REVIEW ARTICLE

THE CHEMOTHERAPY OF TROPICAL DISEASES

PART II. DISEASES CAUSED BY RICKETTSIÆ, BACTERIA, SPIROCHÆTES AND WORMS

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IN Part I of this review recent developments in the chemotherapy of the tropical diseases caused by protozoa were summarised.[1] Part II deals with the more important diseases caused by rickettsiæ, bacteria and worms. The chemotherapy of virus diseases, including lymphogranuloma venereum and trachoma was reviewed recently by Findlay.[2] Gonorrhœa and syphilis, although important diseases of the tropics are outside the scope of the present review.

The most important advance in the treatment of many rickettsial and bacterial infections has been the use of antibiotics. The properties and range of activities of these drugs were summarised in this journal by Abraham.[3]

RICKETTSIAL DISEASES

Louse-borne (epidemic) and murine (endemic) typhus, scrub typhus (tsutsugamushi fever), Rocky Mountain spotted fever, fièvre bouttoneuse, rickettsialpox and Q fever are all diseases caused by rickettsiæ. These parasites are intermediate in size and organisation between the largest viruses and the smallest bacteria. In 1947, it was shown that chloramphenicol had marked activity against experimental rickettsial infections.[4] The first human cases of epidemic and endemic typhus were treated in Mexico,[5] and a team of American Army research workers headed by Smadel, took supplies of chloramphenicol to Malaya for a more extended trial against scrub typhus.[6,7] Fever is controlled very rapidly by the drug, but relapses occur if treatment is begun early in the disease, before the immunity response of the host is well-developed.[6,7,8] The action of the drug is rickettsiostatic and not rickettsiocidal; the immunity and defence mechanisms of the host finally destroy the parasite. Chloramphenicol is too expensive (and perhaps also too toxic[9]) for routine use as a prophylactic, and it is probable that the most satisfactory method of producing immunity will be by means of a living vaccine, with chloramphenicol to control the attack. Aureomycin and terramycin are effective against scrub typhus but chloramphenicol is considered to be the drug of choice.[10] Chloramphenicol is also active in Rocky Mountain spotted fever,[11,12,13] murine typhus[14] and epidemic typhus.[15,16] Aureomycin has given good results in rickettsialpox[17] and fièvre bouttoneuse,[18] and may be more effective than chloramphenicol in epidemic typhus.[15] It has given variable results in Q fever.[19,20] Terramycin is active against all rickettsial infections and has given good results in Rocky Mountain

spotted fever[21] and rickettsialpox.[22] It has high activity in experimental Q fever.[23]

Diseases Caused by Bacteria and Spirochætes

Bacillary Dysentery.

The introduction of the sulphonamides, all of which have some action against the dysentery bacilli, has greatly changed the position with regard to the treatment of this disease. Boyd[24] writes that: "The use of these drugs in bacillary dysentery is one of the major advances in tropical medicine, the advantages of which can be fully appreciated only by those who had experience of dysentery in the days before they were available."

The less readily absorbed sulphonamides such as sulphaguanidine, succinylsulphathiazole and phthalylsulphathiazole are most suitable for use in tropical climates because they have less tendency to produce renal damage when the fluid intake is low.

Plague.

A small epidemic of plague occurred in Taranto in 1945. It was satisfactorily controlled by determined public health measures for the destruction of rats and fleas.[25] In the treatment of the disease, sulphonamides have some action against the plague bacillus, but are not to be relied upon for the treatment of an established infection. They are of value for the prophylaxis of contacts; sulphadimidine and sulphadiazine are the most satisfactory derivatives.[26] The best drug used so far for the treatment of bubonic or septicæmic plague is streptomycin,[26,27,28,29,30,31,32] which rapidly aborts the attack. Streptomycin is of no value as a prophylactic because it is excreted too rapidly. Aureomycin and terramycin are effective against the plague bacillus, but all the antibiotics have the disadvantage of being too expensive for routine use on a large scale.

Cholera.

The problem of the treatment of cholera is a special one because death occurs from extreme loss of body fluids brought about by continued severe diarrhœa and vomiting. Unless the water and electrolyte balance of the patient is corrected, any chemotherapeutic treatment is worthless and may be harmful. In at least one instance, sulphonamides have actually increased the mortality in groups of patients to whom they were given, above the mortality in a control group which received no specific drugs.[33] A number of drugs are active against the cholera vibrio, but they are ineffectual unless given very early in the course of the disease, before serious fluid loss has complicated the picture. Experiments with chloramphenicol and terramycin in mice have shown that animals are protected if a small dose of drug is given within 5 hours of infection, but that enormous doses have no effect if given 7 hours after infection.[34] It has been suggested that chloramphenicol might be useful as a prophylactic in a population exposed to the risk of a cholera epidemic,[35] but this

drug is now known to be dangerous if given for prolonged periods.[9] Researches by Collier and his associates have shown a series of pteridine derivatives to be vibriostatic *in vitro*,[36] and to be effective in the early stages of infection in mice,[37] but no reports of clinical trials have yet appeared.

Enteric Fever.

Enteric fever is not confined to the tropics but is more common in warm countries in which the standards of sanitation are low and the water supplies may be suspect.

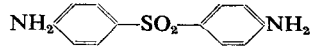
When Smadel and his team of American workers were making clinical trials with chloramphenicol against scrub typhus in Malaya, they noted that the drug also had a dramatic action upon typhoid fever.[7,38,39] At the end of the 3rd or 4th day the fever abated, and if treatment was continued for 14 days, few relapses occurred.[40] The drug has since been used in many areas with excellent results[41,42,43,44,45,46,47] and the mortality from the disease has been greatly reduced. Chloramphenicol is bacteriostatic; it does not prevent the occurrence of perforations or hæmorrhages caused by the separation of sloughs from existing lesions. With streptomycin and aureomycin available, it is now possible to treat complications of typhoid conservatively, but penicillin should not be used because it appears to have an action antagonistic to that of chloramphenicol. Polymyxin and aureomycin have no action against the typhoid bacilli.[39] Relapses are more common in people treated with chloramphenicol than in those which survive and recover from the disease without it, because it interferes in some way with the development of immunity. For the same reason, relapses are especially likely to occur in those who have been treated early in the course of the infection. Promising results have been obtained in the reduction of incidence of relapses, by intensifying the immunity response with injections of T.A.B. vaccine.[46,47] Chloramphenicol often causes vomiting; also, the release of endotoxin from dead typhoid organisms may cause an exacerbation of symptoms, with circulatory failure, early in the course of treatment. It is therefore advisable to begin with small doses of drug, and not with a large "loading dose." Cortisone reduces the effects of typhoid toxin, but increases the danger of perforation. Chloramphenicol has no permanent curative effect upon fæcal carriers of the typhoid bacillus.[39] Evidence is accumulating that in some patients, especially after prolonged administration of chloramphenicol, damage to the blood-forming tissues occurs, resulting in leucopenia or aplastic anæmia. This is likely to be a property of the nitrobenzene radical in the chloramphenicol molecule.[9]

Leprosy.

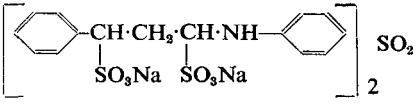
Leprosy usually takes one of two forms: the lepromatous, an active disease with nodules of granulation tissue in the skin and mucous membranes, and the neural in which the peripheral nerves are the main site of attack. Lepromatous leprosy has been treated for many years with chaulmoogra oil and its preparations. When used in large doses

for long periods the disease is controlled, but relapses are very common. Sulphapyridine was tried in leprosy; it produced an erythema nodosum (lepra) reaction, but had no beneficial action in doses which had toxic side-effects. However, the fact that a lepra reaction was produced, gave promise that among compounds related to sulphapyridine a specific for the disease might be found. The leprosy bacillus *Mycobacterium lepræ* is closely allied to *M. tuberculosis* and it is not surprising that the new drugs which have shown promise in tuberculosis have all found their way to clinical trial in leprosy.

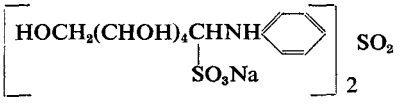
Sulphones. Dapsone (I, diaminodiphenylsulphone) was first tested against streptococcal infections in mice but was considered too toxic for use in man.[48] The less toxic derivatives solapsone (II sulphetrone, cimédone, 3668 R.P.), promin (III) and diasone (IV) followed and were shown to be effective in the treatment of lepromatous leprosy.[49,50,51,52,53,54,55,56]



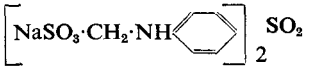
Dapsone (I)



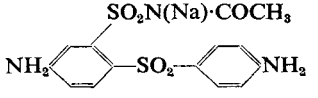
Solapsone (II)



Promin (III)



Diasone (IV)



Promacetin (V)

The substituted sulphones are expensive and large doses are required if they are given by mouth. They are broken down in the alimentary tract to the parent sulphone[57,58] and are wasteful. A return has therefore been made to dapsone itself, which, although more toxic, is cheap and is effective in small doses.

Although clinical improvement often occurs within a few weeks, the sulphones act slowly upon leprosy bacilli. First a change occurs in the morphology of the organisms, their multiplication is suppressed and the lesions regress. The patient frequently shows a lepra reaction, which is a good prognostic sign. The final disappearance of acid-fast material from the lesions may take years of continuous treatment and to ensure that cure is permanent, it is necessary to wait for a further period of 5 or more years because the recovery of surviving organisms and relapse of the disease is also a slow process. Neural leprosy and lepromatous eye lesions respond only poorly to sulphone therapy.

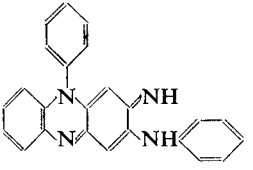
Lowe[59,60,61,62] has used dapsone by mouth in Nigeria and finds it to be cheap, effective, and free from serious toxic side-effects. Similar good results have been reported by Muir from India,[63,64,65] and by French workers.[66,67,68,69] However, the use of dapsone is not without its dangers, and the effective dose is not far removed from the toxic range. Apart from the lepra reaction, exfoliative dermatitis, anæmia, abdominal and joint pains quite frequently occur[67,70,71] and in W. Africa, mononucleosis,[71] toxic hepatitis[72,73] and psychosis have been reported. The patients are weak and depressed during the 2nd month of treatment although many become acclimatised during the 3rd to 8th months.[74] Lepra reactions may be rendered less troublesome by the use of antihistamine drugs, adrenocorticotrophic hormone or cortisone.[56,64,75] Some workers find it most convenient to give dapsone by injection in aqueous suspension,[76] or dissolved in oil, in chaulmoogra oil or its esters.[77,78] In India, where the anti-leprotic oils are much cheaper than the sulphones, advanced lepromatous cases have been given dapsone for 6 months to decrease their infectivity, and thereafter treatment continued with hydnocarpus oil.[79] Cochrane[80,81,82] finds dapsone to be suitable only if patients can be watched carefully for toxic reactions, and considers it too dangerous for mass-treatment in out-patient clinics. He agrees that it is wasteful to use substituted sulphones by mouth, but finds solapsone to be less toxic, and no more expensive than dapsone if it is given by injection. The fate of substituted sulphones given by injection is not yet clear. Solapsone partly dissociates in solution to form a mono-substituted derivative and is excreted as such, without appreciable breakdown into dapsone. It may be that monosubstitution is the normal method of detoxication of dapsone in the body, and if so it would be reasonable to give the substituted derivative by injection instead of risking the toxic effect of the parent sulphone by mouth.[82,83] French workers have reported similar properties for the monosubstituted succinyl derivative "1500 F."[84,85,86] "Sulphone cilag" (4:4′-diaminodiphenylsulphone-*N*-sulphate) and promacetin (V) are also effective; it has been shown that promacetin does not break down appreciably to dapsone in the body.[87]

Antibiotics. Although too expensive for general use, and too toxic for prolonged administration, streptomycin and dihydrostreptomycin have been found to be useful adjuncts to sulphone therapy. They are of particular value in tuberculoid leprosy, in cases with eye lesions, and in people with iodiosyncrasy to the sulphones.[56,88,89,90,91] Aureomycin is also useful for mucous membrane, skin and eye lesions[89,92]. Chloramphenicol is of little value.[93]

Thiosemicarbazone. Thiosemicarbazone is less active in leprosy than the sulphones and although clinical improvement frequently occurs, the bacteria remain and new skin lesions may develop during treatment.[94,95,96,97] It is a useful adjunct, especially in patients who are sensitive to sulphones.[91,98,99] The derivative amithiozone (4-acetylaminobenzalthiosemicarbazone) is also reported to have promising activity.[56]

Other Drugs. *p*-Aminosalicylic acid is not very active in leprosy, but is of use as an adjunct in some patients.[89] It is too early to judge the

value of isoniazid (isonicotinic acid hydrazide) but clinical improvement of lepromatous cases has been reported.[100] The phenazine dye "B283" (VI) has recently been used in Nigeria. Its action appears to be rapid and there have been no toxic side-effects, but it is too early to assess its value with certainty.



B.283 (VI)

Yaws.

This spirochætal disease usually responds rapidly to treatment with neoarsphenamine. A new arsenical preparation "STB" (4-oxy-3-acetyl-aminophenylarsenoxide), which is effective by mouth has recently been used with success,[101,102,103] but side-by-side comparisons with other methods of treatment have not been made. Antibiotics are also valuable in the treatment of yaws, particularly in cases which do not respond to the arsenicals. Procaine penicillin with aluminium stearate in oil is useful for mass treatment and is particularly effective in early cases.[104,105] Aureomycin[106,107,108,109] and chloramphenicol[110,111] are effective by mouth but not in every case. Results with terramycin have also been variable.[112,113]

The antibiotics, both locally and systemically, have given excellent results in the treatment of tropical ulcers.[114,115,116]

Relapsing Fever.

Louse-borne relapsing fever caused by *Treponema recurrentis* usually responds well to treatment with arsenicals. The tick-borne disease, caused by *Tr. duttoni*, is a much more difficult problem. Treatment with neoarsphenamine is rarely successful, unless given very early in the course of the disease.[117] Penicillin has proved disappointing in both the tick-borne and louse-borne infection.[117,118] Streptomycin has been reported effective against a strain of *Tr. duttoni* which was resistant to arsenicals and penicillin,[119] and aureomycin has also given promising results.[120,121] Tests with laboratory infections of *Tr. duttoni* in mice and *Tr. persicum* in rats have shown terramycin to have high curative activity,[122,123] and there is hope that the human infection may also be sensitive to this antibiotic.

Diseases Caused by Worms

Schistosomiasis.

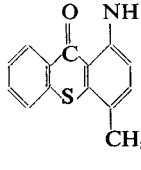
Schistosomes have a life-history similar to that of the liver fluke. The adult worms are found in the blood vessels of man, and the intermediate hosts are snails which live in irrigation canals and water-holes. *Schistosoma hæmatobium* infests mainly the veins of the bladder, and the passage of the spiny eggs through the wall causes inflammation, pain, hæmaturia and anæmia. *S. mansoni* infests mainly the large bowel, and heavy

infections also give rise to pathological changes in the liver and lungs. *S. mansoni* is common in S. America, and both species are widespread among the native populations of Africa and the Middle East; a recent estimate gave a figure of 12 million infected people in Egypt alone.[124] *S. japonicum* infests the small and large intestines and causes similar effects to those of *S. mansoni*; it is a serious public health problem in the Far East and the Pacific area.[125]

Many chemicals have been used to attack the parasite at various stages of its life-history; repellants such as dimethyl phthalate are effective for a time in preventing penetration of the skin by cercariæ, and many substances are used in campaigns against snails.

Organic Antimonials. Until recently, the only drugs of any value in the treatment of the infection in man were the organic antimonials. Tartar emetic, given by intravenous injection is a cheap but toxic remedy; work in Rhodesia has shown that it can be given intensively in short courses of large doses with surprisingly few serious accidents.[126] However, in patients with liver damage resulting from heavy *S. mansoni* infections the toxic effects have been more severe. Less toxic, but rather less efficient remedies are stibophen (fuadin) and anthiomaline which are widely used in Egypt, S. America and the Pacific Islands. Stibophen was introduced by Schmidt[127] in 1930 and the first reports of its use against *S. mansoni* and *S. hæmatobium* in Egypt were encouraging. Later, however, the proportion of failures increased,[128] and the drug has given varying results in the hands of different workers.[129,130,131,132] Against *S. japonicum* stibophen has also given variable results,[133,134,135,136] but schedules of treatment have also varied a great deal. The drug stops the production of eggs by the female worms while it is being given, but if the course is not sufficiently prolonged, the worms recover and relapses occur. Stibophen has the advantage of being less irritant than tartar emetic, and it is given intramuscularly. Anthiomaline has properties similar to those of stibophen, and has given similar results. Quinquevalent antimonials are of very little use in schistosomiasis, but the tervalent compound "triostam" corresponding to sodium stibogluconate (which is used in leishmaniasis[1]) has recently been used in Egypt,[137] Iraq[138] and Brazil. It appears to be less toxic than tartar emetic, but has not yet been used extensively enough for a true assessment of its value to be made.

Xanthone Derivatives. Kikuth and his colleagues have studied the action of a great many substances upon experimental *S. mansoni* infections in mice. They showed that members of a series of xanthone and thioxanthone derivatives were effective when given by mouth.[139,140,141] The most active compound was the thioxanthone derivative lucanthone (VII, miracil D, nilodin, R.P. 3735); the other related xanthone derivatives



Lucanthone (VII)

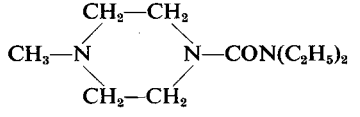
miracils A, B and C were either less potent, or too toxic at therapeutic dose levels to be of use. The series showed a high degree of specificity of action, and if the 4-methyl group of lucanthone was lacking, or was replaced by a chloro- or methoxy-group, the activity was lost. Also, unlike antimalarial drugs which have the same basic side-chain as lucanthone, any alteration in the length of the chain greatly reduced, or abolished activity.[142] Lucanthone has been found to be active against *S. hæmatobium* and *S. mansoni* in man when administered by mouth, provided that sufficiently long courses of treatment are given.[143,144,145,146,147] It has been less successful in *S. mansoni* than in *S. hæmatobium* infections, and from the small number of trials so far made, it appears to be of little value against *S. japonicum.* The drug has the disadvantage of causing gastrointestinal irritation, with nausea, vomiting and other side-effects in therapeutic doses. The side-effects are very much more troublesome among some peoples such as the Egyptians, than among others, and in susceptible individuals it is difficult to administer sufficient drug to cure the disease. A very full study of the action of different preparations of lucanthone was made by the Bilharzia Unit of the Medical Research Council and the Egyptian Ministry of Public Health between 1947 and 1950.[144] The sparingly soluble methylene-bis-hydroxynaphthoate caused less toxic reactions, but was less effective than the hydrochloride; the salicylate gave promise of being the most suitable salt. Enteric-coated tablets caused fewer side-effects, but among some peoples such as those of Rhodesia, produced fewer clinical cures than the uncoated tablets.[148,149] It is a very difficult matter to be certain that a patient has been cured of schistosomiasis, especially under conditions in which there is a constant risk of reinfection. Newsome states that: "If no serious idiosyncrasies appear and care is taken in the treatment of patients with badly damaged livers and kidneys, our impression is that a suitable miracil preparation will prove as effective but much less dangerous than tartar emetic, and more effective and less dangerous than fuadin."[144]

Filariasis.

Filariasis occurs in almost all tropical countries. The adult worms of *Wuchereria bancrofti* live in lymphatics and connective tissue; the larval forms or microfilariæ circulate in the blood. Long-standing occlusion of lymphatic drainage may result in elephantiasis, and where this is advanced, only surgical treatment is of value. *Onchocerca volvulus* lives in nodules in the skin and the microfilariæ are found in the tissue surrounding the nodules. For many years no satisfactory drugs were known for the treatment or prophylaxis of filariasis. Studies upon *Dirofilaria immitis*, a filarial worm of the dog,[150] indicated that organic antimonial compounds reduced the number of microfilariæ, but results of treatment with stibophen and other antimonials in man have been on the whole disappointing. Since 1944, *Litomosoides carinii* of the cotton rat has been used in the study of possible filaricides, and Culbertson[151,152,153] found neostibosan and neostam to be of value both in the laboratory infection and against *W. bancrofti* in man. Neostibosan

received only limited clinical trials because further extensive work with the cotton rat infection by Hewitt and his colleagues[154] led to the discovery of the action of the more active and less toxic piperazine derivatives.

Diethylcarbamazine. The most active compound of this series so far is diethylcarbamazine (VIII, hetrazan, banocide, R.P. 3799), which is now in use in many parts of the world. The drug is active by mouth



Diethylcarbamazine (VIII)

and causes rapid disappearance from the blood of the microfilariæ of most species of filarial worms. The most satisfactory salt to use is the dihydrogen citrate. Hawking, Sewell and Thurston[155] noted that in cotton rats which had received a dose of diethylcarbamazine, the microfilariæ were trapped in the liver sinusoids and attacked there by leucocytes. A similar action takes place with *W. bancrofti*[156] and *Loa loa*[157] in man. The action of the drug upon the larvæ resembles opsonisation, making them susceptible to attack by the host's defence mechanisms. In Puerto Rico,[158] Brazil,[159] Indochina,[160] E. Africa,[161,162] and the Dutch E. Indies,[163] diethylcarbamazine has proved effective in clearing the microfilariæ of *Wuchereria* from the blood; in some early cases elephantiasis has been reduced. There is still doubt as to whether the drug has a lethal effect upon adult worms,[164] but studies in Puerto Rico[165] and the Virgin Islands[166,167] showed that mass treatment of a population with diethylcarbamazine caused a drastic reduction in the percentage of mosquitoes carrying the infection and that the reduction of infection in both man and mosquito was maintained for a considerable time without further treatment. This suggests that there is a prolonged or permanent effect upon the adult worms, because otherwise they would have recovered and produced further broods of microfilariæ to infect the insect vectors.

Diethylcarbamazine sometimes produces headache, nausea and vomiting, but these side-effects are not usually serious. It also has the disadvantage (which must be shared by all drugs which kill filarial worms), that the death of large numbers of worms and the consequent release of foreign proteins may be accompanied by an allergic reaction. This is not usually severe with *W. bancrofti*, but is more troublesome with *W. malayi*[168] and with *Onchocerca.*[169,170] The reaction may be dangerous in *Onchocerca* infections, particularly in cases in which the eye is involved. The incidence of serious reactions may be lessened by administering an antihistamine drug; some workers give the antihistamine prior to the first dose of diethylcarbamazine.[171] Although microfilariæ of *Onchocerca* rapidly disappear from the tissues, diethylcarbamazine has very little action upon the adult worms of this species, which continue to live in the skin nodules.[156,172,173,174] Recent work in Guatemala[175,176] and the Gold Coast[177] has shown that suramin, or suramin together with diethylcarbamazine, are more effective than diethylcarbamazine alone in the

treatment of onchocerciasis. *Loa* infections respond well to diethylcarbamazine; both microfilariæ and adult worms are killed, and the proportion of allergic responses is high.[178,179,180,181] *Acanthocheilonema perstans* infections (which are non-pathogenic) are much more resistant and the drug has very little action upon either microfilariæ or adults.[161,182,183]

Other Drugs. A very large number of compounds has now been tested in experimental filariasis; a few have shown activity warranting clinical trial. Arsenamide (*p*-[bis-(carboxymethylmercapto) arsino] benzamide) which is active against *D. immitis* and *L. carinii*,[184] has been found of use in *W. bancrofti* infections,[185] and is considered to be worthy of further trial in onchocerciasis.[172] The organic antimonial M.Sb[1] has a prolonged prophylactic action in the cotton rat,[186] but has not yet been tried clinically. A number of styrylquinoline and cyanine dyes are effective in experimental filariasis[187,188] but so far none has had any activity in human infections.[188,189] Hawking[189] uses the example of the dye, methylene violet, to point out the desirability of making early clinical trials with any new series of chemotherapeutic substances.

Other Helminth Infestations.

A review of the chemotherapy of helminth infestations has been given by Wigand.[190] Nothing is yet known to act upon hydatids, paragonimus, trichinella, or the circulating larvæ of ascaris.

Tæniasis. Extract of male fern is the standard treatment for tape worm, but other drugs have recently been used. Mepacrine has given good results in some cases,[191,192] but the effective dose is very large and often produces vomiting. *Tænia saginata* has also been successfully treated by the introduction of an emulsion of hexylresorcinol directly into the duodenum.[193] *Diphyllobothrium latum* is sometimes resistant to treatment with male fern, and thymol has been advocated for this parasite.[194]

Ascariasis. Oil of chenopodium is still widely used for expelling round worms; it is effective, but toxic if used in large doses.[195] Diethylcarbamazine has been tried, but reports of its efficacy are conflicting.[196,197]

Enterobiasis. Threadworms are found both in tropical and temperate areas. Gentian violet and diphenan are used against them but neither is entirely satisfactory. Phenothiazine is still used in Germany,[198] although this drug is generally regarded as too toxic for use in man. Recently benzene hexachloride has been reported to give good results.[199]

Ankylostomiasis. Ankylostoma infests a very high proportion of native peoples in the tropics. Like many other helminthic diseases its control is largely a public health problem. Halogenated hydrocarbons such as carbon tetrachloride and tetrachlorethylene are the drugs most widely used against the worm, but are not without danger; it is not considered justifiable to use them for mass-treatment. There is need for an effective and non-toxic substance to eradicate these worms.

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[*Useful summaries, reviews and works of reference are marked with an asterisk.*]

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