PARASITE CHEMOTHERAPY[1]

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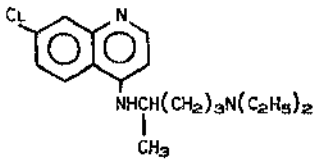
Parasite chemotherapy is being reviewed frequently; consequently, useful summaries of the situation prior to 1963 are available (28, 77, 182, 185). This presentation deals mainly with major developments during the past three or four years. However, drug resistance in malaria is reviewed without time restrictions in an effort to develop a useful perspective of this important subject.

MALARIA

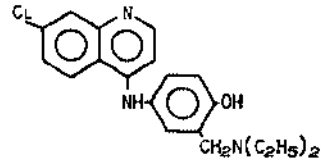
Malaria still is a major health problem in most of the tropical areas of Africa, Latin America, the South Pacific Islands, and Asia. Drug-resistant parasites are of major current interest. In addition, repository drugs are being developed.

A reappraisal of chemotherapy has become necessary with the demonstration that some *Plasmodium falciparum* infections in Southeast Asia and South America are refractory to therapeutic or suppressive doses of chloroquine (I), amodiaquine (II), or quinacrine (III). The potential gravity of the situation is aggravated by the known limitations of alternative drugs. Chlorguanide (IV) and pyrimethamine (V) act too slowly for satisfactory therapeutic effect against acute *falciparum* infections, even when the parasites are normally sensitive to them; moreover, parasite resistance to these drugs not infrequently limits their usefulness as suppressive agents. Quinine (VI), for many years a secondary choice, is now the main drug used in the treatment of *falciparum* malaria caused by chloroquine-resistant parasites. It is too early to assess the effects of resistance on the control and eradication of malaria globally. The interpretation of reports on resistance requires recognition that drug failure is not synonymous with parasite resistance. Distinction between the two is difficult in malaria because drugs, particularly for suppression, are usually used without adequate supervision to assure that they are taken as directed. Furthermore, the recommended doses and regimens of antimalarials are necessarily fixed within relatively narrow limits to provide both safety and efficacy, particularly in nonimmunes; such restrictions allow little deviation below the expected response without suggesting parasite resistance. The World Health Organization (231) has laid down useful guidelines relative to the assessment of resistance. It is not clear in most instances whether resistant parasites represent the extreme in a natural spectrum of sensitivity or have been selected by extensive use of drugs. Experimental studies show the latter is possible, particularly with certain drugs. Informa-

[1] The survey of the literature pertaining to this review was concluded in May 1966.



I CHLOROQUINE



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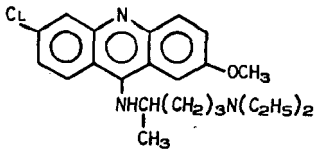
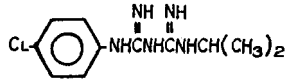
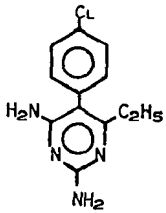


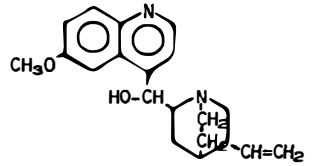
III QUINACRINE



IV CHLORGUANIDE

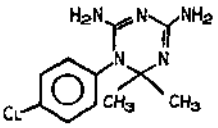


V PYRIMETHAMINE



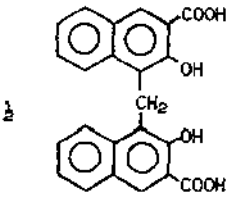
VI QUININE

VII CHLORPROGUANIL



A. HCL

B. PAMOATE



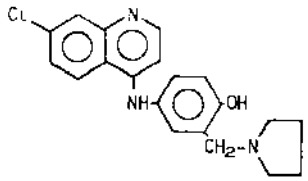
VIII CYCLOGUANIL

tion on the geographical distribution, prevalence, types, and degrees of resistance is inadequate. Even so, enough is known to encourage serious search for new types of therapeutic and suppressive drugs.

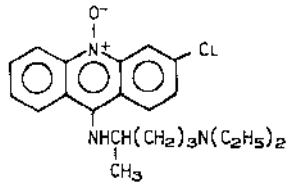
Resistance is generally specific for particular drugs or groups of drugs but multi-resistant strains also occur. Resistance to the antifolic drugs, chlorguanide and pyrimethamine, has been reported most extensively and can be readily induced experimentally. Chlorguanide resistance has been reported in man in many areas and has included *P. falciparum* (3, 67, 76, 79, 104, 123, 139, 187), *Plasmodium vivax* (3, 52, 79, 188, 230), and *Plasmodium malariae* (79). Chlorguanide resistance has been induced in many species of plasmodia in birds, rodents, and monkeys (cf. 13). It persists after passage through mosquitoes (15, 86, 229) and apparently is highly stable (16). The situation is basically the same for pyrimethamine, with reports of resistance in *P. falciparum* (29, 44, 45, 78, 102), *P. vivax* (88, 237), *P. malariae* (236), and many species of plasmodia in animals (cf. 13). Reports of resistance in human malaria have quickly followed the introduction of these drugs into various areas. Cross-resistance usually occurs between them but exceptions are known: some chlorguanide-resistant strains retain sensitivity to pyrimethamine but pyrimethamine-resistant strains typically are resistant to chlorguanide (103, 139). The experimental induction of resistance to these drugs has not resulted in cross-resistance to 4-aminoquinolines, acridines, or quinine (52, 207, 229).

Mention should also be made of two less widely used antifolic compounds, namely, chlorproguanil (VII) and the cycloguanil salts [hydrochloride (VIIIa) and pamoate (VIIIb)]. Chlorproguanil and chlorguanide are grouped together relative to resistance and cross-resistance (231), which is consistent with their close chemical structures. Cycloguanil has been identified as an active metabolite of chlorguanide (53). Resistance to cycloguanil hydrochloride has been induced with *Plasmodium berghei* in mice (10, 156, 208), and cross-resistance to chlorguanide and pyrimethamine was noted (unpublished studies by the author and his colleagues). Chlorguanide- and pyrimethamine-resistant strains of *P. falciparum* are also cross-resistant to cycloguanil pamoate in man (40, 49, 165). Surveillance for the emergence of cycloguanil resistance by *Plasmodium cynomolgi* in monkeys given a repository dose of cycloguanil pamoate yielded negative results (184, 205). Repository compounds produce sustained, low drug blood levels that steadily prevent or inhibit parasite growth (205), while nonrepository agents yield fluctuating levels and less constant suppression. Possibly, these differences make a repository agent less favorable for the emergence of resistance than its nonrepository counterpart; chlorguanide resistance by *Plasmodium gallinaceum* was induced easily while multiplying rapidly but not while multiplying slowly (175).

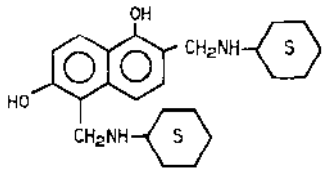
Resistance by *P. falciparum* to 4-aminoquinolines and acridines ranks as one of the greatest surprises in chemotherapy. Except for the poor response to quinacrine by *P. falciparum* in Aitape-Wewak (64), convincing suggestions in this direction had not been recognized during some fifteen years of exten-



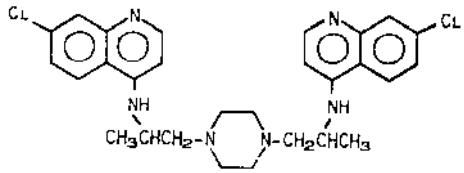
IX AMOPYROQUINE



X PAM 922



XI 377-C-54



XII RP 12,278

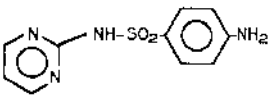
sive use of these drugs. Many of the early experimental attempts (cf. 13) to induce such resistance failed. However, some successful trials had been reported: resistance to quinacrine by *Plasmodium cathemerium* (157), low order of resistance to chloroquine by *P. gallinaceum* (173), and 200-fold resistance to chloroquine by *P. berghei* (171). These results might have served as a warning for the future but apparently were discounted by other failures and by uncertainty regarding extrapolations from animals to man. Recently, many workers (85, 100, 153, 181, 190, 206) have induced *P. berghei* to develop high resistance to chloroquine and to quinacrine (155). Such resistance is unstable, and thus differs from the resistance by *P. falciparum* to these drugs. Chloroquine-resistant *P. falciparum* is generally cross-resistant to other 4-aminoquinolines [amodiaquine and amopyroquine (IX)], acridines [quinacrine and PAM 922 (X)], and the naphthalene 377-C-54 [XI (50, 57, 101, 162, 163, 233, 234)]. Chloroquine-resistant strains of *P. berghei* have been shown to be cross-resistant to amodiaquine, amopyroquine, the bis-4-aminoquinoline RP 12,278 (XII), quinacrine, and PAM 922 (unpublished studies by the author and his colleagues). Cross-resistance to 377-C-54 was exhibited by one chloroquine-resistant strain of *P. berghei* (unpublished studies by the author and his colleagues) but apparently not by another (85); it is not possible to account for this discrepancy. The main difference in cross-resistance by chloroquine-resistant *P. falciparum* and *P. berghei* is in their responses to quinine: *P. falciparum* apparently remains sensitive to quinine but *P. berghei* becomes

resistant to it (100, 153, 206). In addition, a strain of *P. berghei* made resistant to quinine by treatment with the drug was also resistant to chloroquine (100). This difference between *P. falciparum* and *P. berghei* might be caused by the much higher degree of chloroquine resistance possible with the latter, since the drug has a much broader therapeutic index in mice than in man. Although some *P. falciparum* strains in Southeast Asia are resistant to both the antifolic and the 4-aminoquinoline-acridine groups (cf. 161), such multiple resistance is more probably the consequence of distinctly different series of events rather than of cross-resistance. Supporting evidence is the lack of appreciable cross-resistance between these two groups of compounds by a strain of *P. falciparum* from South America (162, 235) and by *P. berghei* (100, 153) and other plasmodia in animals (207, 229).

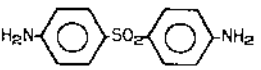
With regard to the global impact of 4-aminoquinoline-acridine resistance, it is important to stress that so far this has been unequivocally demonstrated only in Southeast Asia, Brazil, and Colombia and has been limited to *P. falciparum*. Furthermore, the prevalence of resistant strains in these areas is not known and resistance is typically partial rather than complete: the drugs usually have temporary therapeutic action but, as shown by an early recrudescence, fail to achieve radical cure. However, these features do not diminish the gravity of the problem in localities where the drugs have erratic therapeutic or suppressive action.

The position of quinine has become most important because of the resistance problems with antifolic drugs and the 4-aminoquinoline-acridine compounds (141). Early efforts to induce quinine resistance in the plasmodia of animals were largely unsuccessful (cf. 13), except for the induction of twofold resistance by *P. gallinaceum* (110, 111). Recently, high resistance to quinine by *P. berghei* has been induced via treatment with chloroquine (100, 153, 206) or quinine (100). This suggests a relationship between the actions of quinine and the 4-aminoquinoline-acridine drugs against *P. berghei*. However, a similar relationship has not been recognized in human malaria, as multi-resistant *falciparum* infections typically show a therapeutic response to quinine. Varying amounts of quinine are needed for cure (56), but it is too early to assess the efficacy of quinine against multi-resistant parasites relative to sensitive parasites. In view of the erratic action of quinine in curing *falciparum* malaria generally, failure to achieve cure would be a difficult basis for assessing resistance to it.

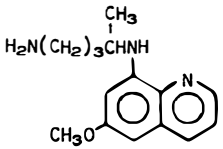
Sulfonamides and sulfones have been known for many years to have anti-



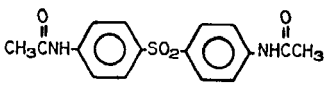
XIII SULFADIAZINE



XIV DDS



XV PRIMAQUINE



XVI DADDS

malarial activity (cf. 161). Interest is now developing in these chemicals as alternative or adjunctive drugs, particularly for use against resistant *P. falciparum*. These compounds are considered together as *p*-aminobenzoic acid (PAB) inhibitors: PAB antagonizes the action of sulfadiazine [XIII (cf. 13)] and of 4,4′-diaminodiphenylsulfone [DDS (XIV) (12)] against plasmodia in animals, and cross-resistance between DDS and sulfadiazine has been demonstrated with *P. berghei* (unpublished studies by the author and his colleagues) and *P. gallinaceum* (14). As reviewed elsewhere (13, 90, 161), complex and at times contradictory observations have been reported on the interrelationships of PAB inhibitors to other antifolic antimalarials. Rollo (174) has postulated a scheme of sequential inhibition of purine and pyrimidine synthesis by these compounds; presumably, the PAB inhibitors interfere with the synthesis of folic acid from PAB or other precursors, and the antifolics (chlorguanide, pyrimethamine, chlorproguanil, and cycloguanil) interfere with the synthesis of folinic acid. Test data indicate that representatives of the two groups are complementary relative to potency against sensitive parasites, broad action against resistant organisms, and less likelihood of the emergence of resistance (208). It is apparent from published and recent oral reports that sulfonamides (121, 122, 136) and sulfones act rather slowly in man, more effectively against *P. falciparum* than against *P. vivax*, and have suppressive action against multi-resistant *P. falciparum*.

The position of 8-aminoquinolines as to drug resistance must be considered relative to the life cycle form and species of parasite. These drugs, notably primaquine (XV), have strong effect in man against tissue forms but weak action against asexual blood forms. Therefore, they are used with a strong schizonticide, usually a 4-aminoquinoline, either for prophylaxis or for radical cure of relapsing malaria. The type of primaquine resistance known experimentally pertains only to its less important schizonticidal activity; this has been induced in *P. berghei* (154, 155, 169), *Plasmodium knowlesi* (172), and *P. vivax* (4). Resistance to pamaquine (a related 8-aminoquinoline) has been induced in asexual blood forms of *P. knowlesi* (73) and *P. gallinaceum* (17). The failure of a primaquine and 4-aminoquinoline combination to act in the expected manner can be interpreted as suggestive of primaquine resistance by tissue forms only when the combination has been used against strains that are fully susceptible to the schizonticide. As many failures (74)

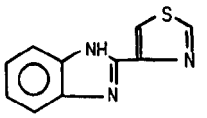
have been in areas of 4-aminoquinoline resistance by *P. falciparum*, resistance by tissue forms to primaquine has not been demonstrated.

Repository antimalarial drugs that prevent or inhibit the growth of plasmodia when given at intervals of several months would greatly extend the horizon of malaria chemotherapy. Systematic research (205) in this direction led to cycloguanil pamoate (CI-501, Camolar). A parenteral dose of the drug protected mice and rats for many weeks against challenges with *P. berghei* trophozoites (205, 223) and monkeys for many months against challenges with *P. cynomolgi* trophozoites (205) or sporozoites (184). An intramuscular dose of cycloguanil also prevented patent infections in men for many months against challenges with *P. vivax* (46, 47) or *P. falciparum* (48, 133). In line with theoretical expectations, cycloguanil pamoate has not been useful against strains that are highly resistant to chlorguanide, pyrimethamine, or both (40, 164, 165). Some reports and a considerable body of data reported from field studies (Department of Clinical Investigation, Parke, Davis & Company, Ann Arbor, Michigan, unpublished data) indicate that (*a*) the drug is active against partially resistant strains, but for a shorter time than against sensitive parasites, (*b*) a concurrent dose of a 4-aminoquinoline is a useful adjunct in areas where the parasites have some degree of resistance to antifolic drugs but are sensitive to 4-aminoquinolines, (*c*) ordinary doses are not toxic and usually provoke only mild to moderate reactions at the injection site when injected properly, and (*d*) larger doses relative to body weight are needed in small children than in adults. The value of cycloguanil pamoate will evidently depend mainly upon the prevalence and degree of resistance to antifolic drugs.

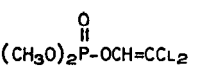
Systematic research for other repository drugs that might complement cycloguanil relative to resistant parasites led to the discovery of long action by 4,4′-diacetyldiaminodiphenyl sulfone [DADDS (XVI) (209)], which on hydrolysis yields DDS. The relationship of such PAB inhibitors to antifolic antimalarials comprises the rationale for a mixture of cycloquanil pamoate and DADDS. A parenteral dose of DADDS protected mice for many weeks against challenges with *P. berghei* and monkeys for many months against challenges with *P. cynomolgi* trophozoites (209, 210) or sporozoites (176). A mixture of cycloguanil pamoate and DADDS showed better activity than either component alone against various drug-resistant plasmodia in animals (176, 209) and man (120). While additional work may be needed to determine the best form and amount of sulfone for use with cycloguanil pamoate, the potential value of this type of repository mixture has been demonstrated.

HELMINTHIASES

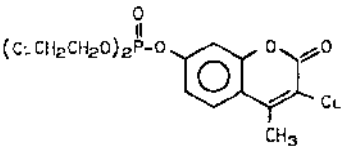
Helminthic diseases of man and domesticated animals collectively pose the most important problems in parasite chemotherapy, both medically and economically.



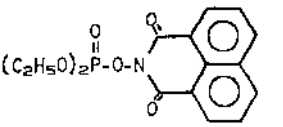
XVII THIABENDAZOLE



XVIII DICHLORVOS



XIX HALOXON



XX MARETIN

Drugs Active Against Intestinal Nematodes

Thiabendazole (XVII).—The subject of more than two hundred reports, thiabendazole (24) is useful for dealing with most of the important gastrointestinal nematodes of herbivores, except *Trichuris*. It has broad action against eggs, larvae, and adult forms. Physiologic disposition studies in animals showed relatively short persistence of the drug in the tissues and pointed to 5-hydroxythiabendazole as a major metabolite in sheep (216, 217). However, thiabendazole is active *in vitro* (119, 198, 199), which suggests that its effects *in vivo* are not dependent upon metabolic activation.

The value of thiabendazole against human helminthiases is being studied. Many reports (21, 69, 95, 142, 147, 180, 191, 220) describe broad action, particularly with multiple doses, in the suppression of egg production by most of the important intestinal nematodes of man, but erratic effect against *Trichuris*. The possibility has been suggested of disproportionate suppression of egg production by hookworms relative to vermifugal action (95). Effective doses frequently cause giddiness, and to a less extent nausea and vomiting (95, 180). Relative to other agents for use against intestinal helminths, thiabendazole is most likely to excel in the treatment of strongyloidiasis, creeping eruption (106, 144, 196, 197), and possibly trichinosis (108, 195).

Organophosphorus compounds.—These substances evidently act, at least in part, via cholinesterase inhibition (112, 129). An interesting development is the incorporation of the volatile and relatively toxic dichlorvos (XVIII) in a resin formulation (Atgard) for use against intestinal nematodes in swine; such formulations apparently reduce toxicity by permitting only a slow release of dichlorvos, but sufficient amounts for high activity against *Ascaris*, *Oesophagostomum*, and *Trichuris* (8, 99).

Haloxon (XIX) appears to be an important new anthelmintic for animal use. It showed low acute oral toxicity in animals (134). In lambs, it had efficacy against *Ostertagia* and *Trichostrongylus* but little effect against *Nematodirus* (6). In cattle, it was effective against *Haemonchus*, *Cooperia*, *Oesophagostomum*, and *Trichostrongylus* (potency varied somewhat according to whether the worms were mature or immature), but it had little action against *Bunostomum* (80).

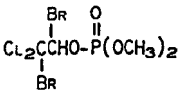
Maretin [(XX) Rametin] has been introduced recently in foreign countries for use against intestinal nematodes in herbivores. In sheep, it had high effect against *Cooperia*, *Haemonchus*, and *Trichostrongylus* but was relatively ineffective against *Chabertia* or *Oesophagostomum* (65). Its anthelmintic spectrum in cattle includes *Bunostomum*, *Cooperia*, *Haemonchus*, *Ostertagia*, *Nematodirus*, *Strongyloides*, and *Trichostrongylus* (51, 194). Maretin exhibited outstanding activity against *Schistosoma mansoni* in mice but was essentially ineffective against this parasite in monkeys (unpublished studies by the author and his colleagues).

In multiple oral doses, 0-1,2-dibromo-2,2-dichloroethyl-0,0-dimethyl phosphate (XXI) has shown encouraging activity in dogs against ascarids, hookworms, and whipworms (131) and against *Dipylidium caninum* (116).

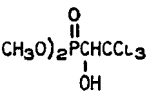
Trichlorophon [(XXII) Dipterex] is active against a variety of gastrointestinal nematodes in sheep and cattle (cf. 63,193). Following an encouraging report of action against intestinal nematodes and schistosomes in man (37), trichlorophon has received considerable attention in Egypt for the oral treatment of human schistosomiasis (211). Tests against *S. mansoni* in mice and monkeys showed insignificant action by large oral doses of the drug (unpublished studies by the author and his colleagues). It is perhaps too early to pass judgment on the clinical value of trichlorophon but its known toxicity for man (87) discourages its use.

Tetramisole (XXIII).—This is a new anthelmintic of unusual interest (215). In contrast to the empirical screening approach which has led to most recent drugs, tetramisole was discovered in the systematic testing of analogues of a metabolite of an active drug. The lead was recognized when chickens were given another anthelmintic: 2-(acetylimino)-3-[2-hydroxy-2-(2-thienyl)-ethyl]-thiazoline. According to a preliminary report (215), tetramisole is active against immature and mature stages of many types of intestinal nematodes in livestock and poultry, against lungworms (*Dictyocaulus* spp.) in sheep and cattle, against *Ascaris lumbricoides* and *Enterobius vermicularis* in man, and is highly potent by either oral or parenteral administration in sheep and cattle. Tetramisole is being sold in some foreign countries for use in sheep.

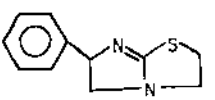
Stilbazium iodide (XXIV).—The structure and spectrum of anthelmintic activity of this new dye (31) is reminiscent of such water-soluble cyanine dyes as pyrvinium and dithiazanine. It is active in one oral dose (31) or by drug diet administration (98) against *Syphacia obvelata* in mice and in multiple



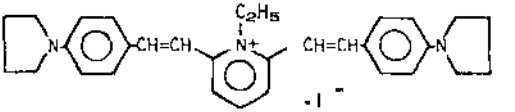
XXI O-1,2-DIBROMO-2,2-DICHLORO-ETHYL-O,O-DIMETHYL PHOSPHATE



XXII TRICHLOROPHON



XXIII TETRAMISOLE



XXIV STILBAZIUM IODIDE

oral doses against ascarids, hookworms, and whipworms in dogs (32). Clinical trials (27, 35, 92, 94, 102, 200, 222) have also given results reminiscent of those reported by numerous workers with the soluble cyanine dyes: high activity in one oral dose against *E. vermicularis* but considerable emetic action unless enteric-coated, strong activity in multiple doses against *Strongyloides stercoralis*, and moderate to slight activity in multiple oral doses against ascarids, hookworms, and whipworms.

Pyrvinium pamoate (*XXV*).—This drug has been used mainly in the single dose treatment of enterobiasis. Although a 5 mg/kg dose has been recommended by the supplier, recent reports (9, 113, 114, 145) indicate that a 2 mg/kg dose in the form of a suspension is highly effective and causes fewer side effects.

Evidence is being accumulated that pyrvinium pamoate, given over a period of one to two weeks, also is useful in the treatment of strongyloidiasis. Therapeutic effects were first observed with the more soluble pyrvinium chloride (25, 138). Pyrvinium pamoate was then found to be effective against *S. stercoralis* in experimentally infected dogs (232). Several reports (137, 212–214, 221, 228) describe therapeutic action by pyrvinium pamoate against strongyloidiasis in man. Further study seems to be warranted, particularly since problems of one type or another arise with the few alternative drugs.

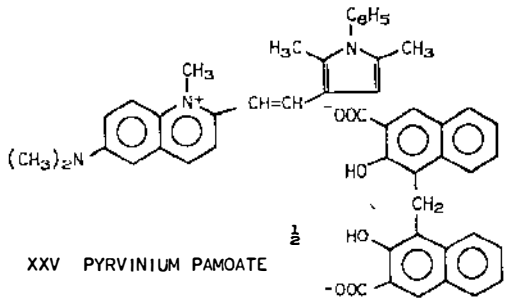
Antifilarial Drugs

Diethylcarbamazine (*XXVI*).—This is the main drug for the treatment of filariasis caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Loa loa* (83, 84). It apparently is moderately active against the adult stages and is highly effective against the microfilariae. It is also very active against the microfilariae of *Onchocerca volvulus* and *Dirofilaria immitis* but lacks appreciable action against adult forms of these parasites. Recent work has demonstrated

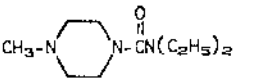
that diethylcarbamazine has prophylactic action against *L. loa* in experimentally infected monkeys (60) and in man (61) and against *D. immitis* in dogs (117). These effects, attained via multiple doses shortly after exposure, might have been anticipated with *L. loa* but not with *D. immitis*. Chemoprophylaxis is especially important in filariasis, as effective treatment commonly is complicated by allergic reactions associated with the killing of microfilariae and adult worms.

Mel W (*XXVII*).—This water-soluble trivalent arsenical derivative is of some current interest in the mass treatment of filariasis caused by *O. volvulus* (70, 71, 128) or *W. bancrofti* (72). It can be given intramuscularly in relatively large doses. Mel W has very little action against microfilariae but is believed to be effective against adult worms. Unfortunately, it is difficult to assess its action in man, as microfilariae persist for many months after treatment and the investigator is faced with the dilemma of judging whether dead worms in excised nodules reflect treatment apart from other factors. Mention should also be made that much experience will be required to assess its benefit-to-risk ratio, particularly with respect to the grave idiosyncratic reactions occasionally associated with trivalent arsenicals.

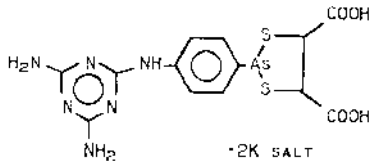
Dithiazanine iodide (*XXVIII*).—Informal reports indicate some use of this drug against the microfilariae of *D. immitis* in dogs. Unsuccessful efforts were made during World War II to develop a cyanine dye that might be used in the treatment of filariasis in man, as many of them had outstanding



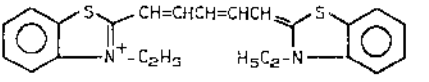
XXV PYRVINIUM PAMOATE



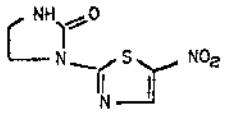
XXVI DIETHYLCARBAMAZINE



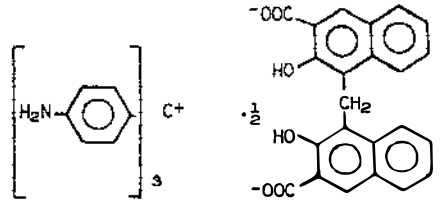
XXVII MEL W



XXVIII DITHIAZANINE IODIDE



XXIX 32,644-Ba



XXX TRIS(p-AMINOPHENYL)CARBONIUM PAMOATE

activity against *Litomosoides carinii* in cotton rats (152). Subsequently, dithiazanine iodide was developed for use against intestinal nematodes in man and animals. However, further experience in man showed that it may occasionally be absorbed in sufficient quantities to cause renal failure and death (55); hence, its human use has progressively declined. Yoshimura et al. (240) found that oral doses of the drug were highly effective against *D. immitis* microfilariae in dogs but not against *W. bancrofti* microfilariae in man. Prophylactic tests of dithiazanine iodide against *D. immitis* in dogs gave negative results (118).

Drugs Active Against Trematodes

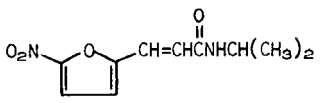
Compound 32,644 Ba [*(XXIX) Ambilhar*].—This new type of antischistosomal drug has been studied extensively, but only a small portion of the results have been published. Unpublished data available to the writer permit some general comments without the usual literature citations.[2] The compound is active *in vitro* (124), although slowly, and has therapeutic action by short-term oral administration in experimental animals (124) or in man (105, 125, 126) against *S. mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. Clinical studies suggest (*a*) greatest utility against *S. haematobium:* (*b*) considerable efficacy against *S. mansoni* but variable curative action, depending upon the severity of infection (105) and perhaps the geographic area; and (*c*) uncertain value against *S. japonicum*, owing to a questionable therapeutic index. This drug is also active by oral administration against intestinal and hepatic amebiasis in animals (115) and man; it also has been reported to be useful against *Drancunculus medinensis* (guinea worm) in man (170). Even though 32,644 Ba evidently has a strong effect against several important parasites, its ultimate place will probably be determined largely by the frequency and severity of side effects. Most of the more frequent side effects—electrocardiographic changes, inhibition of spermatogenesis, nausea, and vomiting—are transient, mild, and probably acceptable. Much less frequent but serious central nervous system reactions manifested by disorientation or convulsions may limit its use.

[2] Following completion of the manuscript, much of these data have been published in *Acta Trop.*, Suppl. **9**, 1–314 (1966) and **23**, 1–80 (1966).

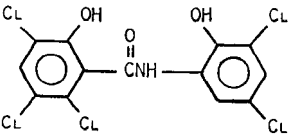
tris(p-*Aminophenyl*) *carbonium pamoate* (*XXX*).—Studies on this antischistosomal compound have been continued since a previous review (63) of its status. Collectively, published and unpublished reports (to the author or the Parke, Davis & Company, Department of Clinical Investigation) indicate that the compound by oral administration is active in man against *S. mansoni* (30, 34, 54), *S. japonicum* (30, 91), *S. haematobium*, and in experimental animals against the first two species; it apparently has not been tested against *S. haematobium* in animals. In man, it appears that the drug must be given during several weeks for strong effects on the worms, although less intensive treatment regularly suppresses egg excretion strongly. Experimental studies show that the drug acts slowly against immature and mature worms (202), inhibits egg production (148, 202), reduces the glycogen content in the cuticular tubercles of male worms, and inhibits acetylcholinesterase in the oral sucker and the acetabulum (182, 183). Prolonged administration of the drug is associated with an increased incidence of tumors in female rats but not in male rats (107); no evidence is known suggesting such effects in other laboratory animals or in people.

Synergistic effects against *S. mansoni* have been observed experimentally under many conditions between tris(*p*-aminophenyl) carbonium pamoate and certain antimonials, without a commensurate increase in joint toxicity for mice (201); furthermore, the coadministration of tris(*p*-aminophenyl) carbonium pamoate and tartar emetic to mice did not discernibly affect the physiologic disposition of antimony (224). It remains to be determined whether the two types of drugs have such favorable joint action against schistosomes in man.

Furapromidium (*XXXI*).—Numerous publications point to much work in China on the chemotherapy of *S. japonicum* infections. Furapromidium (F30066) is the best nonantimonial drug described in this work. It has been found to have prophylactic effects in mice and curative action in rabbits and dogs (192); it kills worms *in vitro* in concentrations of 3–15 γ/ml (96). Studies on the metabolic fate of the drug have been described in mice, rabbits, and man, based on spectrophotometric assays following toluene extraction (96). The most notable features of this and related work were evidences of rapid metabolic decomposition in the presence of liver homogenates or erythrocytes, low transient blood levels, low tissue levels, and low and brief



XXXI FURAPROMIDIUM



XXXII OXYCLOZANIDE

urinary excretion. Following exploratory clinical trials (41, 93), preference was developed for oral treatment regimens of 60–80 mg/kg per day in adults and 80–100 mg/kg per day in children for 20 to 30 days (42), which gave an apparent cure rate of approximately 80 per cent. Major side effects were gastrointestinal disturbances and cramps; mild psychiatric changes were noted occasionally. The various authors consider furapromidium to be a useful alternative when antimonials are contraindicated. This drug also had therapeutic action against clonorchiasis (227) but effective levels caused more side effects than those of 1,4-bis(trichloromethyl) benzene [*infra* (43)]. Furapromidium was ineffective against mature *S. mansoni* in mice when fed on a 0.25 per cent diet concentration for two weeks (unpublished studies by the author and his colleagues).

Dehydroemetine (infra).—Emetine has been known for many years to be moderately useful in the treatment of schistosomiasis. Dehydroemetine has likewise been shown to have considerable action in man against *S. haematobium* and *S. mansoni* (75, 178). The effects were stronger against the former than the latter (75). Dehydroemetine resinate by oral administration was less effective than dehydroemetine hydrochloride by intramuscular or subcutaneous administration (178).

Oxyclozanide [(*XXXII*) *Zanil*].—This new drug for the treatment of fascioliasis in sheep and cattle (109, 226) appears to have a modest safety margin in the removal of adult *Fasciola hepatica* but lacks appreciable activity in safe doses against immature flukes. There are indications that it may be marketed overseas.

Halogenated salicylanilide mixtures.—A 3:1 mixture of 3,5-dibromosalicylic acid 4′-bromanilide and 5-bromosalicylic acid 4′-bromanilide (Diaphene) was found to be effective by oral administration against mature *F. hepatica* implanted under the skin of white rats (130). When a 1:1 mixture of the two compounds (Hilomid) was tested orally against immature and mature *F. hepatica* in experimentally infected sheep, the effective doses were 60 mg/kg and 30 mg/kg against immature and mature flukes, respectively (20). Limited toxicity studies suggested that a 120 mg/kg dose may be tolerated; a 150 mg/kg dose was toxic for uninfected sheep.

1,4-bis(Trichloromethyl) benzene [(*XXXIII*) *Hetol*].—An encouraging, new development is the evidence that 1,4-bis(trichloromethyl) benzene is useful in the treatment of clonorchiasis and opisthorchiasis; no satisfactory drugs have previously been available (193). Following demonstrations of its activity against *F. hepatica* in rodents, sheep, and cattle (127), this drug (also referred to as hexachloroparaxylol and hexachloroparaxylene) has been found to be effective against *Chlonorchis sinensis* in experimentally infected animals (43, 239) and in man (43, 132, 238); a high cure rate without toxicity has been reported in a substantial number of patients. Recent work indicates that 1,4-bis(trichloromethyl) benzene is effective against *Opisthorchis felineus* in cats (160) and against opisthorchiasis in children (59).

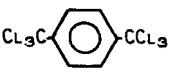
Drugs Active Against Cestodes

Bunamidine hydrochloride (*XXXIV*).—A preliminary report (7) describes broad activity by this compound against many types of cestodes in animals. A further study (81) in dogs and cats indicated high efficacy by a dose of 25 to 50 mg/kg; these doses caused mild gastrointestinal side effects.

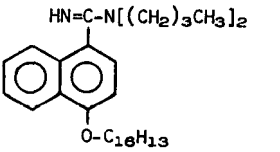
Paromomycin sulfate [(*XXXV*) *Humatin*].—This antibiotic has recently been found to be effective against *Taenia saginata* in man (218, 219); doses of 15 to 45 mg/kg per day for three to five days were used. Animal studies (225) showed that it had inconsequential effect against *Hymenolepis nana* in mice or *Hymenolepis diminuta* in rats but strong action against *Hydatigera taeniaeformis* in experimentally infected cats or *in vitro*.

AMEBIASIS

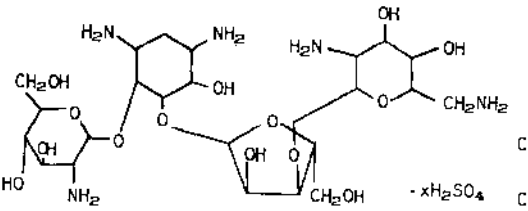
Dehydroemetine (*XXXVI*).—Much current interest is reflected in the European literature in dehydroemetine as a substitute for emetine. Both the racemic dehydroemetine (23) and isomer II (apparently the L-isomer) have been used. Both the racemic mixture (143) and the isomer II (19) have activity comparable to emetine against *Entamoeba histolytica in vitro*. Both forms were more active than emetine against experimenal amebiasis in rats (19, 89). Numerous types of toxicity studies in various species of laboratory animals showed the racemic mixture usually to be somewhat less toxic than emetine on a weight basis (38, 89, 135, 158, 159), although qualitatively



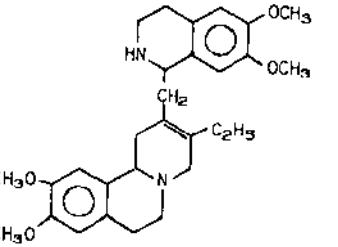
XXXIII 1,4-BIS(TRICHLOROMETHYL)BENZENE



XXXIV BUNAMIDINE



XXXV PAROMOMYCIN SULFATE



XXXVI DEHYDROEMETINE

their toxicities were similar. Comparisons following intraperitoneal administration in guinea pigs showed that racemic 2-dehydroemetine was excreted more than twice as fast as emetine (186). Clinical trials against amebic dysentery (5, 11, 166, 167, 177) or amebic liver abscess (58, 166, 168, 177) have consistently shown therapeutic action by the various forms of dehydroemetine hydrochloride by injection. There are some indications in these studies that dehydroemetine may be given in somewhat higher doses than emetine but further clinical experience is needed for a satisfactory opinion regarding their relative activities and merits on an overall therapeutic index basis. Therapeutic effects against amebic dysentery in patients have also been reported when dehydroemetine was given orally in the form of the resinate (18, 177) or dehydroemetine-bismuthiodide (167).

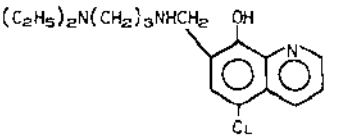
Clamoxyquin hydrochloride and pamoate (*XXXVIIa and b*).—Earlier studies (203) had shown that iodine substitution in 8-quinolinols was not essential for antiamebic activity. Further work led to the water-soluble hydrochloride (26) and the sparingly soluble pamoate salts of clamoxyquin (E. F. Elslager and D. F. Worth, Parke, Davis & Company, unpublished). These salts were moderately active against *E. histolytica in vitro* and against intestinal amebiasis in rats, dogs, and hamsters (26, 97, 204); clamoxyquin hydrochloride also exhibited significant activity by oral administration against amebic hepatitis in hamsters (204). Clinical trials [(36) and unpublished reports, Parke, Davis & Company, Department of Clinical Investigation] indicate that both salts are useful in the treatment of acute or chronic intestinal amebiasis.

Halquinol (*A307*).—This is a mixture comprised of 5,7-dibromo-8-quinolinol (7 parts) and 5,7-dibromo-8-benzoyloxyquinoldine (1 part). It appears from published clinical reports (39, 62, 140, 146, 179) to be moderately useful in the treatment of various forms of intestinal amebiasis.

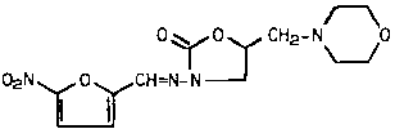
Paromomycin sulfate (supra).—This antibiotic has antibacterial and antiamebic action and is absorbed sparingly from the gastrointestinal tract (68). Most of the published data describing efficacy are based on two or three doses daily (usually 25 mg/kg per day) for five to ten days. The effects of one large dose have been studied recently in patients passing trophozoites or cysts. Substantial proportions of the adults showed a therapeutic response when given a 4 gm dose (149). In children, a 50 mg/kg dose failed frequently (149) but a 70 mg/kg dose had therapeutic effect in most cases (150).

DERMAL LEISHMANIASIS

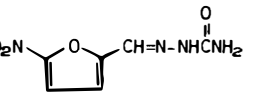
Cycloguanil pamoate (supra).—This repository antimalarial agent has shown promise in the treatment of cutaneous and mucocutaneous leishmaniasis. With the knowledge that the biologically related chlorguanide and pyrimethamine have discernible therapeutic action against cutaneous leishmaniasis in Costa Rica, Peña Chavarria et al. (151) tried an intramuscular injection of cycloguanil pamoate in 30 patients with *Leishmania braziliensis*



XXXVII CLAMOXYQUIN



XXXVIII FURALTADONE



XXXIX NITROFURAZONE

infection. The lesions in most of the patients cleared slowly following one injection. Basically similar results have been obtained in the treatment of *Leishmania mexicanum* infections in Mexico (Dr. F. Biagi and colleagues, personal communication). Both groups of investigators consider that further trials are warranted. Since dermal leishmaniasis occurs mainly among people in remote areas, an effective repository drug would have important advantages over previous methods of treatment, mainly with multiple doses of antimonials.

CHAGAS' DISEASE

Although satisfactory agents for the treatment of Chagas' disease have not been developed, it is appropriate to mention three drugs that may be useful, if given early, against acute infections.

Furaltadone (*XXXVIII*).—The therapeutic effects of this drug against *Trypanosoma cruzi* infections in mice have been described and reviewed (189): it prevented death in otherwise lethal infections but was not demonstrated to be curative. Indications that it may be useful clinically in the treatment of acute infections have been summarized (82).

Nitrofurazone (*XXXIX*).—Encouraging results have been described with this drug in *T. cruzi*-infected mice, particularly on prolonged administration (22). It has shown activity against acute infections in man but caused polyneuritis on long administration (66, 82). It failed to cure chronic infections in man (33).

Amphotericin B.—This antifungal antibiotic has exhibited activity against experimental infections in rats (2). It has also shown evidence of effectiveness against acute Chagas' disease in eight patients, with indications of cure in the three available for a long follow-up (1).

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