Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIPARASITIC AGENTS, ANTIPROTOZOALS

Diseases caused by protozoa affect more people than those brought on by any other biological cause (1). There are over 60,000 species of protozoa, of which some 10,000 are parasitic. In humans, protozoa chiefly infect the gastrointestinal tract, vagina, urethra, blood, and blood-forming organs. Malaria is the most widespread of the protozoan diseases, and is responsible for the greatest number of deaths due to infection. Although protozoan diseases occur throughout the world, they impact most severely on people of tropical areas where there is widespread malnutrition, minimal health education, and poor sanitation. Fatal protozoal infections are occurring to an increased extent in the more developed countries among immunosuppressed individuals, especially those with AIDS. Domesticated and wild animals are also extensively affected and can harbor and propagate infectious protozoa. Protozoan diseases of poultry and ruminants deprive large numbers of people, especially in Africa, of much needed food.

The word protozoa is derived from the Greek *protos* and *zoon*, meaning first and animal, respectively. Protozoa are a highly varied group of one-celled animals that reproduce by both sexual and asexual means. Given suitable conditions, ie, host susceptibility and lack of immunity, their numbers can increase by the tens of thousands in the course of one day. They are eukaryotic (having a well-defined nucleus), are surrounded by a membrane through which nutrients can pass, and their cytoplasm contains organelles that enable them to generate energy, digest nutrients, respire, grow, and reproduce. Protozoa are capable of motility and propel themselves by means of cilia, flagella, or pseudopods. Accurate differentiation and identification of infective protozoa facilitates the choice of treatment, but is frequently a difficult task.

Progress in finding new chemotherapeutic agents to combat protozoal disease has been slow. The urgency of the problem has been dramatized by the realization that AIDS patients usually die from opportunistic diseases, many of which are protozoan in origin. There are no satisfactory treatments for many of the protozoal diseases; where there are proven drugs available, parasites in many parts of the world are developing resistance to them. This resistance has necessitated the continual design, synthesis, and testing of new classes of prophylactic and therapeutic agents. Despite the alarming view by a World Health Organization spokesman in 1990 that the war against tropical diseases is being lost, only a modest proportion of the world's research resources is being devoted to devising new treatments. Unfortunately, most pharmaceutical firms do not anticipate adequate financial reward from solving the health problems of developing countries.

This article discusses the main diseases caused by protozoa and the important chemotherapeutic antiprotozoal agents currently in use or in an advanced state of development. Not all alternative proprietary names are given for each drug. There are excellent sourcebooks on protozoology and parasitology (2–8).

Table 1. Amebiasis Antiprotozoal Agents[a]

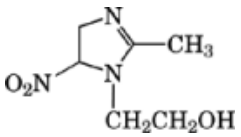
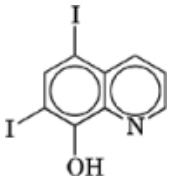
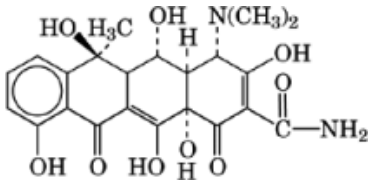
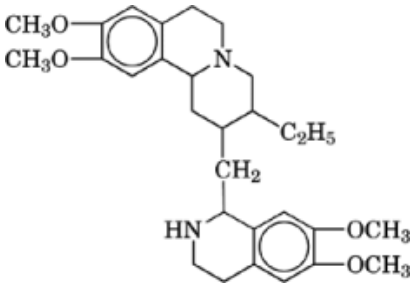
Structure number	Compoundname	CAS Registry Number	Molecular formula	Structure
(**1**)	metrano-dazole[b,c,d,e,f]	[443-48-1]	$C_6H_9N_3O_3$	
(**2**)	iodoquinol[b,d]	[83-73-8]	$C_9H_5I_2NO$	
(**3**)	oxytetra-cycline[b,g,h]	[79-57-2]	$C_{22}H_{24}N_2O_9$	
(**4**)	emetine (HCl)	[316-42-7]	$C_{29}H_{40}N_2O_4 \cdot 2ClH$	

Table 1. ***Continued***

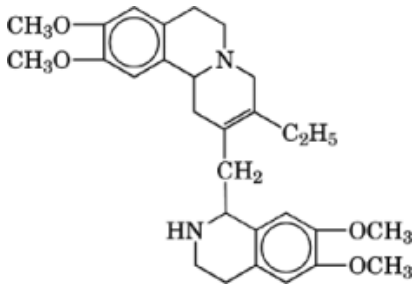
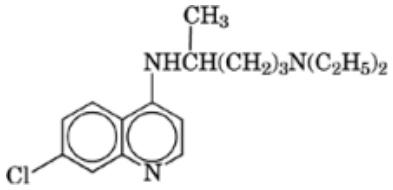
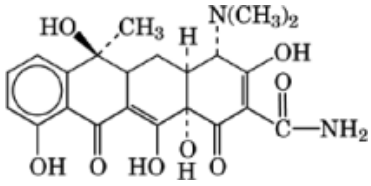
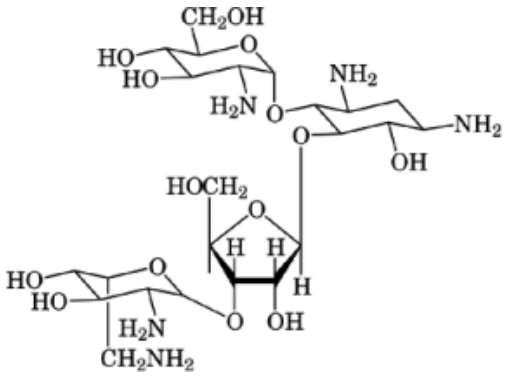
Structure number	Compoundname	CAS Registry Number	Molecular formula	Structure
(**5**)	dehydroemetine	[4914-30-1]	$C_{29}H_{38}N_2O_4$	
(**6**)	chloroquine[g,i,j] (diphosphate)	[50-63-5]	$C_8H_{26}ClN_3 \cdot 2H_3O_4P$	
(**7**)	tetracycline[b,j]	[60-54-8]	$C_{22}H_{24}N_2O_8$	
(**8**)	paromomycin[b,c,k]	[59-04-1]	$C_{23}H_{45}N_5O_{14}$	

Table 1. ***Continued***

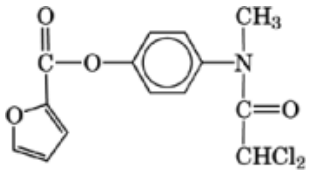
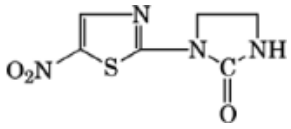
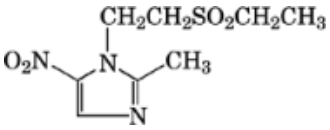
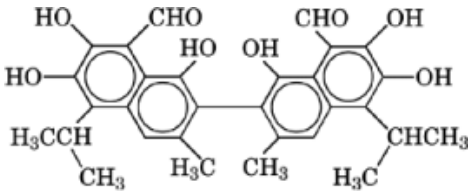
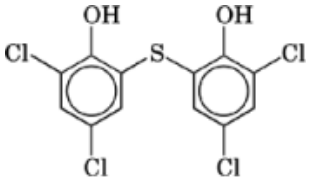
Structure number	Compoundname	CAS Registry Number	Molecular formula	Structure
(**9**)	diloxanide furoate	[3736-81-0]	$C_{14}H_{11}Cl_2NO_4$	
(**10**)	niridazole[f]	[61-57-4]	$C_6H_6N_4O_3S$	
(**11**)	tinidazole[b,c,d,e,f]	[19387-91-8]	$C_8H_{13}N_3O_4S$	
(**12**)	gossypol	[303-45-7]	$C_{30}H_{30}O_8$	
(**13**)	bithionol	[97-18-7]	$C_{12}H_6Cl_4O_2S$	

Table 1. ***Continued***

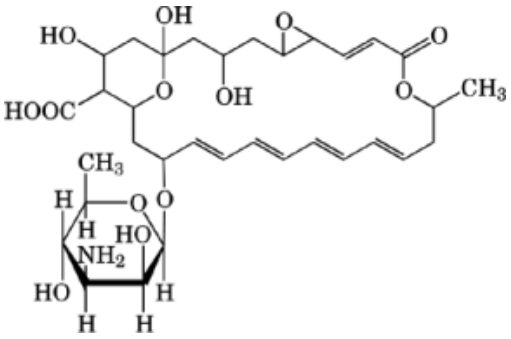
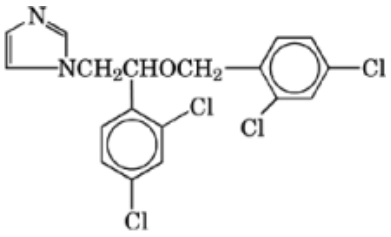
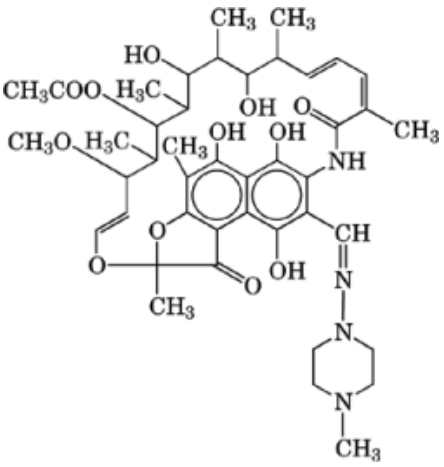
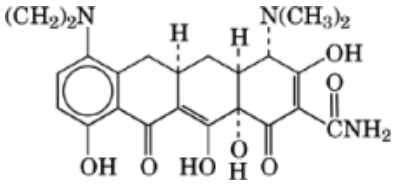
Structure number	Compoundname	CAS Registry Number	Molecular formula	Structure
(**14**)	pimaricin	[7681-93-8]	$C_{33}H_{47}NO_{13}$	
(**15**)	amphotericin B[k]	[1397-89-3]	$C_{47}H_{73}NO_{17}$	in text
(**16**)	miconazole	[22916-47-8]	$C_{18}H_{14}Cl_4N_2O$	
(**17**)	rifampin[j]	[13292-46-1]	$C_{43}H_{58}N_4O_{12}$	

Table 1. ***Continued***

Structure number	Compoundname	CAS Registry Number	Molecular formula	Structure
(**18**)	minocycline (HCl)	[13614-98-7]	$C_{28}H_{27}N_3O_7 \cdot ClH$	

[a] Other applications of these agents are indicated in footnotes to the table.
[b] Balantidiasis.
[c] Giardiasis.
[d] Hexamitosis.
[e] Histomoniasis.
[f] Trichomoniasis.
[g] Anaplasmosis.
[h] Theileriasis.
[i] Babesiasis.
[j] Malaria.
[k] Leishmaniasis.

1. Amebiasis

Amebiasis, a widespread disease of humans, causes an estimated 500 million cases (without the inclusion of China) annually. It is believed to be the third leading cause of death due to parasites. The disease is caused by pathogenic strains of the protozoan *Entamoeba histolytica*, which exists both in a stable infective cyst form and in a more fragile, potentially invasive, trophozoite form. Amebiasis is transmitted by drinking water contaminated with fecal matter from infected individuals or by eating food contaminated by infected humans or flies. Symptoms of the disease are generally centered around the gastrointestinal tract. They include amebic dysentery and sometimes appendicitis or fulminant colitis. The disease of the intestine may range from acute dysentery with chills, fever, and blood or mucoid diarrhea (amoebic dysentery), to mild abdominal discomfort with diarrhea, containing blood or mucus. Its infection is often asymptomatic. Blood-borne propagation can cause liver abscesses, and less commonly, infection of the brain or lungs. Skin ulceration may occur by extension of intestinal lesions. Recently, it was shown that *E. histolytica* has both pathogenic and nonpathogenic strains, with characteristic isoenzyme electrophoresis patterns, that occur in symptomatic and asymptomatic persons, respectively.

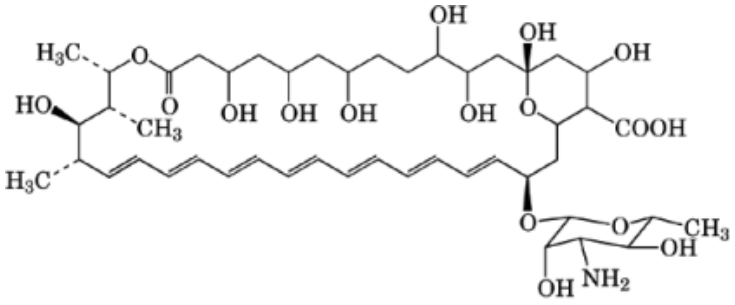
Acute intestinal amebic dysentery is most commonly treated with metronidazole (**1**, Flagyl) (Table 1). An alternative drug is iodoquinol (**2**, diiodohydroxyquin, diiodohydroxyquinoline [83-73-8]), which has also been used advantageously in combination with metronidazole or oxytetracycline (**3**, Terramycin [79-57-2]). For patients too sick to take iodoquinol orally, emetine (**4**) or dehydroemetine (**5**, 2,3-dehydroemetine) hydrochloride is administered either subcutaneously or intramuscularly. The latter sometimes is followed by chloroquine (**6**, Aralen) phosphate or iodoquinol. Because emetine and dehydroemetine cause cardiac arrhythmias, muscle weakness, and inflammation at the injection site, these toxic compounds are used primarily for patients whose lives are threatened by the disease. Antibiotics, such as tetracycline (**7**, Achromycin [60-54-8]) and paromomycin (**8**, Humatin), are also effective against moderate intestinal amebiasis.

Extraintestinal (eg, hepatic) amebiasis is treated with metronidazole and can be followed by iodoquinol or a combination of dehydroemetine or emetine hydrochloride with chloroquine phosphate. Iodoquinol is the drug of choice for asymptomatic amebiasis, whereas diloxanide furoate (**9**, Furamide) has been used successfully to treat symptomatic and asymptomatic intestinal amebic cyst carriers.

Other compounds that have shown promising properties *in vitro* against *E. histolytica* are niridazole (**10**), tinidazole (**11**, Fasigyn, Simplotan), gossypol (**12**), bithionol [(**13**), 2,2′-thiobis(4,6-dichlorophenol)], and pimaricin (**14**, Natamycin [7681-93-8]). The chemotherapy of amebiasis has been reviewed (9).

Related amoeba that cause infections of lower incidence but greater severity are the invasive organisms *Naegleria fowleri* and species of *Acanthamoeba* such as *A. castellanii* and *A. polyphaga*. These amoeba are free-living in the soil or warm fresh water, occur widely, and affect many animals but have no known animal reservoir. Entry of *Naegleria* into the body usually is by the nasal passages, whereas *Acanthamoeba* can enter via the eye, skin, or lung. They cause primary amebic meningoencephalitis (PAM), an infection of the central nervous system that is usually fatal. Symptoms in humans include severe headache, confusion, nausea, seizures, and coma. Frequently the olfactory tract is affected. These infections are considered opportunistic and are seen to a greater extent in immunosuppressed humans (due to AIDS, steroids, radiotherapy, or chemotherapy) than in those who are healthy.

Naegleria is treatable with intravenous amphotericin B (**15**, Fungizone), a toxic drug that must be used with caution.



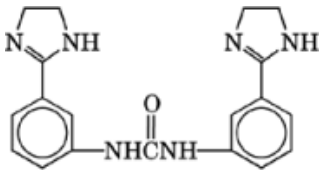
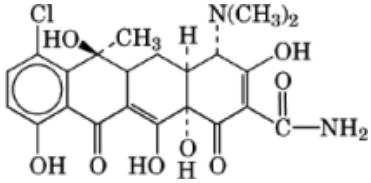
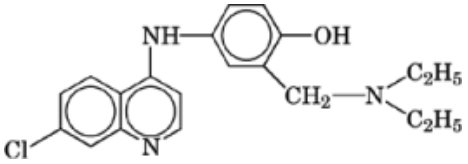
(**15**)

A combination of amphotericin B, miconazole (**16**), and rifampin (**17**) was used to successfully cure one patient. In addition, tetracycline (**7**) and minocycline (**18**) have been recommended although their clinical efficacy have not been established. No proven therapeutic agents exist for treating *Acathamoeba* infections; however, the phenothiazines, trifluoperazine [117-89-5] and chlorpromazine [50-53-3], show promise *in vitro*.

2. Anaplasmosis

Anaplasmosis is a tick-borne disease of cattle and other ruminants, such as deer in the western United States and elk in the former USSR. It is caused by the protozoan *Anaplasma marginale*, so named because the organism appears to be devoid of cytoplasm and resides at the margin within an erythrocyte. At least 30 species of ticks have been shown to be capable of transmitting anaplasmosis under laboratory conditions. Horseflies are also vectors of the disease. Anaplasmosis is mild in young calves and increases in severity, being frequently fatal to cattle above the age of three. Although the disease may be asymptomatic, it is sometimes manifest by anorexia, weakness, fever, anemia, jaundice, reduced milk production, depression, dehydration, difficult respiration, and abortion. Infection can also cause infertility in bulls. The disease in its acute form

Table 2. Anaplasmosis Antiprotozoal Agents[a]

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**19**)	imidocarb[b]	[27885-92-3]	$C_{19}H_{20}N_6O$	
(**20**)	chlortetracycline[b,c,d]	[57-62-5]	$C_{22}H_{23}ClN_2O_8$	
(**21**)	amodiaquine[e]	[86-42-0]	$C_{20}H_{22}ClN_3O$	

[a] Other applications of these agents are indicated in footnotes.
[b] Theileriasis.
[c] Balantidiasis.
[d] Hexamitosis.
[e] Malaria.

occurs frequently in purebred animals and high producing milk cows, which may die in a few hours after the start of infection.

Imidocarb (**19**) dihydrochloride [5318-76-3], the most effective drug against anaplasmosis, is reported to be curative in a single dosage if given early in the infection during the rise in parasitemia. Multiple doses are required if the animals are treated at a later stage or if a relapse occurs (Table 2). Some antibiotics active against the disease include the tetracyclines chlortetracycline (**20**, Aureomycin [57-62-5]) and oxytetracycline (**3**), which are now given in long-acting pharmaceutical dosage forms because of the need for extended treatment. Many other drugs, including arsenicals, antimonials, antimalarials, eg, chloroquine (**6**) and amodiaquine (**21**), the dihydrochloride dihydrate Camoquin [6398-98-7]), and dyes have been employed in the past in an effort to cure or prevent anaplasmosis. α-Ethoxyethylglyoxal dithiosemicarbazone (Gloxazone) has a marked inhibitory effect on *A. marginale* but was found to be too toxic to lactating cattle.

3. Babesiasis

Babesiasis (babesiosis, piroplasmosis), primarily a disease of cattle, is caused by a protozoan related to the malaria parasite. The protozoan, *Babesia microti*, after ingestion by its vector, the ixodid hard-bodied tick, grows inside the gut of the insect and spreads throughout its body. Infection of the vertebrate host, which can be either a wild or domesticated animal, occurs when the tick obtains a blood meal from it. Humans do not appear to be a reservoir for the infection and are not commonly affected by the disease (10). However, they can acquire babesiasis by blood transfusion. The consequences of infection by *B. microti* in humans can range from being asymptomatic to manifestation of a severe and prolonged illness. Typically, there is a gradual onset of fever, chills, sweating, generalized myalgia, fatigue, anemia, and renal insufficiency and failure. Infections by *Babesia divergens* are associated with cattle and are characterized in humans by chills, high fever, nausea, vomiting, and severe hemolytic anemia. Individuals infected with *B. divergens* generally lack functioning spleens and the disease has been fatal in a large percentage of cases. Related infections include *Babesia bigemina*, the cause of Texas cattle fever, and *Babesia bovis*, responsible for hemoglobinuric fever in European cattle.

Babesiasis in humans is frequently self-limiting. Quinine [130-95-0] (**22**) plus clindamycin (**23**) is considered the treatment of choice and has also been used effectively to treat transfusion babesiasis (Table 3). Quinine, either alone or in combination with pyrimethamine (**24**), has failed to eliminate experimental *B. microti* in hamsters. Babesiasis contracted in the United States has been successfully treated with chloroquine (**6**). However, when tested in infected hamsters, chloroquine failed to clear the infection, as did the other antimalarials sulfadiazine (**25**) and pyrimethamine (**24**). There was only a limited response to pentamidine (**26**) and diminazene aceturate [**27**, 4,4′-(diazoamino)dibenzamidine aceturate, Berenil, also diminazene dilactate Babesin]. Pentamidine has been used successfully to treat the symptoms of the disease in humans and in cats infected with *Babesia felis*. Diminazene aceturate is effective against experimental *B. microti* in jirds, but not *in vitro* against *Babesia equi*. Imidocarb (**19**) dipropionate is a therapeutic and prophylactic treatment for babesiasis in cattle, gerbils, and other domestic animals. The urea, amicarbalide (**28**) diisethionate [3671-72-5] (3,3′-diamidinocarbanilide diisethionate, Diampron) is also used for babesiasis in cattle. *Babesia gibsoni* in dogs has been treated effectively with phenamidine isethionate (**29**). Another urea, Babesan, (**30**), 1,3-di-6-quinolinylurea as the bismethosulfate salt ie, quinuronium sulfate, $C_{23}H_{26}N_4O_9S_2$, is used for veterinary purposes.

4. Balantidiasis

Balantidiasis (balantidiosis, balantidial dysentery), an intestinal disease seen almost worldwide, is caused by the large ciliated protozoan, *Balantidium coli*. The organism is usually found in the lumen of the large intestine of humans and animals. Cysts formed in the lumen of the colon or in freshly evacuated feces of humans or domesticated and wild animals, can colonize the colon and terminal ileum of new hosts by the latter's ingestion of contaminated food or water. The hog has been found to be the most heavily parasitized host. Its association with the rat may be a means for maintaining a reservoir infection in the two animals.

Balantidiasis in humans is manifest by chronic episodes of intermittent diarrhea and constipation, symptoms similar to those of amebiasis. The patient may also have abdominal pain, tenderness over the colon, anorexia, nausea, severe weight loss, and weakness. The disease may be fatal and, before the availability of a treatment, was the cause of death in approximately 30% of infected individuals.

Table 3. Babesiasis Antiprotozoal Agents[a]

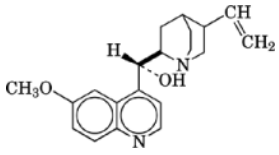
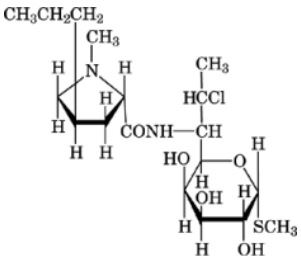
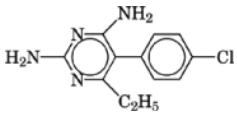
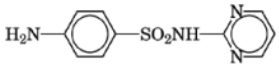
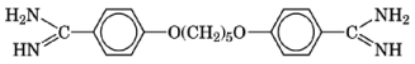
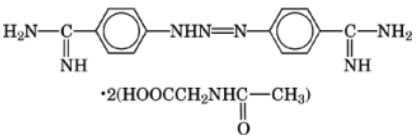
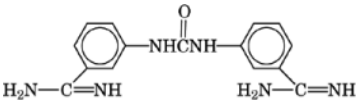
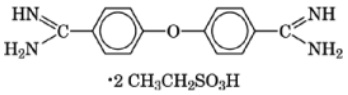
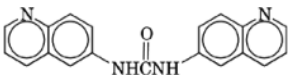
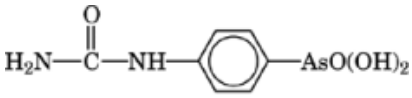
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**22**)	quinine (sulfate)[b]	[804-63-7]	$C_{20}H_{24}N_2O_2 \cdot \frac{1}{2}H_2O_4S$	
(**23**)	clindamycin[b,c,d]	[18323-44-9]	$C_{18}H_{33}ClN_2O_5S$	
(**24**)	pyrimethamine[b,c,d,e]	[58-14-0]	$C_{12}H_{13}ClN_4$	
(**25**)	sulfadiazine[c,d,f]	[68-35-9]	$C_{10}H_{10}N_4O_2S$	
(**26**)	pentamidine[g]	[100-33-4]	$C_{19}H_{24}N_4O_2$	
(**27**)	diminazene aceturate[c,h]	[908-54-3]	$C_{22}H_{29}N_9O_6$	

Table 3. ***Continued***

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**28**)	amicarbalide	[3459-96-9]	$C_{15}H_{16}N_6O$	
(**29**)	phenamidine isethionate	[620-90-6]	$C_{18}H_{26}N_4O_9S_2$	
(**30**)	babesan	[532-05-8]	$C_{19}H_{14}N_4O$	

[a] Other applications are indicated by footnotes.
[b] Malaria.
[c] Pneumocystosis.
[d] Toxoplasmosis.
[e] Coccidiosis.
[f] Balantidiasis.
[g] Leishmaniasis.
[h] Trypanosomiasis (Afrcan trypanosomiasis).

The infection can be cured most readily with tetracycline (**7**), oxytetracycline (**3**), or chlorotetracycline (**20**). Metronidazole (**1**) and iodoquinol (**2**) are also effective. Additional effective drugs include paromomycin (**8**), tinidazole (**11**), sulfadiazine (**25**), and carbarsone [121-59-4] (**31**, *p*-ureidobenzenearsonic acid, $C_7H_9AsN_2O_4$, Ameban).



(**31**)

5. Coccidiosis

Coccidiosis is a widespread disease that occurs most often in fowl, such as chickens and turkeys, and other farm animals (cows, sheep, swine, horses, and rabbits) (11). In chickens the disease has caused severe economic losses. Coccidiosis also occurs in ox, water buffalo, zebu, bighorn sheep, wild goat, alpaca, lion, puma, fox, mink, parakeet, Canada goose, snow goose, and camel, among others. It is seen only rarely in humans, and dogs and cats are only occasionally infected.

Coccidiosis in chickens, as with cattle, is frequently caused by a combination of infective *Eimeria* protozoa. *Eimeria tenella* is the most important, but *Eimeria nectrix* is more common. *Eimeria maxima*, *Eimeria*

acervulina, and *Eimeria mivati* are moderately pathogenic; *Eimeria brunetti* is highly pathogenic, but relatively uncommon. In chickens, young birds become infected by ingesting with their food oocysts shed in the feces of older birds. Diseased birds exhibit diarrhea, emaciation, and anorexia. The disease results in a marked decrease in the production of eggs, as well as a ca 10% mortality caused by the ingestion of a large number of oocysts.

Anticoccidial drugs are administered in the drinking water or feed of poultry and are primarily prophylactic, rather than curative, in nature. The most common ones in use are salinomycin (**32**, Coxistac [53003-10-4]) and monensin (**33**), a carboxylic acid which is used as its water-soluble sodium salt (Coban, Rumensin). These polyether ionophoric antibiotics are capable of complexing and interfacing with specific alkali metal cations to render them lipid-soluble and diffusible across parasite mitochondrial membranes. Related useful polyether antibiotics are narasin [55134-13-9] and lasalocid (**34**, Lasalocid A) (see Antibiotics, polyethers). The potent ionophoric antibiotic maduramicin (**35**, Cygro [84878-61-5]) is currently being evaluated as an alternative for use against resistant strains of *Eimeria* inasmuch as resistance to the entire class of ionophoric compounds is presenting serious problems. Strains resistant to all coccidiostats arise rapidly because of the widespread use of these drugs. Sulfa drugs, such as sulfadimethoxine (**36**) and sulfaquinoxaline (**37**) are members of the first nontoxic class of anticoccidials (see Antibacterial agents, synthetic, sulfonamides). Other types of compounds that have been considered treatments for the control of coccidiosis are the arsenicals, such as roxarsone (**38**, 4-hydroxy-3-nitrophenylarsonic acid [121-19-7]); the alkylidene diphenols; 3,3′-dinitrodiphenyl disulfide; the nitrofurans exemplified by nitrofurazone (**39**, 5-nitro-2-furaldehyde semicarbazone [59-87-0], Amifur, Furacin); the triazinones, diclazuril (**40**) and toltrazuril (**41**, Hycox, Maxicox); the carbanilide complexes such as nicarbazin [**42**, bis(4-nitrophenyl) urea 1:1 complex with 4,6-dimethyl-2(1*H*)-pyrimidone, Nicarb]; pyrimethamine (**24**); clopidol (**43**, Coyden); robenidine {**44**, 1,3-bis[(*p*-chlorobenzylidene)amino]guanidine}; and halofuginone (**45**) and its hydrobromide [64924-67-0], Stenorol (Table 4).

In cattle, infections by a single species of protozoan are unusual; combinations of the protozoa such as *Eimeria zuernii*, *Eimeria bovis*, and *Eimeria auburnensis* are more typical. Bovine coccidiosis occurs mainly in calves from three weeks to six months old. Adult animals are usually the carriers but tend to be asymptomatic. Infection in calves occurs by ingestion of the oocysts with their feed and/or water. As with poultry, the severity of the disease is a function of the number of oocysts ingested. Small numbers may cause no disease, whereas a large profusion ultimately may cause death. Severe disease is marked by anemia, weakness, emaciation, and anorexia. Monensin (**33**) is effective against coccidia in both cattle and sheep. Clopidol (**43**), halofuginone (**45**), and amprolium (**46**) are administered as feed additives. Other coccidiostats that have been employed are nitrofurazone (**39**), lincomycin (**47**), lasalocid (**34**), and salinomycin (**32**). Sulfonamides are only partially effective.

Coccidiosis is seen frequently in puppies and kittens and is responsible for diarrhea and even death if the animals are maintained in unsanitary conditions. For dogs and cats there exists no satisfactory treatment; however, the disease is self-limiting. Human infections can frequently be traced to these animals.

Table 4. Coccidiosis Antiprotozoal Agents

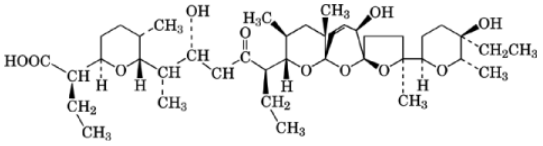
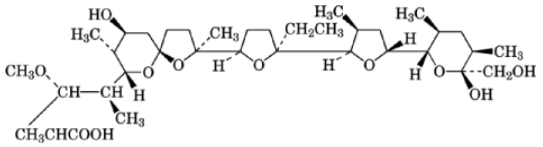
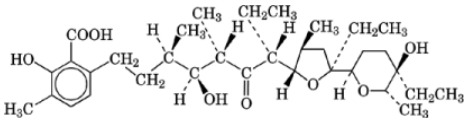
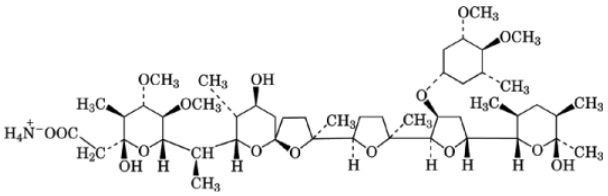
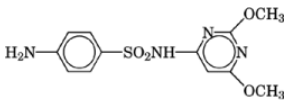
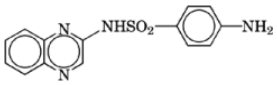
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure	Applications
(**32**)	salinomycin	[53003-10-4]	$C_{42}H_{70}O_{11}$		fowl, cattle, sheep
(**33**)	monensin[a]	[17090-79-8]	$C_{36}H_{62}O_{11}$		fowl, cattle, sheep
(**34**)	lasalocid A	[25999-31-9]	$C_{34}H_{54}O_8$		fowl, cattle, sheep
(**35**)	maduramicin	[84878-61-5]	$C_{47}H_{83}NO_{17}$		fowl
(**36**)	sulfadimethoxine	[122-11-2]	$C_{12}H_{14}N_4O_4S$		fowl
(**37**)	sulfaquinoxaline	[59-40-5]	$C_{14}H_{12}N_4O_2S$		fowl

Table 4. ***Continued***

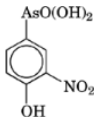
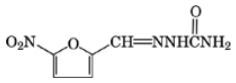
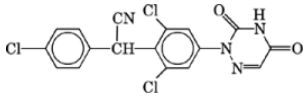
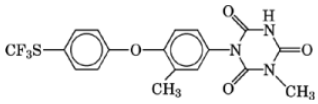
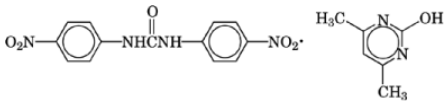
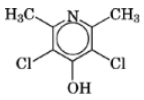
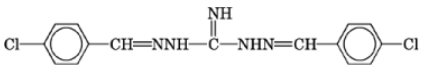
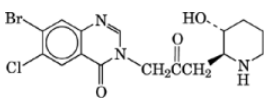
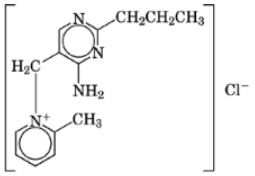
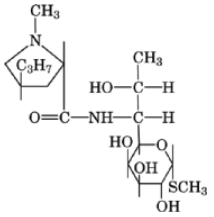
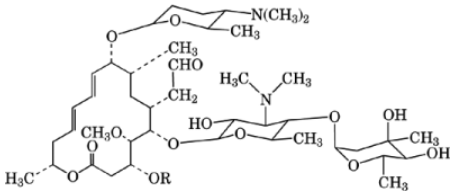
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure	Applications
(**38**)	roxarsone	[121-19-7]	$C_6H_6AsNO_6$		fowl
(**39**)	nitrofurazone	[59-87-0]	$C_6H_6N_4O_4$		fowl, cattle, sheep
(**40**)	diclazuril	[101831-37-2]	$C_{17}H_9Cl_3N_4O_2$		fowl
(**41**)	toltrazuril	[69004-03-1]	$C_{18}H_{14}F_3N_3O_4S$		fowl
(**42**)	nicarbazin	[330-95-0]	$C_{13}H_{10}N_4O_5 \cdot C_6H_8N_2O$		fowl
(**43**)	clopidol	[2971-90-6]	$C_7H_7Cl_2NO$		fowl, cattle, sheep
(**44**)	robenidine	[25875-51-8]	$C_{15}H_{13}Cl_2N_5$		fowl
(**45**)	halofuginone[b]	[55837-20-2]	$C_{16}H_{17}BrClN_3O_3$		fowl, cattle, sheep

Table 4. ***Continued***

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure	Applications
(**46**)	amprolium	[121-25-5]	$C_{14}H_{19}N_4Cl$		cattle, sheep
(**47**)	lincomycin	[154-21-2]	$C_{18}H_{34}N_2O_6S$		cattle, sheep
(**48**)	spiramycin[c]	[8025-81-8]	mixture		

[a] Also used to treat histomoniasis.
[b] Also used to treat theileriasis.
[c] Also used to treat toxoplasmosis.

Cryptosporidiosis, an intestinal infection caused by protozoa of *Cryptosporidium* species is a taxonomically related disease (12). The disease affects animals, such as calves, lambs, and chickens, and infects humans worldwide, especially infants and children in developing countries. Symptoms range from mild self-limiting diarrhea and abdominal pain to a potentially fatal extreme diarrhea that results in weight loss and poor nutritional absorption. Increasingly, this opportunistic disease occurs in those with a suppressed immune system, especially those with AIDS. The only effective treatment for cryptosporidiosis in AIDS patients who do not respond readily to therapy is spiramycin (**48**).

6. Giardiasis

Giardiasis is a water-borne enteric disease of protozoan origin that occurs throughout the world. It is the most prevalent protozoal disease found in humans in the United States; the Rocky Mountain region is a particularly highly endemic area. It is also common in Central America, the former USSR, and India. The infection of the small intestine is caused by the flagellated protozoan, *Giardia lamblia*. The disease is transmitted by drinking water that has been fecally contaminated and poorly purified, or by person-to-person transmission of fecally

contaminated food. Besides humans, the host for the protozoan includes the domesticated dog and certain wild animals, especially the beaver. The disease is more prevalent in children than in adults, and is especially common in those attending daycare centers. It is increasing in prevalence among male homosexuals.

Untreated giardiasis may be self-limiting and may produce no apparent symptoms, regardless of the duration of the infection. Alternatively, it may continue for numerous weeks or months and be extremely debilitating with symptoms that include severe and chronic diarrhea, abdominal cramps, weakness, anorexia, vomiting, fatigue, and weight loss. Because fats and fat-soluble nutrients are malabsorbed, the disease may be responsible for some of the mortality seen in underdeveloped countries. In severe giardiasis, there is inflammation and damage to the duodenal and jejunal mucosa.

Treatment of giardiasis is most successful with quinacrine (**49**, mepacrine) or its hydrochloride eg, Atabrine dihydrochloride. The drug may cause side effects such as dizziness, headache, nausea, vomiting, and reversible yellow staining of the skin. Alternatively, metronidazole (**1**) is recommended by the Centers for Disease Control, but because of its potential for mutagenesis or carcinogenesis should not be administered to children or pregnant women. Failures that occur with both drugs necessitate repetition of the therapy. Another drug reported to be effective is furazolidone (**50**), perhaps even more so in children than quinacrine (**49**) (Table 5). The aminoglycoside paromomycin (**8**) is recommended for pregnant women because the usual drugs are contraindicated. Tinidazole (**11**) has also been used successfully, but its activity could not be confirmed in a murine model. The disease has also been treated with acranil {**51**, 1-[(6-chloro-2-methoxy-9-acridyl)amino]-3-(diethylamino)-2-propanol dihydrochloride}. Further details pertaining to giardiasis are available (13).

7. Hexamitosis

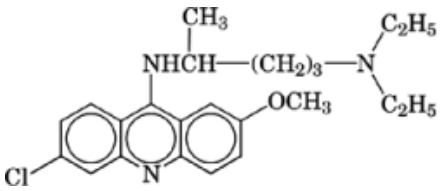
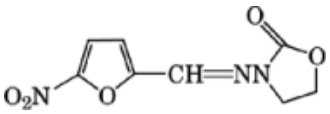
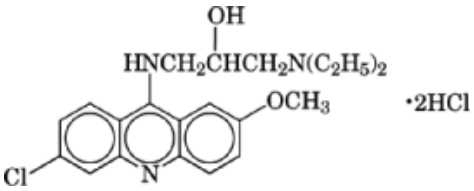
Hexamitosis is a disease of chickens, turkeys, quail, and pheasants in which there is an infectious catarrhal enteritis in the duodenum and small intestine. The disease, caused by the protozoan *Hexamita meleagridis*, occurs in the United States, the United Kingdom, South America, and parts of Europe. It is primarily a disease of young birds under 10 weeks old in which mortality may be as high as 80%. The infected animals develop diarrhea, lose weight rapidly, appear listless and weak, and may eventually die. Hexamitosis is transmitted through contaminated food and water. Carrier birds are adults that have survived earlier infections. Hot weather and overcrowding may exacerbate the severity of the outbreak.

There is no effective treatment for hexamitosis. Penicillin (**52**), oxytetracycline (**3**), chlorotetracycline (**20**), Enheptin (**53**, 2-amino-5-nitrothiazole [121-66-4]), and streptomycin (**54**) sulfate [3810-74-0] were found to have limited value. Hexamitosis in carrier pigeons caused by *Hexamita columbae* was treated successfully with ronidazole (**55**, Dugro) (Table 6). An experimental infection of nude mice with *Hexamita muris* was treated with dimetridazole (**56**, 1,2-dimethyl-5-nitro-1*H*-imidazole [557-92-8]), metronidazole (**1**), tinidazole (**11**), and acranil (**51**). All compounds lowered or suppressed the fecal discharge of cysts, but the latter reappeared when the 1–3 week treatment terminated. In a related study, dimetridazole (**56**) controlled the clinical disease in mice but did not eliminate the infection.

8. Histomoniasis

Histomoniasis (histomonas, enterohepatitis, blackhead disease) is primarily an affliction of chickens and turkeys, but it also affects wild populations of peafowl, guinea fowl, pheasant, grouse, quail, and partridge. The disease occurs throughout the world and extensive outbreaks have been responsible for enormous losses of domesticated fowl; however, good sanitation reduces the number of affected animals. Because chickens are carriers of the disease, they must be separated from turkeys, which are more readily infected. Young turkeys from 3 to 12 weeks of age are particularly susceptible to the disease and may die within three days of the

Table 5. Giardiasis Antiprotozoal Agents[a]

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**49**)	quinacrine[b]	[83-89-6]	$C_{23}H_{30}ClN_3O$	
(**50**)	furazolidone[c]	[67-45-8]	$C_8H_7N_3O_5$	
(**51**)	acranil[d]	[1684-42-0]	$C_{21}H_{28}Cl_3N_3O_2$	

[a] Other applications are indicated in footnotes.
[b] Malaria.
[c] Histomoniasis.
[d] Hexamitosis.

appearance of the first symptoms. Mortality decreases with age. Diseased birds look weak and droopy, may have diarrhea due to enterohepatitis, the head may become darkened, and death may ensue.

Histomoniasis is caused by the protozoan, *Histomonas meleagridis*, found in the liver and cecum of birds. The protozoans from the cecum are more infective than those from the liver. Transmission primarily occurs by ingestion of the eggs of the cecal worm, *Heterakis gallinarium*, which carries the protozoan and can survive several years in the soil.

A favored treatment for histomoniasis is dimetridazole (**56**) (Table 6). Other useful antiprotozoal agents include the thiazoles, Enheptin (**53**), acetylenheptin (**57**, 2-acetamido-5-nitrothiazole [140-40-9], aminitrozole, Enheptin-A), and nithiazide [**58**, 1-ethyl-3-(5-nitro-2-thiazolyl)urea [139-94-6], Hepzide], which are administered continuously into the feed for prevention and suppression. Furazolidone (**50**) and ipronidazole (**59**, Ipropran [14885-29-1]) have also been used. The latter has been evaluated, in addition, as a growth promotant. In an *in vitro* study, metronidazole (**1**), monensin (**33**), and tinidazole (**11**) showed good anti-histomonal activity. Arsenicals that have shown activity are 4-nitrophenylarsonic acid and carbarsone (**31**). The drugs mentioned above, in order to prevent relapses, typically require continuous administration in the drinking water of the poultry until a few days prior to their slaughter, and are responsible for reduced egg production.

Table 6. Hexamitosis and Histomoniasis Antiprotozoal Agents

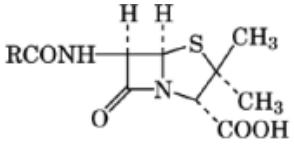
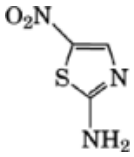
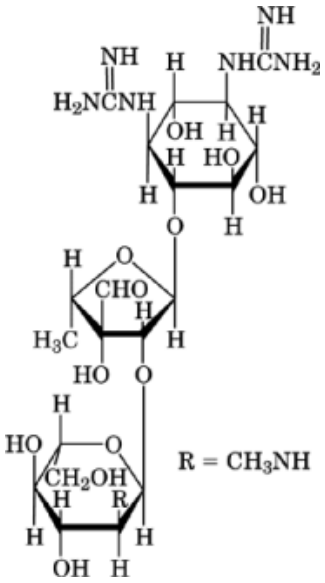
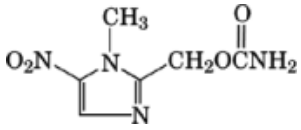
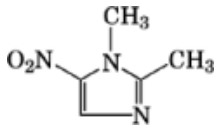
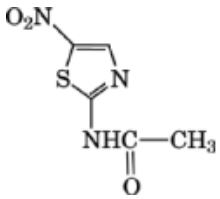
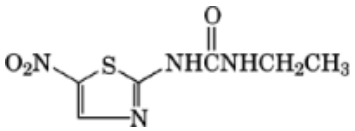
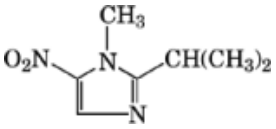
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**52**)	penicillin	[1406-05-9]		
(**53**)	enheptin	[121-66-4]	$C_3H_3N_3O_2S$	
(**54**)	streptomycin	[57-92-1]	$C_{21}H_{39}N_7O_{12}$	
(**55**)	ronidazole	[7681-76-7]	$C_6H_8N_4O_4$	

Table 6. ***Continued***

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**56**)	dimetridazole	[551-92-8]	$C_5H_7N_3O_2$	
(**57**)	acetylenheptin	[140-40-9]	$C_5H_5N_3O_3S$	
(**58**)	nithiazide	[139-94-6]	$C_6H_8N_4O_3S$	
(**59**)	ipronidazole	[14885-29-1]	$C_7H_{11}N_3O_2$	

9. Leishmaniasis

Leishmaniasis affects some 12 million humans annually in an area where 350 million are at risk. It is a complex of at least two protozoan diseases, consisting primarily of cutaneous and visceral forms. A mucocutaneous form is considered by some to be another distinct variety. Clinical manifestations of the disease range from an asymptomatic infection to an infection in which there is considerable destruction of cutaneous tissue and mucous membranes. Leishmaniasis can often be fatal, especially in the visceral form. The seriousness of the disease depends on the state of the immunological system of the host and the species of parasite that inflicts the damage (14). The different species of *Leishmania* that are responsible for the disease can be difficult to distinguish from one another and methods to identify them have occupied the efforts of many researchers. The various species may be localized geographically or may overlap, and each is responsible for somewhat different symptoms. Although the human clinical manifestations may be categorized into different types, infections by more than a single species may be present at one time.

The disease is initiated by a bite from an infected female sand fly of the genus *Phlebotomus*. The injected parasites usually multiply near the site of the original infection, causing a lesion. The sand fly vector becomes infected when it acquires a blood meal from the skin or peripheral blood of a parasitized host and ingests the protozoans in the amastigote stage. The amastigotes develop into promastigotes in the intestine of the sand fly and eventually migrate to its proboscis. The saliva of the sand fly appears to enhance the survival of the injected promastigotes which, after phagocytosis, are transformed into the amastigote phase. The numerous reservoirs for the protozoans include humans, dogs, foxes, cats, rodents, and horses.

Cutaneous leishmaniasis is characterized by one or more slowly healing superficial ulcers that may be painful. These lesions are liable to further infection and may remain as open sores or become hard, wartlike nodules. The form of cutaneous leishmaniasis referred to as New World disease is caused by species of the *Leishmania (Viannia) braziliensis* complex (*L. braziliensis*, *L. guyanensis*, *L. panamanesis*, and *L. peruviana*) and species of the *Leishmania (Leishmania) mexicana* complex (*L. mexicana*, *L. amazonensis*, and *L. venezuelensis*) in the western hemisphere. Old World disease (oriental sore, Delhi or Baghdad boil) is caused by *Leishmania tropica* and *Leishmania major* in Asia, Africa, and southern Europe, and *Leishmania aethiopica*, restricted to eastern Africa. The incubation period for cutaneous leishmaniasis ranges from a few weeks to several months. Spontaneous cures can take place in a period ranging from one month to several years.

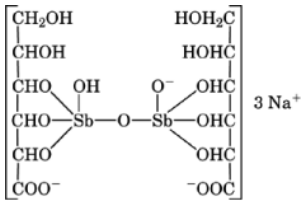
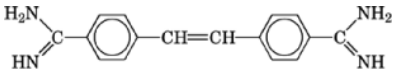
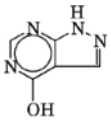
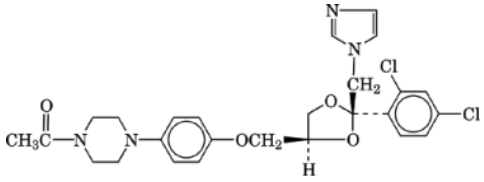
Visceral leishmaniasis is also known as kala azar, meaning black fever or black sickness in Hindi, because of the characteristic pigmentary changes that occur in the skin. The disease is endemic in much of the tropical and subtropical regions of southern Europe and the Mediterranean, the Middle East, India, Africa, and South and Central America. It is caused by species of the *Leishmania (Leishmania) donovani* complex [*L. donovani* (Old World), *L. infantum* (Old World), and *L. chagasi* (New World)]. In this systemic form of leishmaniasis, the parasites invade internal organs. It is characterized in patients by an enlarged liver and spleen, fever, weight loss, hemorrhage, leukopenia, and anemia. There is abdominal discomfort due to the spleen and liver involvement. Death due to severe diarrhea, pneumonia, and gastrointestinal bleeding may ensue if the disease is not treated. Following treatment, patients may relapse with a leishmanial form that solely affects the skin (post-kala azar dermal leishmaniasis). Rarer forms of leishmaniasis include chronic relapsing or recidivans forms of the cutaneous disease and diffuse cutaneous leishmaniasis.

Certain species of the *L. braziliensis* complex may cause mucocutaneous leishmaniasis, a form seen most frequently in northern and central South America. The patient first develops skin infections which later metastasize to produce highly disfiguring mucocutaneous lesions of the oronasopharynx.

Antimony compounds have been used to treat leishmaniasis ever since tartar emetic (antimony potassium tartrate) was discovered early in the 20th century to have efficacy against the mucocutaneous form of the disease. The cutaneous form has been treated with tartar emetic formulated in an ointment. Many side effects have been seen with this trivalent antimonial, some of which can be ascribed to the difficulty of obtaining pure antimony for its manufacture. These side effects include toxicity to the heart, liver, and kidneys. Other promising trivalent antimonials have been abandoned in favor of pentavalent antimonials with lower toxicity.

Pentavalent antimony preparations constitute the primary treatments for all forms of leishmaniasis, the most important of which are sodium stibogluconate (**60**, Pentostam [16037-91-5]) and glucantime (*N*-methylglucamine antimonate, $C_7H_{18}NO_8Sb$, meglumine antimonate) (Table 7). The actual chemical structure of the antimonials is unknown. Studies indicate that they are mixtures of compounds with widely differing molecular weights. Use of glucantime is favored in Latin America and French-speaking countries. Cardio- and hepatotoxicity have been observed when the drug is administered over the typical 3–4 weeks of treatment. Liposome preparations of Pentostam and glucantime substantially increased the activity of these antimonials under experimental conditions. In 1990, an estimated 10,000 out of 200,000 cases of kala azar reported in India were unresponsive to treatment with antimonials; in Kenya, the strains were even more resistant to antimony. Although antimony-resistant strains of leishmania can be treated with diamidines, the latter compounds are more toxic. Pentamidine (**26**) as the isethionate, is the most widely used diamidine and has a high cure rate. Another diamidine, stilbamidine (**61**, 4,4′-diamidinostilbene [122-06-5]), is also effective.

Table 7. Leishmaniasis Antiprotozoal Agents

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**60**)	sodium stibogluconate	[16037-91-5]	$C_{12}H_{20}O_{17}Sb_2 \cdot 9H_2O \cdot 3Na$	
(**61**)	stilbamidine	[122-06-5]	$C_{16}H_{16}N_4$	
(**62**)	allopurinol	[315-30-0]	$C_5H_4N_4O$	
(**63**)	ketoconazole	[65277-42-1]	$C_{26}H_{28}Cl_2N_4O_4$	

Amphotericin B (**15**) is an antifungal macrolide antibiotic produced by *Streptomyces nodosus* that has been used as an alternative, albeit more toxic, drug to the antimonials. It acts as a leishmanicide against the visceral and mucocutaneous forms of the disease. To overcome its potentially severe nephrotoxicity, the drug must be administered over an extended period of time.

Because of the outbreak of antimony-resistant leishmaniasis and the need to develop an orally-administered therapy, the use of many other compounds has been considered. Those that appear to have clinical utility are allopurinol (**62**), ketoconazole (**63**), and both systemically and topically applied paromomycin (**8**) (see Antiparasitic agents, antimycotics).

10. Malaria

Malaria affects an estimated 270 million people and causes 2–3 million deaths annually, approximately one million of which occur in children under the age of five. While primarily an affliction of the tropics and subtropics, it has occurred as far north as the Arctic Circle. The disease essentially has been eradicated in most

temperate-zone countries, but some 1100 cases of malaria in U.S. citizens returning from abroad were reported to the Centers for Disease Control during 1990. Malaria is seen today in Southeast Asia, Africa, and Central and South America. It is on the increase in Afghanistan, Brazil, China, India, Mexico, the Philippines, Sri Lanka, Thailand, and Vietnam. Escalation of the disease is because of the discontinued use of the insecticide DDT which effectively kills mosquito larvae, but has been found to be toxic to livestock and wildlife. Also, chloroquine (**6**), a reliable drug for the prophylaxis and treatment of falciparum malaria, is ineffective in many parts of the world because of the spread of drug-resistant strains.

Malaria is transmitted by the bite of an infected female *Anopheles* mosquito, one of the few species of the insect capable of carrying the human malaria parasite. The responsible protozoa are from the genus *Plasmodium*, of which only four of some 100 species can cause the disease in humans. The remaining species affect rodents, reptiles, monkeys, birds, and livestock. The species that infect humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*. Note that concomitant multiple malaria infections are commonly seen in endemic areas, a phenomenon that further complicates choice of treatment.

An infection by *P. falciparum* has an incubation period (time from mosquito bite to clinical symptoms) of 6–25 days (average 12). Infection from this parasite can result in severe anemia, renal failure, pulmonary edema, shock, jaundice, cerebral malaria, and death. The life cycle of *P. falciparum* begins with a bite by an infected female mosquito in need of a blood meal for the reproductive stage of her life. Some parasites in the sporozoite stage are injected with her saliva, which contains material to prevent rapid clotting of the wound. The sporozoites enter the circulatory system and reach the liver in about one hour. The parasites grow and multiply by asexual division inside liver cells for 5–7 days. Then, as merozoites, having multiplied some 40,000-fold, they leave the liver to enter the bloodstream and invade red blood cells where they grow and further multiply over a period of 1–4 days. The merozoites emerge from the ruptured erythrocytes in a synchronous manner in about 48 hours. This results in the patient experiencing the clinical symptoms of the disease, namely, chills with rising temperatures, followed by fever and intense sweating. In addition, there can be severe headache, fatigue, dizziness, nausea, vomiting, anorexia, and diarrhea. Repetition of these symptoms occur on alternate days in this so-called tertian malaria. The falciparum parasites also cause the red cells to adhere to blood vessels, resulting in clumps that diminish the flow of blood to organs such as the brain, liver, and kidneys. Some released blood forms reinfect other red cells, where they again multiply leading to a further concerted rupturing and a return of the malaria symptoms. Some other merozoites develop into the sexual forms, ie, male or female gametocytes. Repetition of the malaria life cycle begins when gametocytes are acquired by an uninfected mosquito upon biting an infected individual. The gametocytes enter the mosquito stomach, undergo fertilization, and the zygotes thus formed migrate to the salivary glands of the insect where they are capable of being transmitted to another human by a bite. Chloroquine-resistant strains of *P. falciparum* have been found in Southeast Asia, Africa, and South America.

Plasmodium vivax, responsible for the most prevalent form of malaria (benign tertian), has an incubation period of 8–27 days (14 average). A variety seen in northern and northeastern Europe has an incubation period as long as 8–10 months. The disease can cause splenic rupture and anemia. Relapses (renewed manifestations of erythrocytic infection) can occur with this type of malaria. Overall, *P. vivax* is still susceptible to chloroquine; however, resistant strains have been reported from Papua New Guinea and parts of Indonesia. *Plasmodium malariae*, the cause of quartan malaria, has an incubation period of 15–30 days and its asexual cycle is 72 hours. This mildest form of malaria can cause nephritis in addition to the usual symptoms. It is a nonrelapsing type of malaria but the red blood cell infection can last for many years. No resistance to chloroquine by this plasmodium has been reported. *Plasmodium ovale*, responsible for ovale tertian malaria, has an incubation period of 9–17 days (15 average). Relapses can occur in people infected with this plasmodium. No chloroquine resistance has been reported for this parasite.

10.1. Antimalarials

Antimalarials can be categorized according to their mode of action (15).

10.1.1. Tissue Schizonticides

These eradicate the liver stages of the parasite and thereby prevent their entry into the blood. As a class, therefore, they are useful for prophylaxis. Some tissue schizonticides can act on the long-lived tissue forms (hypnozoites) of *P. vivax* and *P. ovale* and thus can cure the latter infections by preventing relapses.

10.1.2. Blood Schizonticides

These destroy the erythrocytic stages of the parasites and are useful for the clinical cure of falciparum malaria or suppression of relapsing infections.

10.1.3. Gametocytocides

These annihilate the sexual forms of the plasmodia (gametocytes) and also destroy the stages of the parasites in the *Anopheles* mosquito.

10.1.4. Sporontocides

These act against the sporozoites and oocysts in the mosquito and thereby prevent the transmission of the disease.

It should be noted that drugs may operate by more than one mechanism, and may possess a specific mode of action against one species of plasmodium but lack efficacy against others. In addition, antimalarial drugs may be classified according to their structural types.

Quinine (**22**), the first known antimalarial, is a 4-quinolinemethanol that has served as a model for the design of numerous antiplasmodial drugs. Its history began in mid-seventeenth century Peru when the Incas told the Jesuits of the medicinal properties of the bark of an evergreen mountain tree they called quina-quina (later called cinchona). The bark, when made into an aqueous infusion, was capable of curing malaria. The use of cinchona spread to Europe and the alkaloid from it, quinine, was isolated in 1820. Quinine, an extremely bitter substance, has been used by millions of malaria sufferers. In recent times, it has been employed successfully to treat chloroquine-resistant strains of *P. falciparum* but it frequently fails to provide a complete cure of the infection. Quinine acts on the asexual blood forms of the plasmodia in a manner slower than many synthetic drugs. Overdoses cause tinnitus and visual disturbances, side effects that disappear on withdrawal of the drug. It can also cause premature contractions in women in late stages of pregnancy. Although quinine is a favored antimalarial for parenteral administration, it is nevertheless hazardous by this route. Quinidine (**64**), has been shown to be even more effective in combatting the disease (Table 8). However, it has undesirable cardiac side effects that reduce its suitability as an antimalarial. Mixtures of cinchona alkaloids, known as totaquine, are easier to produce and have been employed in treatment. Totaquine has been standardized to contain a minimum of 15% quinine.

Table 8. Malaria Antiprotozoal Agents[a]

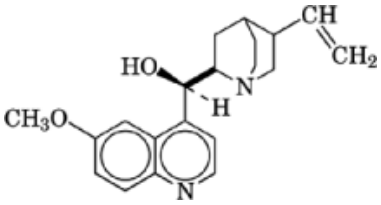
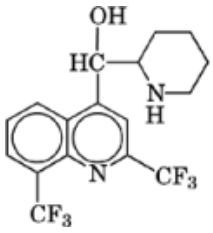
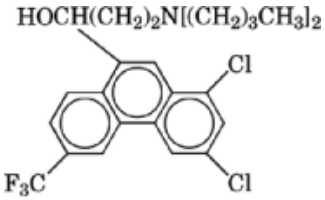
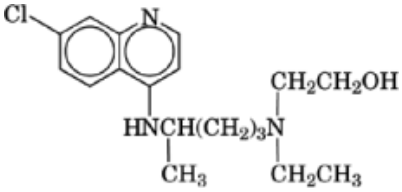
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
			4-Quinolinemethanols	
(**64**)	quinidine (sulfate)	[50-54-4]	$C_{20}H_{24}N_2O_2 \cdot \frac{1}{2}H_2O_4S$	
(**65**)	mefloquine	[53230-10-7]	$C_{17}H_{16}F_6N_2O$	
			Phenanthrene-methanol	
(**66**)	halofantrine	[69756-53-2]	$C_{26}H_{30}Cl_2F_3NO$	
			4-Aminoquinoline	
(**67**)	hydroxy-chloroquine	[118-42-3]	$C_{18}H_{26}ClN_3O$	

Table 8. ***Continued***

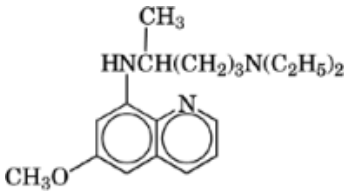
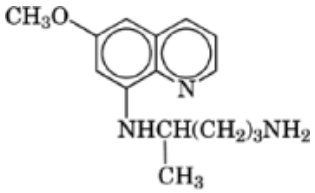
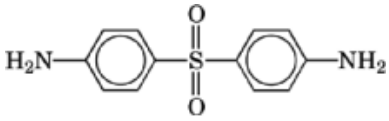
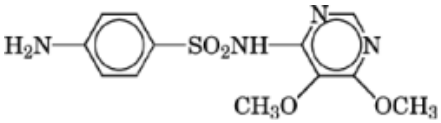
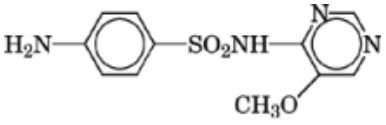
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
			8-Aminoquinolines	
(**68**)	pamaquine[b]	[491-92-9]	$C_{19}H_{29}N_3O$	
(**69**)	primaquine (phosphate)[c,d]	[63-45-6]	$C_{15}H_{21}N_3O{\cdot}2H_3O_4P$	
			Antifolates	
(**70**)	dapsone	[80-08-0]	$C_{12}H_{12}N_2O_2S$	
(**71**)	sulfadoxine[c]	[2447-57-6]	$C_{12}H_{14}N_4O_4S$	
(**72**)	sulfalene[e]	[152-47-6]	$C_{11}H_{12}N_4O_3S$	

Table 8. ***Continued***

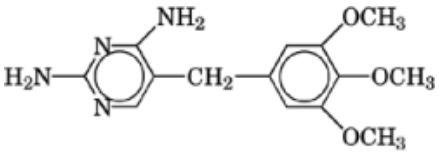
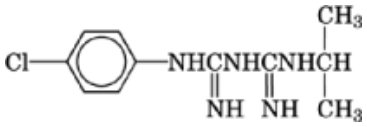
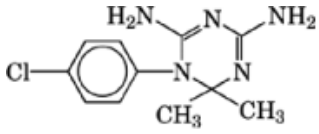
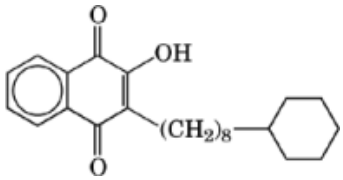
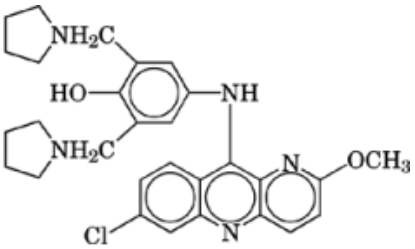
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**73**)	trimethoprim[c,e]	[738-70-5]	$C_{14}H_{18}N_4O_3$	
(**74**)	chlorguanide	[500-92-5]	$C_{11}H_{16}ClN_5$	
(**75**)	cycloguanil	[516-21-2]	$C_{11}H_{14}ClN_5$	
			Others	
(**76**)	menoctone[b]	[14561-42-3]	$C_{24}H_{32}O_3$	
(**77**)	pyronaridine	[74847-35-1]	$C_{29}H_{32}ClN_5O_2$	

Table 8. ***Continued***

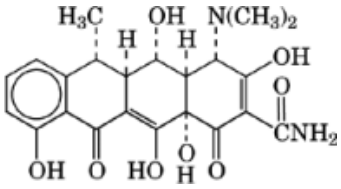
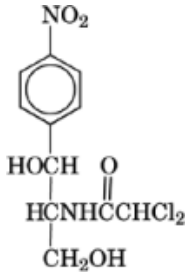
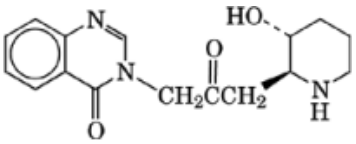
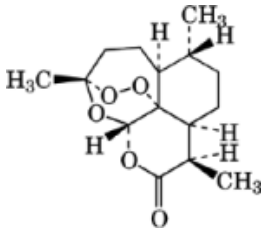
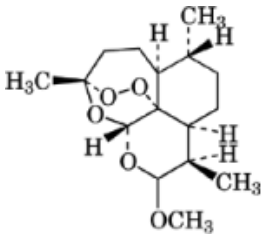
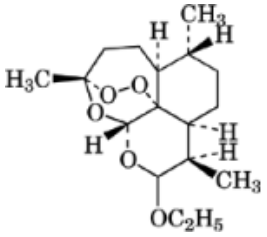
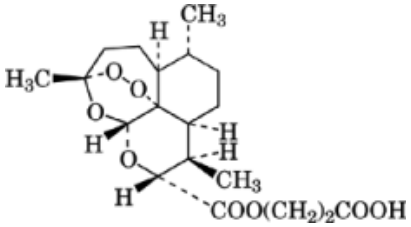
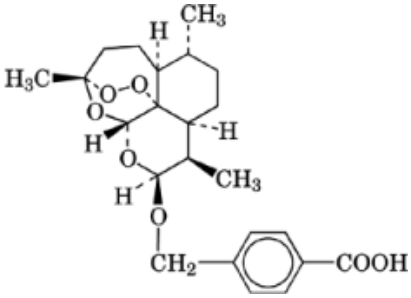
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**78**)	doxycycline	[564-25-0]	$C_{22}H_{24}N_2O_8$	
(**79**)	chloram-phenicol	[56-75-7]	$C_{11}H_{12}Cl_2N_2O_5$	
(**80**)	febrifugine	[24159-07-7]	$C_{16}H_{19}N_3O_3$	
(**81**)	artemisinin	[63968-64-9]	$C_{15}H_{22}O_5$	

Table 8. ***Continued***

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**82**)	artemether	[71963-77-4]	$C_{16}H_{26}O_5$	
(**83**)	arteether	[75887-54-6]	$C_{17}H_{28}O_5$	
(**84**)	artesunic acid	[88495-63-0]	$C_{19}H_{28}O_8$	
(**85**)	artelinic acid	[109637-83-4]	$C_{23}H_{30}O_7$	

[a] Other applications are indicated in footnotes.
[b] Theileriasis.
[c] Pneumocystosis.
[d] American trypanosomiasis.
[e] Toxoplasmosis.

The success of quinine inspired the search for other antimalarials. The greatest impetus for the development of synthetic drugs came this century when the two World Wars interrupted the supply of cinchona bark to the combatants. A structurally related 4-quinolinemethanol is mefloquine (**65**, Lariam [51773-92-3]), which now serves as an effective alternative agent for chloroquine-resistant *P. falciparum*. This is a potent substance that requires less than one-tenth the dose of quinine to effect cures. There are some untoward side effects associated with this drug such as gastrointestinal upset and dizziness, but they tend to be transient. Mefloquine is not recommended for use by those using beta-blockers, those whose job requires fine coordination and spatial discrimination, or those with a history of epilepsy or psychiatric disorders. A combination of mefloquine with Fansidar (a mixture of pyrimethamine and sulfadoxine) is known as Fansimef but its use is not recommended. Resistance to mefloquine has been reported even though the compound has not been in wide use.

The best example of the class of phenanthrene-methanols is halofantrine (**66**, Halfan [36167-63-2]), a drug that is effective against chloroquine-resistant malaria and is now being evaluated in Africa. It produces temporary gastrointestinal disturbances.

Chloroquine (**6**) is the most effective of the hundreds of synthesized 4-aminoquinolines and was the antimalarial of choice until resistance developed to it in Colombia and Southeast Asia in 1962. It is still one of the most important antimalarial agents in use for suppression (prophylaxis) in endemic areas where there remains sensitivity to the drug. It acts as a blood schizonticide and rarely produces serious side effects in individuals taking it prophylactically. Ironically, it was the widespread prophylactic use that most likely led to drug resistance. For treatment of the disease, the phosphate salt is administered orally, or the chloride, parenterally. The minor side effects include gastrointestinal upset, headache, dizziness, blurred vision, and pruritus (itch), but discontinuance of the drug is seldom necessary. Those who have used chloroquine continually for more than 6 years, either for prophylaxis or in the treatment of arthritis, are recommended to have ophthalmologic exams to check for possible retinal damage. It was demonstrated that chloroquine resistance can be reversed *in vitro* by treating *P. falciparum* parasitized erythrocytes with the calcium channel blocking drug verapamil (16). Subsequently, other calcium channel blockers and antihistamines have been found to be effective in overcoming chloroquine resistance *in vitro* and in rodents. Desipramine (Norpramin) and other antidepressants have been shown to reverse chloroquine resistance in monkeys. Alternatives to chloroquine for treatment are amodiaquine (**21**) and hydroxychloroquine (**67**), a chloroquine modification in which one of the ethyl groups on the tertiary nitrogen atom of the side chain is replaced with hydroxyethyl. These compounds are less effective, and amodiaquine is more toxic than chloroquine. The 4-aminoquinolines also act as gametocytocidal agents against *P. vivax*, *P. ovale*, *P. malariae* and immature gametocytes of *P. falciparum*.

The 8-aminoquinolines are effective against both the primary and secondary tissue forms and sexual blood forms of the parasites. At toxic levels they are also active against asexual blood forms in humans. Pamaquine (**68**, plasmochin, plasmoquine), the oldest useful member of the class of 8-aminoquinolines, was synthesized in Germany in the mid-1920s. Primaquine [90-34-6] (**69**), which is less toxic and more effective, is the most widely used of the 8-aminoquinolines. It is gametocytocidal against all species of human malaria parasites and is an antirelapsing drug, but has the undesirable ability to cause severe hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals. This accounts for its recommended administration in limited doses over 1–2 weeks and its low utilization. During pregnancy, it is considered inadvisable for primaquine to be taken as it could be passed on to a G6PD-deficient fetus, thereby causing hemolytic anemia. Primaquine is generally used in conjunction with a blood schizonticide such as chloroquine (**6**), amodiaquine (**21**), or pyrimethamine (**24**) and is used for the prevention of relapses only against *P. vivax* and *P. ovale*.

The drugs known as antifolates act as effective blood schizonticides. Unfortunately, the parasites readily develop resistance to them. Most antifolates show poor oral tolerance, absorption, and host toxicity. They fall into two types depending on the mechanisms by which they operate.

Table 9. Various Antiprotozoal Agents

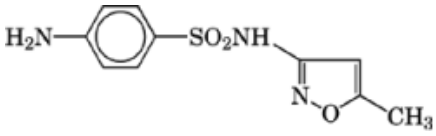
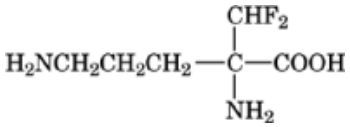
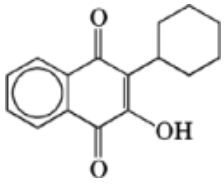
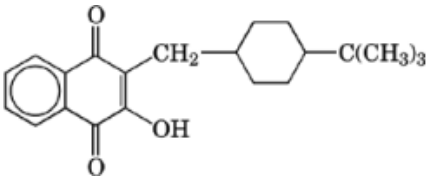
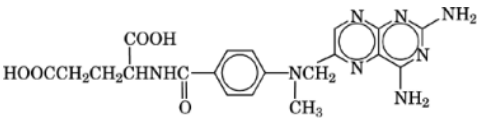
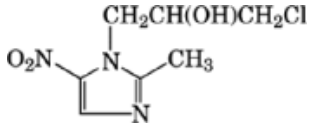
Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
			Pneumocystosis	
(**86**)	sulfamethoxazole[a]	[723-46-6]	$C_{10}H_{11}N_3O_3S$	
(**87**)	eflornithine[b]	[67037-37-0]	$C_6H_{12}F_2N_2O_2$	
			Theileriasis	
(**88**)	parvaquone	[4042-30-2]	$C_{16}H_{16}O_3$	
(**89**)	buparvaquone	[88426-33-9]	$C_{21}H_{26}O_3$	
(**90**)	methotrexate	[59-05-2]	$C_{20}H_{22}N_8O_5$	
			Trichomoniasis	

Table 9. ***Continued***

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
(**91**)	ornidazole	[16773-42-5]	$C_7H_{10}ClN_3O_3$	

[a] Also used for toxoplasmosis.
[b] Also used for African trypanosomiasis.

The first are competitors of PABA (*p*-aminobenzoic acid) and thus interrupt host *de novo* formation of the tetrahydrofolic acid required for nucleic acid synthesis. Examples of drugs that fall into this group are the sulfones and sulfonamides. The most well-known of the sulfones is dapsone (**70**, 4,4′-diaminodiphenyl sulfone, DDS), whose toxicity has discouraged its use. Production of folic acid, which consists of PABA, a pteridine unit, and glutamate, is disturbed by the substitution of a sulfonamide (structurally similar to PABA). The antimalarial sulfonamides include sulfadoxine (**71**, Fanasil [2447-57-6]), sulfadiazine (**25**), and sulfalene (**72**, sulfamethoxypyrazine [152-47-6], Kelfizina). Compounds of this group are rapidly absorbed but are cleared slowly.

The second type of antifolates bind preferentially with, and thus selectively inhibit, the enzyme dihydrofolate reductase contained in the plasmodia. This interferes with the ability of the malaria parasites to convert dihydrofolate to tetrahydrofolic acid. In the erythrocyte host, however, dihydrofolate reductase is considerably less sensitive to these drugs and the blood cells are capable of utilizing exogenous folate. Dihydrofolate reductase inhibitors are potent blood schizonticides that act on the asexual blood stages. Members of this class include the pyrimidines, pyrimethamine (**24**), and trimethoprim (**73**). Pyrimethamine is a slow-acting drug that is not recommended for use in acute attacks and is potentiated by combination with sulfadoxine (**71**) (mixture is called Fansidar), dapsone (**70**) (mixture is called Maloprim), sulfalene (**72**) (mixture is called Kelfimeta or Metakelfin), or chloroquine (**6**) (mixture is called Darachlor). It is an effective suppressant against *P. falciparum*. The mode of action of trimethoprim (**73**) is similar to that of pyrimethamine (**24**). Because it is also slow-acting, it is generally used in combination with the fast-acting sulfonamide, sulfalene (**72**), to give an effective treatment against *P. falciparum*. Related structurally and functionally are the so-called open and cyclic triazines, exemplified by chlorguanide (**74**, proguanil [500-92-5], or the hydrochloride, Paludrine), a biguanide, and cycloguanil (**75**, Camolar [609-78-9]), respectively. The compounds have low toxicity and are also effective as causal prophylactics, ie, they destroy parasites before they enter the red blood cells.

Quinones and naphthoquinones were explored during the World War II Antimalarial Drug Program. Now that chloroquine resistance is a serious problem, compounds of this group such as menoctone (**76**) are being reinvestigated.

Quinacrine (**49**) is an acridine that was used extensively from the mid-1920s to the end of World War II. It acts much like chloroquine and is reasonably effective. Because it causes the skin to turn yellow and, in high doses, causes yellow vision, the drug is no longer in use as an antimalarial. Pyronaridine (**77**), a 1-azaacridine developed in China, appears to be effective against mefloquine-resistant, but not entirely against chloroquine-resistant, strains of *P. falciparum*.

Some antibiotics, such as the tetracyclines, tetracycline (**7**), doxycycline (**78**), and minocycline (**17**), chloramphenicol (**79**), and clindamycin (**23**) have modest antimalarial properties, but are slow-acting.

A Chinese traditional herbal treatment for malaria obtained from the roots of *Dichroa febrifuga* is called Ch'ang Shan and was investigated in the 1940s. Febrifugine (**80**), the alkaloid responsible for its activity, was

isolated and found to be considerably more active than quinine in experimental infections. Unfortunately, the drug caused nausea and vomiting in humans. Synthesized analogues were generally less effective than the parent.

The most promising group of new antimalarials is based on the compound artemisinin (**81**), an unusual sesquiterpene lactone endoperoxide first isolated in China in 1972 and then in the United States from the weed *Artemisia annua* (17). Artemisinin, also called qinghaosu, meaning in Chinese "extract of green herb," is a rapid-acting and relatively nontoxic therapeutic agent. Its low oil and water solubility has been increased by making certain structural modifications to the molecule. Oil-soluble artemether (**82**), the methyl ether of the lactol dihydroartemisinin, has been administered clinically in China by the intramuscular route. The closely related ethyl ether, arteether (**83**), is being developed by the World Health Organization as an alternative oil-soluble analogue. The sodium salts of artesunic acid (**84**) and artelinic acid (**85**) are the most interesting water-soluble modifications of artemisinin. If administered intravenously, these sodium salts could be advantageously applied in the treatment of cerebral malaria where rapid return to consciousness of the comatose patient and reduction of the parasitemia are the primary clinical goals. Although the water-soluble compound sodium artelinate is more stable in aqueous solution than sodium artesunate, only the latter has been tested clinically. Artelinic acid and related compounds effectively eliminated or prevented the establishment of parasitemia in *P. berghei*-infected mice when they were administered by the transdermal route. Artemisinin and its derivatives have been used successfully in China with several thousand *P. falciparum* and *P. vivax* patients; because this class of drugs is new, parasite resistance has not yet been encountered.

11. Pneumocystosis

The organism responsible for pneumocystosis in humans, *Pneumocystis carinii*, having the characteristics of both protozoan and fungi, has defied simple taxonomic classification. Recent evidence suggests that it falls into the fungi category. Acute pneumocystosis rarely strikes healthy individuals, although the organism is harbored by a wide variety of animals and most people without any apparent adverse effect. *P. carinii* becomes active only in those individuals who have a serious impairment of their immunologic systems (18). Typically, this opportunistic disease occurs in AIDS patients, 80% of whom ultimately contract *P. carinii* pneumonia, and is one of the main causes of mortality. The disease also occurs in those being administered immunosuppressive drugs for, eg, organ transplantation or treatment of malignant disease. In addition, pneumocystosis is seen in malnourished infants whose immunological systems are impaired. The disease is characterized by a severe pneumonia caused by a rapid multiplication of the organisms almost exclusively in lung tissue. If left to run its course, the acute disease is generally fatal.

The drug of choice is the antifolate mixture, trimethoprim (**73**)-sulfamethoxazole (**86**) (mixture is called co-trimoxazole, Bactrim, Septra) given orally or intravenously (Table 9). It is well tolerated if given in low doses. Also used is pyrimethamine (**24**) combined with sulfadiazine (**25**) or sulfadoxine (**71**). Pentamidine (**26**) isethionate is administered parenterally but is generally not prescribed for prophylactic use because there is a high incidence of hypotension, renal failure, and pain and tissue injury at the injection site. However, there have been successful prophylactic trials with the drug in the aerosolized form for inhalation. The polyamine-inhibitor eflornithine, (**87**, α-difluoromethylornithine, DFMO; [67037-37-0] the hydrochloride monohydrate is Ornidyl) is undergoing evaluation as a treatment for *P. carinii*. A combination of clindamycin (**23**) and primaquine (**69**) shows great promise against this protozoan in clinical trials when administered for prophylaxis or for therapy in mild to moderately severe pneumocystis pneumonia. Either drug alone is not effective.

12. Theileriasis

Theileriasis (theileriosis) is a tick-transmitted protozoan disease of cattle seen primarily in central and eastern Africa. The disease not only affects domesticated cattle, but also ox, zebu, water buffalo, and African buffalo. The most significant form of the disease is caused by the protozoan *Theileria parva* (*Piroplasma kochi*, *Piroplasma parvum*, *Theileria kochi*, *Theileria lawrencei*) and is known as African Coast fever, East Coast fever, bovine theileriasis, or Corridor disease. The most important vector of the disease is the tick, *Rhipicephalus appendiculatus*, which harbors the protozoan through one molt. About 90–100% adult cattle infected with *T. parva* die, but calves seem to be less susceptible. After receiving a bite from an infected tick, there is an incubation period of 8–25 days before the appearance of the disease. In the acute form, the animals have a fever, cease to eat, may have a nasal discharge and lachrymate, have general weakness, and diarrhea. Rapid and labored breathing precede death.

There are other milder forms of theileriasis that resemble the disease caused by *T. parva* infection. They also primarily affect cattle and are transmitted by ticks. Causative organisms include *Theileria annulata*, responsible for tropical thieleriasis, tropical piroplasmosis, Egyptian fever, and Mediterranean Coast fever. These affect ox, zebu, and water buffalo. Endemic areas include northern Africa, southeastern Europe, the southern part of the former USSR, and Asia. *Theileria mutans* is the cause of benign bovine thieleriasis, Marico calf disease, and mild gall sickness. It affects ox and zebu in Africa, Asia, southern Europe, England, the former USSR, Australia, and North America.

There are no fully effective therapeutic agents for the treatment of theileriasis. Chlorotetracycline (**20**) and oxytetracycline (**3**) have therapeutic activity during the incubation period. Pamaquine (**68**) was reported to have a specific effect on the erythrocyctic forms. Other drugs with limited efficacy are imidocarb (**19**) on *T. annulata*, halofuginone (**45**) on both *T. annulata* and *T. parva*, and the naphthoquinones menoctone (**76**), parvaquone (**88**), and buparvaquone (**89**) on *T. parva*. Methotrexate (**90**) has been found to be active *in vitro* (Table 9).

13. Toxoplasmosis

Toxoplasmosis, a coccidial disease, affects both humans and animals throughout the world. Approximately one-third of the population has antibodies to it but is asymptomatic. Although rare in the past, toxoplasmosis is an increasingly important opportunistic disease that afflicts immunocompromised hosts such as post-transplant patients taking immunosuppressive drugs and AIDS patients. The disease is responsible for a central nervous system infection with symptoms in humans that include fever, headache, swollen lymph glands, cough, sore throat, nasal congestion, anorexia, and skin rash. Complications include neurological abnormalities, seizures, and fatal toxoplasmic encephalitis. In pregnant women, toxoplasmosis can cause miscarriage, premature birth, or blindness in the fetus and is a leading cause of birth defects. In the newborn child, the disease may manifest itself primarily in the eye as chorioretinitis (fetal inflammation of the retina), but it may also cause hydrocephalus, microcephalus, carditis, and hepatitis.

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. In humans, the disease is generally acquired by eating inadequately cooked meat or by association with infected felines. Meat becomes infected when cows or sheep graze in pastures contaminated by fecal matter from infected felines. Cats, the most important reservoir of the disease, become carriers by eating infected rodents or by the ingestion of infected feline feces. Pregnant women are advised to avoid eating insufficiently cooked meat, avoid having close contact with cats, and, especially, avoid cleaning feline litter boxes.

The cyst of *T. gondii* is persistant, making long-term therapy a requirement in patients whose immune systems are compromised. Treatment of cerebral or ocular toxoplasmosis is generally accomplished with antifolate compounds consisting of a combination of pyrimethamine (**24**) and a long-acting sulfonamide such as

sulfadiazine (**25**). Sometimes the latter is replaced by triple sulfonamides or sulfalene (**72**). There is evidence that the related mixture of trimethoprim (**73**) plus sulfamethoxazole (**86**) (mixture is called Bactrim) is nearly as effective but less toxic than the pyrimethamine combinations. Additional drugs for toxoplasmosis treatment are the antibiotics spiramycin (**48**), used alone or in combination with pyrimethamine or a sulfonamide, and clindamycin (**23**). Clindamycin has been used by itself (reportedly not with great success) and in combination with pyrimethamine to treat chorioretinitis and toxoplasmic encephalitis in AIDS patients. It is especially useful for patients who cannot tolerate extended regimens of sulfonamides.

14. Trichomoniasis

Trichomoniasis is a widespread disease of the urogenital tract caused by the protozoan *Trichomonas vaginalis*. This sexually transmitted disease affects humans only and has no known animal reservoirs (19). While it primarily affects women, *T. vaginalis* can infect men as well. The disease is marked in women by the development of purulent, frothy, vaginal discharge with a highly disagreeable odor. The role of *T. vaginalis* in producing inflammation of the male genital tract is not fully understood. The protozoan primarily invades the urethra, but may also enter the seminal vesicles or prostate. In a vast majority of infected males, the disease is asymptomatic, perhaps because they are protected by the high zinc content of prostatic secretions. Successful invasion of the prostate by the protozoan can lead to painful urination.

Treatment by the 5-nitroimidazole class of antiprotozoal agents can destroy most strains of *T. vaginalis*; however, some strains have been reported to be resistant to these drugs. The agent of choice is orally administered metronidazole (**1**), the first systemic antitrichomonal agent, introduced in 1960. Other members of this therapeutic group include niridazole (**10**), tinidazole (**11**), and ornidazole (**91**) but, in general, they offer no distinct advantage over metronidazole (Table 9). It is recommended that both female and male sexual partners be treated simultaneously to avoid reinfecting one another. Nitroimidazoles have been demonstrated to be mutagenic in bacteria and carcinogenic in high doses in laboratory animals. It is advised that pregnant women in the first trimester of pregnancy refrain from taking these drugs even though there is no clinical evidence of fetal abnormalities being caused by them. Other nitro-heterocycles have been synthesized in large number and many show promising *in vitro* activity.

15. Trypanosomiasis

The disease trypanosomiasis has two geographically delineated forms, the so-called African and American varieties. Because of their distinct differences they will be discussed separately (20).

15.1. African Trypanosomiasis

According to the World Health Organization, African trypanosomiasis affects some 25,000 people annually in 36 subSaharan countries where 50 million inhabitants are at risk. It is the cause of sleeping sickness, a disease transmitted by the bite of either the female or male tsetse fly. The tsetse fly is infected by ingesting blood from an animal or human containing trypanosomes. The elimination of these vectors is difficult because they thrive on both domestic cattle and wild animals. Trypanosomiasis in cattle, known as nagana, has seriously limited the production of this primary food source and has thwarted economic growth in endemic areas. African trypanosomiasis is caused by *Trypanosoma brucei* whose subspecies, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, have identical ultrastructures in humans. *T. b. gambiense* is responsible for an unevenly advancing sickness, whereas *T. b. rhodesiense* leads to a more acute form with rapid progression.

A human bitten by an infected tsetse fly develops a small nodule (primary or trypanosomal chancre) at the site of skin penetration from which the organisms may be isolated. These protozoa, whose life cycle is complex, change form, multiply, and invade the bloodstream via the lymphatic system in a matter of weeks or months. The trypanosomes are responsible for causing the clinical form of the disease, which includes severe headache, anemia, local edema, skin rashes, fever, and liver and/or spleen damage. Lymph nodes become enlarged and, in the advanced form of the disease, damage occurs to the central nervous system that causes the sleeping sickness phase. Lesions develop in the brain and, in some instances, in the myocardium. The disease has a high rate of mortality if left untreated. In the case of *T. b. rhodesiense*, death may ensue in several months.

The early stages of African trypanosomiasis, ie, before central nervous system involvement and the sleeping sickness take effect, can be best treated with intravenous suramin sodium (**92**), a compound with a dyelike structure (Table 10). Suramin is most effective against *T. b. rhodesiense*, but has also been used against *T. b. gambiense* infection. The compound causes side effects such as nausea, photophobia, and peripheral neuropathy which disappear shortly after conclusion of administration. Because the drug is unable to pass the blood-brain barrier, prompt treatment of patients is essential. Suramin in combination with tryparsamide (**93**, Tryparsone [554-72-3]) is an alternative that has been investigated. Pentamidine (**26**), as the isethionate or methanesulfonate salt, has been used successfully against *T. b. gambiense*, but the compound also does not enter the central nervous system and is not effective in advanced disease. It can cause severe side effects such as syncope, hypotension, hypoglycemia, vomiting, abdominal pain, and a peripheral neuropathy. Pentamidine (**26**) has been administered to large populations prophylactically against *T. b. gambiense*. This probably accounts for the appearance of resistant strains.

For late-stage disease, in which the central nervous system is implicated, the compound of choice until recently was melarsoprol (**94**, Mel B, Arsobal [494-79-1]) for *T. b. gambiense* or *T. b. rhodesiense*. The drug, administered intravenously, is a solution containing a combination of BAL (2,3-dimercaptopropanol) and the trivalent arsenic compound, melarsen oxide. Not only can the drug cause serious side effects such as intense dermal irritation, myocarditis, and renal and hepatic damage, but it is also responsible for death in 5% of patients. Resistance has developed to melarsoprol.

The first new treatment in 40 years that is showing great promise is eflornithine (**87**). It is an irreversible inhibitor of ornithine decarboxylase that blocks putrescine biosynthesis in *T. brucei in vitro* and inhibits the growth and multiplication of the parasite *in vivo*. The drug, administered orally or parenterally, is relatively nontoxic and is effective in eliminating the parasite *T. b. rhodesiense* and, to a greater extent, *T. b. gambiense*. Late-stage disease is rapidly reversed, causing comatose sleeping sickness patients to regain consciousness. Eflornithine was approved for human use by the FDA in late 1990. Side effects associated with oral administration are diarrhea, nausea, and vomiting. There is a significant relapse rate. A mixture of eflornithine (**87**) and nifurtimox (**95**, Lampit, Bayer 2502) shows good activity against *T. b. gambiense*. The former compound is also reported to potentiate the effect of melarsoprol in infected mice.

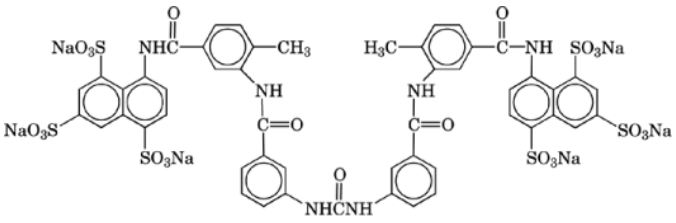
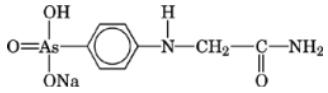
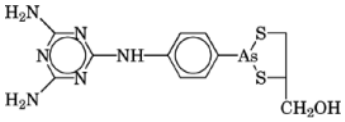
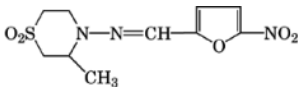
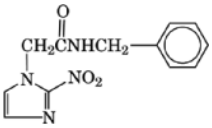
A combination of salicylhydroxamic acid (SHAM) and glycerol, although capable of destroying bloodstream trypanosomiasis, is less effective against infections involving the central nervous system.

16. American Trypanosomiasis

American trypanosomiasis, known as Chagas' Disease, is limited to South and Central America, where it affects 16–18 million people annually in an area where 90 million are at risk. Although only an estimated 1% of infected individuals contract the disease, poverty and poor housing exacerbate it. There is a particularly high incidence of the disease in children.

The protozoan causative agent, *Trypanosoma cruzi*, is harbored in domesticated animals, such as dogs, cats, and pigs, as well as wild animals, eg, rats, bats, foxes, opossums, and monkeys. These reservoirs can infect the vector, the night-feeding, blood-sucking triatomid bug. This insect, after biting a person usually on

Table 10. Trypanosomiasis Antiprotozoal Agents

Structure number	Compound name	CAS Registry Number	Molecular formula	Structure
			African trypanosomiasis	
(**92**)	suramin sodium	[129-46-4]	$C_{51}H_{34}N_6Na_6O_{23}S_6$	
(**93**)	tryparsamide	[554-72-3]	$C_8H_{10}AsN_2NaO_4$	
(**94**)	melarsoprol	[494-79-1]	$C_{12}H_{15}AsN_6OS_2$	
(**95**)	nifurtimox[a]	[23256-30-6]	$C_{10}H_{13}N_3O_5S$	
			American trypanosomiasis	
(**96**)	benznidazole	[22994-85-0]	$C_{12}H_{12}N_4O_3$	

[a] Also used to treat American trypanosomiasis.

the face, defecates near the location of the wound. Parasites from the insect feces may either enter the human host at the point of the bite and/or by fecal contamination of mucus membranes, usually those of the mouth or eyes. This causes a skin lesion (called a primary chagoma) that consists of a small, reddish, slightly painful nodule. One of the eyelids may become swollen. The injected trypanosomes enter many kinds of cells of the host where they multiply and become amastigotes. They then differentiate into trypomastigotes that circulate in the bloodstream and are distributed to all parts of the body. They do not replicate until they enter another cell or are ingested by another blood-sucking insect vector.

The disease has two phases. The acute phase is of approximately two months' duration in which the parasite spreads. Although the disease may be asymptomatic, more typically it is marked by mild fever, colonic

and esophageal dilation, liver and spleen enlargement, erythromatous rash, and acute myocarditis. In children, this phase of the disease can be serious and even fatal. During the chronic phase there is slow tissue destruction that can persist over many years. There may be cardiac and/or digestive involvement, with the former being the primary cause of death in Chagas' Disease. Despite its potential seriousness, the chronic form can also be asymptomatic.

The nitrofuran nifurtimox (**95**) is the most effective drug against *T. cruzi*, being cidal against the trypomastigote and amastigote forms. It is active against both the extra- and intracellular form of the parasite. In combination with corticosteroids it has prevented myocardial inflammation and destroyed the parasites within the heart. Side effects of the drug tend to be mild and include nausea, vomiting, insomnia, nervous excitation, vertigo, and skin rashes. Cardiac symptoms are treated symptomatically. Benznidazole (**96**, *N*-benzyl-2-nitro-1-imidazoleacetamide, RO 7-1051), an alternative drug, can prevent the spread of the parasites from one tissue to another although relapses are common. Primaquine (**69**) can destroy the extracellular trypanosomes in the blood, but is not effective against the intracellular forms of the parasite.

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