CLINICAL MICROBIOLOGY REVIEWS, July 1995, p. 427–439 Vol. 8, No. 3
0893-8512/95/$04.00+0

Human Antiprotozoal Therapy: Past, Present, and Future

MELVIN KHAW AND CLAIRE B. PANOSIAN*

Division of Infectious Diseases, UCLA School of Medicine, Los Angeles, California 90024-1688

* Corresponding author. Mailing address: Division of Infectious Diseases, UCLA School of Medicine, Center for the Health Sciences 37-121, UCLA Medical Center, 10833 Le Conte Ave., Los Angeles, CA 90024-1688. Phone: (310) 206-3096. Fax: (310) 825-3632.

INTRODUCTION

Human protozoal pathogens cause both symptomatic and asymptomatic infections and at some time affect nearly all humans. The significant worldwide impact of diseases resulting from these pathogens is reflected in the long-standing search for antiprotozoal chemotherapy, much of which pre-dates the modern antibiotic era. However, despite the proliferation of antibacterial compounds over the last several decades, many would argue that development of effective treatments for protozoal infections has lagged, being hampered not only by the complexity of protozoan life cycles and host-parasite-drug interactions but also by a low economic incentive to develop new agents. Fortunately, in the 1990s, increased global travel and immigration, as well as heightened awareness of antiprotozoal drug resistance and acute and recrudescent protozoal infections in immunosuppressed hosts, have led to renewed interest in antiprotozoal therapy.

In this review, which is written primarily for nonclinician readers, we have attempted to summarize past and present therapies for common human protozoal infections, as well as promising agents for the future. We have also included brief discussions of pharmacologic mechanisms of action, mechanisms of antiprotozoal drug resistance, and common drug toxicities. For specific antiprotozoal treatment guidelines, including adult and pediatric doses, the reader is referred to a standard pharmacy reference such as the *The Medical Letter* (7). For information regarding the availability of nonlicensed antiprotozoal drugs, the reader is referred to the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA 30333. In addition, nonclinician readers should appreciate that clinical management of patients with protozoal infections often requires diagnostic acumen and judgment in determining appropriate candidates for treatment, as well as adjunct pharmacologic and supportive measures that are beyond the scope of this discussion.

DISEASES CAUSED BY INTESTINAL PATHOGENS

Amebiasis

Entamoeba histolytica is estimated to infect more than 10% of the world's population, primarily in the tropics and regions with poor sanitation. Approximately 10% of those infected will become clinically symptomatic, resulting in an annual toll of 50 million to 100 million cases of invasive colitis and liver abscess and up to 100,000 deaths. Drugs currently used for therapy of amebiasis are iodoquinol, paromomycin, diloxanide furoate, and nitroimidazoles such as metronidazole and tinidazole.

History of chemotherapy. In 1822, Pelletier and Magendie first isolated emetine from ipecac, the Brazil root. After Vedder showed that emetine killed amebae in vitro, successful treatment of humans with both intestinal and hepatic amebiasis by injections of emetine salts was reported in 1912. Many other treatments followed, including chloroquine (in 1948), dehydroemetine (in 1959), tetracyclines, erythromycin, and toxic arsenical compounds (69). More recently, the therapy of amebiasis has been simplified by the introduction of diloxanide furoate (in 1956), paromomycin (in 1959), iodoquinol, and, since 1966, the nitroimidazoles, which are particularly safe and effective in treating invasive forms of infection (122).

Mechanisms of drug action. Iodoquinol (Yodoxin), a halogenated hydroxyquinoline formerly known as diiodohydroxyquin, chelates ferrous ions that are essential for amebic metabolism (69). Diloxanide furoate (Furamide), a directly amebicidal acetanilide, is structurally related to chloramphenicol and may act similarly by inhibiting protein synthesis. Emetine, an alkaloid derived from ipecac, inhibits protein synthesis by affecting movement of ribosomes along mRNA. It is currently believed that metronidazole (Flagyl) affects electron transport and that chemically reactive reduced forms of metronidazole are cytotoxic to parasites (69). Paromomycin (Humatin) is a poorly absorbed aminoglycoside antibiotic whose mechanism of action is unknown.

Current treatment. Agents used to treat amebiasis are divided into tissue amebicides and luminal amebicides. Tissue amebicides such as metronidazole, tinidazole, and emetine kill amebae in host tissues and organs, whereas the poorly absorbed luminal amebicides are active only in the intestinal lumen. The luminal agents currently used are iodoquinol, diloxanide furoate, and paromomycin.

Although many physicians and public health authorities question the need to treat asymptomatic *E. histolytica* cyst passers, the drugs currently available for this indication are iodoquinol and paromomycin, since diloxanide furoate is not licensed in the United States. A course of treatment with iodoquinol is 20 days as opposed to 7 days for the more expensive agent paromomycin (147, 155) and 10 days for diloxanide furoate (178). Diloxanide furoate offers no apparent advantage over the two available agents (90).

Chemotherapy of invasive amebiasis, presenting either as dysentery or as extraintestinal abscess, consists of metronidazole or tinidazole, followed by a luminal amebicide such as iodoquinol or paromomycin. There is no evidence that adding emetine to metronidazole therapy improves the outcome (15). Metronidazole resistance of *E. histolytica* is a theoretical concern which is sometimes mentioned anecdotally in clinical case reports but has not yet been rigorously proven (27, 125).

Drug toxicity. The toxicity of iodoquinol is associated mainly with its iodine component; there have been some reports of neuropathy and blindness after prolonged administration. Diloxanide furoate and paromomycin may cause flatulence and diarrhea. Emetine is a toxic agent associated with cardiac arrythmia, gastrointestinal toxicity, local reactions at injection sites, and neuromuscular reactions. The side effects of metronidazole include nausea, metallic taste, dizziness, intestinal and vaginal yeast overgrowth, and a disulfiramlike reaction (rapid onset of flushing, tachycardia, thirst, nausea, vomiting, hypotension, and blurred vision) when taken concurrently with alcohol. Metronidazole is also potentially carcinogenic, although it has never been conclusively linked to the development of human malignancy.

Drugs on the horizon. Azithromycin, a newly licensed macrolide antibiotic, has shown in vitro activity against *E. histolytica* and has the advantage of enhanced tissue penetration, long half-life, oral administration, and low toxicity (125).

Giardiasis

Giardia lamblia was first recognized by Van Leeuwenhoek in the 1600s and by Vilem Lambl in the 1800s. Although some carriers of *G. lamblia* remain asymptomatic, the organism causes diarrhea worldwide in residents of and travelers to regions with fecally contaminated food and water. In the United States, this protozoan is the most commonly identified intestinal parasite, accounting for 90 waterborne outbreaks of diarrhea between 1964 and 1984 (33). Person-to-person transmission of giardiasis may also occur and has been associated most notably with day care centers, custodial institutions, and oral sexual activity. Drugs used for treatment of giardiasis are quinacrine, furazolidone, paromomycin, nitroimidazoles, and, most recently, the benzimidazoles.

History of chemotherapy. Historically, giardiasis has been treated with mercury, carbon tetrachloride, arsenicals, and bismuth. In the 1930s, quinacrine (Atabrine) became the first truly effective therapy for giardiasis, as well as the leading antimalarial agent used during World War II. Furazolidone and metronidazole were subsequently shown to eradicate *G. lamblia*, along with two other nitroimidazoles, tinidazole and ornidazole (the last two drugs are not currently licensed in the United States). However, many clinicians believe that an ideal drug for *G. lamblia* is still lacking, since quinacrine and metronidazole have frequent side effects and metronidazole and furazolidone are carcinogenic in animals.

Mechanisms of drug action. Quinacrine is an acridine dye derivative which is thought to intercalate into parasite DNA. Metronidazole creates toxic radicals which interfere with DNA replication, and the benzimidazoles affect microtubule formation by targeting β-tubulin (39). The mechanisms of action of furazolidone, a nitrofuran, and paromomycin, a luminally acting aminoglycoside antibiotic, are not known.

Current treatment. Quinacrine was the first effective therapy for giardiasis, achieving cure rates of 95% (179); however, its side effects reduce patient compliance, thereby reducing its overall efficacy. Although still not approved in the United States for treatment of giardiasis, metronidazole is also 85 to 95% effective (78, 180), and the related compounds tinidazole and ornidazole are effective in single doses, thus simplifying therapy (107, 153). Occasional resistance to metronidazole may be mediated by decreased activity of parasite ferrodoxin reductase, resulting in a failure to produce toxic intermediates (165). Furazolidone (Furoxone) is the only agent used to treat giardiasis that is available in a pediatric liquid suspension; the cure rate in children following a 10-day course with this formulation is 92% (102). For treatment of pregnant women with giardiasis, paromomycin has been found safe and effective (71).

Drug toxicity. Compared with other drugs used to treat intestinal protozoa, quinacrine has many side effects, including fever, nausea, vomiting, dizziness, yellow skin discoloration, exacerbation of psoriasis, and psychosis. Metronidazole causes nausea, metallic taste and a disulfiram reaction when taken with alcohol. Furazolidone is associated with nausea, dark urine, diarrhea, mild hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals, and disulfiram reaction; because the drug inhibits monoamine oxidase, patients treated with it must also avoid foods rich in tyramine. Both metronidazole and furazolidone are potentially carcinogenic, although neither drug has been conclusively associated with the development of human malignancies.

Drugs on the horizon. Mebendazole, an antihelmintic benzimidazole introduced in 1971, had a 95% cure rate for giardiasis in one uncontrolled study (3) but no efficacy in another small series (37). A recent trial comparing a single dose and a 5-day course of the more bioavailable related compound, albendazole, found 75 and 97% cure rates, respectively, and minimal side effects (57).

Cryptosporidiosis

Cryptosporidium parvum is a zoonotic coccidian parasite that infects the epithelial cells lining the human digestive tract and causes diarrhea. Cryptosporidiosis is acquired by ingestion of oocysts in contaminated water, by contact with infected animals, and by person-to-person transmission. The true incidence of cryptosporidiosis is unknown, but recent estimates suggest that the organism is a major cause of diarrhea worldwide, causing 250 to 500 million infections annually in Asia, Africa, and Latin America (34). In the immunocompetent host, illness is self-limited; however, in patients with advanced immunosuppression, infection may result in a prolonged, life-threatening cholera-like diarrhea. In Africa and Haiti, up to 50% of patients with AIDS have symptomatic cryptosporidiosis (123), and recent surveys in Baltimore and at the National Institutes of Health have found *C. parvum* infection in 15% of U.S. AIDS patients with diarrhea (75, 149). Although more than 90 drugs have been tried, there is currently no known effective therapy for human cryptosporidiosis.

History of chemotherapy. Some of the therapies recently investigated for treatment of cryptosporidiosis include azithromycin, bovine colostrum, bovine dialyzable leukocyte extract, chloroquine, diclazuril, eflornithine, metronidazole, paromomycin, pentamidine, pyrimethamine, spiramycin, and trimethoprim-sulfamethoxazole. The macrolides and diclazuril, a benzeneacetonitrile derivative, have been shown to be active against related coccidians that infect animals. However, the relationship between host mucosal immunity and successful eradication of *C. parvum*, either spontaneously or pharmacologically, is still poorly understood. In the absence of curative therapy, drugs used for symptomatic treatment of severe diarrhea due to *C. parvum* include opiates, diphenoxylate, loperamide, and somatostatin analogs such as octreotide acetate.

Mechanisms of drug action. The macrolide antibiotics spiramycin and azithromycin target the 50S subunit of the bacterial ribosome, but their specific action on *C. parvum* is unknown (117). The action of paromomycin is also unknown but may affect ribosomal function (88). Bovine dialyzable leukocyte extract, which is prepared from lymph nodes of calves immunized with cryptosporidia, is thought to augment cell-mediated immune response in humans (93). Hyperimmune bovine colostrum contains high titers of anti-cryptosporidium antibodies (bovine immunoglobulin G), which may neutralize intestinal organisms (104).

Current treatment. Spiramycin was the first drug believed to be effective for the treatment of cryptosporidiosis (40, 121); however, subsequent studies have not corroborated this efficacy (116, 176). Some clinical benefit has also been observed with paromomycin (12, 43), eflornithine (α-difluoromethylornithine) (134), hyperimmune bovine colostrum (104, 118, 164), and oral bovine dialyzable extract (93).

Drugs on the horizon. Because azithromycin (with and without paromomycin) has shown promise in treating immunosuppressed rats with cryptosporidiosis (41, 128, 129), a human trial is under way. Letrazuril, a congener of diclazuril with enhanced bioavailability (116), is also undergoing clinical trial. Other drugs with in vitro activity against *C. parvum* are sulfamethoxine (130) and lytic peptides (13).

Microsporidiosis

Microspora are spore-forming intracellular protozoa that cause disease in all five classes of vertebrates, including mammals. The earliest human microsporidial infections due to *Encephalitozoon cuniculi*, *Nosema conori*, *Pleistophora* spp., and *Nosema corneum* were reported in patients with normal immune function or cellular immunodeficiency not related to human immunodeficiency virus coinfection (172). Two new genera and species of microspora, *Enterocytozoon bieneusi* and *Septata intestinalis*, have been identified in intestinal biopsy specimens obtained from $CD4^+$ lymphocyte-depleted AIDS patients with intractable diarrhea similar to that caused by cryptosporidiosis. Rare cases of ocular, respiratory, biliary, hepatic, peritoneal, myositic, renal, and disseminated microsporidian infection have also been reported in AIDS patients. Although there is still no definitive therapy for microsporidiosis, fumagillin blocks replication of *Encephalitozoon cuniculi* in cell culture (145) and clinical reports have described a partial decrease in diarrhea in a small number of AIDS patients with intestinal microsporidiosis treated with metronidazole (23, 108) and octreotide (146). The most promising current therapy for human microsporidiosis due to *Enterocytozoon bieneusi* and *Septata intestinalis* is albendazole, a drug that was recently associated with resolution of diarrhea in 9 of 18 treated AIDS patients and that produced concurrent ultrastructural changes in the parasite in vivo and in vitro (24). (Coinfection with cryptosporidia was found in several nonresponders.) A double-blind placebo-controlled crossover trial of albendazole for intestinal microsporidiosis is under way in two European centers.

DISEASES CAUSED BY INTRAERYTHROCYTIC PATHOGENS

Malaria

Every year, an estimated 120 million clinical cases of malaria occur worldwide, resulting in more than 1 million deaths. Human malaria is caused by four *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, with *P. falciparum* accounting for the majority of deaths. In the United States, approximately 1,000 cases of malaria are reported annually to the Centers for Disease Control and Prevention, divided between returning U.S. travelers and non-U.S. citizens. Between 1980 and 1992, there were 45 reported cases of fatal malaria infection in U.S. civilians, of which 44 (98%) were due to *P. falciparum* and 36 (82%) were acquired in sub-Saharan Africa (28).

Drugs currently available in the United States for prevention or treatment of malaria are chloroquine, quinine, quinidine, tetracycline, pyrimethamine-sulfadoxine (Fansidar), and mefloquine (Lariam). The single most important issue in drug therapy for malaria is single- and multidrug resistance in *P. falciparum*, a growing problem worldwide since the 1960s. Since the 1980s, there has also been evidence for sporadic drug resistance in *P. vivax*.

History of chemotherapy. The modern era of malaria chemotherapy began in the 17th century, when the Countess of Chinchon, wife of a Spanish viceroy in Peru, miraculously recovered from a severe attack of malaria after taking a remedy made from Peruvian tree bark. In 1749, Linnaeus named the tree cinchona to honor the Countess, and in 1820, Caventou and Pelletier isolated the alkaloid quinine from cinchona bark. In 1891, Guttman and Ehrlich discovered that methylene blue had antimalarial activity. Subsequently, many related compounds were synthesized in Germany, resulting in the introduction of quinacrine in 1932. In World War II, quinacrine (Atabrine) was the standard antimalarial agent used by the Allied forces in Asia and the South Pacific. Chloroquine was synthesized in the 1930s and later replaced quinacrine as the drug of choice for the prevention and treatment of malaria. In response to growing chloroquine resistance first noted in the 1960s, quinine has now been reintroduced into widespread use. Other antimalarial drugs currently used worldwide are proguanil (Paludrine), which is not licensed in the United States, tetracyclines, and sulfonamides. The newest agents are mefloquine (Lariam) and halofantrine (Halfan), both developed by the U.S. Army, and artemisinin compounds extracted from the traditional medicinal herb qinghaosu, which has been used for febrile illnesses in China since 341 AD and was rediscovered in 1971 to have antimalarial activity (62).

Mechanisms of drug action. Antimalarial agents are divided into sporonticides, gametocides, and schizonticides. The schizonticides are further divided into blood schizonticides and tissues schizonticides. Blood schizonticides such as quinine, chloroquine, and mefloquine will by themselves treat infection due to *P. falciparum* and *P. malariae*, whereas a tissue schizonticide such as primaquine must be added to achieve radical cure in infections due to *P. vivax* and *P. ovale*, which involve both the bloodstream and the liver.

Quinine, the earliest antimalarial drug, is rapidly active against asexual erythrocytic stages of all *Plasmodium* species that infect humans. It is also gametocidal for all species except *P. falciparum*. Quinine was once thought to kill malaria parasites by intercalation into parasite DNA, thus inhibiting DNA and RNA synthesis. Now it is believed that its mechanism of action is similar to that of chloroquine (see below). Quinidine, an antiarrythmic drug, is the dextrarotary optical isomer of quinine. Because parenteral quinine is no longer available in the United States and quinidine is two- to threefold more active than quinine, intravenous quinidine is often used to treat patients with severe or complicated infection due to *P. falciparum* (95, 175).

Plasmodia derive essential amino acids from the degradation of host erythrocyte hemoglobin. Since ferritoprotoporphyrins (hemoglobin degradation products) are toxic to membranes, the parasite sequesters these products as hemazoin (malarial pigment). It is currently believed that both chloroquine and quinine act by forming a complex with ferritoprotoporphyrin IX, preventing hemazoin sequestration and resulting in cell lysis (50, 135). Chloroquine may also alkalinize malaria food vacuoles, resulting in inhibition of parasite digestive enzymes and decreased parasite growth (73). Resistance to chloroquine in *P. falciparum* occurs by means of accelerated drug efflux, since resistant strains expel chloroquine up to 50 times faster than susceptible strains do (72).

Mefloquine, a synthetic quinolinemethanol which, like quinine, is active against asexual erythrocytic stages of all *Plasmodium* species, binds strongly to erythrocyte membranes. Although its precise antimalarial action is unknown, mefloquine is active against chloroquine-resistant strains, with the exception of certain mefloquine-resistant strains of *P. falciparum* now identified in Southeast Asia (106).

The mechanisms of action of other antimalarial drugs include inhibition of protein synthesis by effects on ribosomal subunits (tetracycline) and the inhibition of folate metabolism (pyrimethamine and sulfonamides). Resistance to antifolate drugs has been linked to specific point mutations in the parasite dihydrofolate reductase-thymidylate synthetase enzyme (56). Halofantrine, a 9-phenanthrenemethanol, is thought to bind to ferritoprotoporphyrin IX like chloroquine but may also

affect mitochondria (5). Artemisinin derivatives are sesquiterpenes which are very rapidly acting schizonticides that react with heme, causing free-radical damage to parasite membranes (94). Primaquine, used only as adjunct therapy for radical cure of infections due to latent liver stages of *P. vivax* and *P. ovale*, is an 8-aminoquinoline derivative of methylene blue whose mechanism of action is unknown.

Current treatment. *P. falciparum* malaria in U.S. travelers and foreign expatriates is a potentially lethal infection, which should be considered a true medical emergency. Consequently, patients must be counselled to obtain prompt medical care if they become ill during or after visiting an area where malaria is endemic, and physicians must perform appropriate diagnostic workup on all travelers and foreign expatriates with a history of exposure to malaria and a compatible clinical syndrome. In selecting treatment, the precise identification of the infecting *Plasmodium* species and a knowledge of current geographic patterns of drug resistance are critical.

The current treatment of choice for malaria due to *P. vivax*, *P. ovale*, and *P. malariae* is chloroquine, which can be administered orally or parenterally. A subsequent course of oral primaquine is recommended for patients with infection due to *P. vivax* and *P. ovale* to prevent recrudescence by exoerythrocytic parasites in the liver. A relatively primaquine-resistant form of *P. vivax* (also known as the Chesson strain) has been present in Asia for several decades (31), and, more recently, chloroquine-resistant *P. vivax* has been reported in Indonesia (19, 133) and Brazil (47).

Because chloroquine-resistant *P. falciparum* is now present in every continent affected by malaria, almost all patients diagnosed with *P. falciparum* in the United States are treated with drugs other than chloroquine. Standard treatment in patients who are not critically ill is oral quinine combined with another drug such as tetracycline (32), clindamycin (97, 142), or pyrimethamine-sulfadoxine (Fansidar), since quinine alone may fail to achieve radical cure in patients infected with strains of *P. falciparum* that are partially quinine resistant (now present in Africa and Asia). In Eastern Thailand, where multidrug resistance is well established, quinine-tetracycline is superior to quinine-Fansidar (126). Mefloquine is also used for treatment of chloroquine-resistant *P. falciparum* (58), although the cure rate when using mefloquine combined with sulfapyrimethamine at a focus of extreme *P. falciparum* resistance at the Thai-Burmese border decreased from 98% in 1985 to 71% in 1990 (106).

Additional drugs for treatment of *P. falciparum*, although not currently available in the United States, are halofantrine and several artemisinin compounds. In early clinical trials, halofantrine produced cure rates of 83 to 100%, with most failures attributed to inadequate drug levels due to poor absorption (25). Compared with quinine, halofantrine has the advantage of a more convenient dosing schedule and better taste, but, like mefloquine, it is expensive. Preliminary data suggest that resistance to mefloquine and halofantrine may be linked (25).

In studies conducted overseas, artemisinin compounds have produced rapid parasite clearance and therapeutic responses in patients with malaria, although late recrudescence of parasitemia has been noted in up to 85% of patients treated for *P. falciparum* and 31% of patients treated for *P. vivax* infection with the oral drug, artemisinin (62). When given to comatose patients with cerebral malaria, artemisinin suppositories were equal in efficacy to intravenous artesunate and intravenous quinine, although neither artemisinin compound was superior to quinine in reducing the duration of coma or the mortality rate (61). At the Thai-Burmese border, treatment of multidrug-resistant *P. falciparum* infection with a 3-day course of oral artesunate combined with mefloquine was 98% effective at 28-day follow-up compared with 69% after treatment with high-dose mefloquine alone (101). Comparative trials of different oral and parenteral compounds in the artemisinin class (artemisinin, artesunate, artemether, arteether, and artelinic acid) have not yet been conducted.

In the United States, treatment of severe infection due to *P. falciparum* consists of intravenous quinidine administered in a cardiac-monitored unit, followed by oral tetracycline or clindamycin. Some authors recommend the use of exchange transfusion in nonimmune expatriates with parasitemias exceeding 15% (95); however, survival without exchange transfusion has been reported in parasitemias exceeding 50% (87). In addition to antimalarial agents, specific therapies and supportive measures for hypoglycemia, pulmonary edema, renal failure, seizures, and coma may be required for the management of severe and complicated malaria (182). Corticosteroids have no proven benefit in *P. falciparum*-infected patients with cerebral malaria (63, 171).

Prophylaxis. Like treatment, the selection of antimalarial chemoprophylaxis is based upon regional patterns of antimalarial drug resistance, which must be regularly monitored. Updated recommendations for malaria chemoprophylaxis may be obtained 24 h a day by calling a travel information line at the Centers for Disease Control and Prevention (404-332-4555). A standard reference for malaria prophylaxis is published yearly by the Centers for Disease Control and Prevention (28).

Currently, weekly chloroquine remains an effective regimen for prophylaxis in Central America, Mexico, and the Middle East. In most other regions, where chloroquine-resistant strains of *P. falciparum* are present, preferred preventive regimens include weekly mefloquine (79, 80), daily doxycycline (109, 110), or weekly chloroquine plus daily proguanil. The last regimen is more effective than chloroquine alone in Africa but has been ineffective in Papua New Guinea and Thailand (28).

Because chloroquine and mefloquine are purely blood schizonticides, they are considered suppressive prophylactic agents. Causal prophylactic agents have tissue schizonticidal activity; examples include doxycycline and primaquine. Following long-term exposure in malarious areas where *P. vivax* or *P. ovale* are present, a 2-week course of primaquine as terminal prophylaxis is recommended to eradicate any remaining liver stages of the parasite. However, primaquine should not be prescribed until laboratory testing has verified that G6PD levels are normal.

In patients who are either unwilling or unable to take standard chemoprophylaxis or those who will have limited access to medical care, a single course of medication for self-treatment of malaria is often provided. Self-treatment is indicated when travelers experience a febrile illness consistent with malaria and are unable to reach medical care within 24 h. In this setting, the drug of choice is Fansidar, unless there is a history of intolerance to sulfonamides. The routine weekly use of Fansidar as a preventive regimen was discontinued in the 1980s following reports of an excessive number of severe cutaneous allergic reactions caused by the long-acting sulfadoxine component of the drug (96). Mefloquine should not be used for self-treatment because of its high frequency of side effects when administered in full treatment dosage. Halofantrine should also not be used for self-treatment because of potentially serious electrocardiographic changes (6). Self-treatment for possible malaria is a temporary measure which must always be followed by professional medical evaluation.

Drug toxicity. In comparison with most other antimalarial agents, quinine is toxic. Side effects include bitter taste, hypersensitivity reactions, tinnitus, decreased hearing, visual distur-

bance, nausea, abdominal pain, and tremors. Overdose can result in coma, cardiac toxicity, and death. Chloroquine causes nausea, diarrhea, dizziness, blurred vision, pruritus, and exacerbation of psoriasis. Primaquine may also cause nausea and abdominal cramps, as well as hemolysis in G6PD-deficient individuals. Side effects of mefloquine include nausea, bradycardia, depression, dysphoria, hallucinations, and psychosis; the drug is currently contraindicated in patients with a history of seizure, psychosis, or cardiac arrythmia or a requirement for fine motor coordination (for example, airline pilots). Sulfonamides cause allergic skin reactions, and tetracyclines produce discoloration of teeth in children, photosensitivity, and yeast overgrowth. Halofantrine has caused electrocardiographic abnormalities, including life-threatening ventricular arrythmia and prolongation of the Q-T interval in patients with preexisting conduction disorders, recent or concurrent mefloquine therapy, and thiamine deficiency (6). Primaquine and tetracycline are contraindicated in pregnancy; the manufacturer of mefloquine also advises against conception during and 6 months following use of the drug, although teratogenicity has not been proven.

Babesiosis

Babesiosis is an intraerythrocytic protozoan infection of mammals and is transmitted to humans by ticks. Serious and sometimes fatal infections due to *Babesia divergens* and *Babesia bovis* were first described in splenectomized patients in Europe in 1956; this was followed in the 1960s by reports of somewhat milder clinical disease due to *Babesia microti* acquired in the northeastern United States. In the ensuing three decades, hundreds of human infections have been acquired through infective tick bites in coastal New England and eastern Long Island, as well as sporadic cases in Wisconsin and California, and transmission of babesiosis by blood products has also occurred (119). Although seroepidemiologic studies suggest that many infections due to *B. microti* in the United States are either asymptomatic or subclinical, severe and even life-threatening infections characterized by malaria-like fevers, hyperparasitemia, and hemolytic anemia are seen in asplenic, immunocompromised, and elderly patients. The current therapy for symptomatic babesiosis is quinine and clindamycin, sometimes supplemented with exchange transfusion.

History of chemotherapy and current treatment. In 1909, trypan blue was the first compound used successfully to treat bovine babesiosis; it was followed by quinoline and aromatic diamidine derivatives such as diminazene and pentamidine. When the first 14 human cases of *B. microti* infection were diagnosed in the United States, almost all were treated with oral chloroquine phosphate, resulting in symptomatic improvement but no apparent change in the degree or duration of parasitemia (137). An immunocompetent patient who failed to defervesce after treatment with chloroquine then received intramuscular diminazene, a regimen that cleared the parasitemia (assessed by an in vivo hamster assay) but resulted in severe ascending polyneuritis (138). Other patients with babesiosis who were treated with pentamidine isethionate have demonstrated clinical improvement and decreased parasitemia but no true eradication of parasites in the hamster assay (45), with the exception of one otherwise healthy patient in France, whose *B. divergens* infection responded promptly to a combination of pentamidine and cotrimoxazole (124).

The current regimen of choice for clinically symptomatic babesiosis in the United States is quinine plus clindamycin, a treatment supported by animal studies and isolated clinical cases that suggest a low likelihood of recurrent parasitemia following treatment with this synergistic combination of drugs (136, 177). However, some immunosuppressed individuals with asplenia, concurrent corticosteroid treatment, and/or human immunodeficiency virus infection have failed to respond to these agents alone (66, 85, 150), instead requiring exchange transfusion to physically clear peripheral parasites. For patients with babesiosis and progressively declining immune function, long-term maintenance with quinine, clindamycin, or tetracycline is sometimes necessary to prevent relapse following treatment of the acute infection.

Drugs on the horizon. Azithromycin, a newly licensed macrolide antibiotic, has suppressed *B. microti* parasitemia in a hamster model of infection when used both singly and in combination with quinine (174). In the same report, the authors relate anecdotal reports of human immunodeficiency virus-infected patients with babesiosis that was successfully treated with quinine and azithromycin (174).

DISEASES CAUSED BY OTHER BLOOD AND TISSUE PATHOGENS

African Trypanosomiasis

Human African trypanosomiasis (sleeping sickness) is a systemic and central nervous system (CNS) infection caused by two geographically distinct subspecies of trypanosomes: *T. brucei gambiense* (West Africa) and *T. brucei rhodesiense* (East Africa). The infection is transmitted by tsetse flies and currently occurs in 36 African countries between latitudes 14°N and 29°S, placing at least 50 million people at risk and resulting in 25,000 new cases every year. Although West African disease is more indolent than East African disease, both infections are ultimately fatal if untreated. Drugs currently used to treat African trypanosomiasis are suramin, pentamidine, melarsoprol, eflornithine, and, experimentally, diminazene and nifurtimox.

History of chemotherapy. Arsenic, a cornerstone of treatment for human trypanosomiasis affecting the CNS, was first used by the famous missionary-explorer David Livingstone to treat the analogous disease in horses (nagana) in 1847 or 1848. Arsenicals were later synthesized for human use by Ehrlich and gradually modified to decrease toxicity; by the end of World War II, melarsoprol B, a trivalent arsenical currently in use, was introduced. Suramin, a sulfated naphthylamine, and pentamidine, an aromatic diamidine, are both effective only against the bloodstream stages of *T. brucei*; they were introduced in 1920 and 1939, respectively. Eflornithine, the only new drug developed and approved for African trypanosomiasis in 40 years, was first used for Gambian sleeping sickness in the mid-1980s (167).

Mechanisms of drug action. Organic arsenicals interfere with protein sulfhydryl groups found in enzymes of carbohydrate metabolism; therefore, it is thought that the primary action of melarsoprol is to disrupt parasite glycolysis. Selectivity has been attributed to preferential binding affinity to parasite pyruvate kinase, greater dependence of the trypomastigote on glycolysis to generate ATP, and higher concentration of the drug in trypomastigotes as opposed to mammalian cells (55). The antitrypanosomal actions of suramin and pentamidine are not fully known, but suramin appears to inhibit enzymes involved in NADH oxidation and pentamidine is a potent inhibitor of nucleic acid biosynthesis (55). Eflornithine is a specific, irreversible inhibitor of ornithine decarboxylase, an enzyme required for parasite polyamine synthesis (148).

Current treatment. Prior to the initiation of antitrypanosomal therapy, it is crucial to determine whether CNS invasion

has occurred. This is accomplished by means of a baseline neurologic examination and cerebrospinal fluid analysis. If there is no indication of CNS involvement, either suramin or pentamidine may be used, although cure rates with pentamidine are lower, especially in infections due to *T. brucei rhodesiense* (20). Suramin must be freshly constituted and administered by slow intravenous injection; the usual adult regimen following a test dose is five individual doses of 1 g each (20). Pentamidine is given intramuscularly or intravenously daily or on alternating days until 10 doses have been administered (20). Diminazene aceturate (Berenil) has also been successful in treatment of early hematolymphatic cases of trypanosomiasis in East Africa (1), but the compound is manufactured for veterinary use only and is not currently recommended for therapy of infected humans.

Melarsoprol crosses the blood-brain barrier and is therefore effective in all stages of trypanosomiasis, but its use has been restricted by severe toxicity, which can include fatal reactive encephalopathy. For this reason, melarsoprol is never used as first-line therapy for non-CNS disease, although it may be indicated for use in relapsing hematolymphatic disease which follows treatment with suramin or pentamidine. Melarsoprol remains the drug of choice for treating late-stage CNS disease due to *T. brucei rhodesiense*. Because it is insoluble in water, melarsoprol must be mixed in propylene glycol for administration; it is given as a daily intravenous injection in 3-day cycles which are repeated at weekly intervals (20). To minimize CNS toxicity, the dose of melarsoprol is sometimes adjusted downward when particularly high cell counts or protein concentrations are present in cerebrospinal fluid (132).

Eflornithine has been highly effective (>90%) in several trials of late-stage (CNS) disease due to *T. brucei gambiense* (38, 98, 113, 156), but it appears to be ineffective in infections due to *T. brucei rhodesiense* because of the high percentage of naturally resistant parasites (17). Its usefulness in Africa is also limited by its relatively high cost and the logistics of drug administration (intravenous dosing every 6 h for the first 2 weeks of treatment, followed by several weeks of oral therapy). However, eflornithine has been effective in treating some patients with West African trypanosomiasis who have failed to respond to initial therapy with melarsoprol (relapse occurs in up to 17% of *T. brucei gambiense* CNS infections) (112). Nifurtimox, an orally administered nitrofuran given at 15 to 30 mg/kg/day for 1 to 2 months, has also produced 31 to 80% cure rates in patients with West African trypanosomiasis who have relapsed after melarsoprol therapy (100, 114, 115).

Drug toxicity. Suramin produces an immediate, idiosyncratic reaction in 1 in 2,000 to 1 in 4,500 recipients, which sometimes leads to cardiovascular collapse and death. More common adverse effects include nephrotoxicity, hemolytic anemia, rash, agranulocytosis, peripheral neuropathy, optic atrophy, and adrenal insufficiency. Patients receiving suramin should be monitored for proteinuria.

Pentamidine is associated with hypoglycemia, nephrotoxicity, orthostatic hypotension and sterile abscess at the site of intramuscular injection.

Melarsoprol is most feared for posttreatment reactive encephalopathy, which occurs in 1 to 10% of treated patients, manifesting with fever, headache, seizures, and coma, with death occurring in as many as 10% of those affected. One proposed mechanism for the pathogenesis of posttreatment reactive encephalopathy is subcurative therapy, leading to persistence of parasites in the CNS (64). Some investigators believe that corticosteroids may suppress posttreatment reactive encephalopathy (112), although this remains controversial (14). Other adverse effects of melarsoprol include phlebitis due to extravasated propylene glycol, Herxheimer reactions, fever, chest pain, abdominal pain, and an altered sense of smell.

Eflornithine, in contrast to other antitrypanosomal drugs, is relatively well tolerated, although mild diarrhea, abdominal pain, anemia, alopecia, and hearing loss have been reported as side effects of treatment. Nifurtimox is believed to have direct central and peripheral neurotoxicity (independent of its effect on CNS trypanosomes), as well as other constitutional side effects and precipitation of hemolysis in G6PD-deficient patients. Chromosomal aberrations have also occurred in children treated with nifurtimox for Chagas' disease (51).

Drugs on the horizon. In an experimental mouse model of *T. brucei* infection, combinations of suramin and eflornithine, melarsoprol and eflornithine, and nifurtimox and melarsoprol have shown promise; suramin plus eflornithine is now being evaluated in humans (67). Other antitrypanosomal compounds with efficacy in the mouse model are the spiroarsoranes (pentavalent arsenicals with less toxicity than trivalent arsenicals) (81) and some newly synthesized dihydroxybenzamides with specific inhibitory activity against trypanosomal alternative oxidase (52).

American Trypanosomiasis (Chagas' Disease)

American trypanosomiasis (Chagas' disease) is caused by the hemoflagellate *Trypanosoma cruzi*, a parasite with a large zoonotic reservoir in South and Central America. The organism is usually transmitted to humans by blood-sucking triatomine (reduvid) bugs that deposit infective feces at the site of a bite or mucosal surface; however, transmission may also occur transplacentally or via human blood products. Resulting clinical syndromes include local inflammation at the site of inoculation, acute myocarditis, encephalitis, and multiorgan infection. Years to decades following initial infection, complications involving the heart and the autonomic nervous system occur in 10 to 30% of seropositive individuals. In areas where the disease is endemic, 10 to 20 million people are currently estimated to be chronically infected with *T. cruzi*, resulting in 50,000 deaths per year; in the United States, the human reservoir includes 50,000 to 100,000 seropositive immigrants (8).

Two experimental drugs, nifurtimox and benznidazole, are partially effective in clearing *T. cruzi* parasitemia during acute infection. Nifurtimox, benznidazole, and allopurinol have also been used for late-stage disease, although the efficacy of treatment for chronic infections remains uncertain. Since blood transfusions constitute an important means of transmission of *T. cruzi* in areas where the disease is endemic, chemoprophylaxis of blood with crystal (gentian) violet is a common practice; other means of blood sterilization with amphotericin B or gamma radiation appear promising on the basis of experimental work (144).

Mechanisms of action and current treatment. Nifurtimox (Lampit, Bayer 2502), a 5-nitrofuran first used in 1976, is thought to cause breaks in parasite DNA, generate superoxide, and inhibit parasite-specific antioxidant defenses (168). Benznidazole (Radamil, Roche 7-1051), introduced in 1978, is a 2-nitroimidazole, less well studied than nifurtimox, that also blocks nucleic acid and protein synthesis (168). Both drugs reduce the duration and clinical severity of acute and congenital *T. cruzi* infection, but they effect total parasite clearance in only 50% of treated patients (68). In addition, both drugs are associated with a marked variation in efficacy according to geographic region, suggesting that parasite strain differences, compounded by inducible drug resistance, may be important factors in treatment outcome (4). During acute infection, ni-

furtimox and benznidazole are given orally for 3 to 4 months and 1 to 4 months, respectively.

For patients chronically infected with *T. cruzi*, treatment is more controversial. The assessment of treatment outcome is confounded by naturally low or undetectable parasitemia, variable seroreactivity, and unpredictable clinical progression on a case-by-case basis. In addition, because the late cardiac and gastrointestinal sequelae of *T. cruzi* infection may be autoimmune mediated (141), late antiparasitic treatment may not truly alter the natural history of disease. Despite these facts, in Latin America, both nifurtimox and benznidazole are used for chronic *T. cruzi* infection without benefit of controlled or prospective data. One retrospective study with an average 8-year follow-up documented a lower frequency of electrocardiographic changes in 131 Argentinian patients treated with benznidazole than was seen in 70 untreated controls (169). In another open study comparing allopurinol (an inhibitor of hypoxanthine oxidase active against *T. cruzi* in mammalian cell culture and experimentally infected mice) (16) with benznidazole and nifurtimox, all three agents were found to reduce parasitemia and induce seronegativity in a group of chronically infected Argentinian patients; however, no long-term benefits were attributed by the authors to any specific therapy (46).

Drug toxicity. Nifurtimox and benznidazole are both associated with significant toxicity, including almost universal gastric upset, anorexia, and weight loss, as well as a high incidence of photosensitive skin rashes, peripheral neuritis, and bone marrow depression. Nifurtimox also induces hemolysis in G6PD-deficient individuals. In rabbits exposed to benznidazole and nifurtimox, invasive lymphomas developed in 42 and 33%, respectively, as opposed to no tumors in control animals (157, 158); however, no comparable pattern of oncogenesis has been observed in humans treated with these drugs. Allopurinol is relatively free of side effects except for allergic skin rashes and other clinical manifestations of drug hypersensitivity.

Drugs on the horizon. *T. cruzi* is susceptible to ergosterol biosynthesis inhibitors such as ketoconazole; however, in murine models of *T. cruzi* infection, the levels of ketoconazole required to prevent mortality and clear parasitemia extrapolate to levels which, in humans, are likely to interfere with the production of steroid hormones, particularly testosterone. This problem has been addressed by combining ketoconazole with a second ergosterol inhibitor, terbinafine, or, alternatively, the glutaryl coenzyme A reductase inhibitor mevinolin (Lovastatin) to produce synergistic killing of *T. cruzi* (86, 166).

Another immunologic strategy to accelerate clearance of *T. cruzi* parasitemia is the use of recombinant gamma interferon (IFN-γ) an agent which has reduced the severity of acute experimental infection in mice (127). To date, two human patients with acute Chagas' disease have received IFN-γ in combination with nifurtimox and have recovered (68).

Leishmaniasis

Every year, according to current World Health Organization estimates, there are 400,000 new cases of human leishmaniasis in Asia, Africa, the Mediterranean basin, the Middle East, and the Americas. The spectrum of clinical syndromes caused by *Leishmania* spp. includes local infections of skin, subcutaneous tissue, and regional lymph nodes (cutaneous leishmaniasis); metastatic infections of the oronasal mucosa (mucocutaneous leishmaniasis, or espundia, found primarily in South America); and disseminated infection involving visceral organs of the mononuclear phagocyte system (visceral leishmaniasis, or kala azar). In each case, the syndrome is initiated by the bite of an infected sandfly which inoculates extracellular (promastigote) forms of the parasite into the skin of the patient; however, once introduced into the mammalian host, the parasite proliferates solely as an intracellular amastigote within cells of the monocyte-macrophage line. Although many cases of cutaneous leishmaniasis do not require specific treatment and some cases of visceral leishmaniasis are clinically latent, drug therapy may be required for any form of the disease. Standard drugs currently used for leishmaniasis include pentavalent antimony, pentamidine, amphotericin B, allopurinol, and the ergosterol inhibitors ketoconazole and itraconazole; in selected cases, topical therapies and immunotherapy have also been used.

History of chemotherapy and mechanisms of drug action. In 1912, the first case of cutaneous leishmaniasis to be successfully treated with tartar emetic (potassium antimony tartrate) was reported by a young Brazilian physician, G. Vianna. A few years later, the same compound was used to treat visceral leishmaniasis in Italy and Asia. Pentavalent antimonials became available in the 1920s, and sodium stibogluconate was introduced in 1945. At present, the pentavalent antimonials sodium stibogluconate (Pentostam) and *N*-methylglucamine antimonate (Glucantime) remain the mainstays of antileishmanial therapy; they act by inhibiting parasite glycolysis and fatty acid oxidation, leading to decreased energy and reducing equivalents for antioxidant defense within the amastigote.

Other drugs currently used to treat leishmaniasis are pentamidine, which may inhibit parasite polyamine synthesis or interfere with kinetoplast DNA; amphotericin B, which increases membrane permeability of leishmaniae by combining with ergosterol; allopurinol, a structural analog of hypoxanthine which inhibits amastigote metabolism by interfering with the production of ATP; and the N-substituted imidazoles ketoconazole and itraconazole, which interfere with parasite-specific demethylation of sterols (168).

Current treatment of cutaneous leishmaniasis. The treatment of cutaneous leishmaniasis is often subdivided according to the geographic origin of the infecting parasite. In general, lesions of Old World cutaneous leishmaniasis, which are caused by *L. tropica*, *L. major*, and *L. aethiopica*, are unlikely to require specific therapy, often healing spontaneously over weeks to months. However, in patients with large or multiple lesions or in patients with lesions in functionally or cosmetically sensitive areas, pentavalent antimonial agents are usually effective when given parenterally at a dose of 10 to 20 mg of antimony per kg per day for 2 to 4 weeks. Intralesional sodium stibogluconate and local heat therapy have also been used with some success, although controlled trials are lacking. The orally administered imidazoles, ketoconazole and itraconazole, have been promising in limited human studies (2, 173). Diffuse cutaneous leishmaniasis, a syndrome unique to Ethiopia and Kenya which results from the absence of specific cell-mediated immunity to leishmanial antigens, is often refractory to treatment with antimony and may require prolonged weekly injections of pentamidine for clinical regression or cure.

New World cutaneous leishmaniasis is caused primarily by parasites of the species *L. mexicana* and *L. braziliensis*; infection by organisms of the latter group may lead to destructive oral, nasal, or pharyngeal lesions called mucocutaneous leishmaniasis or espundia. As with Old World cutaneous infections, antimony is the drug of choice, but recent clinical experience favors the higher dose of 20 mg/kg/day (60). Some strains of New World cutaneous leishmaniasis are resistant to antimony (53); when resistance is clinically or microbiologically suspected, pentamidine (2 mg/kg every other day for four to seven doses) is often an effective alternative (151, 152). The experience with imidazoles is more limited and contradictory: in Central America, ketoconazole cured 16 of 21 patients in-

fected with *L. panamensis* and 8 of 9 patients infected with *L. mexicana* (103, 140), but 20 patients with *L. panamensis* infection acquired in Panama treated with itraconazole had no better outcome than did nontreated controls (152). Because of its greater virulence and potential for metastatic spread, most authors recommend that *L. braziliensis* infection be treated only with parenteral antimony or pentamidine or, in the case of clinical relapse, amphotericin B.

Current treatment of visceral leishmaniasis. As with other agents of leishmaniasis, the first line of treatment for infections due to the visceralizing species *L. donovani* and *L. chagasi* is pentavalent antimony. Because of increasing antimony resistance, the minimum course for a typical case is 20 mg of antimony per kg per day for ≥20 days (181); in India, where resistance occurs in at least 10% of all cases, a regimen of 20 mg of antimony per kg per day for ≥40 days is currently recommended (159). The addition of allopurinol to antimony has produced variable results in small clinical trials in Kenya, India, and the Mediterranean, although synergy of the two drugs has been demonstrated in vitro (36).

Pentamidine is also effective in visceral leishmaniasis when used at a dose of 4 mg/kg thrice weekly (160). In patients who previously failed to respond to antimony therapy, a comparative trial of pentamidine (4 mg/kg every other day for ≥40 days) and amphotericin B (0.5 mg/kg/day for 2 weeks) resulted in 77 and 98% cure rates, respectively (99). Most recently, an Indian trial evaluating amphotericin B (total dose, 20 mg/kg) as a first-line drug for visceral leishmaniasis found a 6-month cure rate of 100% in 75 patients (162).

Because T-cell suppression leads to reduced levels of interleukin-2 and IFN-γ in patients with visceral leishmaniasis, recombinant IFN-γ has been added to pentavalent antimony in small clinical trials in Brazil and Kenya (18, 154). These early studies suggest that the addition of IFN-γ may cure patients previously unresponsive to multiple courses of antimony alone and that the addition of IFN-γ may also accelerate the clearance of splenic parasites in first-time-treated patients. The major drawback of immunotherapy is expense. IFN has been unsuccessful in treating visceral leishmaniasis in one patient coinfected with the human immunodeficiency virus (82).

Drug toxicity. The major toxicity associated with pentavalent antimony is cardiac, often manifesting with acute electrocardiographic changes and arrythmia directly related to the cumulative dose of drug administered. Other side effects include sterile abscesses at sites of intramuscular injection, venous thrombosis after intravenous administration, renal and hepatic effects, myalgia, arthralgia, anorexia, vomiting, and headache. Pentamidine can lead to sterile abscesses, hypoglycemia, nephrotoxicity, and orthostatic hypotension. Amphotericin B, a drug which is administered only intravenously, frequently produces acute fever, chills, phlebitis, and hypotension during its infusion, as well as hypokalemia, hypomagnasemia, and cumulative dose-related nephrotoxicity. The major adverse effects of allopurinol are skin rash and hypersensitivity reactions. The orally administered imidazoles produce nausea, vomiting, hepatotoxicity, and, in the case of ketoconazole specifically, decreased testosterone levels leading to male gynecomastia and diminished libido.

Drugs on the horizon. Ketoconazole has been used in isolated cases of visceral leishmaniasis with variable success (36), including in some patients with antimony- and pentamidine-resistant infections (170). Aminosidine, also known as paromomycin, is an aminoglycoside with significant antileishmanial activity in vitro and in animal models; use of the drug either singly or in combination with antimony has yielded favorable results in patients with *L. donovani* infections acquired in Kenya, India, the Sudan, and the Mediterranean region (36, 143, 161). Liposomal amphotericin B was successful in treating visceral leishmaniasis in two human immunodeficiency virus-positive Spanish patients (163). A final drug in the early stages of clinical evaluation for treatment of visceral leishmaniasis is the oral 8-aminoquinolone, WR 6026 (36).

Toxoplasmosis

Toxoplasma gondii is a worldwide zoonotic pathogen whose definitive host is the cat. Secondary hosts include humans and a broad range of herbivorous and carnivorous mammals that can acquire toxoplasmosis directly by ingestion of fecal oocysts shed by infected cats or, indirectly, by ingestion of cyst-containing meat. In addition, transmission of *T. gondii* to humans can occur by congenital passage of organisms, organ transplantation, blood transfusion, and laboratory accident (self-inoculation) (22). After the acute phase of infection, infected humans have tissues cysts 10 to 200 μm in diameter, most frequently located in the myocardium, skeletal muscle, and CNS. Reactivation of chronic infection from latent cysts occurs almost exclusively in patients with severe, underlying immunosuppression.

In immunocompetent adults, only 10 to 20% of acute *Toxoplasma* infections are symptomatic. However, congenitally infected neonates and immunodeficient hosts with acute or reactivation disease may have severe multiorgan involvement affecting the brain, heart, liver, lungs, and eyes. In patients with AIDS, toxoplasmic encephalitis is one of the most frequent CNS infections, affecting 3 to 10% of AIDS patients in the United States and 25 to 50% of AIDS patients in Europe, Africa, and Haiti; it usually occurs when the $CD4^+$ lymphocyte count falls below 100/mm^3 (83). The primary drugs used for treatment of toxoplasmosis are pyrimethamine, sulfadiazine, and clindamycin.

History of chemotherapy. In 1955, sulfonamides were first used alone and in combination with pyrimethamine to treat experimental murine toxoplasmosis. In subsequent animal studies, trimethoprim-sulfamethoxazole was shown to be less effective than pyrimethamine-sulfonamide (54). In the 1980s, the macrolide antibiotics clindamycin and spiramycin were commonly used in mild cases of toxoplasmosis. However, with the increasing number of AIDS- and immunosuppression-related infections, pyrimethamine in combination with either sulfadiazine or clindamycin is now the regimen of choice. Although these combinations are considered synergistic, pyrimethamine as sole therapy compared with pyrimethamine-sulfadiazine or pyrimethamine-clindamycin has never been studied in a controlled, prospective fashion. Other drugs recently used for toxoplasmosis are atovaquone, trimetrexate, dapsone, azithromycin, and clarithromycin.

Mechanisms of drug action. Of the folate antagonists, sulfadiazine and dapsone inhibit dihydropteroate synthetase and pyrimethamine and trimetrexate inhibit dihydrofolate reductase, thereby killing or inhibiting extracellular forms of *T. gondii*. Although clindamycin exerts antibacterial effects by inhibition of protein synthesis (74), the mechanism of action of clindamycin and other macrolides (clarithromycin, azithromycin, and roxithromycin) against *T. gondii* is unknown. Atovaquone, a hydroxynaphthoquinone, is thought to interfere with electron transport and pyrimidine synthesis. With the possible exception of atovaquone and azithromycin, no antimicrobial agent has been effective against the tissue cyst form of *T. gondii* (11, 65).

Current treatment and prophylaxis. Immunocompetent hosts with acute acquired toxoplasmosis rarely require treat-

ment, unless there is evidence of severe visceral organ involvement or a prolonged systemic illness. One notable exception is infection acutely acquired during pregnancy, when spiramycin (available from the U.S. Food and Drug Association) in a dose of 3 g/day appears to reduce fetal infection by 60% (44). Although a detailed discussion of the treatment of congenital toxoplasmosis is beyond the scope of this article, there is new evidence to support the benefits of prolonged treatment with pyrimethamine, sulfadiazine, and leucovorin during the first year of life (92). Ocular toxoplasmosis, which is almost invariably the result of reactivation, responds well to a 1-month course of pyrimethamine and sulfadiazine in approximately 70% of cases (48).

The efficacy of therapy for toxoplasmic encephalitis in HIV-infected patients, although ultimately palliative rather than curative, is usually measured by the acute regression of clinical symptoms and radiographic abnormalities on computed tomography or magnetic resonance imaging scans. The regimen of pyrimethamine-sulfadiazine-leucovorin, which is still the standard by which all other experimental regimens are judged, has been associated with clinical improvement in 68 to 95% of patients (59, 76, 120), but adverse effects of therapy have led to discontinuation of treatment in up to 40%. For acute therapy, pyrimethamine-clindamycin is also effective (83), yielding comparable clinical results and toxicity to those seen with pyrimethamine-sulfadiazine (35), although higher rates of relapse occur during secondary prophylaxis (131). In small trials, trimethoprim-sulfamethoxazole and pyrimethamine-clarithromycin have been clinically beneficial (42, 105), although trimethoprim is less effective than pyrimethamine in vitro and in experimental models (22). Patients treated solely with trimetrexate as salvage therapy have shown early response followed by relapse during therapy, suggesting possible drug resistance (89). In patients intolerant of folate antagonists, atovaquone has produced clinical response in 66 to 75%, although relapses have occurred in approximately 50% of patients receiving maintenance doses following a successful induction course (70).

In the initial therapeutic trials for toxoplasmosis in AIDS patients, relapse frequently occurred after therapy was discontinued, so continuous maintenance therapy became necessary. Pyrimethamine-sulfadiazine, pyrimethamine-clindamycin, and pyrimethamine-dapsone have all proven effective for long-term suppression of toxoplasmosis (30, 49, 111). AIDS patients receiving trimethoprim-sulfamethoxazole for long-term prevention of pneumocystis infection have also been protected against *Toxoplasma* encephalitis (26). Clarithromycin and spiramycin have not proven successful for prophylaxis (77, 139).

Drug toxicity. The folate antagonist combinations have frequent adverse effects, including skin rash, nausea, leukopenia, and thrombocytopenia. To counteract the bone marrow toxicity associated with these agents, folinic acid (leucovorin) is usually given as an adjunct to therapy. In addition, sulfadiazine can cause crystalluria and clindamycin predisposes patients to pseudomembranous colitis (21). Dapsone has been associated with rash, agranulocytosis, and, in G6PD-deficient individuals, hemolysis. Atovaquone causes rash, nausea, and diarrhea.

Drugs on the horizon. Pyrimethamine-dapsone is currently undergoing clinical evaluation as a regimen for patients intolerant of or unresponsive to pyrimethamine-sulfadiazine (91). The newer macrolides azithromycin and roxithromycin are effective in murine toxoplasmosis (10, 29), as is the folate antagonist pitrexin in combination with a sulfonamide (9). Another experimental agent that appears to interfere with purine salvage pathways of *T. gondii* is aprinocid (84).

REFERENCES

1. **Abaru, D. E., D. A. Liwo, D. Isakina, and E. E. Okori.** 1984. Retrospective long-term study of effects of berenil by follow-up of patients treated since 1965. Trop. Med. Parasitol. **35:**148–150.
2. **Al-Fouzan, A. S., Q. A. Al Saleh, N. M. Najem, and A. I. Rostom.** 1991. Cutaneous leishmaniasis in Kuwait: clinical experience with itraconazole. Pharmacol. Ther. **30:**519–521.
3. **Al-Waili, N. S., B. H. Al-Waili, and K. Y. Saloom.** 1988. Therapeutic use of mebendazole in giardial infections. Trans. R. Soc. Trop. Med. Hyg. **82:**438.
4. **Andrade, S. G., A. Rassi, J. B. Magalhaes, F. F. Filho, and A. O. Luquetti.** 1992. Specific chemotherapy of Chagas disease: a comparison between the response in patients and experimental animals inoculated with the same strains. Trans. R. Soc. Trop. Med. Hyg. **86:**624–626.
5. **Anonymous.** 1989. Halofantrine in the treatment of malaria. Lancet **ii:**537–538.
6. **Anonymous.** 1993. Drug alert: halofantrine. Change in recommendations for use. Weekly Epidemiol. Rec. **68:**269–270.
7. **Anonymous.** 1993. Drugs for parasitic infections. Med. Lett. Drugs Ther. **35:**111–112.
8. **Appleman, M. D., I. A. Shulman, S. Saxena, and L. V. Kirchoff.** 1993. Use of a questionnaire to identify potential donors at risk for infection with *Trypanosoma cruzi*. Transfusion **33:**61–64.
9. **Araujo, F. G., D. R. Guptill, and J. S. Remington.** 1987. In vivo activity of pitrexin against *Toxoplasma gondii*. J. Infect. Dis. **156:**828–830.
10. **Araujo, F. G., D. R. Guptill, and J. S. Remington.** 1988. Azithromycin, a macrolide antibiotic with potent activity against *Toxoplasma gondii*. Antimicrob. Agents Chemother. **32:**755–757.
11. **Araujo, F. G., J. Huskinson-Mark, W. E. Gutteridge, and J. S. Remington.** 1992. In vitro and in vivo activities of the hydroxynapthoquinone 566C50 against the cyst form of *Toxoplasma gondii*. Antimicrob. Agents Chemother. **36:**326–330.
12. **Armitage, K., T. Flanigan, J. Carey, I. Frank, R. R. MacGregor, P. Ross, R. Goodgame, and J. Turner.** 1992. Treatment of cryptosporidiosis with paramomycin, a report of five cases. Arch. Intern. Med. **152:**2497–2499.
13. **Arrowood, M. J., J. M. Jaynes, and M. C. Hedley.** 1991. Hemolytic properties of lytic peptides active against the sporozoite of *Cryptosporidium parvum*. J. Protozool. **38:**161S–163S.
14. **Arroz, J. O. L.** 1987. Melarsoprol and reactive encephalopathy in *Trypanosoma brucei rhodesiense*. Trans. R. Soc. Trop. Med. Hyg. **81:**192.
15. **Aucott, J. N., and J. I. Ravdin.** 1993. Amebiasis and "nonpathogenic" intestinal protozoa. Infect. Dis. Clin. North Am. **7:**467–485.
16. **Avila, J. L., and A. Avila.** 1981. *Trypanosoma cruzi*: allopurinol in the treatment of mice with experimental acute Chagas disease. Exp. Parasitol. **51:**204–208.
17. **Bacchi, C. J., H. C. Nathan, T. Livingston, G. Valladares, M. Saric, P. D. Sayer, A. R. Njogu, and A. B. Clarkson.** 1990. Differential susceptibility to DL-alpha-difluoromethylornithine in clinical isolates of *Trypanosoma brucei rhodesiense*. Antimicrob. Agents Chemother. **34:**1183–1188.
18. **Badaro, R., E. Falcoff, F. S. Badaro, E. M. Carvalho, D. Pedral-Sampaio, A. Barral, J. S. Carvalho, M. Barral-Netto, M. Brandely, L. Silva, J. C. Bina, R. Teiseira, R. Falcoff, H. Rocha, J. L. Ho, and W. D. Johnson.** 1990. Treatment of visceral leishmaniasis with pentavalent antimony and intereferon gamma. N. Engl. J. Med. **322:**16–21.
19. **Baird, J. K., H. Basri, Purnomo, M. J. Bangs, B. Subianto, L. C. Patchen, and S. L. Hoffman.** 1991. Resistance to chloroquine by *Plasmodium vivax* in Irian Jaya, Indonesia. Am. J. Trop. Med. Hyg. **44:**547–552.
20. **Bales, J. D.** 1991. African trypanosomiasis, p. 617–628. *In* G. T. Strickland (ed.), Hunter's tropical medicine. The W. B. Saunders Co., Philadelphia.
21. **Bartlett, J. G., T. W. Chang, M. Gurwith, S. L. Gorbach, and A. B. Onderdonk.** 1978. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N. Engl. J. Med. **298:**531–534.
22. **Beaman, M. H., R. E. McCabe, S.-Y. Wong, and J. S. Remington.** 1995. *Toxoplasma gondii*, p. 2455–2475. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases. Churchill Livingstone, Inc., New York.
23. **Beaugerie, L., M. F. Teilhac, A. M. Deluol, J. Fritsch, P. M. Girard, W. Rozenbaum, Y. Le Quintrec, and P. D. Chatelet.** 1992. Cholangiopathy associated with Microsporidia infection of the common bile duct mucosa in a patient with HIV infection. Ann. Intern. Med. **117:**401–402.
24. **Blanshard, C., D. S. Ellis, S. P. Dowell, G. Tovey, and B. G. Gazzard.** 1993. Electron microscopic changes in *Enterocytozoon bieneusi* following treatment with albendazole. J. Clin. Pathol. **46:**898–902.
25. **Bryson, H. M., and K. L. Goa.** 1992. Halofantrine: a review of its antimalarial activity, pharmacokinetic properties and therapeutic potential. Drugs **434:**236–258.
26. **Carr, A., B. Tindall, B. J. Brew, D. J. Marriott, J. L. Harkness, R. Penny, and D. A. Cooper.** 1992. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. Ann. Intern. Med. **117:**106–111.
27. **Cedeno, J. R., and D. J. Krogstad.** 1983. Susceptibility testing of *Entamoeba histolytica*. J. Infect. Dis. **148:**1090–1095.
28. **Centers for Disease Control.** 1994. Health information for travel. U.S.

Government Printing Office, Washington, D.C.
29. **Chang, H. R., and J. C. F. Pechere.** 1987. Effect of roxithromycin on acute toxoplasmosis in mice. Antimicrob. Agents Chemother. **31:**1147–1149.
30. **Clotet, B., G. Sirera, J. Romeu, J. M. Gimeno, A. Jou, M. J. Condom, J. Tor, and M. Foz.** 1991. Twice-weekly dapsone-pyrimethamine for preventing PCP and cerebral toxoplasmosis. AIDS **5:**601–602.
31. **Coatney, G. R., and M. Getz.** 1962. Primaquine and quinocide as curative agents against sporozoite-induced Chesson strain vivax malaria. Bull. W. H. O. **27:**290–293.
32. **Colwell, E. J., R. L. Hickman, M. R. Intraprasert, and C. Tirabutana.** 1972. Minocycline and tetracycline treatment of acute falciparum malaria in Thailand. Am. J. Trop. Med. Hyg. **21:**144–149.
33. **Craun, G.** 1986. Waterborne giardiasis in the United States, 1965–1984. Lancet **ii:**513–514.
34. **Current, W. L., and L. S. Garcia.** 1991. Cryptosporidiosis. Clin. Microbiol. Rev. **4:**325–358.
35. **Dannemann, B., A. McCutchan, D. Israelski, D. Antoniskis, C. Leport, B. Luft, J. Nussbaum, N. Clumeck, P. Morlat, J. Chiu, J. L. Vilde, M. Orrelllana, D. Feigal, A. Bartok, P. Heseltine, J. Leedom, J. Remington, and California Collaborative Treatment Group.** 1992. Treatment of toxoplasmic encephalitis in patients with AIDS. Ann. Intern. Med. **116:**33–43.
36. **Davidson, R. N., and S. L. Croft.** 1993. Recent advances in the treatment of visceral leishmaniasis. Trans. R. Soc. Trop. Med. Hyg. **87:**130–131.
37. **di Martino, L., A. Nocerino, and M. P. Mantovani.** 1991. Mebendazole in giardial infections: confirmation of the failure of this treatment. Trans. R. Soc. Trop. Med. Hyg. **85:**557–558. (Letter.)
38. **Doua, F. F. Y. Boa, P. J. Schecter, T. W. Miezan, D. Diai, S. R. Sanon, P. De Raadt, K. D. Haegele, A. Sjoerdsma, and K. Konian.** 1987. Treatment of human late stage gambiense trypanosomiasis with alpha-difluoromethylornithine (eflornithine): efficacy and tolerance in 14 cases in Cote d'Ivoire. Am. J. Trop. Med. Hyg. **37:**525–533.
39. **Edlind, T. D., T. L. Hang, and P. R. Chakraborty.** 1990. Activity of the antihelmintic benzimidazoles against *Giardia lamblia* in vitro. J. Infect. Dis. **162:**1408–1409.
40. **Fafard, J., and R. LaLonde.** 1990. Long-standing symptomatic cryptosporidiosis in a normal man: clinical response to spiramycin. J. Clin. Gastroenterol. **12:**190–191.
41. **Fayer, R., and W. Ellis.** 1993. Glycoside antibiotics alone and combined with tetracyclines for prophylaxis of experimental cryptosporidiosis in neonatal BALB/c mice. J. Parasitol. **79:**553–558.
42. **Fernandez-Martin, J., C. Leport, P. Morlat, M. C. Meyohas, J. P. Chauvin, and J. L. Vilde.** 1991. Pyrimethamine-clarithromycin combination for therapy of acute *Toxoplasma* encephalitis in patients with AIDS. Antimicrob. Agents Chemother. **35:**2049–2052.
43. **Fichtenbaum, C. J., D. R. Ritchie, and W. G. Powderly.** 1993. Use of paromomycin for treatment of cryptosporidiosis in patients with AIDS. Clin. Infect. Dis. **16:**298–300.
44. **Forestler, F.** 1991. Les foetopathies infectieuses—prevention, diagnostic prenatal, attitude pratique. Presse Med. **20:**1448–1454.
45. **Francioli, P. B., J. S. Keithly, T. C. Jones, R. D. Brandstetter, and D. J. Wolf.** 1981. Response of babesiosis to pentamdine therapy. Ann. Intern. Med. **94:**326–330.
46. **Gallerano, R. H., J. J. Marr, and R. R. Sosa.** 1990. Therapeutic efficacy of allopurinol in patients with chronic Chagas disease. Am. J. Trop. Med. Hyg. **43:**159–166.
47. **Garavelli, P. L., and E. Corti.** 1992. Chloroquine resistance in *Plasmodium vivax*: the first case in Brazil. Trans. R. Soc. Trop. Med. Hyg. **86:**128.
48. **Ghosh, M., P. Levy, and I. H. Leopold.** 1965. Therapy of toxoplasmic uveitis. Am. J. Ophthalmol. **59:**55–61.
49. **Girard, P. M., R. Landman, C. Gaudebout, R. Olivares, A. G. Saimot, P. Jelazko, C. Gaudebout, A. Certain, F. Boue, E. Bouvet, T. Lecompte, and J. P. Couland.** 1993. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. N. Engl. J. Med. **328:**1514–1520.
50. **Goldberg, D. E., A. F. Slater, R. Beavis, B. Chait, A. Cerami, and G. B. Henderson.** 1991. Hemoglobin degradation in the human malaria pathogen *Plasmodium falciparum*: a catabolic pathway initiated by a specific aspartic protease. J. Exp. Med. **173:**961–969.
51. **Gorla, N. B., O. S. Ledesma, G. P. Barbieri, and I. B. Larripa.** 1989. Thirteenfold increase of chromosomal aberrations in chagasic children treated with nifurtimox. Mutat. Res. **224:**263–267.
52. **Grady, R. W., E. J. Bienen, H. A. Dieck, M. Saric, and A. B. Clarkson, Jr.** 1993. *N-n*-alkyl-3,4-dihidroxybenzamides as inhibitors of the trypanosome alternative oxidase: activity in vitro and in vivo. Antimicrob. Agents Chemother. **37:**1082–1085.
53. **Grogl, M., T. N. Thomason, and E. D. Franke.** 1992. Drug resistance in leishmaniasis: its implication in systemic chemotherapy of cutaneous and mucocutaneous disease. Am. J. Trop. Med. Hyg. **47:**117–126.
54. **Grossman, P. L., and J. S. Remington.** 1979. The effect of trimethoprim and sulfamethoxazole on *Toxoplasma gondii* in vitro and in vivo. Am. J. Trop. Med. Hyg. **28:**445–455.
55. **Gutteridge, W. E.** 1985. Existing chemotherapy and its limitations. Br. Med. Bull. **41:**162–168.
56. **Gyang, F. N., D. S. Peterson, and T. E. Wellems.** 1992. *Plasmodium falciparum*: rapid detection of dihydrofolate reductase mutations that confer resistance to cycloguanil and pyrimethamine. Exp. Parasitol. **74:**470–472.
57. **Hall, A., and Q. Nahar.** 1993. Albendazole as treatment for infections with *Giardia duodenalis* in children in Bangladesh. Trans. R. Soc. Trop. Med. Hyg. **87:**84–86.
58. **Harinasuta, T., D. Bunnag, R. Lasserre, R. Leimer, and S. Vinijanont.** 1985. Trials of mefloquine in vivax and of mefloquine plus Fansidar in falciparum malaria. Lancet **i:**885–888.
59. **Haverkos, H. W.** 1987. Assessment of therapy for *Toxoplasma* encephalitis. Am. J. Med. **82:**907–914.
60. **Herwaldt, B. L., and J. D. Berman.** 1992. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. Am. J. Trop. Med. Hyg. **46:**296–306.
61. **Hien, T. T., K. Arnold, H. Vinh, B. M. Cuong, N. H. Phu, T. T. H. Chau, N. T. M. Hoa, L. V. Chuong, N. T. H. Mai, N. N. Vinh, and T. T. M. Trang.** 1992. Comparison of artesunate suppositories with intravenous artesunate in the treatment of cerebral malaria. Trans. R. Soc. Trop. Med. Hyg. **86:**582–583.
62. **Hien, T. T., and N. J. White.** 1993. Qinghaosu. Lancet **341:**603–608.
63. **Hoffman, S. L., D. Rustama, N. H. Punjabi, B. Surampaet, B. Sanjaya, A. J. Dimpudus, K. T. McKee, Jr., F. P. Paleologo, J. R. Campbell, H. Marwoto, and L. Laughlin.** 1988. High-dose dexamethasone in quinine-treated patients with cerebral malaria: a double-blind, placebo-controlled trial. J. Infect. Dis. **158:**325–331.
64. **Hunter, C. A., F. W. Jennings, J. H. Adams, M. Murray, and P. G. E. Kennedy.** 1992. Subcurative chemotherapy and fatal post-treatment reactive encephalopathies in African trypanosomiasis. Lancet **339:**956–958.
65. **Huskinson-Mark, J., F. G. Araujo, and J. S. Remington.** 1991. Evaluation of the effect of drugs on the cyst form of *Toxoplasma gondii*. J. Infect. Dis. **164:**170–177.
66. **Jacoby, G. A., J. V. Hunt, K. S. Kosinski, Z. N. Demirjian, C. Huggins, P. Etkind, L. C. Marcus, and A. Spielman.** 1980. Treatment of transfusion-transmitted babesiosis by exchange transfusion. N. Engl. J. Med. **303:**1098–1100.
67. **Jennings, F. W.** 1993. Combination chemotherapy of CNS trypanosomiasis. Acta Trop. **54:**205–213.
68. **Kirchoff, L. V.** 1993. Chagas disease: American trypanosomiasis. Infect. Dis. Clin. North Am. **7:**487–502.
69. **Knight, R.** 1980. The chemotherapy of amoebiasis. J. Antimicrob. Chemother. **6:**577–593.
70. **Kovacs, J. A.** 1992. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. Lancet **340:**637–638.
71. **Kreutner, A. K., V. E. DelBene, and M. S. Amstey.** 1981. Giardiasis in pregnancy. Am. J. Obstet. Gynecol. **140:**895–901.
72. **Krogstad, D. J., I. Y. Gluzman, D. E. Kyle, A. M. Odoula, S. K. Martin, W. K. Milhous, and P. H. Schlesinger.** 1987. Efflux of chloroquine from *Plasmodium falciparum*: mechanism of chloroquine resistance. Science **238:**1283–1285.
73. **Krogstad, D. J., and P. H. Schlesinger.** 1986. A perspective on antimalarial action: effects of weak bases on *Plasmodium falciparum*. Biochem. Pharmacol. **35:**457–462.
74. **Kucers, A., N. Bennett, and R. Kemp.** 1987. Lincomycin and clindamycin, p. 819–850. *In* A. Kucers, N. Bennett, and R. Kemp (ed.), The use of antibiotics. Heinemann, London.
75. **Laughon, B. E., D. A. Druckman, A. Vernon, R. Quinn, B. F. Polk, J. F. Modlin, R. H. Yolken, and J. G. Bartlett.** 1988. Prevalence of enteric pathogens in homosexual men with and without AIDS. Gastroenterology **94:**984–993.
76. **Leport, C., F. Raffi, S. Matheron, C. Katlama, B. Regnier, A. G. Saimot, C. Marche, C. Vedrenne, and J. L. Vilde.** 1988. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Am. J. Med. **84:**94–100.
77. **Leport, C., J. L. Vilde, C. Katlama, B. Regnier, S. Matheron, and A. G. Saimot.** 1986. Failure of spiramycin to prevent neurotoxoplasmosis in immunosuppressed patients. JAMA **255:**2290. (Letter.)
78. **Levi, G. C., C. Armando de Avila, and V. A. Neto.** 1977. Efficacy of various drugs for treatment of giardiasis. Am. J. Trop. Med. Hyg. **26:**564–565.
79. **Lobel, H. O., K. W. Bernard, S. L. Williams, A. W. Hightower, L. C. Patchen, and C. C. Campbell.** 1991. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine. JAMA **265:**361–364.
80. **Lobel, H. O., M. Miani, T. Eng, K. W. Bernard, A. W. Hightower, and C. C. Campbell.** 1993. Long-term malaria prophylaxis with weekly mefloquine. Lancet **341:**848–851.
81. **Loiseau, P. M., J. G. Wolf, and P. Gayral.** 1992. Spiroarsoranes of second generation: evaluation of trypanocidal properties against *Trypanosoma brucei brucei*. Trop. Med. Parasitol. **44:**32–36.
82. **Lothorlary, O., D. Mechali, D. Christiaens, M. Gougerot Pocido, M. Brandley, and P. Babinet.** 1990. Interferon-gamma associated with conventional

therapy for recurrent visceral leishmaniasis in a patient with AIDS. Rev. Infect. Dis. **12:**370–371.
83. **Luft, B. A., R. Hafner, A. H. Korzun, C. Leport, D. Antoniskis, E. M. Bosler, D. D. Bourland, R. Uttamchandani, J. Fuhrer, J. Jacobson, P. Morlat, J. L. Vilde, and J. S. Remington.** 1993. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. N. Engl. J. Med. **329:**995–1000.
84. **Luft, B. J., and J. S. Remington.** 1992. Toxoplasmic encephalitis in AIDS. Clin. Infect. Dis. **15:**211–222.
85. **Machtinger, L., S. R. Telford, C. Inducil, E. Klapper, S. H. Pepkowitz, and D. Goldfinger.** 1993. Treatment of babesiosis by red blood cell exchange in an HIV-positive, splenectomized patient. J. Clin. Apheresis **8:**78–81.
86. **Maldonado, R. A., J. Molina, G. Payares, and J. A. Urbina.** 1993. Experimental chemotherapy with combinations of ergosterol biosynthesis inhibitors in murine models of Chagas' disease. Antimicrob. Agents Chemother. **37:**1353–1359.
87. **Marik, P. E.** 1989. Severe falciparum malaria: survival without exchange transfusion. Am. J. Trop. Med. Hyg. **41:**627–629.
88. **Marshall, R. J., and T. P. Flanigan.** 1992. Paramomycin inhibits *Cryptosporidium* infection of a human enterocyte cell line. J. Infect. Dis. **165:**772–774.
89. **Masur, H., M. A. Polis, C. U. Tuazon, D. Ogata-Arakaki, J. Kovacs, D. Katz, D. Hilts, T. Simmons, I. Feuerstein, B. Lundgren, et. al.** 1993. Salvage trial of trimetrexate-leucovorin for treatment of cerebral toxoplasmosis in AIDS patients. J. Infect. Dis. **167:**1422–1426.
90. **McAuley, J. B., B. L. Herwaldt, S. L. Stokes, J. A. Becher, J. M. Roberts, M. K. Michelson, and D. D. Juranek.** 1992. Diloxanide furoate for treating asymptomatic *Entamoeba histolytica* cyst passers: 14 years' experience in the United States. Clin. Infect. Dis. **464:**464–468.
91. **McCabe, R., and V. Chirurgi.** 1993. Issues in toxoplasmosis. Infect. Dis. Clin. North Am. **7:**587–604.
92. **McCauley, J., K. Boyer, D. Patel, M. Mets, C. Swisher, N. Roizen, C. Wolters, L. Stein, M. Stein, W. Schey, et al.** 1994. Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago collaborative treatment trial. Clin. Infect. Dis. **18:**38–72.
93. **McMeeking, A., W. Borkowsky, P. H. Klesius, S. Bonk, R. S. Holzman, and H. S. Lawrence.** 1990. A controlled trial of bovine dialyzable leukocyte extract for cryptosporidiosis in patients with AIDS. J. Infect. Dis. **161:**108–112.
94. **Meshnick, S. R., Y. Z. Yang, V. Lima, F. Kuypers, S. Kamchonwongpaisan, and Y. Yuthavong.** 1993. Iron-dependent free radical generation from the antimalarial agent artemisinin (Qinghaosu). Antimicrob. Agents Chemother. **37:**1108–1114.
95. **Miller, K. D., A. E. Greenberg, and C. C. Campbell.** 1989. Treatment of severe malaria in the United States with a continuous infusion of quinidine gluconate and exchange transfusion. N. Engl. J. Med. **321:**65–70.
96. **Miller, K. D., H. O. Lobel, R. F. Satriale, J. N. Kuritsky, R. Stern, and C. C. Campbell.** 1986. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. Am. J. Trop. Med. Hyg. **35:**451–458.
97. **Miller, L. H., R. H. Glew, D. J. Wyler, W. A. Howard, W. E. Collins, P. G. Contacos, and F. A. Neva.** 1974. Evaluation of clindamycin in combination with quinine against multi-drug resistant strains of *Plasmodium falciparum*. Am. J. Trop. Med. Hyg. **23:**565–569.
98. **Milord, F., J. Pepin, L. Loko, L. Ethier, and B. Mpia.** 1992. Efficacy and toxicity for treatment of *Trypanosoma brucei gambiense* sleeping sickness. Lancet **340:**652–655.
99. **Mishra, M., U. K. Biswas, D. N. Jha, and A. B. Khan.** 1992. Amphotericin versus pentamidine in antimony-unresponsive kala-azar. Lancet **340:**1256–1257.
100. **Moens, F., M. De Wilde, and N. Kila.** 1984. Essai de traitement au nifurtimox de la trypanosomiase humaine africaine. Ann. Soc. Belg. Med. Trop. **64:**37–43.
101. **Mosten, F., C. Luxemburger, F. O. ter Kuile, C. Woodrow, J. Pa Eh, T. Chongsuphajaisiddhi, and N. J. White.** 1994. Treatment of multidrug-resistant *Plasmodium falciparum* with 3-day artesunate-mefloquine combination. J. Infect. Dis. **170:**971–979.
102. **Murphy, T. V., and J. D. Nelson.** 1983. Five versus ten days' therapy with furazolidone for giardiasis. Am. J. Dis. Child. **137:**267–270.
103. **Navin, T. R., B. A. Arana, F. E. Arana, J. D. Berman, and J. F. Chajon.** 1992. Placebo-controlled trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. J. Infect. Dis. **165:**528–534.
104. **Nord, J., P. Ma, D. DiJohn, S. Tzipori, and C. O. Tacket.** 1990. Treatment with bovine hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients. AIDS **4:**581–584.
105. **Norrby, R., T. Eilard, A. Svedhem, and E. Lycke.** 1975. Treatment of toxoplasmosis with trimethoprim-sulfamethoxazole. Scand. J. Infect. Dis. **7:**72–75.
106. **Nosten, F., F. ter Kuile, T. Chongsuphajaisiddhi, C. Luxemburger, H. K. Webster, M. Edstein, L. Phaipun, K. L. Thew, and N. J. White.** 1991. Mefloquine-resistant falciparum malaria on the Thai-Burmese border. Lancet **337:**1140–1143.
107. **Oren, B., E. Schgurensky, M. Ephros, I. Tamir, and R. Raz.** 1991. Single-dose ornidazole versus seven-day metronidazole therapy of giardiasis in kibbutzim children in Israel. Eur. J. Clin. Microbiol. Infect. Dis. **10:**963–965.
108. **Orenstein, J. M., J. Chang, W. Steinberg, P. D. Smith, H. Rotterdam, and D. P. Kotler.** 1990. Intestinal microsporidiosis as a cause of diarrhea in human immunodeficiency virus-infected patients. Hum. Pathol. **21:**475–481.
109. **Pang, L., N. Limsomwong, and P. Singharaj.** 1988. Prophylactic treatment of vivax and falciparum malaria with low-dose doxycycline. J. Infect. Dis. **158:**1124–1127.
110. **Pang, L. W., N. Limsomwong, E. F. Boudreau, and P. Singharaj.** 1987. Doxycycline prophylaxis for falciparum malaria. Lancet **i:**1161–1164.
111. **Pedrol, E., J. M. Gonzalez-Clemente, J. M. Gatell, J. Mallolas, J. M. Miro, F. Graus, R. Alvarez, J. M. Mercader, J. Bereguer, M. T. Jimenez de Anta, M. E. Valls, and E. Soriano.** 1990. Central nervous system toxoplasmosis in AIDS patients: efficacy of an intermittent maintenance therapy. AIDS **4:**511–517.
112. **Pepin, J., F. Milord, C. Guern, B. Mpia, L. Ethier, and D. Mansina.** 1989. Trial of prednisolone for the prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. Lancet **i:**1246–1250.
113. **Pepin, J., F. Milord, C. Guern, and P. J. Schecter.** 1987. Difluoromethylornithine for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness. Lancet **ii:**1431–1433.
114. **Pepin, J., F. Milord, F. Meurice, L. Ethier, L. Loko, and B. Mpia.** 1992. High-dose nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness: an open trial in central Zaire. Trans. R. Soc. Trop. Med. Hyg. **86:**254–256.
115. **Pepin, J., F. Milord, B. Mpia, F. Meurice, D. Degroof, and H. Bruneel.** 1989. An open clinical trial of nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness in central Zaire. Trans. R. Soc. Trop. Med. Hyg. **83:**514–517.
116. **Petersen, C.** 1992. Cryptosporidiosis in patients infected with the human immunodeficiency virus. Clin. Infect. Dis. **15:**903–909.
117. **Pilla, A. M., M. J. Rybak, and P. H. Chandrasekar.** 1987. Spiramycin in the treatment of cryptosporidiosis. Pharmacotherapy **7:**188–190.
118. **Plettenberg, A., A. Stoehr, H. J. Stellbrink, H. Albrecht, and W. Meigel.** 1993. A preparation from bovine colostrum in the treatment of HIV-positive patients with chronic diarrhea. Clin. Invest. **71:**42–45.
119. **Popovsky, L. M., M. E. Lindberg, A. L. Syrek, and P. L. Page.** 1988. Prevalence of *Babesia* antibody in a selected blood donor population. Transfusion **28:**59–61.
120. **Porter, S. B., and M. A. Sande.** 1992. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. N. Engl. J. Med. **327:**1643–1648.
121. **Portnoy, D., M. E. Whiteside, E. Buckley, and C. L. MacLeod.** 1984. Treatment of intestinal cryptosporidiosis with spiramycin. Ann. Intern. Med. **101:**202–204.
122. **Powell, S. J., I. MacLeod, A. J. Wilmot, and R. Elsdon-Dew.** 1966. Metronidazole in amoebic dysentery and amoebic liver abscess. Lancet **ii:**1329–1331.
123. **Quinn, T. C., J. M. Mann, J. W. Curran, and P. Piot.** 1986. AIDS in Africa: an epidemiologic paradigm. Science **234:**955–963.
124. **Raoult, D., L. Soulayrol, B. Toga, H. Dumon, and P. Casanova.** 1987. Babesiosis, pentamidine and cotrimoxazole. Ann. Intern. Med. **107:**944. (Letter.)
125. **Ravdin, J. I., and J. Skilogiannis.** 1989. In vitro susceptibilities of *Entamoeba histolytica* to azithromycin, CP-63,956, erythromycin, and metronidazole. Antimicrob. Agents Chemother. **33:**960–962.
126. **Reacher, M., C. C. Campbell, J. Freeman, E. B. Doberstyn, and A. D. Brandling-Bennett.** 1981. Drug therapy for *Plasmodium falciparum* malaria resistant to pyrimethamine-sulfadoxine (Fansidar). Lancet **ii:**1066–1069.
127. **Reed, S. G.** 1988. In vivo administration of recombinant IFN-gamma induces macrophage activation, and prevents acute disease, immune suppression and death in experimental *Trypanosoma cruzi* infections. J. Immunol. **140:**4342–4347.
128. **Rehg, J. E.** 1991. Activity of azithromycin against *Cryptosporidium* in immunosuppressed rats. J. Infect. Dis. **163:**1293–1296.
129. **Rehg, J. E.** 1994. Comparison of anticryptosporidial activity of paromomycin with that of other aminoglycosides and azithromycin in immunosuppressed rats. J. Infect. Dis. **170:**934–938.
130. **Rehg, J. E., M. L. Hancock, and D. B. Noodmansee.** 1988. Anticryptosporidial activity of sulfadimethoxine. Antimicrob. Agents Chemother. **32:**1907–1908. (Letter.)
131. **Remington, J. S., and J. L. Vilde.** 1991. Clindamycin for toxoplasma encephalitis in AIDS. Lancet **338:**1142–1143. (Letter.)
132. **Rew, R. S.** 1986. African trypanosomiasis, p. 129–137. *In* W. C. Campbell and R. S. Rew (ed.), Chemotherapy of parasitic diseases. Plenum Press, New York.
133. **Rieckmann, K. H., D. R. Davis, and D. C. Hutton.** 1989. *Plasmodium vivax* resistance to chloroquine? Lancet **ii:**1183–1184.
134. **Rolston, K. V. I., V. Fainstain, and G. P. Bodey.** 1989. Intestinal cryptospo-

ridiosis treated with eflornithine: a prospective study among patients with AIDS. J. Acquired Immune Defic. Syndr. **2:**426–430.
135. **Rosenthal, P. J., and R. G. Nelson.** 1992. Isolation and characterization of a cysteine protease gene of *Plasmodium falciparum*. Mol. Biochem. Parasitol. **51:**143–152.
136. **Rowin, K. S., H. B. Tanowitz, and M. Wittner.** 1982. Therapy of experimental babesiosis. Ann. Intern. Med. **97:**556–558.
137. **Ruebush, T. K., P. B. Cassady, H. J. Marsh, S. A. Lisker, D. B. Voorhees, E. B. Mahoney, and G. R. Healy.** 1977. Human babesiosis on Nantucket Island: clinical features. Ann. Intern. Med. **86:**6–9.
138. **Ruebush, T. K., R. H. Rubin, E. R. Wolpow, P. B. Cassady, and M. G. Schultz.** 1979. Neurologic complications following treatment of human *Babesia microti* infection with diminazene aceturate. Am. J. Trop. Med. Hyg. **28:**184–189.
139. **Ruf, B., D. Schurmann, and H. D. Pohle.** 1992. Failure of clarithromycin in preventing toxoplasmic encephalitis in AIDS patients. J. Acquired Immune Defic. Syndr. **5:**530–531.
140. **Saenz, R. E., H. Paz, and J. D. Berman.** 1990. Efficacy of ketoconazole against *Leishmania braziliensis panamensis* cutaneous leishmaniasis. Am. J. Med. **89:**147–155.
141. **Santos-Buch, C. A., and A. R. L. Texeira.** 1974. The immunology of experimental Chagas' disease. III. Rejection of allogeneic heart cells in vitro. J. Exp. Med. **169:**641–652.
142. **Seaberg, L. S., A. R. Parquette, I. Y. Guzman, G. W. Phillips, Jr., T. F. Brodasky, and D. J. Krogstad.** 1984. Clindamycin activity against chloroquine-resistant *Plasmodium falciparum*. J. Infect. Dis. **150:**904–911.
143. **Seaman, J., D. Pryce, H. E. Sondorp, A. Moody, A. D. M. Bryceson, and R. N. Davidson.** 1993. Epidemic visceral leishmaniasis in Sudan: a randomized trial of aminosidine plus sodium stibogluconate versus sodium stibogluconate alone. J. Infect. Dis. **168:**715–720.
144. **Schmunis, G. A.** 1991. *Trypanosoma cruzi*, the etiologic agent of Chagas' disease: status in the blood supply in endemic and nonendemic countries. Transfusion **31:**547–557.
145. **Shadduck, J. A.** 1980. Effect of fumagillin on in vitro multiplication of *Encephalitozoon cuniculi*. J. Protozool. **27:**202–208.
146. **Simon, D., L. M. Weiss, H. B. Tanowitz, A. Cali, J. Jones, and M. Wittner.** 1991. Light microscopic diagnosis of human microsporidiosis and variable response to octreotide. Gasteroenterology **100:**271–273.
147. **Simon, M., H. B. Shookhoff, H. Terner, B. Weingarten, and J. G. Parker.** 1967. Paramomycin in the treatment of intestinal amebiasis: a short course of therapy. Am. J. Gastroenterol. **48:**504–511.
148. **Sjoerdsma, A., and P. J. Schecter.** 1984. Chemotherapeutic implications of polyamine biosynthesis inhibition. Clin. Pharmacol. Ther. **35:**287–300.
149. **Smith, P. D., C. H. Lane, V. J. Gill, J. F. Manischewitz, G. V. Quinn, A. S. Fauci, and H. Masur.** 1988. Intestinal infections in patients with the acquired immunodeficiency syndrome (AIDS). Ann. Intern. Med. **108:**328–333.
150. **Smith, R. P., A. T. Evans, M. Popovsky, L. Mills, and A. Spielman.** 1986. Transfusion-acquired babesiosis and failure of antibiotic treatment. JAMA **256:**2726–2727.
151. **Soto, J., P. Buffet, M. Grogl, and J. Berman.** 1994. Successful treatment of Colombian cutaneous leishmaniasis with four injections of pentamidine. Am. J. Trop. Med. Hyg. **50:**107–111.
152. **Soto-Mancipe, J., M. Grogl, and J. D. Berman.** 1993. Evaluation of pentamidine for the treatment of cutaneous leishmaniasis in Colombia. Clin. Infect. Dis. **16:**417–425.
153. **Speelman, P.** 1985. Single-dose tinidazole for the treatment of giardiasis. Antimicrob. Agents Chemother. **27:**227–229.
154. **Squires, K. E., F. Rosenkaimer, J. A. Sherwood, A. L. Fornia, J. B. O. Were, and H. W. Murray.** 1993. Immunochemotherapy for visceral leishmaniasis: a controlled pilot trial of antimony versus antimony plus interferon-gamma. Am. J. Trop. Med. Hyg. **48:**666–669.
155. **Sullam, P. M., G. Slutkin, A. B. Gottlieb, and J. Mills.** 1986. Paramomycin therapy of endemic amebiasis in homosexual men. Sex. Transm. Dis. **131:** 151–155.
156. **Taelman, H., P. J. Schecter, L. Marcelis, J. Sonnet, G. Kayzumba, J. Dasnoy, K. D. Haegele, A. Sjoerdsma, and M. Wery.** 1987. Difluoromethylornithine, an effective new treatment of Gambian trypanosomiasis: results in five patients. Am. J. Med. **82:**607–614.
157. **Texeira, A. R. L., J. C. Cordova, I. Souto Maior, and E. Solorzano.** 1990. Chagas disease: lymphoma growth in rabbits treated with benznidazole. Am. J. Trop. Med. Hyg. **43:**146–158.
158. **Texeira, A. R. L., R. Silva, E. Cunha Neto, J. M. Santana, and L. V. Rizzo.** 1990. Malignant, non-Hodgkin's lymphomas in *Trypanosoma cruzi*-infected rabbits treated with nitroarenes. J. Comp. Pathol. **103:**37–48.
159. **Thakur, C. P., M. Kumar, P. Kumar, B. N. Mishra, and A. K. Pandey.** 1988. Rationalization of regimens of treatment of kala-azar with sodium stibogluconate in India: a randomized study. Br. Med. J. **296:**1557–1561.
160. **Thakur, C. P., M. Kumar, and A. K. Pandey.** 1991. Comparison of regimens of treatment of antimony resistant kala azar patients: a randomized study. Am. J. Trop. Med. Hyg. **45:**435–441.
161. **Thakur, C. P., P. Olliaro, S. Gothoskar, S. Bhowmick, B. K. Choudury, S. Prasad, M. Kumar, and B. B. Verma.** 1992. Treatment of visceral leishmaniasis (kala-azar) with aminosidine (paramomycin)-antimonial combinations, a pilot study in Bihar, India. Trans. R. Soc. Trop. Med. Hyg. **86:**615–616.
162. **Thakur, C. P., G. P. Sinha, V. Sharma, A. K. Pandey, M. Kumar, and B. B. Verma.** 1993. Evaluation of amphotericin B as a first line drug in comparison to sodium stibogluconate in the treatment of fresh cases of kala-azar. Indian J. Med. Res. Sect. A **97:**170–175.
163. **Torres-Cisneros, J., J. L. Villanueva, J. M. Kindelan, R. Jurado, and P. Sanchez-Guijo.** 1993. Successful treatment of antimony-resistant visceral leishmaniasis with liposomal amphotericin B in patients infected with human immunodeficiency virus. Clin. Infect. Dis. **17:**625–627.
164. **Ungar, B. L. P., D. J. Ward, R. Fayer, and C. A. Quinn.** 1990. Cessation of *Cryptosporidium*-associated diarrhea in an AIDS patient after treatment with hyperimmune bovine colostrum. Gastroenterology **98:**486–489.
165. **Upcroft, J. A., P. Upcroft, and P. F. L. Boreham.** 1990. Drug resistance in *Giardia intestinalis*. Int. J. Parasitol. **20:**489–496.
166. **Urbina, J. A., K. Lazardi, E. Marchan, G. Visbal, T. Aguirre, M. M. Piras, R. Piras, R. A. Maldonado, G. Payares, and W. De Souza.** 1993. Mevinolin (Lovostatin) potentiates the anti-proliferative effects of ketoconazole and terbinafine against *Trypanosoma* (*Schizotrypanum*) *cruzi*: in vitro and in vivo studies. Antimicrob. Agents Chemother. **37:**580–591.
167. **Van Nieuwenhove, S., P. J. Schecter, J. Declercq, G. Bone, J. Burke, and A. Sjoerdsma.** 1985. Treatment of gambiense sleeping sickness in Sudan with oral DFMO (DL-alpha-difluoromethylornithine), an inhibitor of ornithine decarboxylase: first field trial. Trans. R. Soc. Trop. Med. Hyg. **79:**692–698.
168. **Van Voorhis, W. C.** 1990. Therapy and prophylaxis of systemic protozoan infections. Drugs **40:**176–202.
169. **Viotti, R., C. Vigliano, H. Armenti, and E. Segura.** 1994. Treatment of chronic Chagas disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up. Am. Heart J. **127:**151–162.
170. **Wali, J. P., P. Aggarwal, U. Gupta, S. Saluja, and S. Singh.** 1992. Ketoconazole in the treatment of antimony- and pentamidine-resistant kala-azar. J. Infect. Dis. **166:**214–215.
171. **Warrell, D. A., S. Looareesuwan, M. J. Warrell, P. Kasemsarn, R. Intraprasert, D. Bunnag, and T. Harinasuta.** 1982. Dexamethasone proves deleterious in cerebral malaria. N. Engl. J. Med. **306:**313–319.
172. **Weber, P., R. T. Bryan, D. A. Schwartz, and R. L. Owen.** 1994. Human microsporidial infections. Clin. Microbiol. Rev. **7:**419–461.
173. **Weinrauch, L., R. Livshin, Z. Even-Paz, and J. El-On.** 1983. Efficacy of ketoconazole in cutaneous leishmaniasis. Arch. Dermatol. Res. **275:**353–354.
174. **Weiss, L. M., M. Wittner, S. Wasserman, H. S. Oz, J. Retsema, and H. B. Tanowitz.** 1993. Efficacy of azithromycin for treating *Babesia microti* infection in the hamster model. J. Infect. Dis. **168:**1289–1292.
175. **White, N. J., S. Looaresuwan, D. A. Warrell, T. Chongsuphajaisiddhi, D. Bunnag, and T. Harinasuta.** 1981. Quinidine in falciparum malaria. Lancet **ii:**1069–1071.
176. **Wittenberg, D. F., N. M. Miller, and J. van den Ende.** 1989. Spiramycin is not effective in treating *Cryptosporidium* diarrhea in infants: results of a double-blind randomized trial. J. Infect. Dis. **159:**131–132.
177. **Wittner, M., K. S. Rowin, H. B. Tanowitz, J. F. Hobbs, S. Saltzman, B. Wenz, R. Hirsch, E. Chisholm, and G. R. Healy.** 1982. Successful chemotherapy of transfusion babesiosis. Ann. Intern. Med. **96:**601–604.
178. **Wolfe, M. S.** 1973. Nondysenteric intestinal amebiasis: treatment with diloxanide furoate. JAMA **224:**1601–1604.
179. **Wolfe, M. S.** 1975. Giardiasis. JAMA **233:**1362–1365.
180. **Wolfe, M. S.** 1992. Giardiasis. Clin. Microbiol. Rev. **5:**93–100.
181. **World Health Organization.** 1990. Control of the leishmaniases. Technical report series no. 793. World Health Organization, Geneva.
182. **World Health Organization.** 1990. Severe and complicated malaria. Trans. R. Soc. Trop. Med. Hyg. **84**(Suppl. 2)**:**1–65.