bisquaternary ammonium compounds also possess marked antibacterial and antifungal activity, although they may be devoid of any appreciable surface-active properties. Examples of this are the polymethylene-bisquinolinium and -bisisoquinolinium salts, of which perhaps the most important is hedaquinium chloride (Teoquil) [XXXIV]. This compound has been shown to possess good antibacterial activity (Collier, Potter and Taylor, 1953) and it is also effective as a fungistatic agent *in vitro* over a wide spectrum of pathogenic fungi (Collier, Potter and Taylor, 1955); additional observations on the biological properties of hedaquinium have been published by Collier, Cox, Huskinson and Robinson (1959). Clinical studies have shown hedaquinium to be effective in the topical treatment of fungal infections, especially those due to *Trichophyton* species, both in man (Colin-Jones, 1958) and in animals (Gold and Jones, 1958; McPherson, 1959a, b). Hedaquinium is probably the most active antifungal agent *in vitro* of the quaternaries, and has been selected as a reference standard in the evaluation of the activity of other potential antifungal agents (Renzi, Garner and Burger, 1958).

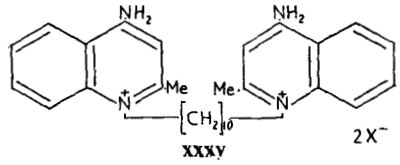
Dequalinium (Dequadin) [XXXV] is a further bisonium compound with a very wide antimicrobial spectrum, being active against both Gram-positive and Gram-negative bacteria and many pathogenic fungi (Babbs, Collier, Austin, Potter and Taylor, 1956; Collier and Grimshaw, 1958; Collier and others, 1959). The main indications for the use of dequalinium, which has recently been reviewed (Wilkinson, 1959), are in the treatment of bacterial and fungal infections of the mouth, throat and skin (Coles, Grubb, Mathuranayagam and Wilkinson, 1958); in addition

dequalinium is of considerable value in the treatment of specific fungal infections, notably Lingua nigra—"Black hairy tongue" (Stockdale and Banks, 1959), and of the varied forms of monilial infestation. Roddie (1958) and Levinson (1959) have found dequalinium to be effective in the treatment of trichomoniasis in women, whilst Catterall (1960) has shown that moderately satisfactory results in the treatment of trichomonal urethritis in the male can be obtained by urethro-vesical irrigations with solutions of dequalinium chloride.

The veterinary use of dequalinium for the local treatment of wounds has been favourably described by Fowler and Jones (1957). In addition an interesting development in the possible application of dequalinium has been the demonstration that this agent is effective against *Candida albicans* and *Pityrosporum ovale* (D'Arcy, Cox, Hedge and Wilkinson, 1960; Cox and D'Arcy, 1961). The latter yeast-like organism is associated with dandruff in man, and although there is much contention whether it is the specific infective agent causing dandruff, or whether it is a saprophyte only on human scurf causing allergic skin reactions, it is certain that its continued presence on the human scalp is far from desirable. In initial clinical investigations dequalinium has proved highly effective in seborrhoea and infective dandruff (Colin-Jones, private communication). Other quaternaries have shown some activity against dandruff, and this use has been reported by Lesser (1952) in his excellent review on the cause and treatment of dandruff.



XXXIV



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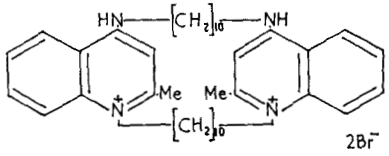
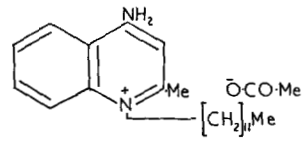


XXXVI



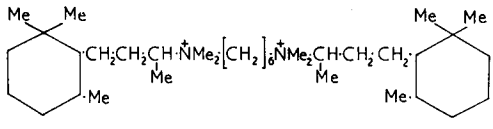
XXXVII

Kasparek and Stark (1960) have described the toxicity of an onium salt [XXXVI], closely related in structure to dequalinium, but as yet no information on its antimicrobial activity has been reported.

Recently, it has been shown that monoquaternary derivatives of 4-aminoquinaldine, which resemble half the dequalinium molecule, especially 4-aminoquinaldinium laurylacetate (Laurodin) [XXXVII], have marked antibacterial and antifungal properties (Cox and D'Arcy, 1959). In a comparative survey of a series of common skin antiseptics under ward conditions, Verdon (1961) has reported the efficacy of a solution of this substance as a standard pre-injection skin disinfectant. Recent studies

by Caldwell, Cox, D'Arcy and Rowe (1961) have shown that the analogous 4-aminoquinolinium salts have also good antimicrobial activity although they are slightly less potent than the corresponding quinaldinium salts.

So far, attention has been drawn only to those quaternary salts that have achieved therapeutic application; but much other work has been reported which indicates that there may be several onium salts yet to be introduced into this field. Thus Gadebusch and Cavallito (1957) have described the broad antimicrobial spectrum of a series of diquaternary salts of α,ω-bis-(2,2′-dipyridylamino)alkanes, while Schnitzer, Grunberg, DeLorenzo and Bagdon (1959) have reported the local antimicrobial activity of an interesting derivative of β-ionone, triclobisonium chloride (Triburon) [XXXVIII].



XXXVIII

Onium salts have obviously an important and widening rôle in the control and treatment of localised infective conditions. Although there are few reviews on this general topic, the antifungal activity of onium salts has been included in a recently published review (Taylor and D'Arcy, 1961).

Surface-active Agents

During the past 20 years, a vast range of synthetic materials, including many onium compounds, has been introduced to displace soap from its formerly unique position as the sole available detergent. Many onium salts have both antimicrobial and detergent properties and this valuable combination of activities is being widely used in cosmetic formulations, although this application is comparatively recent. The use of quaternary ammonium compounds in cosmetics has been reviewed by Lincoln (1954).

Prophylactic deodorants function by killing or inactivating the bacteria which are normally responsible for the decomposition of perspiration into odoriferous products. Arising from this, onium compounds have been found useful in antiperspirant formulations, and are often the only active odour inhibitors in various deodorant preparations. In addition, many skin dusting powders now contain a proportion of an antimicrobial quaternary.

Recently attention has been drawn in the medical press (Anon, 1958; Boheimer, 1958), to the failure of detergents to disinfect. This is of particular importance in connection with the disinfection of hospital wards, bedding and linen, since much concern is now felt over the comparatively widespread development and dissemination of bacterial strains, particularly Staphylococcal, resistant to many of the antibiotics in current use (Gillespie, Simpson and Tozer, 1958; Timbury, Wilson, Hutchison and Govan, 1958; Finland, Jones and Barnes, 1959; Hassall and

Rountree, 1959; Koch, Kastensen and Resnick, 1959; Elias-Jones, Gordon and Whittaker, 1961). It is considered that inefficiently disinfected blankets may serve as a continual reservoir for re-infection (Thomas, Liddell and Carmichael, 1958; Anderson and Sheppard, 1959). A further source of hospital infection is from the noses of healthy individuals, which probably form by far the largest breeding-ground for the pathogenic staphylococci (Williams, Jevons, Shooter, Hunter, Girling, Griffiths and Taylor, 1959), whilst localised infections (for example, boils) in theatre staff may also give rise to post-operative wound infections in patients (Mitchell, Timbury, Pettigrew and Hutchison, 1959). It would seem that onium salts could be useful in this field, both as topical agents for skin application and as general disinfectants for all-purpose cleansing; however, the choice of the correct onium salt is obviously of prime importance since it is well known that many Gram-negative bacilli, especially *Pseudomonas pyocyanea*, are unaffected by some quaternaries (Anon, 1958). The importance of the whole question of the prevention of infection in hospitals is emphasised by the fact that the entire January (1961) issue of the *Journal of Clinical Pathology* was devoted to this subject. The use of onium salts in this context receives favourable comment.

Several good reviews of the general use of onium compounds as germicides are available for more detailed study, for example Lawrence (1950) and de Benneville (1956); Sykes (1958) has fully discussed the whole field of disinfection and sterilisation. Several other publications deal with the evaluation of disinfectant and surface-active agents (Cook, 1959; British Standard 3286, 1960; Anon, 1960), while Hugo (1957), in a most interesting review, discussed the mode of action of antiseptics.

Antiparasitic Agents

Modern improvements in the facilities for world travel have caused a wide distribution of many diseases and infections previously localised in comparatively obscure regions. One of the few tangible benefits of the Second World War was the stimulation of organised effort in the search for new drugs in the chemotherapy of tropical diseases. The ubiquitous biological activity of the onium compounds has made them an obvious choice for detailed examination as antiparasitic agents and many have been shown to have activity.

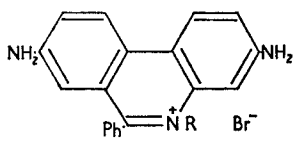
Trypanosomiasis

Trypanosomes have a notable place in the history of chemotherapy, being the causative agents of a group of diseases widely distributed in man and animal species. There are two main forms of trypanosomiasis in man; one is African sleeping sickness, caused by *Trypanosoma gambiense* and *T. rhodesiense*, and the other, prevalent in South America, is Chagas' disease caused by *T. cruzi*. Horses and cattle in certain tropical areas are also subject to trypanosomiasis, due mainly to infections by *T. brucei*, *T. congolense*, *T. vivax*, *T. equiperdum*, *T. equinum* and *T. evansi*. Infection of cattle is often very widespread and large areas, especially in tropical Africa, are held back from full development because of this.

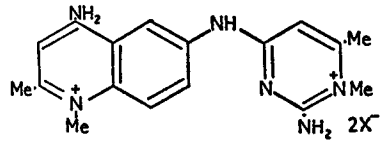
Thus in addition to the obvious rôle played by antitrypanosome agents in the clinical treatment of man and animals, the successful use of these drugs exerts a large economic and sociological influence. The nature of the problems of animal husbandry and management in these tropical areas has made the development of very long acting prophylactic or therapeutic drugs a major consideration in the chemotherapy of this disease. In the treatment of man also, the nomadic habits of many of the indigenous peoples renders continued treatment equally difficult.

One of the earliest observations on trypanocidal activity of onium salts was made by Browning, Cohen, Ellingworth and Gulbransen (1929), who investigated the properties of various styrylquinolines and their derivatives, which although promising in their activity were rejected after field trials. One of the most important steps in the application of onium compounds to the treatment of trypanosomiasis was the introduction of the phenanthridinium compounds. The first compounds of this type were synthesised by Morgan and Walls (1938) and examined by Browning, Morgan, Robb and Walls (1938). In 1948, Browning, Calver and Adamson described the high trypanocidal activity of 2,7-diamino-9-phenyl-10-methylphenanthridinium bromide (Dimidium) [XXXIX, R = Me], the preparation of which had earlier been reported by Walls (1947); this substance was widely used and achieved considerable success in the treatment of cattle trypanosomiasis. In subsequent years, a wide variety of phenanthridinium compounds was investigated for trypanocidal activity, but it was not until 1952 that the remarkable effect of changing the quaternising group of Dimidium from methyl to ethyl was discovered. In this year, Watkins and Woolfe (1952) first described homidium bromide (Ethidium) [XXXIX, R = Et], which although differing from Dimidium only in this one respect, proved much more active in laboratory experiments and in field trials in cattle infected with *T. congolense*.

Meanwhile other workers were following up leads originally developed by Jensch (1937, 1950) and as a result Curd and Davey (1949, 1950)



XXXIX



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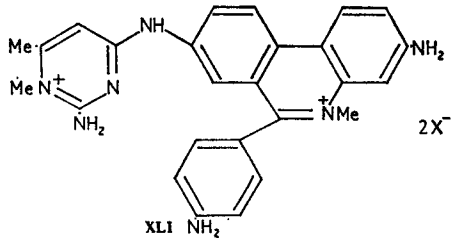


described the very active compound quinapyramine (Antrycide) [XL]. This drug is very useful since apart from the curative action of its readily soluble methosulphate, the less soluble chloride is more slowly absorbed and therefore possesses potent prophylactic properties. This has particular application to the problem of drug treatment of trypanosomiasis, which is three fold, involving (*a*) the treatment of early cases, (*b*) the treatment of advanced cases and (*c*) prophylaxis. A number of drugs are effective in combating early infections, but only a few penetrate into the central nervous system to kill the parasite. In cattle trypanosomiasis, prophylaxis is of vital importance, since it enables the cattle to be driven from the raising area through the wide belt of tsetse fly infestation to new grazing grounds or to market with safety.

An interesting development has been reported by Watkins and Woolfe (1956), when they first described the use of Prothidium [XLI] for the prophylactic treatment of trypanosome infections in cattle; this drug combines certain structural features of both Dimidium and quinapyramine. Robson (1958) has described a field trial in Zebu cattle in which he compares the prophylactic activity of homidium, quinapyramine and Prothidium. Homidium, although effective, produced severe local reactions, whereas Prothidium, at single dosage, and quinapyramine, at repeated dosage at 2-monthly intervals, gave good protection without severe reactions.

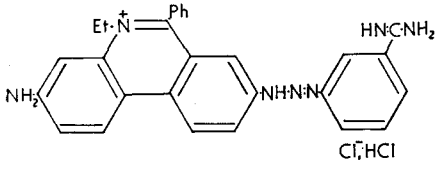
In 1958, Wragg, Washbourn, Brown and Hill described a new derivative of homidium prepared by coupling *m*-amidinobenzenediazonium chloride and homidium chloride. An approximately equal mixture of two isomers was obtained, one purple, the other red, which these authors originally thought to differ only in the position of the diazoamino group. The red isomer was found to be the more active against *T. congolense* infection in mice, both therapeutically and prophylactically. In practice, however, the mixture of the two isomers, which has been assigned the common name of Metamidium chloride hydrochloride, has proved to be the most promising trypanocide since it shows excellent prophylactic properties at a dose one ninth that of the LD50 value. This is of interest, since neither the parent compound homidium nor the non-quaternary drug Berenil, with which Metamidium shows some structural similarities, has any appreciable prophylactic activity at a dose equivalent to one-third of the LD50. Stephen (1960) has shown that Metamidium is a successful prophylactic agent against trypanosomiasis in cattle.

Further chemical study (Berg, 1960) has shown that the formulae provisionally suggested for the two isomers present in Metamidium (Wragg and others, 1958) have to be modified. The red isomer is now shown to be 7-*m*-amidinophenyldiazoamino-2-amino-10-ethyl-9-phenylphenanthridinium chloride hydrochloride [XLII], a structure which was originally assigned to the purple compound. Recent investigations into the structure of the latter have revealed it to be an isomeric aminoazo compound. Concurrently, the original coupling reaction has been studied and conditions have been established under which the red isomer is the main product formed, the ratio of red : purple being as high as 9 : 1; the pure

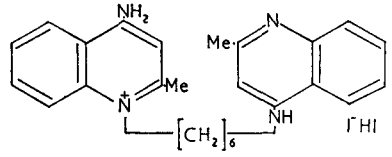
red product can be readily isolated by standard procedures. This red isomer is now termed isoMetamidium and its trypanocidal activity has been confirmed in cattle, the results of field trials in Africa being encouraging (Berg, 1960).

In the course of their systematic study on the chemotherapeutic activity of polymethylenebisquaternaryammonium salts, Austin, Collier, Potter, Smith and Taylor (1957) described the trypanocidal activity of bisonium derivatives of 4-aminoquinaldine. The hexamethylene member of this series was at first thought to be highly active against *T. congolense* in mice, but it was later shown that this activity was due to the presence of an isomeric impurity, the hydriodide of 6-(4-quinaldylamino)hexyl-4-aminoquinaldinium iodide (Tozocide) [XLIII]. This compound was highly effective in both therapeutic and prophylactic experiments, the latter studies being made with the suramin salt. In field trials in Africa however, the prophylactic activity was disappointing although the therapeutic action was confirmed in cattle. At this point attention may be drawn to the potential prophylactic value of suramin salts of most trypanocidal agents. This concept of fortifying the trypanocidal activity of an agent and simultaneously producing an insoluble form suitable for use in depot therapy was developed by Williamson and Desowitz (1956), following an original study by Guimaraes and Lourie (1951). Nowadays, it would seem to be routine practice to prepare and examine the suramin derivative of any new trypanocidal agent.

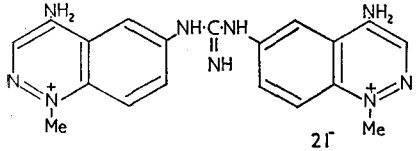
A further compound which also showed promising activity in initial studies was the cinnoline compound 528 [XLIV], described by Keneford, Lourie, Morley, Simpson, Williamson and Wright (1948) and by Lourie, Morley, Simpson and Walker (1951). This substance was found to be an active trypanocidal agent against *T. congolense* infections in mice, with a therapeutic index not significantly different from that of quinapyramine; however, it does not appear to have survived the rigours of field trials.



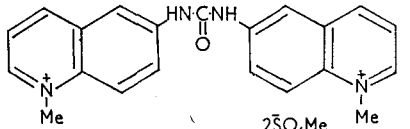
XLII



XLIII



XLIV



XLV

A most interesting feature in the development of many synthetic trypanocidal onium compounds is, that often the final active compound of a series has eventually been shown to have a constitution different from that originally ascribed to it, the activity proving to be due to the presence of

an impurity in the original material submitted for testing. This occurred with quinapyramine, Tozocide and Cinnoline 528; there was also some confusion between the Metamidium isomers.

In addition to this outline of the activity of trypanocidal onium salts, further details are given in excellent general reviews by Walls (1951), Ing (1953) and Davey (1957); furthermore, an excellent general review dealing with the African trypanosomiasis problem as a whole has been published by Nash (1960).

Babesiasis

Babesiasis (piroplasmosis) is an endoparasitic disease of cattle and other mammals (surprisingly enough, man appears to be immune) which is caused by species of *Babesia* and *Theileria.* Bovine redwater, one of the most common forms, is the name given to a condition due to *B. bovis* infestation. Piroplasmosis in its various forms is widely distributed in many animal species throughout the world. It has been observed that many trypanocidal compounds are quite active against babesiasis, in particular against *Babesia* infections in mice (*B. rodhaini*). Thus Beveridge (1956), when investigating the activity of more than 200 phenanthridine and phenanthridinium compounds against *B. rodhaini* in mice, found that the general requirements of chemical structure for babesicidal activity were similar to those for trypanocidal action. Similarly, Taylor, Terry and Godfrey (1956) showed that quinapyramine and homidium were effective against babesiasis in mice, although certain other known trypanocidal agents were found to be ineffective. In our laboratories, Spurling finds Tozocide to be only slightly active against *B. rodhaini* in mice.

The agent currently used for over 25 years in the treatment of British bovine redwater is quinuronium sulphate (Acapron, Babesan, Pirevan, Piroparv) [XLV], first described by Kikuth (1935–36). However, quinuronium has the disadvantage that even in therapeutic doses it produces toxic effects associated with parasympathetic stimulation (Ashley, Berg and Lucas, 1960).

In an excellent review on the chemotherapy of babesia infections, Ryley (1957) described, *inter alia*, the properties of two new babesicidal compounds,4-amino-6-(2-amino-1,6-dimethylpyrimidinium-4-amino)2-phenyl-1-methylquinolinium dichloride (compound 10,073), and 1,1′-dimethyl-4,4′-dimethylamino-6,6′-diquinaldiniumamino dimethylsulphate (compound 14,911). The latter is somewhat similar to quinuronium in constitution, whilst compound 10,073 is related to quinapyramine; both substances are highly active against *B. rodhaini* infections in mice, whilst in splenectomised calves and dogs, compound 10,073 was shown to have excellent activity after a single subcutaneous dose against *B. bovis* and *B. canis* respectively.

Very recently, Berg and Lucas (1961) have described a new babesicidal onium salt, 6-(*m*-amidinophenyldiazoamino)-4-amino-1,2-dimethylquinazolinium chloride hydrochloride, [XLVI], which, it is interesting to note, incorporates the *m*-amidinophenyldiazoamino structure present in iso-Metamidium, the trypanocidal agent which originated from the same

laboratories. This compound is active against *B. canis* infections in dogs.

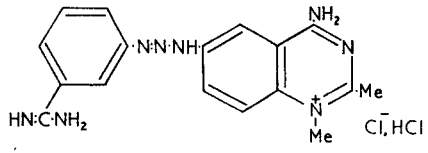
Although it is by no means an ideal drug, quinuronium has not been superceded in general veterinary practice; but, it must be emphasised that in this field much research is being carried out on non-onium babesicidal agents, particularly 3,3'-diamidinocarbanilide di-isethionate (Amicarbalide) (Ashley and others, 1960; Beveridge, Thwaite and Shepherd, 1960; Lucas, 1960).

Rodhain (1951), Ryley (1957) and Canache Mata (1959) have reviewed the progress of babesiasis and its chemotherapy in small laboratory animals, whilst Wright and Woodford (1958) have presented a brief review of bovine piroplasmosis in this country.

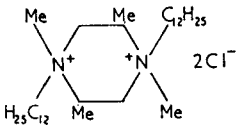
Helminthiasis

In 1947, Stoll surveyed the helminth parasites of man, and came to the startling conclusion that the number of helminthic infections in the world was 2,257,100,000; this figure was greater than the total world population at that time, and illustrates the principle that "wormy" people frequently harbour several different species of helminth at the same time. It is estimated that over 800,000,000 people throughout the world are infected with helminths.

As in other fields, World War II proved to be a stimulus to research, and workers have continued to focus their attention on chemotherapeutic studies of helminthic diseases; several new compounds, including some onium salts, have achieved some success. Although efficacy and safety are of prime importance in an anthelmintic compound, cheapness is also desirable, since in general, in human infections the hosts are often members of the lowest economic group of a poor country. Furthermore, worm infestation of cattle also presents a serious problem to the economy of under-developed areas. Helminth diseases both human and animal, are caused by a wide variety of parasites; these have been enumerated by Brown (1960) in a comprehensive article surveying the actions and uses of anthelmintics. A good anthelmintic must therefore possess a wide spectrum of activity since the worm burden of both man and beast may include several different species of parasite.



XLVI



XLVII

Piperazine and its salts, which have been widely used over the past 10 years, are amongst the best established chemotherapeutic agents in this field. More recently, mono- and bis-quaternary piperazines have been investigated, principally by Harfenist and his colleagues (Harfenist, Fanelli, Baltzly, Brown, Hussey and Chan, 1957; Brown, Hussey, Chan,

Harfenist, Fanelli and Magnien, 1959). The most successful compound reported by this group is the highest-melting isomer of 1,4-(2,5-*trans*)-tetramethyl-1,4-bis-dodecylpiperazinium dichloride [XLVII], which was found to be very effective *in vivo* against the mouse pinworm, *Syphacia obvelata*; so far, there have been no clinical reports of the activity of this drug in man or cattle.

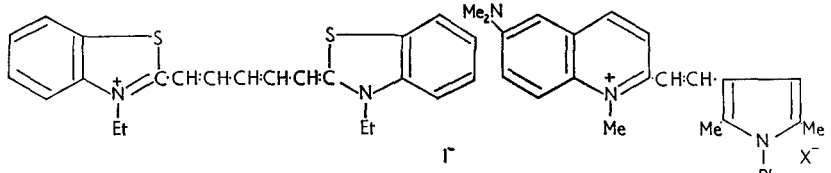
Some polymethylene-bisonium compounds possess appreciable anthelmintic activity, in particular against filarial infections and against the tapeworm, *Hymenolepsis nana*. Thus Hawking and Terry (1959) and Taylor and Terry (1960) have investigated the antifilarial activity of a number of onium salts against *Litomosoides carinii* in the cotton rat; these compounds were mainly polymethylene-bisisoquinolinium salts of chain lengths varying from dodecamethylene to tetracontylene. The octadecamethylene and eicosylene compounds were the most effective in these laboratory studies although later toxicity trials in dogs in our laboratories indicated that these compounds caused severe venous irritation and were therefore unlikely to be of practical value. The eicosylene member was also examined, amongst other compounds, by Sen and Hawking (1960) for *in vitro* cesticidal activity against the tapeworm *Hymenolepsis nana*, and was found to be one of the most active of the compounds studied.

The cyanines constitute an interesting group of onium salts which were originally developed for use in the photographic industry. Two members of this series, dithiazanine iodide (Abminthic, Delvex) [XLVIII] and viprynium salts (Pyrvinium, Vanquin) [XLIX], have quite recently achieved success in the treatment of anthelmintic infections. Cyanine dyes as a class are sparingly soluble and poorly absorbed from the gastrointestinal tract; their high concentrations in the intestine after oral administration exert an inhibitory effect on the anaerobic metabolic reactions of certain intestinal helminths.

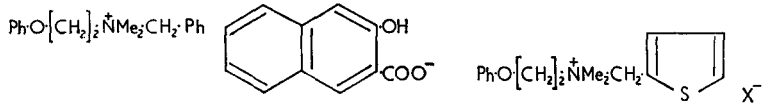
Dithiazanine has achieved clinical success against several worm infestations of man, although in others it is less effective. Thus, it is extremely active against *Strongyloides stercoralis*, and in this respect is superior to many other anthelmintics (Brumpt and Ho-Thi-Sang, 1959; Lloyd, 1959). It is also active in the treatment of trichuriasis in man (Brumpt and Ho-Thi-Sang, 1959; Paine, Lower and Cooper, 1959), and against *Trichuris vulpis*, the canine whipworm (Bueding, Kmetec, Swartzwelder, Abadie and Saz, 1961). Dithiazanine is highly effective against pinworm infections, but since its use is associated with a much higher incidence of gastrointestinal side-effects than is therapy with piperazine, the latter agent is considered preferable (Brown, 1960). Dithiazanine is inferior, however, to piperazine in the treatment of ascariasis and is ineffective in patients with ancylostomiasis (Brumpt and Ho-Thi-Sang, 1959).

Pyrvinium chloride was shown by Weston, Thompson, Reinertson, Fisken and Reutner (1953), to be effective against pinworm in laboratory animals, whilst Bumbalo, Plummer and Warner (1958), found this drug to be effective in the treatment of enterobiasis in children. However, these authors consider that piperazine is still the drug of choice for the

treatment of this infection. More recently, Beck, Saavedra, Antell and Tejeiro (1959), concluded that both pyrvinium chloride and pyrvinium pamoate are comparable in curative value against enterobiasis in children, but that the pamoate was only about one-quarter as toxic as the chloride in animal tests. A marked advance over the customary multiple dosage was the cure rate of 96 per cent achieved by a single dose of the pamoate; similar results have been recorded by other workers (Biguet, Deblock, Capron and Machez, 1959; Komiya, Kobayashi, Ogawa and Kumada, 1960; Bisley, Davidson, Stewart, Wheatley and Wilson, 1961). Sanders and Hall (1960) have compared dithiazanine iodide and pyrvinium pamoate in the treatment of enterobiasis in both children and adults. Many of those treated with dithiazanine iodide vomited and did not complete the



XLVIII XLIX



L LI

course of treatment, but in those who completed the course, eradiction of the pinworm was generally achieved. In a series of 29 individuals given a single dose of pyrvinium pamoate, vomiting occurred in only one and the treatment eliminated the pinworms in the remaining 28 patients.

One of the most recent developments in the anthelmintic field was the discovery of bephenium (Alcopar) hydroxynaphthoate [L] by Copp, Standen, Scarnell, Rawes and Burrows (1958), which, as will be seen, is structurally related to the hypotensive onium salt bretylium. These authors reported that the bephenium series of compounds was highly active against a wide spectrum of helminths, but was relatively more effective against the mucosa-dwelling species of parasitic nematodes than against those living more freely in the lumen of the gut. Reporting on clinical trials against hookworm infection (*Necator americanus*) of man, Goodwin, Jayewardene and Standen (1958) found that bephenium was particularly suitable for the treatment of patients with advanced anaemia, diarrhoea, and heavy hookworm infection, because of its low toxicity and because no purge was necessary; similar results to these have also been reported by Gillies, Watson-Williams and Worlledge (1961). This drug was also found to be effective against roundworm (*Ascaris* species), which was present as a concurrent infection in many of these patients.

Simultaneously, Rogers (1958) investigated the excretion of bephenium salts in the urine of volunteers. Jayewardene, Ismail and Wijayaratnam (1960), have more recently reported on the use of this drug in the treatment of ascariasis in children, and found that the only disagreeable side-effect directly attributable to the drug was vomiting, which was significantly more in children under four years of age. However, the small dose recommended for the treatment of ascariasis could be safely given to any age group without causing anxiety.

The application of bephenium to the veterinary field has been widely studied by various workers. Thus, Rawes and Scarnell (1959), have recommended that this agent be used in the prevention and treatment of nematodiriasis and other forms of parasitic gastroenteritis in the unweaned lamb. Gibson (1960) has compared the efficacy of bephenium hydroxynaphthoate and bephenium embonate with those of two organic phosphorus compounds, Trolene and Neguvon, against *Trichostrongylus axei* in sheep. He supports the general view that both the phosphorus compounds are ineffective against this organism in sheep, and also finds that both the bephenium salts are less efficient than is phenothiazine against this infection. The hydroxynaphthoate is preferable to the embonate in the control of nematodiriasis since it has superior activity against trichostrongylid worms other than *Nematodirus* species. The anthelmintic activity of bephenium hydroxynaphthoate against the more common gastrointestinal *strongyles* found in Nigerian Zebu cattle has been investigated by Armour and Hart (1960). The drug is highly effective against *Cooperia* species and *Oesophagostomum radiatum* at all dosage levels used, but is only fully active against *Haemonchus* species and *Bunostomum phlebotomum* at the highest doses (225 mg./kg.). At this dose, *Trichostrongylus* species were satisfactorily eliminated in most animals, but not in all. In addition to its use in the treatment of human and cattle infections, bephenium hydroxynapthoate has proved to be highly effective in hookworm in dogs, but its introduction into this veterinary usage has been severely hampered by its emetic properties in the dog (Rawes and McIntyre, reported by Burrows, Clapham, Rawes, Copp and Standen, 1960). These latter authors have reported a series of compounds related to bephenium, one of which, 611C55 [LI], has been extensively tested in larger animals in the form of its *p*-chlorobenzenesulphonate. This drug is marginally more effective against *Ancylostoma caninum* and *Uncinaria stenocephala* in the dog, but is only minimally emetic at therapeutic doses. It also appears to be more effective against *Toxocara canis* and *Toxascaris leonina*. In contrast, compound 611C55 is substantially less effective than bephenium against some of the gastrointestinal *Trichostrongyles* in sheep. However, the development of compound 611C55 as an antihookworm drug in the dog is of considerable interest, since it combines high efficiency with only mild emetic properties in this vomit-prone animal; clinical trials of this drug against human hookworm infections are planned.

Several excellent reviews have recently appeared, which although primarily dealing with other compounds, have described the use of a

diverse number of onium salts as anthelmintic agents; the following are particularly worthy of mention: Watkins (1958); Cavier (1960); Brown (1960), and Watson (1960).

Amoebiasis

In view of the extraordinarily wide field of chemotherapeutic activity of the onium salts, it is interesting to note that very little has been reported on the activity of these compounds on two of the major scourges of mankind, malaria and amoebic dysentery. For some time the treatment of malaria with synthetic drugs has been the object of sustained investigation by many groups of workers; some of the recently introduced antimalarials are so highly potent, and have proved so successful, that the possible application of onium salts in this context would appear fruitless. However, it may well be that onium salts have a potential use in the treatment of amoebic dysentery, especially in view of their notably poor absorption from the gastro intestinal tract, which would be a positive advantage in the treatment of this condition. Some preliminary indications of activity of onium salts against *Entamoeba histolytica* have been found in the authors' laboratories; thus dequalinium is slightly effective when administered orally to young rats infected with *E. histolytica*,and Laurodin is also slightly effective but only at near toxic levels. Tetramethylenebis-7-aminoisoquinolinium salts also possess some *in vivo* activity (Austin, Lunts, Potter and Taylor, 1959).

A comprehensive review on the chemotherapy of tropical diseases has been published by Goodwin (1952), in which he deals *inter alia* with amoebiasis as well as a most detailed survey of all other important tropical diseases.

Comments and Conclusions

This review has summarised principally the activities of onium compounds in those human and veterinary spheres in which these agents have achieved some measure of experimental or clinical success. It is apparent that onium salts have a wide and diverse spectrum of activity extending from neuromuscular and ganglionic blockade, through anti-acetylcholine and anticholinesterase action, antimicrobial and antiparasitic activity to detergent and cosmetic adjuvant applications; activities that do not seem to have any well defined common mechanism of action. In spite of this versatility, it is obvious that there are many fields in which onium compounds are not effective. So far as is possible to ascertain, onium salts have found little, if any, use as local anaesthetics, antihistamine drugs, antiemetics, analgesics, tranquillisers, or antitussives; neither have they found application as CNS depressants nor as analeptics or CNS stimulants. It is difficult to envisage, with the wide interest that has been shown in onium compounds, that they have not been investigated for these actions; it is more probable that they have been fully examined and found wanting. Absence of specific activity in these instances may arise from, in part, the well known parenteral toxicity of onium salts as a class, and also to

their poor absorption after doses given by mouth, factors that automatically exclude many onium salts from the usual methods of administration. At this point, it may be worthwhile to mention that the poor intestinal absorption of onium compounds is a subject of current investigation; thus, Levine and Pelikan (1961) have studied the absorption of a single selected onium salt, benzomethamine. In unanaesthetised rats, using single- and multiple-loop preparations, they found that absorption was increased above control levels by fasting the animals and by perfusing the intestinal lumen with small quantities of water before the beginning of the experiments. Absorption was unaffected by mild mechanical manipulation of the gut; the amount of benzomethamine absorbed was found to be greatest in the intestinal segments closest to the pylorus. The presence of intestinal mucous material in the drug solutions uniformly decreased the amount of benzomethamine absorbed per quantity administered. It would also seem that where good *in vivo* activity is shown by onium salts, the mechanism of action does not involve the central nervous system. Therefore it may well be that these agents find difficulty in reaching central nervous tissue and would consequently not show any pharmacological effect in conditions which require the drug to act in the brain.

In the major sphere of their biological activity, quaternary ammonium compounds can be roughly classified into those with pronounced pharmacodynamic action, and those with anti-infective properties. In the former class, the future of onium salts, in our opinion, lies (*a*) in the development of new, safe hypotensive and ganglionic blocking agents, more predictable in their therapeutic use, and (*b*) in the discovery of new non-depolarising neuromuscular blocking agents. These latter agents must be short in action, easily controllable, and be capable of reversal by a harmless antagonist. Their fate in the body should not be affected by pathological changes, and their breakdown products should not exert any neuromuscular blocking action.

As anti-infective agents, perhaps the major requirement of onium salts is the discovery of a potent drug with a broad spectrum of antimicrobial action, devoid of toxic effects and unwanted pharmacological activity, but sufficiently well absorbed to produce effective blood and tissue levels of the drug when administered either orally or parenterally. This target, although formidable, should not present an unsurmountable problem, since many quaternary ammonium compounds, at present employed in the treatment of local infective conditions, are markedly effective against a diverse range of microbial species and many are active even in the presence of blood, serum, pus and tissue exudate. To our knowledge, strains of bacteria initially susceptible to onium salts do not subsequently become resistant. Only the potential toxicity and poor absorbability of the onium salts currently available prevent their use in general systemic therapy. In this field it would seem that research should be directed, not necessarily towards the development of more potent antimicrobial agents, but towards the transition of their known local activity to oral and systemic use.

Apart from the field of oral and systemic antimicrobial agents, an almost

equally important application of onium salts would seem to be in the treatment of the tropical diseases, and in this respect there are many indications of the potential efficacy of these salts. Undoubtedly there is still a tremendous need for cheap, long-acting and, if possible, single dose, anthelmintics, trypanocides and other antiprotozoal agents.

One problem to which there is, as yet, no complete solution, is the erection of a barrier between the sick patient and the airborne or dust-carried bacteria. Currently there are many reports of the incidence of bacterial infection in hospital wards, due to a variety of causes, not the least of which is the emergence of strains of bacteria resistant to the common antibiotics. Many of the so-called disinfectant-detergents fail to prevent the dissemination of bacteria, and it would seem that what is required is a really effective, but cheap onium compound, suitable for washing crockery, blankets, walls and floors, and also suitable for spraying into the air of the ward. It is appreciated that many onium salts may either possess undesirable, or lack suitable, properties for general disinfectant use. Thus, many are antagonised by anionic agents such as soaps, others have low solubilities in water, and several are expensive. On the other hand most onium salts are stable in aqueous solution, many are detergents as well as antiseptics, and a large proportion of these are highly active against bacteria in low concentration. One further possible application of onium salts, which has not yet received much attention, lies in the prevention of secondary infection after skin burns. It would seem that many onium salts could have particular application to this use because of their protein precipitating properties, since they would provide a sterile deposit of protein on the raw or exposed tissue surface. It must be emphasised however, that many such onium salts also delay wound healing when applied in high concentration, and ideally therefore a balance between these two contrasting effects must be sought.

The centenary of the first description of the biological activity of the onium salts by Crum Brown and Fraser will occur in less than 10 years time; in view of the very rapid development of medicinal chemistry during the post-war period, it is interesting to speculate on the advances that have yet to be made in the development of onium salts and their application to medicine. In the light of the current trend in research, new quaternary ammonium compounds should certainly have become well established in the treatment of tropical diseases, in the treatment of local, and possibly systemic, infective conditions and ought still to maintain their commanding position in pharmacodynamics.

Since this manuscript was written, we have received a copy of *Progress in Drug Research*, Volume 2, 1960, which contains *inter alia* an excellent article by Cavillito and Gray entitled "Chemical Nature and Pharmacological Action of Quaternary Ammonium Salts".

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