53 Antiprotozoal Drugs

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DRUG LIST

Protozoal and helminthic infections are a major cause of disease in many parts of the world. Although some of these diseases are endemic to the United States or can be found in migrant workers or individuals returning from an endemic area, many other such infections are rarely seen in the United States. However, physicians should be aware of these diseases and seek advice from those experienced in their diagnosis and treatment.

Although the mode of action of many antiprotozoals is not well understood, Table 53.1 summarizes the assumed or known modes of action of a number of the agents. The treatment of malaria is discussed at the end of this chapter.

PROTOZOAL DISEASES

Amebiasis and Balantidial Dysentery

The protozoan *Entamoeba histolytica* causes amebiasis, an infection that is endemic in parts of the United States. The parasite can be present in the host as either an encysted or a trophozoite form. Initial ingestion of the cyst may result either in no symptoms or in severe amebic dysentery characterized by the frequent passage of bloodstained stools. The latter symptom occurs after invasion of the intestinal mucosa by the actively motile and phagocytic trophozoite form of the protozoan.

TABLE 53.1 Chemotherapeutic Agents Used in Treatment of Protozoal Disease

Drug	Specific Effects	Mode of Action
Arsenicals (melarsoprol, tryparsamide), antimonials	Binds with SH groups; selectively inhibits pyruvate kinase or phosphofructokinase	Affects cellular structure, function, synthesis or energy production
Paromomycin	Interferes with initiation complex; causes misreading of mRNA	Affects protein structure, function, synthesis
Diamidines (pentamidine)	Binds to kinetoplast DNA	Affects synthesis or structure of nucleic acids
Metronidazole	Inhibits DNA replication	Affects synthesis or structure of nucleic acids
Nifurtimox	Generation of toxic oxygen radicals	Unknown
Suramin	Binds to plasma proteins; inhibits glucose utilization	Unknown
Iodoquinol	Steadily liberates inorganic iodine in the lumen	Unknown
Diloxanide furoate	Unknown	Unknown
Eflornithine	Inhibits ornithine decarboxylase and biosynthesis of polyamines	Affects cell division, differentiation

SH, sulfhydryl; mRNA, messenger RNA

Trophozoites may spread to the liver through the portal vein and produce acute amebic hepatitis, or more rarely, the trophozoites may encyst and produce an amebic liver abscess many years later. On rare occasions, amebic abscesses are found in other organs, such as the lungs or the brain.

Many patients continue to excrete cysts for several years after recovery from the acute disease and therefore are a hazard to themselves and other persons; the public health risk is greatest when persons employed as food handlers are affected. More recently, it has been recognized that infection can be transmitted by sexual activities.

Balantidium coli is the largest of the protozoans that infect humans. The trophozoite form is covered with cilia, which impart mobility. Infection is acquired through the ingestion of cyst-contaminated soil, food, or water. The trophozoite causes superficial necrosis or deep ulceration in the mucosa and submucosa of the large intestine. Otherwise healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea, whereas debilitated or nutritionally stressed patients may develop severe dysentery.

Trichomoniasis and Giardiasis

Trichomoniasis is a genital infection produced by the protozoan *Trichomonas vaginalis.* Infections frequently are asymptomatic in the male, whereas in the female vaginitis characterized by a frothy pale yellow discharge is common. Relapses occur if the infected person's sexual partner is not treated simultaneously.

Giardiasis is caused by the protozoan *Giardia lamblia* and is characterized by gastrointestinal symptoms ranging from an acute self-limiting watery diarrhea to a chronic condition associated with episodic diarrhea and occasional instances of malabsorption. The parasite is similar to *E. histolytica* in that it exists in two forms, an actively motile trophozoite (usually confined to the upper small bowel) and a cyst (commonly excreted in the feces).

Leishmaniasis and Trypanosomiasis

The flagellate leishmania is transmitted to humans by the bite of the female sandfly of the genus *Phlebotomus.* Three principal diseases result from infection with *Leishmania* spp. *L. donovani* causes visceral leishmaniasis (kala-azar); *L. tropica* and *L. major* produce cutaneous leishmaniasis, and *L. braziliensis* causes South American mucocutaneous leishmaniasis. In visceral leishmaniasis, the protozoan parasitizes the reticuloendothelial cells, and this results in an enlargement of the lymph nodes, liver, and spleen; the spleen can become massive. Cutaneous leishmaniasis remains localized to the site of inoculation, where it forms a raised disfiguring ulcerative lesion. South American leishmaniasis is variable in its presentation. It is characterized by ulceration of the mucous membranes of the nose, mouth, and pharynx; some disfiguring skin involvement also is possible.

African trypanosomiasis follows the bite of *Glossina,* a tsetse fly infected with the protozoan *Trypanosoma brucei.* The ensuing illness (*sleeping sickness*) is initially characterized by the hemolymphatic stage of fever, headache, and lymph node enlargement. These symptoms are followed by meningoencephalopathic involvement, with wasting, mental disturbances, and drowsiness as the disease progresses. This latter more

serious stage requires different, more potentially toxic drugs than does the hemolymphatic stage. There are geographical variations of the disease. *Rhodesian sleeping sickness,* acquired in the savannah and woodlands of East Africa from *Glossina morsitans,* is a much more acute and rapidly progressive disease than *Gambian sleeping sickness,* acquired in riverine areas of West Africa from *Glossina palpalis,* in which the incubation period can be more prolonged and the disease more protracted.

Chagas' disease, the South American variety of trypanosomiasis, is caused by *Trypanosoma cruzi.* It is quite different from African trypanosomiasis in its clinical and pathological presentation and in its failure to respond to many agents effective in that disease. It has both an acute and chronic phase. The latter frequently results in gastrointestinal and myocardial disease that ends in death.

ANTIPROTOZOAL DRUGS

Metronidazole

Metronidazole (*Flagyl, Metrogel*) exerts activity against most anaerobic bacteria and several protozoa. The drug freely penetrates protozoal and bacterial cells but not mammalian cells. Metronidazole can function as an electron sink, and because it does so, its 5-nitro group is reduced. The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug. Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.

Antimicrobial Spectrum

Metronidazole inhibits *E. histolytica, G. lamblia, T. vaginalis, Blastocystis hominis, B. coli,* and the helminth *Dracunculus medinensis.* It is also bactericidal for obligate anaerobic gram-positive and gram-negative bacteria except *Actinomyces* spp. It is not active against aerobes or facultative anaerobes. Drug resistance is infrequent; the mechanism of resistance is not understood. Tinidazole, a 5-nitroimidazole closely related to metronidazole, is effective against vaginal trichomoniasis resistant to metronidazole.

Absorption, Metabolism, and Excretion

Absorption from the intestinal tract is usually good. Food delays but does not reduce absorption. The drug is distributed in body fluids and has a half-life of about 8 hours. High levels are found in plasma and cerebrospinal fluid (CSF). Less than 20% binds to plasma proteins. Metronidazole is metabolized by oxidation and glucuronide formation in the liver and is primarily excreted by the kidneys, although small amounts can be found in saliva and breast milk. Dose reduction is generally unnecessary in renal failure.

Clinical Uses

Metronidazole is the most effective agent available for the treatment of individuals with all forms of amebiasis, with perhaps the exception of the person who is asymptomatic but continues to excrete cysts. That situation calls for an effective intraluminal amebicide, such as diloxanide furoate, paromomycin sulfate, or diiodohydroxyquin. Metronidazole is active against intestinal and extraintestinal cysts and trophozoites.

Although quinacrine hydrochloride has been used for the treatment of giardiasis, many physicians prefer metronidazole. Furazolidone is an alternate choice.

Metronidazole is the drug of choice in Europe for anaerobic bacterial infections; concern about possible carcinogenicity has led to some caution in its use in the United States. Recently it has been found to be effective in treating *D. medinensis* (Guinea worm) infections and *Helicobacter pylori.*

Adverse Effects

The most frequently observed adverse reactions to metronidazole include nausea, vomiting, cramps, diarrhea, and a metallic taste. The urine is often dark or red-brown. Less frequently, unsteadiness, vertigo, ataxia, paresthesias, peripheral neuropathy, encephalopathy, and neutropenia have been reported. Since metronidazole is a weak inhibitor of alcohol dehydrogenase, alcohol ingestion should be avoided during treatment. A psychotic reaction also may be produced. Metronidazole interferes with the metabolism of warfarin and may potentiate its anticoagulant activity. Phenobarbital and corticosteroids lower metronidazole plasma levels by increasing its metabolism, whereas cimetidine raises levels by impairing metronidazole metabolism. The drug is not recommended for use during pregnancy.

Iodoquinol

Iodoquinol (diiodohydroxyquin, *Yodoxin, Moebiquin*) is a halogenated 8-hydroxyquinoline derivative whose precise mechanism of action is not known but is thought to involve an inactivation of essential parasite enzymes. Iodoquinol kills the trophozoite forms of *E. histolytica, B. coli, B. hominis,* and *Dientamoeba fragilis.*

Iodoquinol is absorbed from the gastrointestinal tract and is excreted in the urine as glucuronide and sulfate conjugates. Most of an orally administered dose is excreted in the feces. Iodoquinol has a plasma half-life of about 12 hours.

Iodoquinol is the drug of choice in the treatment of asymptomatic amebiasis and *D. fragilis* infections. It is

also used in combination with other drugs in the treatment of other forms of amebiasis and as an alternative to tetracycline in the treatment of balantidiasis.

Adverse reactions are related to the iodine content of the drug; the toxicity is often expressed as skin reactions, thyroid enlargement, and interference with thyroid function studies. Headache and diarrhea also occur. Chronic use of clioquinol, a closely related agent, has been linked to a myelitislike illness and to optic atrophy with permanent loss of vision.

Diloxanide Furoate

Diloxanide furoate (*Furamide*) is an amebicide that is effective against trophozoites in the intestinal tract. In mild or asymptomatic infections, cures of 83 to 95% have been achieved; in patients with dysentery, cure rates may be less impressive. The drug is administered only orally and is rapidly absorbed from the gastrointestinal tract following hydrolysis of the ester group. It is remarkably free of side effects, but occasionally flatulence, abdominal distention, anorexia, nausea, vomiting, diarrhea, pruritus, and urticaria occur. Diloxanide is excreted in the urine, largely as the glucuronide. It is not available in the United States.

Antibiotics

Several antibiotics have been used to treat intestinal protozoal infections. Erythromycin and tetracycline do not have a direct effect on the protozoa; they act by altering intestinal bacterial flora and preventing secondary infection. Tetracycline also reduces the normal gastrointestinal bacterial flora on which the amebas depend for growth.

The aminoglycoside paromomycin (*Humatin*) has a mode of action identical to that of the other aminocyclitols and is directly amebicidal. It is not absorbed from the intestinal tract and thus has its primary effect on bacteria, some amebas (e.g., *E. histolytica*), and some helminths found in the lumen of the intestinal tract. Side effects are limited to diarrhea and gastrointestinal upset.

Amphotericin B, a polyene, is discussed more fully in Chapter 52. It has produced healing of the mucocutaneous lesions of American leishmaniasis, but its potential for nephrotoxicity makes it a drug of second choice. On the other hand, liposomal amphotericin B, approved by the U. S. Food and Drug Administration (FDA) for treatment of visceral leishmaniasis, is considered the drug of choice for that indication and is much less toxic than pentavalent antimonials or amphotericin B.

Pentamidine

Pentamidine (*Pentam 300*) binds to DNA and may inhibit kinetoplast DNA replication and function. It also may act by inhibiting dihydrofolate reductase and interfering with polyamine metabolism. An effect on organism respiration, especially at high doses, also may play a role.

Pentamidine is not well absorbed from the intestinal tract after oral administration and generally is given by intramuscular injection. The drug binds to tissues, particularly the kidney, and is slowly excreted, mostly as the unmodified drug. It does not enter the central nervous system (CNS). Its sequestration in tissues accounts for its prophylactic use in trypanosomiasis.

Pentamidine is active against *Pneumocystis carinii,* trypanosomes, and leishmaniasis unresponsive to pentavalent antimonials. It is an alternative agent for the treatment of *P. carinii* pneumonia. Although it is more toxic than trimethoprim–sulfamethoxazole, it has been widely used in patients with acquired immunodeficiency syndrome (AIDS), in whom *P. carinii* infection is common.

Pentamidine is an alternative drug for visceral leishmaniasis, especially when sodium stibogluconate has failed or is contraindicated. Pentamidine is also a reserve agent for the treatment of trypanosomiasis before the CNS is invaded. This characteristic largely restricts its use to Gambian trypanosomiasis.

Adverse reactions occur frequently. Rapid drug infusion may produce tachycardia, vomiting, shortness of breath, headache, and a fall in blood pressure. Changes in blood sugar (hypoglycemia or hyperglycemia) necessitate caution in its use, particularly in patients with diabetes mellitus. Renal function should be monitored and blood counts checked for dyscrasias.

Suramin

Suramin (*Germanin*) is a derivative of a nonmetallic dye whose antiparasitic mechanism of action is not clear. It appears to act on parasite specific α-glycerophosphate oxidase, thymidylate synthetase, dihydrofolate reductase, and protein kinase but not on host enzymes.

Suramin is not absorbed from the intestinal tract and is administered intravenously. Although the initial high plasma levels drop rapidly, suramin binds tightly to and is slowly released from plasma proteins, and so it persists in the host for up to 3 months. Suramin neither penetrates red blood cells nor enters the CNS. It is taken up by the reticuloendothelial cells and accumulates in the Kupffer cells of the liver and in the epithelial cells of the proximal convoluted tubules of the kidney. It is excreted by glomerular filtration, largely as the intact molecule.

Suramin is used primarily to treat African trypanosomiasis, for which it is the drug of choice. It is effective in treating disease caused by *Trypanosoma gambiense* and *T. rhodesiense* but not *T. cruzi* (Chagas'

disease). It can be used alone prophylactically or during the initial hemolymphatic stages of the disease. Later stages, particularly those involving the CNS, are more commonly treated with a combination of suramin and the arsenical melarsoprol.

When CNS involvement occurs, the poor penetration of suramin and pentamidine into the CSF requires alternative forms of chemotherapy, such as melarsoprol in combination with suramin. In treating *Onchocerca volvulus* infections, suramin kills adult worms and is an alternative to ivermectin. Suramin is used after initial treatment with diethylcarbamazine, which is used to kill the microfilariae. It produces favorable results in pemphigus and prolongs the time to disease progression in hormone-refractory prostate cancer.

It is important to test for drug sensitivity by administering a small (200 mg) dose by slow intravenous injection before giving the full amount of suramin. Since adverse reactions occur with greater frequency and severity among the malnourished, greater caution is necessary for patients with advanced trypanosomiasis. An acute reaction in sensitive individuals results in nausea, vomiting, colic, hypotension, urticaria, and even unconsciousness; fortunately, this reaction is rare. Rashes, photophobia, paresthesias, and hyperesthesia may occur later; these symptoms may presage peripheral neuropathy. Mild albuminuria is not uncommon, but hematuria with casts suggests nephrotoxicity and the need to stop treatment.

Eflornithine

Eflornithine (difluoromethyl ornithine, *Ornidyl*) is a unique antiprotozoal agent in that its mode of action involves inhibition of a specific enzyme, ornithine decarboxylase. In eukaryotes, decarboxylation of ornithine is required for biosynthesis of polyamines, which are important in cell division and differentiation.

Eflornithine is given intravenously, and about 80% of the drug is excreted in the urine within 24 hours. It does not bind significantly to plasma proteins and has a terminal plasma half-life of about 3 hours. It crosses the blood-brain barrier and is one of the drugs of choice for treating the hemolymphatic and meningoencephalitic stage of *T. brucei-gambiense.* The most significant side effects are anemia and leukopenia. Oral therapy is associated with considerable gastrointestinal toxicity. Diarrhea, thrombocytopenia, and seizures are occasionally reported.

Arsenicals

Melarsoprol (trivalent) and tryparsamide (pentavalent) are organic compounds containing arsenic that bind to sulfhydryl groups in proteins, thereby affecting cellular structure and function. The action of arsenic is nonspecific, and any selective toxicity achieved is related to differences in drug permeability and sulfhydryl content of the affected structure or enzyme. Melarsoprol shows some selectivity for the trypanosome enzymes phosphopyruvate kinase and trypanothione reductase. These drugs are administered intravenously. Resistance has started to emerge among trypanosomes responsible for African trypanosomiasis.

The arsenicals are trypanocidal. Melarsoprol is highly active against all stages of trypanosomiasis, but its toxicity restricts its application to the meningoencephalitic phase of the disease. Their value lies in their ability to penetrate the CNS; hence, they are useful in treating meningoencephalitis caused by trypanosomes. The drugs are rapidly eliminated.

Vomiting and abdominal cramping occur but may be minimized by slow injection in the supine fasting patient. Great care should be taken to prevent painful drug extravasation into the tissue. The most frequently observed adverse reaction is encephalopathy, which develops on or about the third day of therapy and can be fatal. Other side effects include fever, rashes, proteinuria, peripheral neuropathy, and rarely, agranulocytosis. Since the overall incidence of side effects to tryparsamide is quite high, it largely has been replaced by melarsoprol in the treatment of trypanosome infestation.

Nifurtimox

Nifurtimox (*Lampit*) is a nitrofuran derivative whose likely mechanism of action for killing of trypanosomes is through the production of activated forms of oxygen. Nifurtimox is reduced to the nitro anion radical, which reacts with oxygen to produce superoxide and hydrogen peroxide. The free radical metabolites, an absence of parasite catalase, and a peroxide deficiency lead to lipid peroxidation and cell damage. This production of activated oxygen results in toxicity to the protozoal cells.

The drug is given orally and is well absorbed from the gastrointestinal tract. It is rapidly metabolized, and only low levels are found in blood and tissues. The drug is excreted in the urine, primarily in the form of metabolites.

Nifurtimox is trypanocidal and exerts an effect on the trypomastigote and amastigote forms of *T. cruzi.* It is effective in the treatment of the acute form of Chagas' disease but is less effective once the disease becomes chronic. The drug is moderately well tolerated, and treatment generally lasts 3 to 4 months. Cure rates of 80 to 90% have been reported. Since much of the tissue damage caused by the disease is irreversible, early diagnosis and treatment are important. Nifurtimox has also been used in *T. gambiense* infection with meningoencephalopathic involvement.

Although side effects occur in approximately half the patients treated with nifurtimox, it is necessary to

discontinue treatment in only a minority. Nausea, vomiting, abdominal pain, skin rashes, headache, insomnia, convulsions, and myalgia all have been reported.

Antimonials

Sodium stibogluconate (*Pentostam, Triostam*) and meglumine antimonate (*Glucantime*), both pentavalent antimonials, bind to sulfhydryl groups on proteins and may form thio antimonides. Some evidence suggests that the pentavalent form may be reduced in vivo to the trivalent antimonial before binding. Trivalent antimonials inhibit phosphofructokinase, a rate-limiting enzyme in glycolysis, and organisms whose growth is dependent on the anaerobic metabolism of glucose cannot survive without the active enzyme. Whether this is the mechanism by which pentavalent antimonials inhibit protozoa is unclear.

Antimonials are irritating to the intestinal mucosa and therefore are administered by intramuscular or slow intravenous injection. Peak blood concentrations occur in 2 hours. These drugs bind to cells, including erythrocytes, and are found in high concentrations in the liver and spleen. As compared with the trivalent antimonials, which are no longer used, the pentavalent antimonials bind to tissue less strongly. This results in higher blood levels, more rapid excretion, and lowered toxicity. Pentavalent antimonials are rapidly excreted in the urine, with up to one-half of the administered dose excreted in 24 hours.

No pentavalent antimonial is licensed for use, but sodium stibogluconate is available from the Parasitic Disease Drug Service of the Centers for Disease Control (CDC) for treatment of leishmaniasis. While the pentavalent antimony compounds can be given intravenously or intramuscularly, local infiltration of the lesion in cutaneous leishmaniasis is highly effective. Because of the lower toxicity of liposomal amphotericin B, this drug is considered a first-line choice for visceral leishmaniasis rather than the antimonials.

Adverse reactions particularly associated with the trivalent antimonials are coughing, occasional vomiting, myalgia, arthralgia, and changes in the electrocardiogram. Sodium stibogluconate occasionally causes rashes, pruritus, abdominal pain, diarrhea, and anaphylactoid collapse. Liver damage with jaundice is a rare side effect. Toxic reactions are more common with repeated courses of treatment. Biochemical evidence of pancreatitis is usual (97%), but severe or fatal pancreatitis is extremely infrequent.

MALARIA

Malaria is a parasitic disease endemic in parts of the world where moisture and warmth permit the disease vector, mosquitoes of the genus *Anopheles,* to exist and multiply. The emergence of both drug-resistant strains of malarial parasites and insecticide-resistant strains of *Anopheles* has contributed significantly to the extensive reappearance of this infection. The annual global incidence of malaria is estimated to be approximately 200 million cases, and in tropical Africa alone, malaria is responsible for the yearly deaths of more than 1 million children younger than 14 years. Malaria ranks as a leading cause of mortality in the world today.

Most cases of malaria in the United States result from individuals who have contracted the disease before they entered this country. It is also possible to contract malaria during a blood transfusion if the transfused blood has been taken from a malaria-infected individual. Additionally, hypodermic needles previously contaminated by blood containing malarial parasites can be the source of an infection; this has occurred when needles are shared among drug addicts.

Effective treatment of malaria depends on early diagnosis. Since the patient's symptoms are often relatively nonspecific, it is crucial to examine stained blood smears for the presence of the parasite. Even this procedure may be inconclusive during the early stages of the infection, since the levels of parasitemia can be quite low. Thus, it is important to repeat the blood smear examination several times if malaria is suspected.

Once the presence of malarial parasites has been confirmed, it is vital to identify the particular plasmodial strain involved, since appropriate use of chemotherapy depends on the particular species responsible for the acute attack. Unfortunately, mixed infections, that is, simultaneous infections with more than one species of plasmodia, are often observed. If more than a single species is involved, treatment appropriate for the elimination of all strains must be instituted to avoid delayed attacks or misinterpretations.

Life Cycle of the Malarial Parasite

The malarial parasite is a single-cell protozoan (plasmodium). Although more than 100 species of plasmodia have been identified, only four are capable of infecting humans (*Plasmodium malariae, P. ovale, P. vivax,* and *P. falciparum*); the rest attack a variety of animal hosts. *P. falciparum* and *P. vivax* malaria are the two most common forms.

P. vivax malaria is the most prevalent type of infection and is characterized by periodic acute attacks of chills and fever, profuse sweating, enlarged spleen and liver, anemia, abdominal pain, headaches, and lethargy. Hyperactivity of the reticuloendothelial system and hemolysis are the principal causes of the enlarged spleen and liver; these effects often result in anemia, leukopenia, thrombocytopenia, and hyperbilirubinemia. The cyclical nature of the acute attacks (48 hours for

P. vivax, P. ovale, and *P. falciparum*) is characteristic of malaria and reflects the relatively synchronous passage of the parasites from one red blood cell stage in their life cycle to another. If *P. vivax* malaria is not treated, the symptoms may subside for several weeks or months and then recur. These relapses are due to a latent liver form of the parasite (see the following section), which is not present in *P. falciparum* strains. Although the fatality rate of *P. vivax* malaria is low, it is an exhausting infection and renders the patient more susceptible to other diseases.

Unchecked *P. falciparum* malaria is the most serious and most lethal form of the disease. It is responsible for 90% of the deaths from malaria. The parasitemia achieved can be quite high and will be associated with an increased incidence of serious complications (e.g., hemolytic anemia, encephalopathy). *P. falciparum* malaria produces all of the symptoms listed for *P. vivax* malaria and in addition can cause renal failure and pulmonary and cerebral edema. The tissue anoxia occurring in *P. falciparum* infections results from the unique sequestering of infected erythrocytes deep in the capillaries during the last three-fourths of the intraerythrocytic cycle.

Members of the genus *Plasmodium* have a complex life cycle (Fig. 53.1). A sexual stage occurs within the *Anopheles* mosquito, while asexual stages take place in the host. Malaria is actually transmitted from one human to another through the insect vector. Initially, a female mosquito is infected by biting a human with the disease whose blood contains male and female *gamete* forms of the parasite. Fertilization takes place in the mosquito gut, and after differentiation and multiplication, the mature *sporozoite* forms migrate to the insect's salivary glands. At the mosquito's next feeding, the sporozoites are injected into the bloodstream of another human to begin the asexual stages. After a relatively brief residence (less than an hour) in the systemic circulation, the sporozoites invade liver parenchymal cells, where they divide and develop asexually into multinucleated *schizonts.* These are the primary exoerythrocytic tissue forms of the parasite. When this primary stage of development is completed (6–12 days), the schizonts will rupture, releasing *merozoites* into the

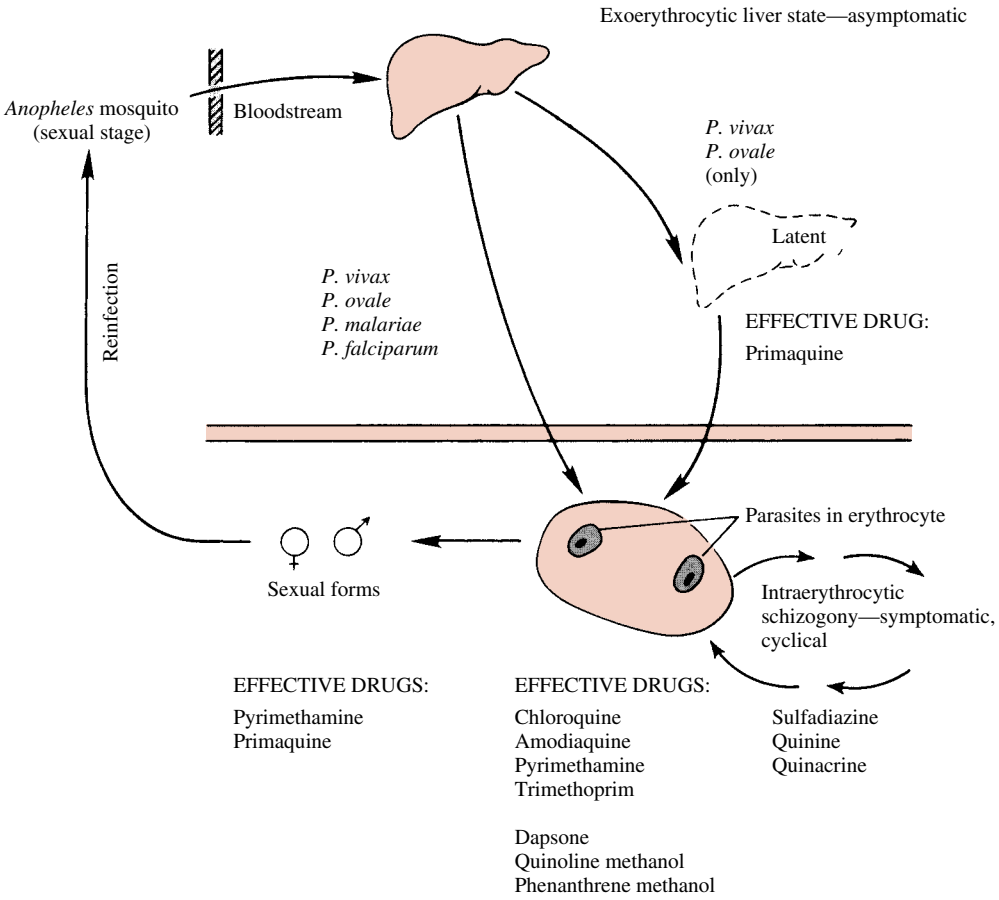

FIGURE 53.1
Life cycle of malaria parasites and locations where specific drugs are effective. The life cycles are not identical for every species.

blood. These latter forms invade host erythrocytes, where they again grow and divide asexually (*erythrocytic schizogony*) and become red cell schizonts. Some of the parasites differentiate into sexual (male and female) forms, or *gametocytes.* If the diseased human is bitten by a mosquito at this time, the gametes will be taken up into the organism's gut to repeat the sexual cycle. The gametocytes and the exoerythrocytic liver forms of *Plasmodium* spp. are not associated with the appearance of clinical symptoms of malaria.

The asexual intraerythrocytic parasites, that is, those that do not differentiate into gametocytes, also multiply and grow until they rupture the cells in which they reside; these new merozoites are released into the bloodstream. This occurrence not only sets up the subsequent cyclical red blood cell stages of the cycle but also gives rise to the symptoms associated with malarial infections. The recurrent chills and fever are thought to be related to the lysis of erythrocytes and the accompanying release of lytic material and parasite toxins into the bloodstream. Although the appearance of a cyclic fever is useful for diagnosis, this symptom may not occur during the early stages of the infection.

In individuals infected with either *P. vivax* or *P. ovale,* the exoerythrocytic tissue (e.g., liver) forms can persist after a latent period and give rise to relapses. In *P. falciparum* and *P. malariae* malaria, however, there do not appear to be any persistent secondary liver forms. Thus, in both of these forms of malaria, the physician must contend only with the asexual erythrocytic forms and the gametes, not with the latent liver forms found in *P. vivax* and *P. ovale.*

Patients who have blood transfusion malaria are infected with the asexual erythrocytic parasites only; exoerythrocytic tissue forms apparently do not develop. *Plasmodium malariae* has been known to produce an infection after transfusion, even when the blood was obtained from a person whose only contact with malaria was 40 years previous to the donation of blood.

Therapeutic Considerations

The main objective in the clinical management of patients suffering from an *acute* malaria attack is the prompt elimination of the parasite form responsible for the symptoms, that is, the asexual erythrocytic form. Drugs that are particularly effective in this regard are called *schizonticidal,* or *suppressive,* agents. They include such compounds as amodiaquine, chloroguanide, chloroquine, hydroxychloroquine, pyrimethamine, quinine, and tetracycline. These drugs have the potential (excluding any drug resistance) for effecting a *clinical cure;* that is, they can reduce the parasitemia to zero. The term *radical cure* also has been used, and it, in contrast to clinical cure, implies the elimination of all parasite forms from the body.

Once the primary therapeutic objective has been achieved, attention can be focused on such additional considerations as elimination of the gametocytes and the tissue forms of the parasite. Success in these areas would help to ensure that relapses do not occur. Since no latent liver forms are associated with mosquito-induced, drug-sensitive *P. falciparum* malaria, administration of chloroquine for up to 3 months after the patient leaves a malarious area will usually bring about a complete or radical cure *unless* the organism is resistant to chloroquine.

The emergence of parasites resistant to chloroquine is an increasingly important problem. Several strains of chloroquine-resistant *P. falciparum* have been identified. This resistance would lead to the reappearance of overt symptoms of *P. falciparum* malaria.

P. falciparum malaria may be accompanied by an infection caused by one of the other three plasmodial forms (*mixed infection*). As long as all of the parasites are drug sensitive, the parasitemia can be eliminated. However, it must be remembered that even though *P. falciparum* malaria may be ameliorated or eliminated, relapses due to *P. vivax* and *P. ovale* still can occur.

Antimalarial Drugs

Chloroquine

Chloroquine (*Aralen*) is one of several 4-aminoquinoline derivatives that display antimalarial activity. Chloroquine is particularly effective against intraerythrocytic forms because it is concentrated within the parasitized erythrocyte. This preferential drug accumulation appears to occur as a result of specific uptake mechanisms in the parasite. Chloroquine appears to work by intercalation with DNA, inhibition of heme polymerase or by interaction with Ca^{++}–calmodulin-mediated mechanisms. It also accumulates in the parasite's food vacuoles, where it inhibits peptide formation and phospholipases, leading to parasite death.

The drug is effective against all four types of malaria with the exception of chloroquine-resistant *P. falciparum.* Chloroquine destroys the blood stages of the infection and therefore ameliorates the clinical symptoms seen in *P. malariae, P. vivax, P. ovale,* and sensitive *P. falciparum* forms of malaria. The disease will return in *P. vivax* and *P. ovale* malaria, however, unless the liver stages are sequentially treated with primaquine after the administration of chloroquine. Chloroquine also can be used prophylactically in areas where resistance does not exist. In addition to its use as an antimalarial, chloroquine has been used in the treatment of rheumatoid arthritis and lupus erythematosus (see Chapter 36), extraintestinal amebiasis, and photoallergic reactions.

The absorption of chloroquine from the gastrointestinal tract is rapid and complete. The drug is distributed widely and is extensively bound to body tissues,

with the liver containing 500 times the blood concentration. Such binding is reflected in a large volume of distribution (V_d). Desethylchloroquine is the major metabolite formed following hepatic metabolism, and both the parent compound and its metabolites are slowly eliminated by renal excretion. The half-life of the drug is 6 to 7 days.

Dizziness, headache, itching (especially in dark-skinned people), skin rash, vomiting, and blurring of vision may occur following low doses of chloroquine. In higher dosages these symptoms are more common, and exacerbation or unmasking of lupus erythematosus or discoid lupus, as well as toxic effects in skin, blood, and eyes can occur. Since the drug concentrates in melanin-containing structures, prolonged administration of high doses can lead to blindness. Chloroquine should not be used in the presence of retinal or visual field changes.

Hydroxychloroquine

Hydroxychloroquine (*Plaquenil*), like chloroquine, is a 4-aminoquinoline derivative used for the suppressive and acute treatment of malaria. It also has been used for rheumatoid arthritis and discoid and systemic lupus erythematosus. Hydroxychloroquine has not been proved to be more effective than chloroquine. Adverse reactions associated with its use are similar to those described for chloroquine. The drug should not be used in patients with psoriasis or porphyria, since it may exacerbate these conditions.

Amodiaquine

Amodiaquine (*Camoquin*) is another 4-aminoquinoline derivative whose antimalarial spectrum and adverse reactions are similar to those of chloroquine, although chloroquine-resistant parasites may not be amodiaquine-resistant to the same degree. Prolonged treatment with amodiaquine may result in pigmentation of the palate, nail beds, and skin. There is a 1:2000 risk of agranulocytosis and hepatocellular dysfunction when the drug is used prophylactically.

Primaquine

Primaquine is the least toxic and most effective of the 8-aminoquinoline antimalarial compounds. The mechanism by which 8-aminoquinolines exert their antimalarial effects is thought to be through a quinoline–quinone metabolite that inhibits the coenzyme Q–mediated respiratory chain of the exoerythrocytic parasite.

Primaquine is an important antimalarial because it is essentially the only drug effective against the liver (exoerythrocytic) forms of the malarial parasite. The drug also kills the gametocytes in all four species of human malaria. Primaquine is relatively ineffective against the asexual erythrocyte forms. *Primaquine finds its greatest use in providing a radical cure for* P. vivax *and* P. ovale *malaria.*

Primaquine is readily absorbed from the gastrointestinal tract, and in contrast to chloroquine, it is not bound extensively by tissues. It is rapidly metabolized, and the metabolites are reported to be as active as the parent drug itself. Peak plasma levels are reached in 4 to 6 hours after an oral dose, with almost total drug elimination occurring by 24 hours. The half-life is short, and daily administration is usually required for radical cure and prevention of relapses.

Although primaquine has a good therapeutic index, a number of important side effects are associated with its administration. In individuals with a genetically determined glucose 6-phosphate dehydrogenase deficiency, primaquine can cause lethal hemolysis of red cells. This genetic deficiency occurs in 5 to 10% of black males, in Asians, and in some Mediterranean peoples. With higher dosages or prolonged drug use, gastrointestinal distress, nausea, headache, pruritus, and leukopenia can occur. Occasionally, agranulocytosis also has been observed.

Pyrimethamine

Pyrimethamine (*Daraprim*) is the best of a number of 2,4-diaminopyrimidines that were synthesized as potential antimalarial and antibacterial compounds. Trimethoprim (*Proloprim*) is a closely related compound.

Pyrimethamine is well absorbed after oral administration, with peak plasma levels occurring within 3 to 7 hours. An initial loading dose to saturate nonspecific binding sites is not required, as it is with chloroquine. However, the drug binds to tissues, and therefore, its rate of renal excretion is slow. Pyrimethamine has a half-life of about 4 days. Although the drug does undergo some metabolic alterations, the metabolites formed have not been totally identified.

The only antimalarial drugs whose mechanisms of action are reasonably well understood are the drugs that inhibit the parasite's ability to synthesize folic acid. *Parasites cannot use preformed folic acid and therefore must synthesize this compound* from the following precursors obtained from their host: *p*-aminobenzoic acid (PABA), pteridine, and glutamic acid. The dihydrofolic acid formed from these precursors must then be hydrogenated to form tetrahydrofolic acid. The latter compound is the coenzyme that acts as an acceptor of a variety of one-carbon units. The transfer of one-carbon units is important in the synthesis of the pyrimidines and purines, which are essential in nucleic acid synthesis.

Whereas the sulfonamides and sulfones inhibit the initial step whereby PABA and the pteridine moiety combine to form dihydropteroic acid (see Chapter 44), *pyrimethamine and trimethoprim inhibit the conversion of dihydrofolic acid to tetrahydrofolic acid, a reaction*

catalyzed by the enzyme dihydrofolate reductase. The basis of pyrimethamine selective toxicity resides in the *preferential binding* of the drug to the parasite's reductase enzyme.

The combined use of sulfonamides or sulfones with dihydrofolate reductase inhibitors, such as trimethoprim (*Bactrim, Septra*) or pyrimethamine (*Fansidar*), is a good example of the synergistic possibilities that exist in multiple-drug chemotherapy. This type of impairment of the parasite's metabolism is termed *sequential blockade. Using drugs that inhibit at two different points in the same biochemical pathway produces parasite lethality at lower drug concentrations than are possible when either drug is used alone.*

Pyrimethamine has been recommended for prophylactic use against all susceptible strains of plasmodia; however, it should not be used as the sole therapeutic agent for treating acute malarial attacks. As mentioned previously, *sulfonamides should always be coadministered with pyrimethamine* (*or trimethoprim*), since the combined antimalarial activity of the two drugs is significantly greater than when either drug is used alone. Also, resistance develops more slowly when they are used in combination. Sulfonamides exert little or no effect on the blood stages of *P. vivax,* and resistance to the dihydrofolate reductase inhibitors is widespread.

In addition to its antimalarial effects, pyrimethamine is indicated (in combination with a sulfonamide) for the treatment of toxoplasmosis. The dosage required is 10 to 20 times higher than that employed in malarial infections.

Relatively few side effects are associated with the usual antimalarial dosages. However, signs of toxicity are evident at higher dosages, particularly those used in the management of toxoplasmosis. Many of these reactions reflect the interference of pyrimethamine with *host* folic acid metabolism, especially that occurring in rapidly dividing cells. Toxic symptoms include anorexia, vomiting, anemia, leukopenia, thrombocytopenia, and atrophic glossitis. CNS stimulation, including convulsions, may follow an acute overdose. The side effects associated with the pyrimethamine–sulfadoxine combination include those associated with the sulfonamide and pyrimethamine alone. In addition, there is evidence of a greater incidence of allergic reactions, particularly toxic epidermal necrolysis and Stevens-Johnson syndrome, with the combination. This carries an estimated mortality of 1:11,000 to 1:25,000 when used as a chemoprophylactic.

Chloroguanide (Proguanil)

Chloroguanide hydrochloride (*Paludrine*) is activated to a triazine metabolite, cycloguanil, which also interferes with parasite folic acid synthesis. It is a dihydrofolate reductase inhibitor that is used for the prophylaxis of malaria caused by all susceptible strains of plasmodia. Chloroguanide is rapidly absorbed from the gastrointestinal tract. Peak plasma levels occur 2 to 4 hours after oral administration, and the drug is excreted in the urine with an elimination half-life of 12 to 21 hours. Its side effects and spectrum of antimalarial activity are quite similar to those of pyrimethamine. The conversion of chloroguanide to the active metabolite is decreased in pregnancy and also as a result of genetic polymorphism in 3% of whites and Africans and 20% of Asians.

Quinine

Quinine is one of several alkaloids derived from the bark of the cinchona tree. The mechanism by which it exerts its antimalarial activity is not known. It does not bind to DNA at antimalarial dosages. It may poison the parasite's feeding mechanism, and it has been termed a general protoplasmic poison, since many organisms are affected by it.

Quinine is rapidly absorbed following oral ingestion, with peak blood levels achieved in 1 to 4 hours. About 70 to 93% of the drug is bound to plasma proteins, depending on the severity of the infection. Quinine is extensively metabolized, with only about 20% of the parent compound eliminated in the urine.

The primary present-day indication for quinine and its isomer, quinidine, is in the intravenous treatment of severe manifestations and complications of chloroquine-resistant malaria caused by *P. falciparum.*

Aside from its use as an antimalarial compound, quinine is used for the prevention and treatment of nocturnal leg muscle cramps, especially those resulting from arthritis, diabetes, thrombophlebitis, arteriosclerosis, and varicose veins.

Cinchonism describes the toxic state induced by excessive plasma levels of free quinine. Symptoms include sweating, ringing in the ears, impaired hearing, blurred vision, nausea, vomiting, and diarrhea. Quinine is a potent stimulus to insulin secretion and irritates the gastrointestinal mucosa. Also, a variety of relatively rare hematological changes occur, including leukopenia and agranulocytosis. Quinine is potentially neurotoxic in high dosages, and severe hypotension may follow its rapid intravenous administration.

Quinacrine

Quinacrine is no longer used extensively as an antimalarial drug and has been largely replaced by the 4-aminoquinolines.

Dapsone

Although dapsone (*Avlosulfon*) was once used in the treatment and prophylaxis of chloroquine-resistant *P. falciparum* malaria, the toxicities associated with its administration (e.g., agranulocytosis, methemoglobinemia, hemolytic anemia) have severely reduced its use.

Occasionally dapsone has been added to the usual chloroquine therapeutic regimen for the prophylaxis of chloroquine-resistant *P. falciparum* malaria. It is also used in combination therapy for leprosy.

Mefloquine

Mefloquine (*Lariam*) is a 4-quinolinemethanol derivative used both prophylactically and acutely against resistant *P. falciparum* malaria. It is ineffective against the liver stage of *P. vivax* malaria.

While its detailed mechanism of action is unknown, it is an effective blood schizonticide; that is, it acts against the form of the parasite responsible for clinical symptoms. Orally administered mefloquine is well absorbed and has an absorption half-life of about 2 hours; the elimination half-life is 2 to 3 weeks. Among its side effects are vertigo, visual alterations, vomiting, and such CNS disturbances as psychosis, hallucinations, confusion, anxiety, and depression. It should not be used concurrently with compounds known to alter cardiac conduction or prophylactically in patients operating dangerous machinery. It should not used to treat severe malaria, as there is no intravenous formulation.

Atovaquone

Atovaquone is a naphthoquinone whose mechanism of action involves inhibition of the mitochondrial electron transport system in the protozoa. Malaria parasites depend on de novo pyrimidine biosynthesis through dihydroorotate dehydrogenase coupled to electron transport. Plasmodia are unable to salvage and recycle pyrimidines as do mammalian cells.

Atovaquone is poorly absorbed from the gastrointestinal tract, but absorption is increased with a fatty meal. Excretion of the drug, mostly unchanged, occurs in the feces. The elimination half-life is 2 to 3 days. Low plasma levels persist for several weeks. Concurrent administration of metoclopramide, tetracycline, or rifampin reduces atovaquone plasma levels by 40 to 50%.

Atovaquone has good initial activity against the blood but not the hepatic stage of *P. vivax* and *P. ovale* malaria parasites. It is effective against erythrocytic and exoerythrocytic *P. falciparum,* and therefore, daily suppressive doses need to be taken for only 1 week upon leaving endemic areas. When used alone, it has an unacceptable (30%) rate of recrudescence and selects for resistant organisms. It and proguanil are synergistic when combined and no atovaquone resistance is seen. This combination (*Malarone*) is significantly more effective than mefloquine, amodiaquine, chloroquine, and combinations of chloroquine, pyrimethamine, and sulfadoxine. In addition to using the combination of atovaquone and proguanil for the treatment and prophylaxis of *P. falciparum* malaria, atovaquone is also used for the treatment and prevention of *P. carinii* pneumonia and babesiosis therapy.

Atovaquone is well tolerated and produces only rare instances of nausea, vomiting, diarrhea, abdominal pain, headache, and rash of mild to moderate intensity.

DRUGS IN DEVELOPMENT

Chinese scientists have isolated several compounds with antimalarial activity from species of *Artemisia.* These include artemisinin (*Qinghaosu*), artesunate, and artemether. These sesquiterpene peroxides are potent and rapidly acting antimalarial drugs that show relatively low human toxicity. They are active against blood stages, especially in patients with severe manifestations, such as cerebral malaria and chloroquine-resistant malarial infections. They possess activity against the erythrocytic stages of human malaria and have no effect on the liver or exoerythrocytic stage of the parasite; their gameticidal activity is not clear. They are most useful in treating life-threatening cerebral edema. At present artemisinin, artesunate, and artemether are available outside the United States.

SELECTION OF DRUGS

The particular agent employed in the treatment of acute malarial infections will depend on the severity of the infection, the strain of the infecting organism, and the degree to which the organism is drug resistant. In addition, *chemoprophylaxis* is considered a valid indication for the use of antimalarial drugs when individuals are traveling in areas where malaria is endemic. The following paragraphs may provide useful guidelines in the therapeutic management and prevention of malarial infections.

Prophylactic Measures for Use in Endemic Areas

Chloroquine may be the drug of choice, but only in areas where chloroquine-sensitive *P. falciparum* organisms are present. Chloroquine prophylaxis is no longer effective for travel to many regions. Daily atovaquone–proguanil appears to be the first choice for chemoprophylaxis for travel to areas of chloroquine resistance. Prophylactic drugs, such as chloroquine or mefloquine, should be started 2 to 4 weeks prior to travel and continued for 6 to 8 weeks after leaving the endemic areas. The atovaquone–proguanil combination is the exception in that it is started 1 to 2 days prior to departure and is continued 1 week after return.

Treatment of an Acute Uncomplicated Attack

Chloroquine phosphate, administered orally, is again the drug of choice unless one suspects the presence of a chloroquine-resistant organism. Oral mefloquine or

Malarone is indicated for uncomplicated infections resistant to chloroquine. For severe infections, parenteral administration of quinidine is indicated with hourly monitoring of serum glucose levels.

Mechanism of Chloroquine Resistance

A particular protein (P_{170} glycoprotein) has been identified in the resistant parasite that appears to function as a drug-transporting pump mechanism to rid the cell of drug. This resistance mechanism is similar to the multidrug resistance system in cancer. Thus, when drug enters the organism, it is rapidly removed before it can exert its toxicity. Drug therapy directed at inhibiting this pump mechanism may be able to reverse this resistance. This is a potentially important new approach to the chemotherapy of malaria.

Treatment of Chloroquine-Resistant *P. Falciparum* Infection

In areas where chloroquine-resistant *P. falciparum* is common, a combination of a rapidly acting blood schizonticide and pyrimethamine–sulfadoxine may be the treatment of choice. An acute attack of malaria caused by chloroquine-resistant *P. falciparum* complicated by renal failure or cerebral manifestations may be terminated with parenteral quinidine gluconate alone or with oral pyrimethamine and sulfadiazine. Oral mefloquine has been used in place of chloroquine in uncomplicated infections with chloroquine-resistant organisms, but serious CNS side effects (e.g., flashbacks) are frequently seen with its use. Consequently, the atovaquone–proguanil combination is now considered as effective as and better tolerated than mefloquine.

Mixed Infections

Every patient with malaria should be examined for simultaneous infection with more than one species of *Plasmodium.* Infections with both *P. falciparum* and *P. vivax* are among the most commonly encountered mixed infections. In patients with falciparum malaria, attacks of *P. vivax* malaria may later develop; it is important not to misinterpret this delayed *P. vivax* form as a relapse of *P. falciparum* infection. If a mixed infection is identified, a combination of 4-aminoquinoline and primaquine should be administered, since the primaquine helps to eliminate any persisting tissue forms of *P. vivax.*

Study Questions

1. A 35-year-old medical entomologist comes to the hospital with chief complaints of fever, headache, and photophobia. This illness began about 6 days prior to admission, when he returned from a 2-month visit to the jungles of Central and South America. On his return flight, about 6 days prior to admission, he described having fever and shaking chills. He saw his physician 2 days prior to admission; the physician made a diagnosis of influenza and prescribed tetracycline. On the day of admission, the patient had shaking chills followed by temperature elevation to 104°F (40°C). Physical examination revealed a well-developed man who appeared ill. There is some left upper quadrant tenderness but no organomegaly; blood pressure, 126/90; pulse, 120; and respirations, 22. Laboratory findings were hemoglobin, 14.5 mg/dL (normal, 13.4–17.4 mg/dL); hematocrit, 45% (normal, 40–54%); Giemsa-stained blood smear (thick and thin) revealed *Plasmodium vivax.* What is the oral drug of choice to rid the blood of plasmodia?
(A) Primaquine
(B) Chloroquine
(C) Sulfadiazine
(D) Quinine
(E) Mefloquine

2. A 27-year-old ecologist went to his physician with an ulcer on his left wrist 8 weeks after returning from Panama. The patient noted a small pink papule that was pruritic (itchy) and enlarged and developed a crusted appearance. This in time fell off, leaving an oozing shallow ulcer about 2 cm in diameter with indurated margins. He applied over-the-counter topical agents without clinical improvement. No fever or lymphadenopathy was present. Scrapings were taken from the raised margins of the ulcer and stained with Giemsa, revealing intracellular and free small, round and oval bodies measuring 2 to 5 μm in diameter. While this is suggestive of the *Leishmania* amastigote stage in the vertebrate host, culture confirmed it to be *L. braziliensis panamensis.* The patient had New World cutaneous leishmaniasis. What is the drug of choice?
(A) Praziquantel
(B) Pyrimethamine–sulfadoxine
(C) Pentavalent antimonials
(D) Pyrantel pamoate
(E) Primaquine phosphate

3. The patient is 43-year-old Agency for International Development worker with chief complaints of fever and headache. He recently returned from a trip to western Kenya and Tanzania. While traveling

cross-country through the woodland and savanna by Land Rover, he indicated that the cab appeared to be filled with tsetse flies of the genus *Glossina.* He was bitten on the forearm and developed a painful chancre with some exudate. Physical examination showed the patient to be febrile, with a temperature of 102°F (38.8°C); he had tachycardia, with a pulse of 120 beats per minute, and appeared acutely ill and lethargic. Low-grade posterior cervical lymphadenopathy was present. There was no edema of the extremities, no organomegaly, and no abnormalities in his neurological examination. Renal and hepatic functions were normal. Giemsa-stained thick and thin blood smears examined to rule out malaria revealed trypomastigotes. Parasites were also found in a drop of exudate from a needle aspiration of the chancre. A lumbar puncture revealed CSF having one white blood cell and two red blood cells with normal glucose and protein levels. No parasites were seen in a centrifuged sample of CSF. What treatment is indicated for this patient?

(A) Sulfadoxine–pyrimethamine
(B) Chloroquine
(C) Suramin
(D) Melarsoprol
(E) Metronidazole

4. A 52-year-old real estate salesperson has a 2-week history of watery diarrhea without blood. The patient states that 4 to 5 weeks ago she and her husband visited Aspen, Colorado, on a backpacking vacation and on occasion drank water from mountain streams. They were sure the water was potable, as the unspoiled, pristine area abounded with fish, beaver, and plant life. She states she has enjoyed perfect health except that she takes antacids for what she describes as gastroesophageal reflux disease. Her physical examination produced unremarkable findings. Examination of liquid stool revealed trophozoites and cysts of *G. lamblia.* Which of the following is the correct treatment for this disease?

(A) Melarsoprol
(B) Mefloquine
(C) Mebendazole
(D) Metronidazole
(E) Meglumine antimonate

5. The patient is a 12-year-old boy with fever and vomiting. The fever began a month prior to admission, spiking to approximately 104°F (40°C) each day. The family physician for a time entertained a presumptive diagnosis of chloroquine-resistant malaria and prescribed mefloquine followed by a week of doxycycline, without effect. Then, 2 days prior to admission, the patient began vomiting after eating. About 4 months earlier the family visited their home of origin in Bihar state in northeast India. Physical examination revealed a thin, acutely ill child with a temperature of 103°F (39.4°C), pulse of 130, and respirations of 36. Positive finding on physical examination was a nontender distended abdomen with a liver edge palpable 5 finger breadths below the costal margin and a smooth, firm spleen extending to the umbilicus (hepatosplenomegaly). The skin was dry and darkly pigmented. Laboratory findings revealed hemoglobin of 8.5 mg/dL (normal, 13.4–17.4 mg/dL), white blood cell count 3900 cells/mm^3 (normal, 4000–12,000 cells/mm^3), platelet count 99,000 cells/mm^3 (normal, 150,000–400,000 cells/mm^3). A bone marrow aspirate revealed characteristic amastigotes of *L. donovani.* Which of the following is the drug of choice for visceral leishmaniasis?

(A) Liposomal amphotericin B
(B) Albendazole
(C) Atovaquone
(D) Pyrimethamine–sulfadoxine
(E) Proguanil

ANSWERS

1. B. The drug of choice for clinical cure of *P. vivax* malaria is oral chloroquine. The only isolated reports of chloroquine-resistant *P. vivax* are from the western Pacific, not Central and South America. The patient should become afebrile in 24 to 48 hours, and parasitemia should decline in 72 hours. Since *P. vivax,* known as benign tertian malaria, responds well to chloroquine, there is no need to resort to parenteral quinine or quinidine or oral mefloquine; these agents have cardiotoxic and neurotoxic side effects. *P. vivax* also does not respond as well to the sulfonamides. In *P. vivax* and *P. ovale* infections, treatment with a blood schizonticide will result only in clinical cure, but radical cure requires additional treatment with a tissue schizonticide, primaquine, to destroy exoerythrocytic stages responsible for relapses. The patient should be checked for glucose 6-phosphate dehydrogenase deficiency before taking primaquine. Also, primaquine is not effective against erythrocytic schizonts at pharmacological levels, so it cannot be used in place of chloroquine.

2. C. The first-line drug for cutaneous or mucocutaneous leishmaniasis is sodium stibogluconate (*Pentostam*) or meglumine antimonate (*Glucantime*). Antimonials have not been approved by the U. S. Food and Drug Administration, but sodium stibogluconate is obtained from the Centers for Disease Control and Prevention. Clinical response is determined by species and resistance patterns of *Leishmania* and by host immunity. These drugs are given by intravenous or intramuscular injection. Phlebitis and pain are reduced when these drugs

are given intravenously. In advanced mucocutaneous leishmaniasis amphotericin B may be an alternative, especially in areas of resistance to antimony drugs. Liposomal amphotericin B is the drug of choice for visceral leishmaniasis and has been used successfully in the treatment of cutaneous and mucocutaneous disease. Pentamidine, ketoconazole, and itraconazole have been used effectively to treat the cutaneous but not visceral form of leishmaniasis. Pyrantel pamoate is a roundworm treatment and not indicated here. Primaquine phosphate is used to prevent relapses in tertian malaria, and praziquantel is the drug of choice in treating tapeworm and fluke infections. Pyrimethamine–sulfadoxine is used to treat malaria and is sometimes combined with quinine sulfate in chloroquine resistance. It is also used to treat toxoplasmosis when it is accompanied by leucovorin (folinic acid).

3. **C.** Suramin is the drug of choice for the hemolymphatic stage of *T. rhodesiense* and *T. gambiense* with a normal CSF examination. This drug is almost 100% effective in eliminating trypanosomes from the blood of patients in the early stage of disease. Epidemiologically this patient appears to have East African trypanosomiasis caused by *T. rhodesiense.* Pentamidine isethionate results in lower cure rates in *T. rhodesiense* infections than those with suramin. Suramin does not cross the blood-brain barrier, so it is not effective for patients with meningoencephalopathic involvement. Somnolence, or inability to concentrate, may be seen before the CNS is involved. Treatment for CNS late-stage trypanosomiasis is melarsoprol; however, because of potential toxicity, this drug is reserved for late-stage disease only. Metronidazole is used to treat amebiasis, not trypanosomiasis. Sulfadoxine–pyrimethamine and chloroquine are antimalarial and are not used for this indication. Sulfadoxine–pyrimethamine with leucovorin (folinic acid) can also be used to treat *Toxoplasma gondii.*
4. **D.** Metronidazole is the drug most frequently recommended for treatment of this infection. Quinacrine has been used in the past, but because of toxicity and lack of availability it is not a first choice. Albendazole, not mebendazole, has been used with a good outcome in giardiasis. Mebendazole is used to treat roundworm infections. Melarsoprol is used to treat advanced-stage CNS African trypanosomiasis. Mefloquine is an oral drug used to treat chloroquine-resistant malaria. Meglumine antimonate (*Glucantime*) or sodium stibogluconate (*Pentostam*) is used to treat cutaneous or mucocutaneous leishmaniasis by the IV route. Giardiasis, which may be chronic and the cause of malabsorption, sometimes requires multiple stool examinations or a duodenal aspirate. Infection may be through contaminated food or beverages or may be acquired through surface water contaminated by mammals such as beavers. The risk of human infection appears increased in those with reduced gastric acid production.
5. **A.** Liposomal amphotericin B was approved by the U.S. Food and Drug Administration to treat visceral leishmaniasis. Pentavalent antimony compounds, pentamidine, amphotericin B, and aminosidine (paromomycin) have all been demonstrated efficacious here. The liposomal amphotericin appears to be better taken up by the reticuloendothelial system, where the parasite resides, and partitions less in the kidney, where amphotericin B traditionally manifests its toxicity. In addition to being better tolerated by patients, it has proved to be very effective in India, where resistance to antimony drugs is widespread. This patient appears to have acquired his infection there, where many infected patients develop darkening of the skin, hence the name kala-azar, or black sickness. Albendazole, an anthelmintic, has no role here. Atovaquone, a naphthoquinone, is used to treat malaria, babesiosis, and pneumocystosis. Pyrimethamine–sulfadoxine is used to treat malaria and toxoplasmosis. Proguanil inhibits the dihydrofolate reductase of malaria parasites and is used in combination with atovaquone.

SUPPLEMENTAL READING

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CASE Study Malaria and Travel

A 57-year-old medical missionary developed fever, diarrhea, headache, vomiting, and dark urine about 10 days after returning to the United States from a month-long trip to East Africa. The patient has been taking chloroquine and proguanil chemoprophylaxis. On physical examination the patient is feverish, agitated, sweating, weak, and in mild distress, with a blood pressure 95/60 (normal, 120/80), a pulse of 120 (normal, 60–100), and temperature of 104°F (40°C) (normal, 98.6°F, 37°C). Laboratory findings are a hematocrit of 25% (normal for male, 40–54%); platelet count 29,000 (normal, 150,000–400,000/mm^3); parasitemia 6% (*P. falciparum*); serum creatinine 3.5 mg/dL (Normal for male, 0.8–1.5 mg/dL); and plasma glucose 39 mg/dL (Normal fasting, 65–110 mg/dL). What is the best choice of drug therapy?

ANSWER: The first and most important step in managing a patient with fever and occasional gastrointestinal symptoms upon return from a malaria-endemic area is to include it prominently in the differential diagnosis. Any delay in the diagnosis and proper treatment places the patient in peril. Untreated *P. falciparum* in a nonimmune individual can quickly overwhelm the patient in a very short time; hence the name malignant tertian malaria. Severe manifestations heralding unfavorable prognosis include hyperparasitemia greater than 5%, hyperpyrexia above 04°F (40°C), unrousable coma or declining neurological status, severe anemia with a hematocrit below 15%, hypoglycemia with blood glucose less than 40 mg/dL, circulatory collapse with systolic blood pressure less than 70 mm Hg in adults or 50 mm Hg in children, renal failure with serum creatinine more than 3 mg/dL, jaundice with serum bilirubin greater than 3 mg/dL. The treatment of choice in this setting is parenteral quinidine gluconate with frequent monitoring of serum glucose. Quinidine and quinine, as well as hyperparasitemia, can depress circulating glucose levels; this must be corrected. Daily determinations of parasitemia are necessary to follow recovery. If this patient was seen while the parasitemia was low and there were no complications, oral atovaquone–proguanil might have been a therapeutic first choice or mefloquine as a second choice. This case underscores the need to avoid inappropriate chemoprophylaxis in countries where known resistance patterns dictate, since the initiation of aggressive therapy with indicated drugs can be lifesaving. *P. falciparum* does not have persistent liver stages to cause relapses, so there is no need to administer primaquine unless one suspects a mixed infection of *P. vivax*.