PARASITE CHEMOTHERAPY

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Parasite chemotherapy is considered for the present purposes to deal with the chemotherapy and chemoprophylaxis of infections caused by protozoa and helminths. A great variety of parasites produce infection in man, livestock, poultry, and pets. Moreover, the number of chemicals known to have some type or degree of antiparasitic activity is large and increases each year. Hence, parasite chemotherapy is an unusually broad subject. However, only a small proportion of the reported antiparasitic chemicals qualify as medicaments for the treatment of infections. The presentation, organized on an infection basis, is restricted to areas in which important new advances seem apparent. Adequate documentation of new drugs usually requires several years; therefore, this review, covering a varying number of years, may include some items that will not stand the test of time, and naturally may omit emerging important developments.

MALARIA

In spite of eradication or impressive control in many areas, malaria still annually affects 200 million people and causes one million deaths [Russell (111)]. Moreover, further reduction will be impeded by the increasing problem of anopheline resistance to residual insecticides. Consequently, antimalarial drugs still are important, particularly in vast areas where other control measures are inadequate or impractical.

Recent progress in malaria chemotherapy stems mainly from appropriate recognition of the following factors: (*a*), Susceptibility to drug action differs according to the life cycle forms of the parasites; no single drug is highly effective against all forms even of the same species. Stated most briefly, the stages to be considered relative to available drugs are primary tissue, secondary tissue (absent in falciparum) and asexual blood forms, and falciparum gametocytes. (*b*), Variable goals exist: clinical cure, radical cure, suppression to prevent patent infections, interruption of transmission, or prevention of an established infection. (*c*), The choice of therapy is further influenced by the species of parasite, the status of immunity, and such drug factors as potency, physiologic disposition, and toxicity liabilities relative to the regimen. Consequently, drugs are being used more intelligently. Only a few new compounds, primarily schizonticides, have emerged recently.

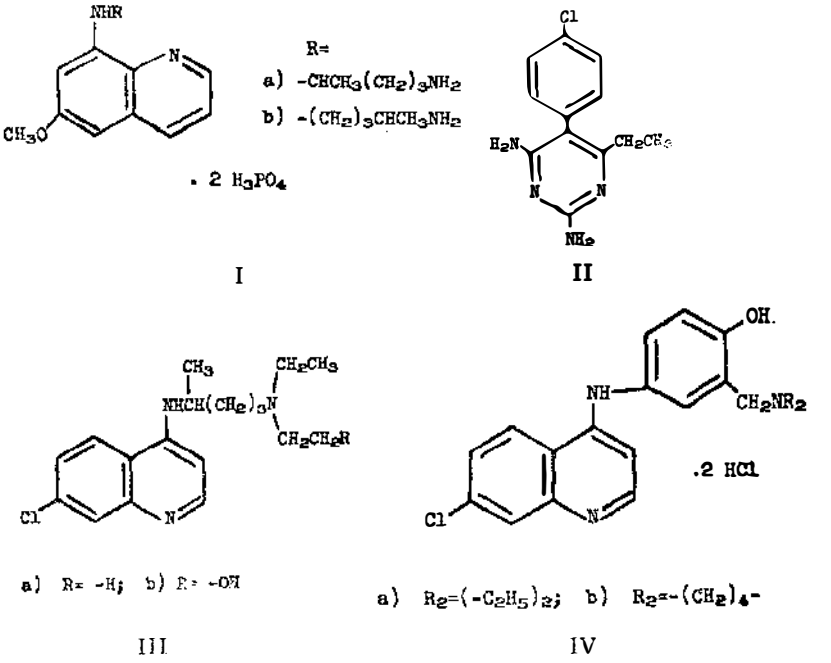
The effects of primaquine (Ia) in intermittent doses are of major current interest. Primaquine continues to be the preferred 8-aminoquinoline (2) even though quinocide (Ib) has attracted considerable attention in Russia (19). Much of the work on intermittent administration of primaquine is presented and the background of the drug is reviewed by Alving *et al.* (2). The previous

standard course of a suppressive drug together with 15 mg of primaquine daily for 14 days could not be exceeded without the risk of hemolytic anemia in primaquine-sensitive patients. Yet this treatment was dependably curative for only certain strains of *Plasmodium vivax*. A general reluctance to use primaquine in most dark-skinned races resulted. Recent work showed that effect against vivax tissue stages is increased, toxic liabilities are reduced (2), and activity against falciparum gametocytes is retained [Jeffery *et al.* (78)] when primaquine is given intermittently rather than daily. Adults tolerated well 60 mg once weekly for eight weeks (2). These findings, greatly extending the horizon of primaquine, may be the most important advance in malaria chemotherapy since the introduction of pyrimethamine (Daraprim) (II). Already, they have led to a combination of complementary drugs (*infra*) that is safe and has a wider range of uses than any single compound.

Justifiably, the trend is toward combinations of drugs. Combination therapy with a 4-aminoquinoline and primaquine has been evaluated under a variety of controlled conditions. Chloroquine (Aralen) (IIIa) and primaquine, in respective weekly doses of 300 and 45 mg for eight weeks, has been recommended for the radical cure of vivax malaria (2). Amodiaquine (Camoquin) (IVa) and primaquine (this combination is called Camoprima) in respective amounts of 300 and 30 mg weekly or biweekly, in a course of 10 doses cured vivax malaria, and in 18 doses (eight before exposure) prevented patent vivax infections [Courtney *et al.* (37)]. Therapeutic weekly doses of Camoprima were administered for several weeks without toxic effects to American children [Hodgkinson *et al.* (74)] and to primaquine-sensitive African children [Charles (25)]. Camoprima, which has met the requirements of the U. S. Food and Drug Administration, proved to be highly useful when given weekly in a large field trial in Tanganyika [Clyde (27)]. The above 4-aminoquinolines, recognized for some years as the best schizonticides, with primaquine constitute the most potent combination for action against tissue stages, asexual blood forms, and gametocytes. The ultimate doses, regimens, and uses of each would depend upon the goals and other factors mentioned previously.

Other combinations of current interest are chloroquine with pyrimethamine or with chlorproguanil (Lapudrine) (Vb). Unfortunately, documented evidence of efficacy from controlled studies with these combinations has not been reported. Presumably, each moiety would exert its characteristic action without interference by the other. Chlorproguanil has similar antimalarial action to chlorguanide (Va) but persists longer in the body [Archibald *et al.* (4)]. The chief uncertainties of these combinations are dependable radical curative efficacy against *P. vivax* (owing to erratic activity against secondary tissue stages) and the liability of pyrimethamine or chlorproguanil-resistant strains. Resistance has emerged to pyrimethamine when it was given with a borderline dose of chloroquine [Schneider *et al.* (112)].

Another development of much practical significance is the demonstration that chloroquine phosphate or pyrimethamine may be administered adequately and safely by incorporation in table salt used in the daily prepara-

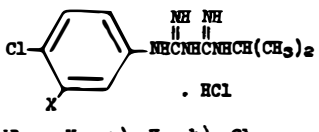


I. (a) Primaquine; (b) Quinocide. II. Pyrimethamine. III. (a) Chloroquine; (b) Hydroxychloroquine. IV. (a) Amodiaquine; (b) Amopyroquin.

tion of food; the concentration is such as to result in weekly intakes of 300 mg of chloroquine or of 25 mg of pyrimethamine [Coatney *et al.* (28)]. Subject to the following problems, this method of treatment has considerable potential in the mass suppression of malaria in areas where the supply of salt is under centralized control. First, chloroquine given in table salt has not been demonstrated to be excreted sufficiently in breast milk to protect vulnerable infants. Second, chloroquine phosphate is reputed to be so hygroscopic that much of the drug is lost by leaching in highly humid environments. Third, pyrimethamine-resistant strains continue to develop in new geographic areas. Hence, a more suitable antimalarial for use in salt is needed.

Aside from quinocide and chlorproguanil, most of the drugs of relatively recent origin are schizonticides [Russell (110), Thompson (126)]. Hydroxychloroquine (Plaquenil) (IIIb) is less toxic than chloroquine and has similar antimalarial activity, orally or parenterally. Amopyroquin (Propoquin) (IVb) is relatively nontoxic and is particularly useful intramuscularly. Cycloquine (VI), a relative of amodiaquine developed in the U.S.S.R., has been used on a small scale in field trials with apparent success. Azacrine (VII) is active orally but estimates of its potency relative to the better schizonticides have varied. The acridine N-oxide PAM-922 (CI-423) (VIII) is a more potent schizonticide in animals than quinacrine and is unlikely to

stain the skin [Thompson *et al.* (129)]; this compound has strong suppressive action in man [Gunders (70a)]. The substituted naphthalene 377-C-54 (IX) is one-half to one-third as potent as the better 4-aminoquinolines. Diaminodiphenylsulfone (X) is useful in the treatment of falciparum and quartan malaria in natives living in hyperendemic areas [Archibald & Ross (5)]. The eventual position of these new drugs in malaria chemotherapy depends, of



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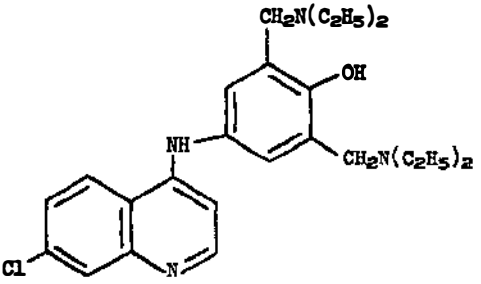
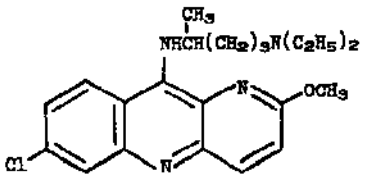
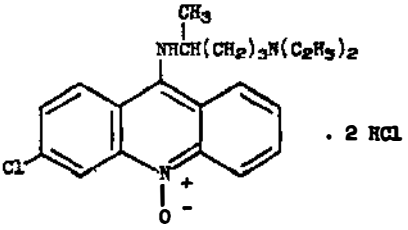


VI

V. (a) Chlorguanide; (b) Chlorproguanil.
VI. Cycloquine.



VII



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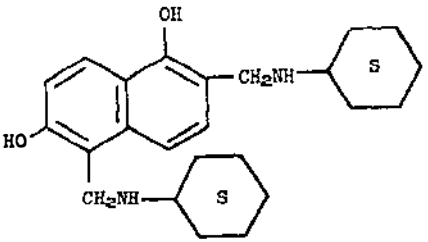
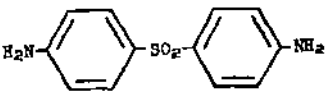


IX



X

VII. Azacrine.
VIII. PAM-922.
IX. 377-C-54.
X. Diaminodiphenylsulfone.

course, upon many factors. They, at least, constitute an alternative group that may be drawn upon if the current schizonticides become less useful.

Drug-fast strains have been a problem with certain drugs—chlorguanide and pyrimethamine—in some areas in the past [Goodwin & Rollo (68)]. Published and oral reports indicate many new areas of pyrimethamine resistance. Indications are that drug-fastness will be an even more important consideration in the future. A chloroquine-fast strain of *P. falciparum* in Colombia has been reported [Moore & Lanier (92)]. It is not known whether this fastness has been acquired or was an innate property, comparable to a quinacrine-refractory strain of *P. falciparum* encountered in the South Pacific area (68). Previous work (68) indicated that acquired resistance to quinacrine or a 4-aminoquinoline is most improbable but the induction of a chloroquine-fast strain of *P. berghei* has been reported recently [Ramakrishman (105)].

An important defect among available drugs is that none in a single dose will protect against patent malaria for more than about three weeks. A repository drug capable of suppression for several months is urgently needed; it would expand greatly the available approaches to the control and eradication of malaria.

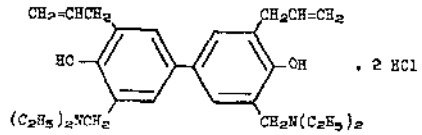
Amebiasis

In agreement with recent detailed reviews (3, 7, 49, 54) no single compound is dependably effective against amebae irrespective of whether they occur in the lumen of the colon, the wall of the colon, or extra-intestinally. A paramount defect seems to be that the physiologic distribution of any one drug in tolerable doses is inadequate for all forms of the disease. Hence, most drugs can be classified as mainly intestinal or hepatic amebicides.

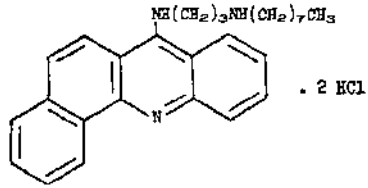
The hepatic amebicides are selectively concentrated and held in the liver for many days. As reviewed elsewhere [Thompson (126)], amodiaquine (IVa), quinacrine, biallylamicol (Camoform) (XI) and a substituted benz[c]acridine (PAA-2056, CI-344) (XII) have definite potential in the therapy of hepatic amebiasis. None of these is known, however, to be superior to emetine or chloroquine for the treatment of amebic abscess of the liver in man. Indeed, the limitations of either emetine or chloroquine alone are such that emetine followed by chloroquine now is recommended [Wilmot *et al.* (142)].

Several new intestinal amebicides have been developed recently. The antibiotic paromomycin (XIII) [Haskell *et al.* (71)], has both high antibacterial and direct antiamebic potency [Coffey *et al.* (29); Thompson *et al.* (127); Fisher *et al.* (58)]. Used as the sulfate salt, it is absorbed poorly from the gastrointestinal tract and is tolerated well. Clinical experience indicates paromomycin sulfate (Humatin) to be useful in the treatment of acute and chronic intestinal amebiasis as well as many types of bacterial enteritis [Courtney *et al.* (36)].

The dichloracetamides are of considerable current interest. Chlorbetamide (Win 5047, Mantomide) (XIV) was developed first [Dennis & Berberian (45); Loughlin & Mullin (85)]. This was soon followed by entamide (XV) [Bristow



XI



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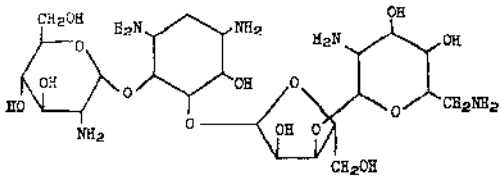
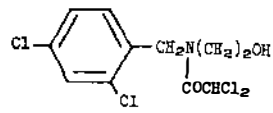
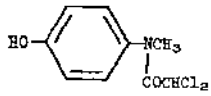


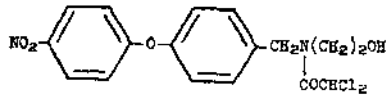
XIII



XIV



XV



XVI

XI. Biallylamicol. XII. PAA-2056. XIII. Paromomycin. XIV. Chlorbetamide. XV. Entamide. XVI. Chlorphenoxamide.

et al (13)] and quite recently by the benzoate, piperazine sulfate, and furoate salts of this compound [Marsden (89); Woodruff & Bell (144); Shaldon (116)]. Another recent member of the group is chlorphenoxamide (Mebinol) (XVI) [De Carneri (43)]. The consensus of clinical reports (*loc. cit.*) is that these drugs are tolerated well and are useful mainly in the treatment of chronic rather than acute intestinal amebiasis. No indication of their efficacy against hepatic amebiasis has appeared.

Another new type of amebicide is 4,7-phenanthroline-5,6-quinone (Ciba 11,925, Entobex) (XVII) and its monosemicarbazone (Ciba 11,925C). These substances, particularly the former, are moderately effective against both chronic and acute intestinal amebiasis but they cause more gastrointestinal side effects than the pentavalent arsenicals and dichloracetamides [Younes (150); Chowdhury & Chowdhury (26)].

Glaucarubin (Glaumeba), a glycoside of plant origin [Del Pozo & Algaraz (44); Van Assendelft *et al.* (133)] and biallylamicol [Taylor (125); Bustamente y Rivera (24)] are relatively new drugs that are tolerated well and moderately effective against both chronic and acute intestinal amebiasis.

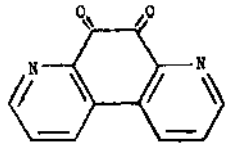
Drug combinations, particularly of chloroquine with a pentavalent arsenical or halogenated 8-quinolinol, are being offered but convincing evi-

dence is lacking that any of these approximates ideal therapy for all forms of amebiasis.

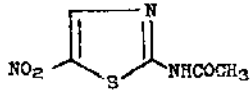
Trichomoniasis

No parasitic infection is known to be as common among women of the temperate zones as vaginal trichomoniasis; the prevalence is particularly high among women of the lower socio-economic groups (73, 132, 140). Like many other parasitoses, it provokes such a feeble immune response that cure is largely dependent upon chemotherapy. Topical medicaments, reviewed recently [Willcox (140); Goldman (64)], are palliative but rarely curative parasitologically. Their failure stems more from the inaccessibility of the foci of infection to topical treatment than to a lack of potent antitrichomonal ingredients [Willcox (140)].

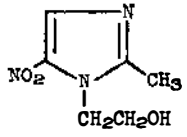
Recent advances in trichomoniasis chemotherapy are the emergence of orally-active drugs and confirmation that systemic treatment, alone or adjunctively, enables a superior rate of parasitologic cure. The first solid encouragement toward systemic therapy was provided by aminitrozole (Tritheon) (XVIII); however, even at levels causing side effects this substance conferred in women only erratic effect [Willcox (140); Plentl *et al.* (103)] and was ineffective in men [Feo & Fetter (57)]. Further confirmation of the oral treatment approach has occurred with the use of metronidazole (Flagyl) (XIX). More than a score of clinical reports (50) attest to an en-



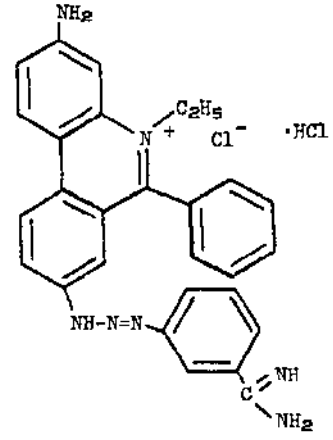
XVII



XVIII



XIX



XX

XVII. Entobex.
XVIII. Aminitrozole.
XIX. Metronidazole.
XX. Isometamidium.

couraging degree of efficacy and good tolerance in both men and women given metronidazole orally. In some later studies [Scott-Gray & Murrell (113)], the failure rate after oral administration was sufficiently high that a tendency toward both oral and topical treatment of women with metronidazole is becoming manifest and so far is yielding excellent results [Sylvestre & Gallai (123); Fortier (59)]. The antibiotic trichomycin seems to be inadequate in either women [Goldman (64)] or men [Sylvestre *et al.* (124)] when given only by the oral route but moderately promising in women when given both orally and intravaginally [Gaudefroy (63)].

Trypanosomiasis

Trypanocides have been reviewed quite recently (64, 67, 118). Trypanosomes have such a remarkable capacity to become drug-resistant [Bishop (12)] that new types of drugs are needed. Puromycin [Trincao *et al.* (131)] and 5-nitro-2-furaldehyde semicarbazone (Nitrofurazone) [Evans *et al.* (56)] have shown sufficient effect to suggest consideration of them as alternatives or supplements to the older drugs used for the treatment of African sleeping sickness. Isometamidium (M and B 4180A) (XX) is the more active moiety of the isomeric mixture homidium (Metamidium) and is active in cattle [Berg (11)]; its efficacy in cattle relative to older phenanthridiniums has not been described.

The stubborn endemicity of the trypanosomiases makes chemoprophylaxis of prime importance. Acceptable substances must have long action, low toxicity, and small likelihood of permitting drug-fastness; these requirements still have not been met. Complexes of the acid suramin (Bayer 205) and of basic trypanocides (ethidium, dimidium, antrycide, berenil, etc.) are of recent interest in animals as they act longer than either component alone [Williamson (141); Desowitz (46)]. Suramin-ethidium is too irritating for use in cattle [Stephen & Williamson (121)], but suramin-antrycide and antrycide dimethylsulfate are useful in protecting pigs against *Trypanosoma simiae* [Stephen & Gray (120); Watson & Williamson (138)]. Prothidium protects cattle for five to eight months and ethidium (Homidium) is effective against prothidium-resistant strains [Lyttle (87)].

The need persists for drugs that have specific therapeutic effect against acute and chronic forms of American trypanosomiasis (Chagas' disease). None of the various substances [Goldman (64)] that are variably active against *T. cruzi* in animals has been shown to be worthy of recommendation for the treatment or prevention of the disease in man.

Coccidiosis

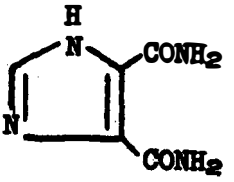
The chemoprophylaxis of coccidiosis in poultry continues to attract much interest; responsible factors include the great economic importance of the poultry industry and the emergence of strains of coccidia resistant to nitrophenide, nitrofurazone, and sulfaquinoxaline [Cuckler & Malanga (41)]. A useful review of anticoccidial substances has appeared recently [Goldman (64)]. Glycarbylamide (Glycamide) (XXI) [Cuckler *et al.* (40)] has been

introduced for use in broilers but not in laying hens. Recently in Canada, Zoalene (Zoamix) (14) (XXII) has been introduced, but use so far is restricted to broilers. A synergistic mixture of 2,2′-thiobis[4,6-dichlorophenol](XXIII) with 4,6-diamino-1-(4-methylthiophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (XXIV) (35) is being offered under the name Trithiadol. A new group of thiamine-reversible coccidiostats has been described [Rogers *et al.* (108)]; these include many 1-(2-alkyl-4-amino-5-pyrimidinylmethyl)-alkylpyridinium salts and analogous 3-thiazolium compounds. Amprolium (XXV) has been developed and is being marketed as Amprol.

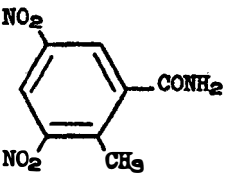
The action of various sulfonamides against *Eimeria tenella* is potentiated by certain pteridines [Horton-Smith *et al.* (75)], as well as by various diaminopyrimidines and dihydrotriazines [Ball (8); Lux (86)].

Intestinal Helminthiases of Man

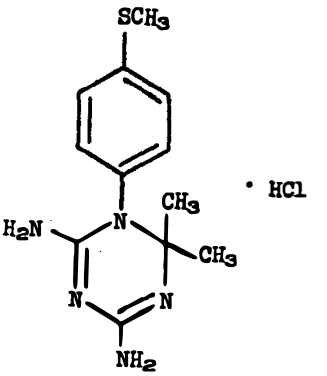
The world-wide prevalence of intestinal helminthic infections in man has been estimated by Stoll (122) to approach the staggering figure of two billion. The substantial progress made in the development of new anthelmintics during the past 10 years has recently been reviewed (6, 9, 18, 21, 98).



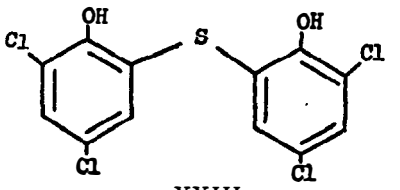
XXI



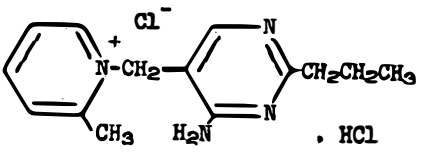
XXII



XXIV



XXIII



XXV

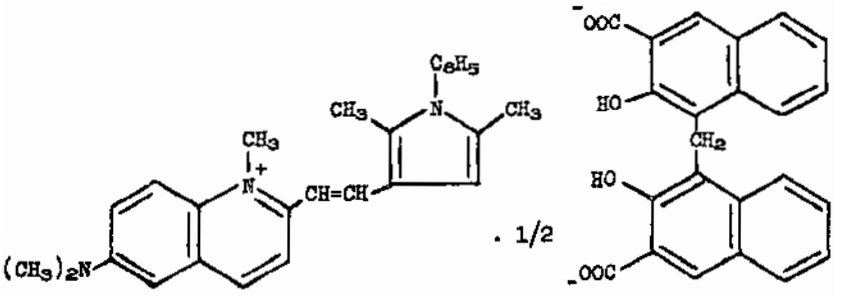
XXI. Glycarbylamide. XXII. Zoalene. XXIII. Bithionol.
XXIV. Methiotriazamine. XXV. Amprolium.

The introduction of piperazine for the treatment of ascariasis and oxyuriasis (pinworms) represented an important advance in helminth chemotherapy [Goodwin & Standen (69)]. More recently, several cyanine dyes have received widespread use in the treatment of intestinal helminthiases of man. Pyrvinium chloride is active against a variety of intestinal nematodes of laboratory animals and man [Weston *et al.* (139); Thompson *et al.* (130)], but attempts to develop a pyrvinium chloride suspension suitable for use in children were thwarted by variability among lots of drug as to taste and reputedly as to gastrointestinal tolerance. A search for a superior pharmaceutical form led to pyrvinium pamoate (Povan, Vanquin) (XXVI), which has proved to be a highly curative and well-tolerated antioxyurid in man when administered in a single oral dose of 5 mg/kg [Beck *et al.* (10)]. With the advent of such a single-dose regimen, the removal of pinworms as a personal and public health problem may well be in sight.

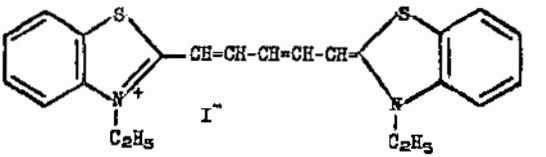
Following reports that dithiazanine (Delvex) (XXVII) was effective against various helminths in experimental animals [McCowen *et al.* (91)], the drug was demonstrated to be effective for the treatment of trichuriasis, strongyloidiasis, ascariasis, and enterobiasis in man [Frye *et al.*(61); Brown (18)]. Because of an over-all incidence of gastrointestinal side-effects of about 30 per cent, and rare, but more serious reactions attributed to drug idiosyncrasy (119), a major manufacturer has recommended that dithiazanine be discontinued in the treatment of enterobiasis (pinworms), used only when other therapy fails in ascariasis, and reserved for infections caused by *Strongyloides stercoralis* or heavy and clinically significant infection with *Trichuris trichiura.*

A group of quaternary ammonium compounds has recently been shown to have activity against a wide range of nematodes in laboratory and domestic animals and in man [Copp *et al.* (34)]. Preliminary clinical trials in Ceylon [Goodwin *et al.* (66)] demonstrated that bephenium hydroxynaphthoate (Alcopar), when administered in a single dose of 2 or 3 g of base or in multiple doses given on successive days or three times on the same day, compared favorably in effectiveness with tetrachloroethylene against *Necator americanus.* The drug was also effective against concurrent *Ascaris* infections. Unfavorable results were obtained with bephenium bromide and bephenium embonate (XXVIII). Subsequent clinical studies have confirmed that bephenium hydroxynaphthoate is active against *Ascaris lumbricoides, Ancylostoma duodenale* and *N. americanus* infections, although tolerance and efficacy against *N. americanus* have varied among investigators (76, 79, 149). It is only moderately effective against *T. trichiura* [Young *et al.* (151); Hsieh *et al.* (76)]. The drug usually is tolerated relatively well and side effects (7 to 42 per cent) consist principally of nausea, vomiting, and abdominal pain.

The trichlorophenol salt CI-416 (XXIX) has broad action against intestinal nematodes in animals and man at nontoxic levels [Peña Chavarria *et al.* (102), Wagner (134a), Kayhoe *et al.* (80)]. A single oral dose of 50 mg/kg in 10 patients caused respective mean egg count reductions of 99, 96, and 73 per cent for *Ascaris, Necator* and *Trichuris* (102). Single or multiple

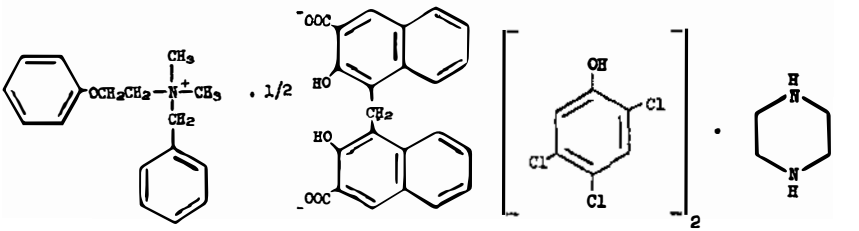


XXVI

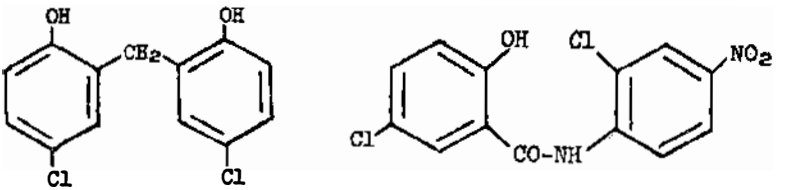


XXVII

XXVI. Pyrvinium pamoate. XXVII. Dithiazanine.



XXVIII XXIX



XXX XXXI

XXVIII. Bephenium embonate.
XXIX. CI–416.
XXX. Dichlorophen.
XXXI. Yomesan.

doses of 0.75 to 3.0 g, given to 53 patients, had strong effect against *Ascaris* and hookworms, moderate effect against *Enterobius*, and slight effect against *Strongyloides* and *Trichuris* (134a). The drug also removed *Trichostrongylus orientalis* in three patients refractory to treatment with several other anthelmintics (80).

The most prevalent cestodes in man are the three large tapeworms, *Taenia saginata*, *T. solium*, and *Diphyllobothrium latum*, and the dwarf tapeworm *Hymenolepis nana*. At present quinacrine (Atabrine) is regarded as the drug of choice for the removal of taenias, but it is not satisfactory against the dwarf tapeworm. Several new anthelmintics for cestode therapy have recently been reported, although additional confirmation of their safety and efficacy utilizing a critical standard procedure is needed. Amodiaquine (Camoquin) (IVa) has been reported to be useful against taenias [van Grunderbeeck & Penson (134)]. Dichlorophen (Di-phenthane 70, G–4) (XXX), introduced by Craige and Kleckner (38) as a remedy for dog tapeworms, has received widespread use in human taeniasis in the past five years. Seaton (114) indicates that a large, single oral dose of the drug is nontoxic and highly effective against *T. saginata* infections without ancillary treatment. Several instances of jaundice and one death indicate that this drug is potentially dangerous when the standard dose is exceeded [Jackson (77)].

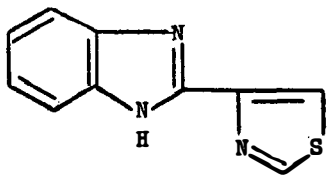
A new taeniacide Yomesan (XXXI) has been described by Gönnert and Schraufstätter (65). The drug is well tolerated by experimental animals and man (72) and early clinical reports indicate that the drug is effective against *H. nana* in man [Donckaster *et al.* (47)].

Intestinal Helminthiases of Animals

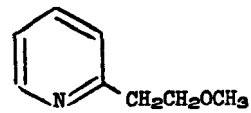
Approximately 300 kinds of internal parasites are of economic importance to the livestock industry of the United States alone; losses to this country in livestock and poultry production from internal parasites approach one-half billion dollars annually (84). Approximately one-half of these losses are due to intestinal helminths.

Intensive efforts to develop new anthelmintics for treating livestock, poultry, and other animals have yielded a variety of promising new drugs. Brown *et al.* (17) recently announced that thiabendazole (XXXII) and related benzimidazoles possess broad spectrum activity against intestinal helminths in sheep, goats, cattle, horses, swine, dogs and poultry at well-tolerated doses. A single oral dose of 50 mg/kg removed from sheep more than 95 per cent of the worms belonging to ten genera (*Trichostrongylus, Cooperia, Nematodirus, Ostertagia, Haemonchus, Oesophagostomum, Bunostomum, Strongyloides, Chabertia, Trichuris*). In addition to removing adult parasites, the drug inhibits the production of eggs and interferes with the development of larval forms. The drug is also reported to be effective against the migrating parasitic stages of *Ascaris* and kidney worm in swine. Its vermifugal action in dogs includes action against hookworms, roundworms, and whipworms.

Another new drug with unusual anthelmintic properties is methyridine (Promintic) (XXXIII) (16, 70, 137). During extensive trials in cattle and sheep, a single 200 mg/kg dose, administered orally or subcutaneously, gave excellent results against *Trichostrongylus* spp. in the abomasum, *Ostertagia*, *Cooperia*, and *Nematodirus* spp. in the small intestine, and *Trichuris* spp. in the caecum and large intestine [Walley (137); Groves (70)]. The drug has good activity against *Bunostomum*, *Chabertia*, and *Oesophagostomum* spp. but erratic effect against *Haemonchus* and *Ostertagia* in the abomasum. Immature and mature worms appear to be equally susceptible to the compound. At the recommended dose, no untoward general effects have been reported apart from occasional dullness, although twice this dose may cause death from respiratory depression. The drug sometimes produces a local swelling after injection, particularly in cattle. Methyridine is rapidly absorbed and distributed throughout the tissues following injection. Appreciable amounts pass into the alimentary canal and are sustained there until metabolism in



XXXII



XXXIII

XXXII. Thiabendazole.
XXXIII. Methyridine.

the tissues causes the blood concentration to fall, at which time re-absorption takes place. The passage of methyridine from the blood to the alimentary canal along its entire length favors the exposure of various stages of a worm to contact with the drug, including those lying deep in the mucosa. This remarkable property contributes to its broad-spectrum of activity. Methyridine passes through the cuticle of living worms and paralyzes them by causing a neuromuscular block which cannot be reversed by acetylcholine [Broome (15)]. The compound is rapidly eliminated from the tissues; approximately 24 hours after administration no drug residues can be found in milk or carcass. Most of the drug is metabolized to pyridine-2-acetic acid, which, together with traces of other metabolites and unchanged drug, is excreted in the urine.

Bephenium embonate (XXVIII) and hydroxynaphthoate are active against certain intestinal worms of cattle and sheep when administered in a single oral dose of 250 mg/kg, and are well-tolerated. Rawes & Scarnell (106) and Marquardt *et al.* (90) found bephenium embonate to be effective in removing adult and larval stages of *N. battus* and *N. filicollis* and adult *N. spathiger* and *Marshallagia marshalli* in sheep. Little or no effect was demonstrated against *O. circumcinata*, *T. colubriformis*, *H. contortus*, and *T. axei*.

In cattle, bephenium hydroxynaphthoate removed *O. ostertagi*, *T. axei*, *N. helvetianus*, *C. oncophora*, *Oe. radiatum*, and *Chabertia ovina* [Eisa & Rubin (51)].

A single 15 mg/kg dose of diethylcarbamazine (Hetrazan, Caricide) (XXXIV) reduced egg production and adult populations of *H. contortus* in lambs; doses of 250 to 500 mg/kg gave results against *T. axei* and *T. columbriformis* comparable to 1000 mg/kg doses of phenothiazine [Wood *et al.* (143)]. These studies suggest that the anthelmintic effect of diethylcarbamazine is not a direct function of its piperazine content as piperazine has been reported inactive against these nematodes.

Several organic phosphorus compounds exhibit anthelmintic activity in cattle and sheep, although toxicity problems may limit their usefulness. In cattle, high efficiency was obtained with Neguvon (Bayer L13/59, Dipterex) (XXXV) against mature *H. placei*, *Oe. radiatum*, *B. phlebotomum*, *T. axei*, and *Cooperia spp.*; the drug was also effective against the immature stages of all but *T. axei* [Rieck (107)]. Neguvon has not been promising in sheep: although it removes *H. contortus* and has some effect against *Ostertagia* spp., it has little usefulness against *Trichostrongylus* or *Oesophagostomum* spp. [Southcott (117)]. Studies in cattle with Ruelene (XXXVI) indicate good removal of *H. placei*, *O. ostertagi*, *Oe. radiatum*, and *Cooperia* spp., fair removal of *T. axei*, and little or no effect on *B. phlebotomum* [Landram (83)]. Douglas & Baker (48) found a 200 mg/kg dose of Ruelene to be well-tolerated in sheep and highly efficient against *Ostertagia*, *Nematodirus*, *T. axei*, and *T. vitrinus*, but inadequate against *T. colubriformis*. However, Galvin *et al.* (62) encountered signs of intoxication in lambs at this and higher doses; they concluded that well-tolerated doses of 100 mg/kg left too many parasites in the gastrointestinal tract to recommend Ruelene for use in mixed infections.

Among swine anthelmintics, the antibiotic hygromycin [Mann & Woolf (88)] (XXXVII) has a broader spectrum of anthelmintic activity than sodium fluoride or piperazine as it eliminates whipworms in addition to large roundworms and nodular worms [Colglazier & Enzie (30)].

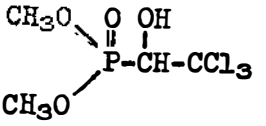
Disophenol (XXXVIII) has recently been introduced for the treatment of dogs infected with hookworms, including *Ancylostoma caninum*, *A. braziliense*, and *Uncinaria stenocephala*. The drug is administered by a single subcutaneous injection and is well-tolerated. Disophenol is primarily effective against adult hookworms. Early results indicate that *A. caninum* is more susceptible to the drug than *U. stenocephala* [Koutz & Groves (81)].

The bephenium analog 611C55 (XXXIX) is more effective than bephenium against *A. caninum*, *U. stenocephala*, *Toxocara canis*, and *Toxascaris leonina* in the dog, and is much less emetic [Burrows *et al.* (23)].

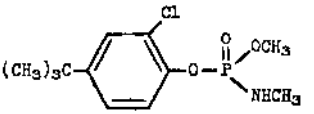
Lungworm Infections of Domestic Animals

Lungworm diseases cause great livestock losses throughout the world in the form of poor weight gains, lowered production, secondary invasion by debilitating bacterial and viral infections, and in some instances, death. The uncomplicated infection is often transient and self-limiting. Hence, spon-

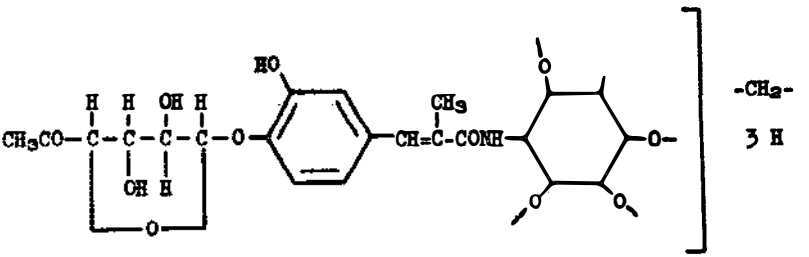
XXXIV



XXXV

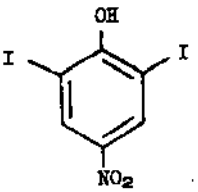


XXXVI

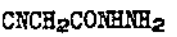


XXXVII

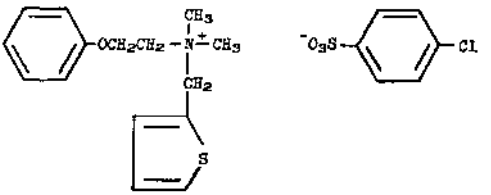
XXXIV. Diethylcarbamazine.
XXXV. Neguvon.
XXXVI. Ruelene. XXXVII. Hygromycin.



XXXVIII



XL



XXXIX

XXXVIII. Disophenol.
XXXIX. 611C55
XL. Cyanacethydrazide.

taneous recovery—stemming from immunological reactions and improved dietary, sanitary, or other management practices—requires carefully controlled studies in the evaluation of drugs against lungworm infections.

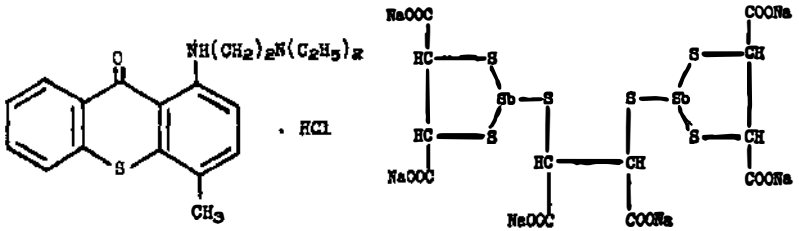
Walley (135) reported cyanacethydrazide (Dictycide, Helmox) (XL) to be active orally, subcutaneously, or intramuscularly against certain nematodes that normally live in the air passages: *Dictyocaulus viviparus* in cattle, *D. filaria* in sheep and goats, *Protostrongylus rufescens* in sheep, and *Metastrongylus apri* in swine. It was ineffective against migrating larvae or *Muellerius capillaris* and *Neostrongylus linearis* in lung tissue. Parker *et al.* (100, 101) found diethylcarbamazine (Hetrazan, Franocide) (XXXIV) to be somewhat useful in removing adult and larval stages of *D. viviparus* from cattle. The clinical response was good provided the drug was administered before lung damage was severe. Methyridine (XXXIII) has some activity against *Dictyocaulus* spp. in cattle and sheep [Walley (137)] but is not recommended alone as a specific treatment for severe parasitic bronchitis. All three drugs appear to be tolerated well at the recommended doses.

The ideal lungworm drug should be effective against the migrating immature worms and against both mature and immature worms in the air passages of the lungs. Conflicting reports (101, 136, 137) that cyanacethydrazide and diethylcarbamazine give excellent results in some trials but are relatively ineffective in others suggest that neither drug is adequate for all purposes.

Schistosomiasis

Some 200 million people are infected with schistosomes and on a global basis this group of diseases is spreading. The degree of prevalence, the seriousness of infection, and the lack of adequate drugs make these diseases one of the greatest challenges in medical parasitology today. Several impressive new leads have been discovered in experimental animals, but the usefulness of these compounds in human schistosomiasis has yet to be adequately evaluated. Therefore, one still must rely on the antimonials with some assistance from lucanthone hydrochloride (Miracil D, Nilodin) (XLI) in the case of *Schistosoma haematobium* and some strains of *S. mansoni*.

No new trivalent antimony compounds appear to be available at this time that are markedly superior to those in use for many years (antimony potassium tartrate, antimony sodium tartrate, sodium antimony III bis-pyro-catechol-2,4-disulfonate, lithium antimony thiomalate, sodium antimony III gluconate). Antimony dimercaptosuccinate, sodium salt (TWSb/6, Ro 4-1544/6, Astiban) (XLII) may provide effective treatment in a shorter period of time (60, 82, 93). The necessity of repeated parenteral administrations of antimonials is one of their most serious disadvantages, and due caution must be taken concerning the well-known contraindications in their use and the possibility of severe reactions following even short-term courses. In China, tartar emetic has been administered on a large scale orally with relatively good therapeutic results, but with considerable side effects [Yung-Chi *et al.* (146)].



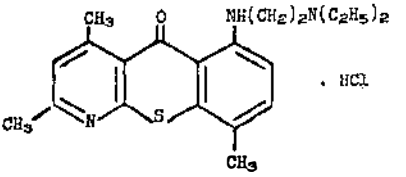
XLI XLII

XLI. Lucanthone hydrochloride.
XLII. Antimony dimercaptosuccinate.

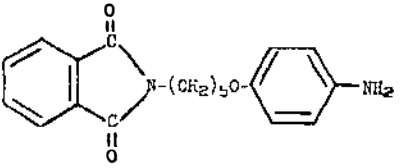
Hundreds of compounds related to lucanthone hydrochloride have been prepared and tested. Many of these are active in experimental animals, but none has been demonstrated to be superior to lucanthone hydrochloride in man (97, 109, 115). Davis (42) encountered less frequent and less severe side effects with resinates of lucanthone than with lucanthone hydrochloride, yet, the usual degree of efficacy against *S. haematobium* and *S. mansoni* was obtained. The administration of combinations of tartar emetic and lucanthone hydrochloride or compound 17581 (XLIII) at one-half the usual therapeutic dose of each was reported to diminish side effects while maintaining a therapeutic response in *S. haematobium* patients [Nagaty *et al.* (94)]. Further combination studies appear warranted.

Following the independent discovery by Raison & Standen (104) and by Collins *et al.* (33) that certain α,ω-di(*p*-aminophenoxy)alkanes were highly active against experimental schistosomiasis, hundreds of related compounds were prepared and tested. Although many of these possessed marked antischistosome activity, the more promising compounds also produced retinotoxicity in cats which precluded human use. Recently a related compound, N-[5-(*p*-aminophenoxy)pentyl]phthalimide (M and B 2948 A, 6,171 R.P.) (XLIV), was selected for clinical trial because it showed a very low incidence of ocular disturbances in cats [Collins *et al.* (32)]. Preliminary clinical reports indicate that M and B 2948 A produces a definite therapeutic response in *S. haematobium* infections at doses that are fairly well-tolerated, although visual disturbances were reported in several patients [Alves *et al.* (1); El-Bitash *et al.* (53)]. Further trials are needed to accurately assess the safety and efficacy of this drug.

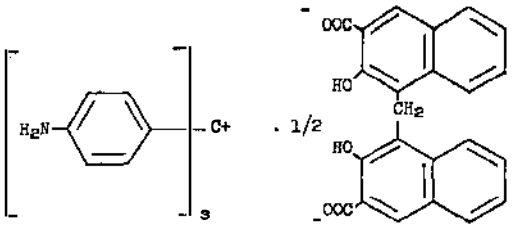
It has recently been reported that commercial samples of pararosaniline hydrochloride exhibit a lethal effect on *S. mansoni* and *S. japonicum* in experimental animals [Elslager *et al.* (55), Thompson *et al.* (128) & Yea-Lin (145)]. Purification of the commercial dye led to the isolation of a highly purified form of tris(*p*-aminophenyl)carbonium chloride which had both curative and protective activity in mice and monkeys. This compound is schistosomicidal *in vitro* and appears to act by interfering with the nutrition of the worms rather than by specific organ or tissue toxicity. Although it is well-tolerated in mice and monkeys at levels necessary for antischistosomal



XLIII



XLIV



XLV

XLIII. 17581.
XLIV. M and B 2948A.
XLV. CI-403A.

activity, such amounts cause emesis and gastritis in dogs. The pamoate (CI-403A) (XLV) is less emetic than the chloride in dogs (128) and has been demonstrated to be orally effective against *S. haematobium*, *S. japonicum* and *S. mansoni* in man at well-tolerated doses (22, 128). The pamoate appears to be worthy of expanded clinical trials in schistosomiasis for the purpose of cure, protection against infection, and prevention of egg excretion.

Extensive research on schistosomiasis in China has recently been reviewed (96).

Paragonimiasis

An authoritative review on all aspects of this trematode infection has recently been published by Yokogawa *et al.* (147). So far paragonimiasis has proved to be relatively resistant to effective chemotherapy although many drugs have been tried. Some favorable results have been obtained with chloroquine (IIIa), and combinations of emetine with sulfa drugs or chloroquine (147). Buck *et al.* (20) conclude that the erratic response to chloroquine therapy is related to the duration of the disease and the location of the parasite in the host. Park (99) has reported that certain chloroquine-resistant cases respond to treatment with PAA-2056 (XII).

When dogs infected with *Paragonimus kellicotti* are treated orally with tris(*p*-aminophenyl)carbonium chloride or the pamoate (XLV), egg production by the worms is markedly decreased and many of the eggs appear abnormal [Elslager *et al.* (55); Najarian *et al.* (95)]. The chloride also induces the worms to produce abnormal eggs *in vitro*. The chemotherapeutic evaluation of these substances in human paragonimiasis appears warranted (95).

Probably the most outstanding new development in paragonimiasis chemotherapy is the demonstration that bithionol (XXIII) is active against *P. westermanni in vitro*, in experimental animals, and in man [Yokogawa *et al.* (148, 149)]. The compound has demonstrable killing action against the worms under experimental conditions. It cleared all of 13 patients through a six months follow-up after five to fifteen oral doses of 50 mg/kg/day; side effects, primarily gastrointestinal, were mild and transient.

Clonorchiasis

Chloroquine (IIIa) (39, 52) exerts some beneficial effect on *Clonorchis sinensis* infections but there is a great need for a more effective drug to combat this trematode. which infects some 19,000,000 people.

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