REVIEW ARTICLE

THE CHEMOTHERAPY OF TROPICAL DISEASES

PART I. PROTOZOAL INFECTIONS

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THE chemotherapy of tropical diseases has seen great advances during the last ten years. The need to maintain armies in the tropics during the war, and increasing interest in Colonial development, has stimulated the search for new drugs. The latest edition of Findlay's *Recent Advances in Chemotherapy*[1] has had to be accommodated in four volumes, the first two of which deal almost exclusively with tropical diseases.

The assessment of the value of new drugs in the tropics is not a simple matter. The course of a disease in a native population is influenced by social and hygienic conditions, the state of nutrition, the presence of other infections in the same host and many other factors. Improvement of hygiene and the destruction of intermediate hosts of disease often make it difficult to estimate the value of chemotherapy given concurrently. After treatment, exposure to reinfection is often the rule; it is also difficult to follow treated patients for any length of time. The practice of using experimentally infected human volunteers, as in the study of malaria, is yielding very valuable results and reliable comparisons of the activities of drugs.

MALARIA

Fairley and his team of workers at Cairns, N. Australia, made important tests with antimalarial drugs upon experimentally infected normal men.[2] These tests paved the way for further controlled comparisons of drugs, especially in the U.S.A., and for many field trials. They also gave further evidence for the existence of tissue stages in the development of plasmodia infecting man. Shortt and his colleagues recently demonstrated[3] that the earliest stages of development of *Plasmodium vivax* and *P. falciparum* occur in the cells of the liver. These stages are very important from the point of view of chemotherapy.[4] All of the drugs used against malaria cause the death of trophozoites in the red blood cells; only a few have activity against primary or secondary tissue forms, or against the gametocytes which infect mosquitoes. The present views upon the value of drugs in the treatment of malaria are summarised in a number of reports.[5,6,7]

Quinine. Quinine is still used in the treatment of acute malaria because it acts so rapidly. It acts mainly upon trophozoites and has no appreciable effect upon *P. falciparum* gametocytes or upon tissue parasites. Quinine has the disadvantage of precipitating attacks of blackwater fever in some circumstances.

Mepacrine. Mepacrine has been widely used as a suppressant, and also for the treatment of acute malaria. It acts only upon trophozoites.[8]

It rarely causes toxic side-effects, although these have been well documented.[9]

Proguanil. The research upon the antimalarial activity of pyrimidine compounds which led to the discovery of proguanil is well known.[10] Since the war, the suppressant and curative properties of this drug have been tested in many parts of the world. It has a wide margin of safety, it cures most strains of *falciparum* malaria and suppresses all other species. It has some inhibitory effect upon the primary tissue forms of *P. vivax*,[11,12] but is not a certain cure, and relapses frequently occur when the medication stops.[13] Its action is slower than that of quinine, mepacrine and the new 4-aminoquinoline derivatives, and it is therefore not a good drug for the initial treatment of acute malaria.[14,15,16,17,18] Strains of parasite vary greatly in their sensitivity to proguanil, and unduly resistant strains have been encountered in West Africa,[17,19,20] Eritrea,[21] the Philippines,[22] and elsewhere. The sensitivity of the parasite to the drug may also be decreased by the presence of secondary infections such as infestation by worms.[23] By giving increasing sub-curative doses of proguanil it is easy to produce strains that are very resistant to the action of the drug. This has been shown with *P. gallinaceum*[24,25] in chicks, *P. relictum*[26] in pigeons, *P. cynomolgi*[27,28] in monkeys and *P. vivax*[29,30] and *P. falciparum*[31] in man. The resistance survives repeated and rapid passage,[32] and mosquito transmission.[33,34,35] Prolonged exposure of the exoerythrocytic forms of *P. gallinaceum*[36] or *P. vivax*[37] to proguanil (by giving full suppressive doses) has failed to produce detectable drug-resistance in the strain when it relapsed after the end of treatment; the resistance is therefore only produced in the trophozoites. Recent work with *P. cynomolgi*[38] suggests that the exoerythrocytic forms of this species may also become resistant. There is some evidence that human malaria in some parts of the world may be increasing slightly in resistance to proguanil.[39,40,41,42] In Malaya it has been recommended that other drugs should be used alternately with proguanil as suppressants, to minimise the risk of making drug-fast strains.[43] Gametocytes are not morphologically affected by proguanil in the mammalian host, but lose their power to develop in the mosquito.[44]

4-*Aminoquinolines.* A number of years ago German workers prepared a series of quinoline derivatives which included sontochin (I, nivaquine C, M, or R) and resochin (II, chloroquine, aralen, nivaquine B).[45] This series was re-examined in the U.S.A. during the war, and careful comparisons of activity and toxic side-effects were made. A new synthesis of chloroquine was devised[46] and large amounts of the drug are now manufactured. Sontochin and chloroquine are about equal in activity to mepacrine, and act more rapidly in acute malaria.[47,48,49,50] They have fewer toxic side-effects than mepacrine, and do not stain the skin. Chloroquine is usually effective against strains resistant to proguanil; it may be given by intramuscular[51] or intravenous[52] injection if the patient is too ill to swallow the dose. It is a good suppressant,[53,54,55] and in some areas is superior to proguanil.[55,56] The action of sontochin and chloroquine is upon the trophozoites, and there is no effect on

exoerythrocytic parasites or gametocytes. Camoquin (III), another member of the series, has similar properties to chloroquine but acts slightly less rapidly.[57] It has given good results as a suppressant and for treatment of acute malaria in Egypt,[58] South America,[59,60,61] the Philippines[62] and India.[63]

8-*Aminoquinolines.* This series of drugs has the property (which is not shared by any other known group of antimalarials) of killing the tissue stages of *P. vivax.* Pamaquin has long been known to do this, and when used with quinine or another schizonticide, effectively puts an end to relapses of *vivax* malaria in about 90 per cent. of cases.[64,65] Pamaquin has toxic effects and must be used with care. Pentaquine (IV) has properties similar to pamaquin and has been used with quinine or chloroquine for the cure of *vivax* malaria.[66,67,68,69] Isopentaquine (V) has activity equal to pamaquin but is less toxic.[70] The primary amine, primaquine (VI) is less toxic still, and is probably the best of the series of 8-aminoquinolines so far discovered.[70]

Other Drugs. A great survey of drugs was made in the United States during the war,[71] and many groups of compounds were shown to have antimalarial activity. Sulphonamides act upon young trophozoites in the blood cells; sulphapyrazine has been shown to be a useful suppressant.[72] Metachloridine [*N'*-(5-chloro-2-pyrimidyl) metanilamide] has an effect upon the sporozoites and early tissue forms of *P. gallinaceum*[73] but has proved very disappointing in human malaria. A new derivative of proguanil has been prepared which has higher activity upon exoerythrocytic parasites in experimental animals.[74] Proguanil itself is metabolised in the body to produce a highly active dihydro-triazine derivative; recent work has shown that the related compound, 2 : 4-diamino-1-(3 : 4-dichloro-phenyl)-1 : 6-dihydro-6 : 6-dimethyl-1 : 3 : 5-triazine is about 100 times as active as proguanil against *P. gallinaceum.*[75] One of a new series of 2 : 4-diaminopyrimidines has shown activity 50 to 200 times as great as that of proguanil[76] in laboratory infections; preliminary field trials in West Africa show that it also has very great activity against the schizonts of *P. falciparum.*[77]

There are still many problems to be attacked in the chemotherapy of malaria. There is as yet no prophylactic which affords complete protection against *P. vivax*, and no satisfactory drug is known which will protect by killing sporozoites as they are injected by the mosquito. There is also the great unsolved problem of the best way of treating native populations in hyperendemic areas, where the aim must be to assist the children to reach a stage of premunition or tolerance to the infection, without rendering the strains of parasite resistant to antimalarial drugs. Attempts have been made to do this in Java,[78] Indochina,[79] and elsewhere, but there is much truth in the closing remarks of a review of hyperendemic malaria by Bagster Wilson, Garnham and Swellengrebel[80]: "The optimum dosage of antimalarial drugs, and the choice of drug in the treatment of infants in order so to modify their attacks that mortality is eliminated and morbidity reduced to a minimum (without extermination of parasites) is in urgent need of study; for at present there is wide diversity of practice in this respect."

TRYPANOSOMIASIS

African Trypanosomiasis

The problem of the treatment of trypanosomiasis with drugs is threefold: (*a*) treatment of early cases, (*b*) treatment of advanced cases, and (*c*) prophylaxis. A number of drugs are effective in early infections but there are very few which penetrate into the central nervous system to kill the trypanosomes in advanced cases. Prophylaxis is now being tried in many areas with apparent success, but it is as yet too soon to know to what extent this will lead to cryptic infection. A useful general review of trypanocides was given recently by Walls.[81]

Suramin. Suramin has been in use for many years and is effective in the early stages of trypanosomiasis. It is especially valuable in *Trypanosoma rhodesiense* infections. It has no action in advanced sleeping sickness but it is used to supplement treatment with tryparsamide (see below). Suramin combines with plasma proteins and remains in the circulating blood for long periods; a dose given as a prophylactic is effective for 3 months. Suramin also has an inhibitory effect on enzymes; its properties have been studied by Wormall and his collaborators in a systematic attempt to discover the mode of action of the drug.[82,83]

Aromatic Diamidines.

Pentamidine. This drug has a powerful effect in early cases of *T. gambiense* sleeping sickness.[84,85,86,87,88,89] In *T. rhodesiense* infections it is said to be less effective than suramin,[90] but there are very few reports upon the use of pentamidine in this form of the disease. Against "intermediate" cases of *T. gambiense* sleeping sickness, pentamidine has given good results in some areas,[91,92] but it is not to be relied upon when an increased cell-count and protein content of the cerebrospinal fluid indicates that the central nervous system has become involved.[93,94] There is always a danger in such cases that a cryptic infection will continue and produce nervous lesions without trypanosomes appearing in the blood or lymphatics. Pentamidine is often effective in relapses after arsenical treatment,[95] but in advanced cases it is of no value alone, and must be given together with tryparsamide.[87,88,92] Pentamidine has some effect upon early cases when given by mouth, but produces diarrhœa and vomiting in some patients; the parenteral route is preferable. Pentamidine is now used widely as a prophylactic in African populations exposed to the risk of trypanosomiasis. Although in laboratory animals the protective effect of an injection lasts only for a month, it appears that in man it will protect for 4 to 12 months.[96,97,98,99,100,101] However, it is very important that a full survey of the population is made before the first prophylactic injection, because there is a likelihood that some people will be already harbouring the disease. These must be treated at once with a full course of drugs, or the infection may become cryptic and the opportunity for curing the patients easily will have been missed. Pentamidine is given by intramuscular or intravenous injection, either as the isethionate or the methanesulphonate (Lomidine). It has an irritant

effect when given intramuscularly but this is to be preferred to the alarming symptoms which occasionally follow intravenous injection and which are caused by the fall in blood pressure which the drug produces. It is dangerous to give the drug intrathecally.[86] It has recently been shown that many of the immediate pharmacological effects of pentamidine are greatly reduced when it is given together with suramin. The therapeutic action of the two trypanocides in combination is not likely to be affected, because they kill trypanosomes over much longer periods and at much lower concentrations in the blood than are required for the immediate effect upon smooth muscle and neuromuscular transmission.[102]

Propamidine. Propamidine is more toxic than pentamidine and may cause abortion when given to pregnant women.[103,104] Prophylaxis with propamidine has been reported to produce a high incidence of cryptic infections,[105] and the drug is now rarely used in trypanosomiasis.

Arsenicals.

Tryparsamide. Tryparsamide, which is reduced in the body to the active trivalent form, has the power of crossing the "blood-brain barrier" and killing trypanosomes in nervous tissue. It is still the mainstay of treatment for advanced cases, and is usually given together with pentamidine or suramin.[87,88,92,106] Unfortunately there is an increasing number of strains of trypanosomes found to be resistant to tryparsamide, especially in the Belgian Congo.

Melarsen, Melarsen Oxide, Mel. B. Organic arsenical compounds containing the melamine nucleus were introduced by Friedheim.[107,108] Melarsen (VII) is very active in early and intermediate cases[96] but has given variable results in more advanced cases.[109,110] Doses large enough to be useful sometimes produce serious toxic side-effects.[101,110] Melarsen oxide (VIII) is also of value in early cases,[111] and against tryparsamide-resistant strains,[101] but there is diversity of opinion as to its effectiveness in the later stages. Melarsen and melarsen oxide have been tried orally with good results in some cases, but they are more certainly effective when injected.[110] Mel. B (IX) is a compound of melarsen oxide with dimercaprol (B.A.L.); it has given good results in advanced cases and in infections which are refractory to all other forms of treatment.[92,112,113,114] Mel. B is usually effective against tryparsamide-resistant strains,[115,116] but will itself produce drug-resistance if the dose given is not large enough. Inadequate treatment with melarsen or melarsen oxide also renders trypanosomes resistant to Mel. B, and such strains are resistant to tryparsamide.[116] The disadvantage of Mel. B is that it sometimes produces serious toxic side-effects and in some trials, a high proportion of fatalities has occurred.[92,114,117] Attempts to control the toxic effects have been made using novocaine or *p*-aminobenzoic acid in animals, and by supplementary injections of dimercaprol itself in man, but there is no doubt that the drug should be given under close supervision in hospital and that it is unsuitable in its present form for general use in field dispensaries.[92,115] Some of the toxic effects and variations of therapeutic action of this group of drugs may be caused by difficulties in the

manufacture of batches of uniform quality. It is important that every batch should be controlled by biological tests.[118] It is too early to judge the future of the compounds, but Mel. B. is likely to be the most useful member of the series.[115,118] A melaminyl derivative of antimony "M Sb." (X) has shown promise in laboratory animals as a prophylactic[119] but there have been as yet only limited clinical trials.[113,115]

Butarsen (XI). This was introduced by Eagle[120] as a result of extensive experiments in the laboratory. The results of clinical trials have been disappointing because although it is active in the early stages of *T. gambiense* infections butarsen has no effect when the central nervous system is involved.[88,109,121]

South American Trypanosomiasis

Infection with *T. cruzi* is responsible for deaths in children and chronic heart disease in adults. It is found in South American populations living under poor conditions where the bug which is the vector of the disease flourishes. No drug is known which is really effective against the chronic stage of the disease. "Bayer 7602 (Ac)" (XII)[122] has proved to be of value in the acute stage in children,[123] but the drug is very irritant on injection and it has no effect on trypanosomes in the heart muscle. Butarsen has some effect, in the early stages of the disease only. In laboratory infections of *T. cruzi* in mice, activity has been shown with pentaquine,[124] and with some phenanthridine derivatives.[125,126] Only one of these compounds, 3-amino-9-*p*-carbethoxyaminophenyl-10-methyl-phenanthridinium sulphate, has so far been tried clinically.[127]

Trypanosomiasis in Cattle

The outstanding problem in cattle trypanosomiasis is the control of infections of *T. congolense* and *T. vivax*. These parasites are practically unaffected by all the trypanocides used in human sleeping sickness, and until the introduction of phenanthridinium compounds, the only drugs of any value were tartar emetic, stibophen and surfen C. The antimonials were of low activity and surfen C had undesirable toxic side-effects. The two phenanthridine derivatives phenidium, "897" (XIII) and dimidium, "1553" (XIV) were first used in the field about 10 years ago; dimidium was found to be the more effective drug.[128,129] The trypanocidal effect of dimidium has been proved in many areas, but the drug has the disadvantage of being irritant at the site of injection. Also, in some areas therapeutic doses cause considerable losses due to a toxic action, probably upon the liver, which may be accompanied by symptoms resembling photosensitisation of the skin. Phenanthridine compounds have no real prophylactic value. Further compounds of the series have recently been tried on a limited scale in the field.[118] The introduction of antrycide (XV)[130] gave reason to hope that the scourge would at last be effectively controlled, and that a mixture of antrycide methylsulphate and chloride given at 6-monthly intervals might be useful as a prophylactic. Antrycide has given good results as a curative drug,[130,131] but it is not without toxic side-effects in ill-nourished animals, and the effect

of the prophylactic mixture lasts for less than 90 days in areas where the tsetse fly density is high.[118] Also, resistant strains of trypanosomes are making their appearance and there is evidence that these are also resistant to dimidium.[132] Antrycide probably acts as a growth inhibitor of trypanosomes, and produces changes in the nucleoproteins of the cytoplasm.[133] It inhibits different enzyme systems from those affected by suramin. Trypanocidal cinnoline derivatives have recently been prepared,[118,134] but have not yet been tried in the field. There is still much to be done in the prophylaxis and treatment of bovine trypanosomiasis.

LEISHMANIASIS

Visceral Leishmaniasis (Kala azar)

Quinquevalent organic antimonials are still the most commonly used drugs for the treatment of kala azar. Aromatic diamidines are also effective, and of especial value in infections resistant to antimony. These two groups of compounds serve for the cure of almost all cases of kala azar.[135] In spite of much research upon laboratory infections no other series of drugs has yet been found to have any action in visceral leishmaniasis.

Antimony Compounds.

Derivatives of Stibanilic Acid. Probably the most widely used stibanilic acid derivative is urea stibamine, which is manufactured and used in India in large quantities. The drug is a mixture of compounds of phenylstibonic acid, and batches must be controlled for toxicity by biological tests. It is usually given by intravenous injection twice weekly; it has recently been given intensively in an intravenous drip. Other well-established phenylstibonic acid derivatives are neostibosan and stibamine glucoside. A new member of the series introduced recently is pentastib, the *p*-aminophenylstibonate of *N*-methylglucamine. This has had only limited trials.[136]

Quinquevalent "Emetic Type" Compounds. In stibanilic acid, the antimony atom is joined directly to a carbon atom of the phenyl ring. In tartar emetic the antimony atom is joined to carbon through oxygen. Antimony pentachloride reacts with a number of organic compounds rich in hydroxyl groups, such as gluconic acid, to form quinquevalent "emetic type" compounds of high solubility in water, and low toxicity. Such compounds are excreted rapidly, and are active in leishmaniasis. The first of these compounds to be used in kala azar was solustibosan, which had high activity in experimental leishmaniasis,[137] in spite of the fact that its action upon trypanosomes was very slight. Sodium stibogluconate replaced solustibosan during the war, and is now used extensively under various trade names. It is effective in all forms of kala azar,[138,139,140] even the Sudanese variety which is notoriously difficult to cure with antimony.[141] Schmidt[142] has taken pains to point out that sodium stibogluconate B.P.C. is "an uncertain approximation to solustibosan." It nevertheless gives good results. Sodium stibogluconate

rarely produces serious toxic side-effects, although rigors have been observed in one series of cases. An oily suspension of solustibosan has been used in Spain.[143,144] A similar "emetic type" compound is glucantime, the antimoniate of *N*-methyl glucamine. This has been used mainly in Algeria,[145,146,147] but has also been tried in Italy[148] and India.[149] Glucantime is superior to the corresponding stibanilic acid derivative, pentastib. It is very rapidly excreted in the urine.[145,150] Enormous doses of antimony have been given as glucantime with safety, but occasional toxic effects have been recorded. Tartar emetic itself was recently tried in large doses in an attempt to give a short, intensive, curative course for kala azar.[151] Apart from its cheapness, tartar emetic has little to recommend it now that safer remedies are available.

Aromatic Diamidines.

The diamidine first used in kala azar was stilbamidine, but although it was effective, especially in antimony-resistant cases, it was found that exposure to light rendered solutions of stilbamidine very toxic.[152,153] The toxic substance was shown to be the dimer, 1 : 2 : 3 : 4-tetraphenyl*cyclo*-butane.[154,155] Even freshly prepared solutions of stilbamidine have a toxic action on nervous tissue,[156] and the clinical use of the drug sometimes produces neuropathy, especially of the trigeminal nerve, which appears during the year following treatment with the drug and seems to be permanent.[157,158,159] For this reason, stilbamidine is now very rarely used. Pentamidine is used instead[135,160,161] and has approximately the same activity. It does not produce nerve lesions and is more stable. Phenamidine has also been found effective in kala azar.[162]

Another important development is the treatment of cancrum oris, a fatal complication of kala azar, with penicillin.[163,164] This controls secondary bacterial infection, and greatly improves the prognosis.

Mucocutaneous Leishmaniasis (Espundia)

South American Leishmaniasis is more resistant than kala azar to chemotherapy. Antimonials have been tried, sometimes with success, but relapses frequently occur.[165,166] A similar condition found in the Sudan usually responds to treatment with antimonials or pentamidine. In South America, a large variety of drugs has been tried, including mepacrine, sodium formaldehyde sulphoxylate and arsenicals. Penicillin has no effect in this condition.

Dermal Leishmaniasis (Oriental Sore)

Leishmaniasis of the skin has been treated with X-rays, local injections of berberine, or by intravenous antimonials. More recent treatments include the local injection of mepacrine or of solustibosan. None is entirely satisfactory.

AMŒBIASIS

Papers and review articles upon methods of treatment for amœbiasis frequently appear in the press.[167,168] This is evidence that although there are many remedies for the disease, none is entirely satisfactory. A fair

statement of the present position is given in the review by Anderson and Hansen.[167] There are three main types of amœbic infection:—

(1) The symptomless carrier state in which the host passes cysts in the fæces.
(2) Amœbic dysentery in which the amœbæ form extensive ulcers in the bowel wall.
(3) Spread of the infection from the intestine to the liver, producing amœbic hepatitis or abscess.

A number of drugs are effective against amœbic dysentery, and when supplemented with antibiotics to control secondary bacterial infections, the clinical response to treatment is nearly always good. However, relapses are common, and the host often passes cysts for many years and is a potential danger to the community. Such chronic infections are difficult to eradicate.

Emetine. This alkaloid is still the most potent remedy known against *Entamœba histolytica.* It is toxic to the host in therapeutic doses and produces unpleasant side-effects upon the gastrointestinal tract and the heart. When given by injection emetine is effective in acute amœbic infections and in amœbic hepatitis, but rarely produces permanent cures. Treatment must be supplemented with doses of emetine bismuth iodide, or emetine in enteric coated capsules[169] by mouth. A large number of schemes have recently been devised in which emetine, halogenated hydroxyquinolines, arsenicals, sulphonamides and antibiotics are all given in a "blunderbuss" treatment.[170,171]

Conessine. Kurchi (*Holarrhena antidysenterica*) and its constituent alkaloid conesine have been favourite remedies in India for many years. Recently French workers have used the alkaloids extracted from *H. africana*[172] and *H. floribunda.*[173] There are a number of enthusiastic reports upon the efficacy of conessine,[174,175,176] but in most of these trials the patients were not examined for long enough to ensure that the infection had been eradicated. A number of workers have observed toxic effects[176,177,178] and some have used phenergan to counteract the sleeplessness caused by conessine.[176] It appears that conessine will be of value when given together with emetine[178] or other amœbicides, and also in patients who are unable to tolerate emetine. The hydrobromide is considered to be the most suitable salt.[176]

Halogenated Hydroxyquinolines. Vioform, chiniofon and diodoquin are widely used in amœbic infections. Diodoquin (XVI) is of low toxicity and is probably the best drug at present available for the treatment of chronic infections.[179,180] It is often given together with sulphonamides and with other amœbicides. Studies upon the blood iodine levels produced by doses of these iodoquinolines showed that all were absorbed to some extent,[181,182,183] and that diodoquin gave the highest blood level.[182] It is likely that the main action of the compounds is upon the amœbæ and the bacterial flora in the lumen of the bowel.

Arsenicals. Carbarsone and acetarsone are well-tried remedies and are usually given together with other amœbicidal drugs. A bismuth

derivative of *p*-N-glycolylarsanilic acid (XVII) was introduced under the name of "Wia" in 1943,[184] and has recently been re-examined as "Milibis" or "Win 1011."[185,186,187] It is claimed to have good effect in chronic cyst-passers but is of little value in acute amœbiasis. Other new arsenical preparations are the thioarsenites "CC914" (XVIII) and "CC1037" (XIX) introduced by Anderson,[188,189] and the sulphonamido derivative (XX) tested by Schneider and Montezin.[190]

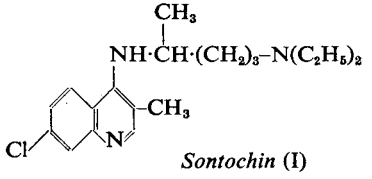
Antibiotics. The invasive power of *E. histolytica* is probably related to the presence of certain bacteria in the gut. Amœbic ulcers become secondarily infected with bacteria and the local tissue reaction may prevent access of amœbicides in adequate concentration to kill the amœbæ. The introduction of penicillin and sulphonamides to supplement treatment with emetine and other amœbicides[191] was a great step forward in the control of acute infections. Most of the available antibiotics have now been tried. Chloramphenicol is of little value,[192] but streptomycin and bacitracin[192,193] are useful. Aureomycin is the most promising antibiotic tried so far, because not only does it affect the bacterial flora of the gut, but it probably has a direct amœbicidal action of its own.[194] Treatment with aureomycin rapidly alleviates acute dysentery, but relapses frequently occur.[195,196,197,198] It is best to use aureomycin together with other amœbicides. Terramycin has also been tried,[199,200,201] but it does not appear to be more active than aureomycin.

Chloroquine. Chloroquine, like emetine, is selectively concentrated in liver tissue. It has proved to be very useful in the treatment of amœbic hepatitis and liver abscess,[202,203,204,205] although it is of little value in intestinal amœbiasis. Chloroquine is much less toxic than emetine, and has given good results in cases in which treatment with emetine and other remedies had failed. Sontochin is also active in hepatic amœbiasis.[206]

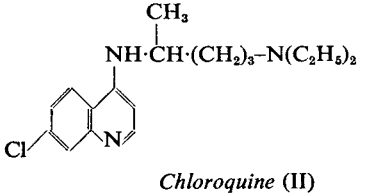
In spite of a great deal of work upon *E. histolytica* in experimental animals and in culture, a safe and powerful remedy for chronic amœbic infections is still lacking.

Antimalarials

New 4-aminoquinoline derivatives

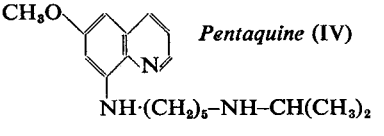


Sontochin (I)

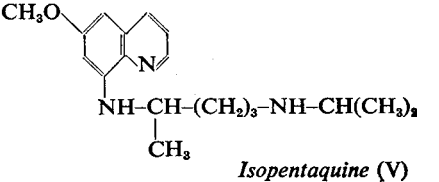


Chloroquine (II)

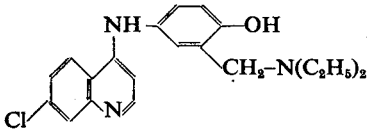
New 8-aminoquinoline derivatives



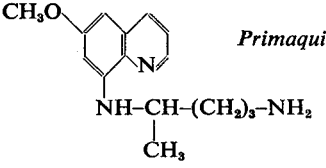
Pentaquine (IV)



Isopentaquine (V)

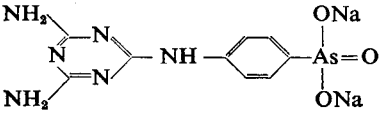


Camoquin (III)

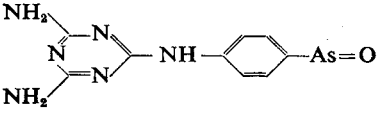


Primaquine (VI)

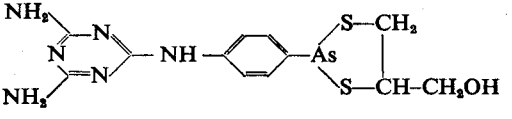
Trypanocides



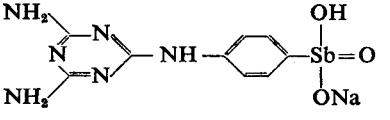
Melarsen (VII)



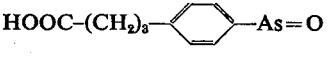
Melarsen oxide (VIII)



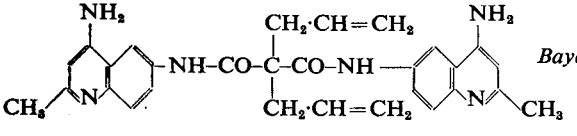
Mel. B (IX)



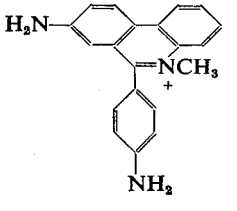
MSb. (X)



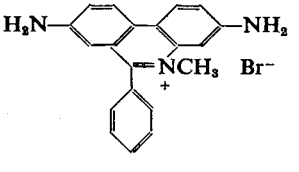
Butarsen (XI)



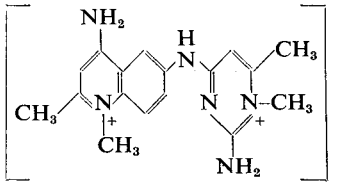
Bayer 7602 (*Ac*) (XII)



Phenidium (XIII)

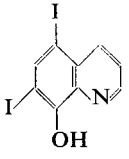


Dimidium (XIV)

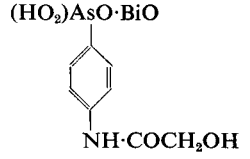


Antrycide (XV)

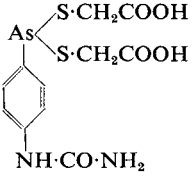
Amœbicides



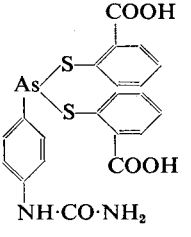
Diodoquin (XVI)



Milibis (XVII)



*CC*914 (XVIII



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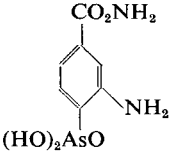

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