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МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
ХАРКІВСЬКИЙ ДЕРЖАВНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

TROPICAL DISEASES

Manual
for medical students and interns

ТРОПІЧНІ ХВОРОБИ

Навчальний посібник
для студентів медичних ВНЗ і лікарів-інтернів

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The material contained in the manual reviews the fundamental questions of tropical diseases (etiology, epidemiology, pathogenesis, clinical manifestations and treatment). It would be helpful for medical students and interns.

Матеріал, що міститься в навчальному посібнику, розглядає фундаментальні питання тропічних хвороб (етіологію, епідеміологію, патогенез, клінічну картину та лікування). Навчальний посібник рекомендований для студентів медичних ВНЗ і лікарів-інтернів.

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INTRODUCTION

In the tropics and subtropics there are two main disease patterns. The first, caused chiefly by protozoan or helminthes parasites, will probably be unfamiliar to medical workers practicing in temperate climates. The second includes almost the whole range of diseases which are commonplaces the world over.

Essential features of infectious diseases in these regions are the increased lethal effects of the commoner bacterial and viral diseases, and the enormous degree of morbidity occasioned by those due to parasites. Communicable diseases, including the parasitic infections, account for about one third of all recorded deaths, but the degree of mortality caused directly by parasites is difficult to estimate.

Parasitic infestation is usually multiple. According to recent estimates intestinal helminthes probably affect at least 1.000 million; about 300 million are exposed to schistosomiasis, and 250 million to filariasis, not counting another 50 million at risk of acquiring onchocerciasis and river blindness. Of these helminthiases it is suggested that about 13% are transmitted by arthropods, 46% are soil-borne and 7% are transmitted through snails. Malaria, according to a recent WHO estimate, is still endemic in areas occupied by 800 million people (21% of the world's population). In Africa 50 million inhabitants face the threat of trypanosomiasis, and a similar number are exposed to Chagas' disease in the New World, while at least 7 million in various continents live in areas where leishmaniasis is present.

The diagnosis of tropical disease is complicated by lack of medical services, undernutrition and other socio-economic factors. These make correct diagnosis difficult, and may result in medical treatment being cursory, if not impossible. A further complicating factor is the need for preventive work to be carried out on a communal scale, in order to avoid reinfection of individuals.

This book is basically a ready reference to the commoner tropical diseases, and a guide to their etiology, epidemiology, pathology, clinical manifestations and treatment. It would be helpful to medical students from the tropics and subtropics. At the same time, it would prove useful to those who will work in temperate climates, for whom tropical diseases are a curious and exotic.

High speed air travel has resulted in the spread of many diseases beyond their natural geographical boundaries. Thus, patients may arrive in Ukraine, for example, with schistosomiasis or with Ebola fever. Etiologic agents of these infections may be transmitted to other individuals and medical workers would be able to recognize the signs and to treat the infected patient's symptoms.

PROTOZOAL INFECTIONS

MALARIA

Definition. Malaria – is a group of protozoan endemic diseases transmitted by the bite of infected Anopheles mosquitoes and characterized by periodic attacks of fever, associated with anemia, enlargement of spleen and liver.

Etyology. Malaria is caused by species of the obligate intracellular protozoa classified in the genus Plasmodium within the class Sporozoa. Although a large number of *Plasmodium spp.* naturally infect a variety of animals, such as monkeys, rodents, birds, and reptiles, only four species infect humans: *P. falciparum, P. vivax, P. malariae*, and *P. ovale*. Each species has certain morphologic characteristics by which the parasite is identified.

Epidemiology. Malaria is transmitted by the bites of infected female anopheline mosquitoes or by inoculation of infected blood (e.g. transfusion malaria, congenital malaria). Malaria parasites, which grow and develop inside the mosquito, need warmth to complete their growth before they are mature enough to be transmitted to humans. So malaria occurs in over 100 countries and territories in tropical and subtropical regions. 41% of the world's population lives in areas with malaria risk (parts of Africa, the Middle East, the Indian subcontinent, Southeast Asia, large areas of Central and South America, Hispaniola, and Oceania).

P. vivax is more common in Central America and the Indian subcontinent (India, Pakistan, Bangladesh, Sri Lanka), while *P. falciparum* infections occur much less frequently in these countries. *P. vivax* occurs rarely in Africa because of the resistance of most blacks, presumably because they lack the appropriate erythrocyte receptors associated with the Duffy blood group. *P. falciparum* predominates in Africa, Haiti, and New Guinea. The prevalence of *P. falciparum* and *P. vivax* malaria is approximately equal in South America, Southeast Asia, and Oceania. *P. ovale* occurs primarily in Africa, with rare cases on other continents. *P. malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less common. In some areas, such as in northern India, Sri Lanka, Southeast Asia, Ethiopia, southern Africa, and Madagascar, malaria behaves like an epidemic disease

Travel to endemic areas by European civilians and travel to the Europe by citizens from malarious areas are responsible for imported cases. Since the anopheline mosquito vectors continue to be present in large numbers in the United States and some European countries, transmission of parasites from imported cases of malaria is a continual risk. Congenital and transfusion malaria remain infrequent problems. Immunity against disease is hard won, full protective immunity is not acquired.

Pathogenesis. In the life cycle of plasmodia, asexual reproduction occurs in humans, and sexual reproduction occurs in the mosquito. Human infection begins when a female anopheline mosquito inoculates plasmodial sporozoites from its

salivary glands into subcutaneous capillaries during a blood meal. These infective forms circulate to the liver, where they invade hepatic parenchymal cells and begin a period of asexual reproduction.

During amplification process in the liver (known as intrahepatic or preerythrocytic schizogony) parasites multiply in stages called exoerythrocytic forms (EE forms) and become hepatic schizonts. After 1-2 weeks of development, the hepatic schizonts rupture, and each releases thousands of daughter merozoites, which enter the circulation and invade erythrocytes; at this point the symptomatic stage of the infection begins. In *P. falciparum* and *P. malariae*, all EE forms rupture more or less at the same time, and none persist chronically in the liver. In contrast, EE forms in *P. v*ivax and *P.ovale* exist in two types: the primary exoerythrocytic forms that develop and rupture, resulting in an initial wave of parasitemia within weeks after infection, and the latent exoerythrocytic dormant forms (also called hypnozoites) that may remain in the liver for months or years before they rupture, resulting in relapses of erythrocytic infection. Once the parasites enter the erythrocytic stage, they never reinvade the liver. Therefore, blood-induced infections (e.g., transfusion malaria) never result in development of exoerythrocytic forms.After entry into the bloodstream, merozoites rapidly invade erythrocytes and become trophozoites. The invasion depends on the interaction between specific surface receptors on merozoites and those on the surface of erythrocytes. Thus, for example, persons whose erythrocytes are Duffy blood-group negative (Most West Africans and people with origins in that region) are resistant to *P. vivax* infection.

The age of the erythrocyte is an important determinant of its susceptibility to invasion by different species of the parasite. Only young erythrocytes are infected by *P. vivax* and *P. ovale*, and only mature erythrocytes are susceptible to *P. malariae*. The magnitude of parasitemia is, therefore, limited in malarial infections due to these species. In contrast, *P. falciparum* can develop in erythrocytes of all ages, and parasitemia can reach very high levels, so infection with *P. falciparum* is frequently fatal if left untreated. Protection against falciparum malaria have the persons with genetic disorders affecting the red cells (sickle cell disease, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency). The development of *P. falciparum* is suppressed in the presence of fetal hemoglobin, hemoglobin S (HbS), and possibly also in the presence of certain other abnormal hemoglobins.

On entering the erythrocyte, merozoites acquire the appearance of ring forms. As development of the asexual parasite proceeds, the cytoplasm increases in quantity; at this stage the forms are called trophozoites. When nuclear division occurs, the parasites become known as schizonts. By the end of the 48-h intraerythrocytic life cycle (72 h for *P. malariae*), parasite progressively consumes and degrades intracellular proteins, principally hemoglobin. The red cell becomes more irregular in shape, more antigenic, less deformable. Nonspecific defense mechanisms activated.

Splenic immunologic and filtrative clearance functions are increased in malaria, and the removal of both parasitized and uninfected erythrocytes is accelerated.

Schizonts rupture to release 6 to 30 daughter merozoites. Within seconds the merozoites attach to and penetrate new erythrocytes and repeating the cycle. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures. The material released induces the activation of macrophages and the release of proinflammatory mononuclear cell-derived cytokines, which cause fever and exert other pathologic effects. Temperatures of 40°C are schizonticidal.

In *P. falciparum* infections in the second 24 h of the asexual cycle, membrane protuberances appear on the erythrocyte's surface, which extrude a high-molecular-weight, antigenically variant, strain-specific, adhesive protein that mediates attachment to receptors on venular and capillary endothelium and adhere to uninfected red cells to form rosettes. The processes of cytoadherence and rosetting are central to the pathogenesis of falciparum malaria. Thus the infected erythrocytes sequester inside the small blood vessels (particularly in brain and heart), where they interfere with microcirculatory flow and metabolism.

In the other three "benign" malarias, sequestration does not occur, and all stages of the parasite's development are evident on peripheral blood smears.

The disease in human beings is caused by the direct effects of red cell invasion and destruction by the asexual parasite and the host's reaction. During this process, some parasites develop into morphologically distinct sexual forms (gametocytes, still within the erythrocytes), which are long-lived. Parasites may persist in the blood for months (or, in the case of *P. malariae*, for many years) if treatment is not given.

After being ingested in the blood meal of a biting female anopheline mosquito, the male and female gametocytes form a zygote in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which then migrate in the hemolymph to the salivary gland of the mosquito to await inoculation into another human at the next feeding. This process of sporogony requires approximately 10 days.

Neither the presence of sporozoites or exoerythrocytic forms nor gametocytes are directly harmful to the host, and only the asexual intraerythrocytic parasites cause disease. The pathogenic mechanisms involved in establishing clinical illness can be divided into four basic processes: fever and its physiologic consequences; anemia; tissue hypoxia resulting from anemia and alterations in the microcirculation; initiation of immunopathologic events.

The basis of malarial fevers is schizont rupture. It has been postulated that endogenous pyrogen is secreted by tissue macrophages, which ingest erythrocyte and parasite debris released at the time of schizont rupture. Anemia is a common complication of malaria, and extensive hemolysis may occur in association with very

high parasitemias. Hemolysis results from rupture of infected erythrocytes during schizogony, splenic sequestration of erythrocytes, autoimmune mechanisms. When massive hemolysis and hemoglobinuria occur the condition is referred to as blackwater fever. A number of other serious complications can occur in *P. falciparum* malarial infections, including acute renal failure, pulmonary edema, and cerebral dysfunction. A common basis for these complications includes tissue hypoxia, which results from the anemia and alterations in the microcirculation.

Pathogenic mechanisms:

I. Fever and its physiologic consequences (endogenous pyrogen secreted by tissue macrophages, parasite debris released at the time of schizont rupture);
II. Extensive hemolysis and anemia (rupture of infected erythrocytes during schizogony, splenic sequestration of erythrocytes, autoimmune mechanisms);
III. Tissue hypoxia (anemia and alterations in the microcirculation);
IV. Initiation of immunopathologic events (antibody-mediated splenic sequestration of platelets, glomerulonephritis and nephrotic syndrome, immunosuppression, etc.)

Clinical manifestations. A primary malarial attack normally develops after an incubation period of 10-14 days. In tropical malaria the incubation period tends to be shorter and may only be five days. In naturally transmitted vivax and ovale malaria, especially in Europe, there may be latent period of several months before symptoms appear – latent malaria. The latent period usually covers the winter months. Many patients experience a prodromal period one to several days before the onset of the paroxysms and may complain of nonspecific symptoms, such as malaise, headache, myalgia, arthralgia and fatigue that are easily mistaken for a viral illness. In some cases it may be a prominence of headache, chest pain or diarrhea.

Quite a large proportion of malarial paroxysms “come off” between midnight and noon or in the early afternoon. Acute malarial paroxysm is divided into three phases: 1) cold phase, 2) hot phase and 3) sweating phase. One or even all these stages may be absent on occasions.

Cold phase of peripheral vasoconstriction lasts within minutes to 1-2 hours. The first symptoms are high fever, chills and rigors. The feeling of cold is intense and is purely subjective, because the temperature is rapidly rising. Patient shivers from head to foot. The teeth chatter. Vomiting may be most distressing. The cold, pale skin with cyanosis of the lips and nail beds and cutis anserina (goose flesh) attest to marked sympathetic discharge.

Hot phase may last from three to four hours. The temperature rises to 40-41°C, rarely higher, and the patient's skin becomes warm, hyperemic and dry. The shivering decreased and gives place to sensations of great heat. Tachycardia, tachypnea, cough, severe headache, backache, abdominal pain, nausea, vomiting, and delerium are characteristic of this phase.

Sweating phase usually lasts from two to four hours. The patient breaks out into profuse perspiration. With sweating the fever rapidly declines to subnormal. Headache, thirst and distress give place to a feeling of relief and tranquillity. Orthostatic hypotension resulting from a decrease in effective intravascular volume in the setting of marked peripheral vasodilatation commonly occurs. Euphoria and fatigue give way to sleep. Patients may be remarkably asymptomatic between paroxysms, in contrast to many other febrile illnesses. The total duration of the fever cycle may be from six to ten hours.

Primary *P. vivax* or *P. ovale* malaria produces a remittent or irregular fever before assuming the classical intermittent character with regular intervals every 48 hours. In *P. falciparum* malaria temperature never become regular and remains elevated between paroxysms.

On physical examination, patients frequently are found to have moderate splenomegaly. In nonimmune individuals the spleen takes several days to become palpable. Spontaneous rupture of the spleen, even after therapy is instituted, has been reported especially in *P. vivax* malaria. Vigorous palpation of the spleen may be dangerous and should be avoided. Tender hepatomegaly is also common, particularly among young children. Mild jaundice may develop in patients with falciparum malaria and usually resolves over 1 to 3 weeks.

Other physical findings that have been described in association with malaria but occur with less frequency include urticaria, petechial rash, conjunctival suffusion, scleral icterus, retinal vasospasm and hemorrhage, and herpes labialis. Auscultation of the chest may reveal scattered rales in some patients or, rarely, evidence of pulmonary consolidation. Cardiac examination is generally normal except for tachycardia. Fever and anemia may result in flow murmurs and may precipitate congestive heart failure in patients with underlying heart disease. The abdomen may be tender. Despite complaints of myalgia and arthralgia, neither muscle tenderness nor joint effusions are present. Peripheral edema is usually absent. In uncomplicated cases, the neurologic examination is normal, with the exception of delirium and other minor behavioral changes that may result from high fever.

A variety of abnormalities in routine laboratory tests may be encountered in patients with malaria. In addition to a normochromic, normocytic hemolytic anemia, leukopenia due to a decrease in granulocytes and lymphocytes is often present However, in the first few days of infection, a transient increase in the percentage of band forms is not unusual. Relative and absolute monocytosis frequently occurs, and monocytes may contain malarial pigment; erythrophagocytosis of normal and parasitized cells may occasionally be recognized. Platelet counts may reach very low levels (less than 50,000/mm3), but this rarely results in spontaneous hemorrhage and is rapidly reversible with the appropriate antimalarial chemotherapy. Malaria does not cause eosinophilia.

Urinalysis frequently reveals small amounts of protein, probably related to the effects of fever, and is otherwise normal. In the presence of acute tubular necrosis, casts can be seen in the sediment. Children with nephrotic syndrome due to *P. malariae* have marked proteinuria and may also have casts. Elevation in the blood urea nitrogen level may reflect fever and dehydration, but if serum creatinine levels rise disproportionately, renal failure must be considered. Electrolyte balance may be altered by several factors, such as dehydration, vomiting, tissue hypoxia, tachypnea, renal failure, and homeostatic responses to a decrease in effective plasma volume. Repeated serum electrolyte and blood gas determinations are important in assessing the changing status in severely ill patients. Liver function tests may reveal abnormalities, which include elevated transaminase levels and a mild to moderate increase in bilirubin (mostly indirect) but usually normal alkaline phosphatase levels. Marked abnormalities in liver function tests should suggest an associated illness or centrilobular necrosis complicating malaria. Hypoglycemia may complicate certain cases of malaria.

Complications include: cerebral malaria, hypoglycemia, lactic acidosis, acute renal failure, noncardiogenic pulmonary edema, hematologic abnormalities, aspiration pneumonia, superinfections, tropical splenomegaly, quartan malarial nephropathy, Burkitt's lymphoma and EBV infection

Cerebral malaria occurs as a complication of *P. falciparum* infection, although tissue hypoxia resulting from any malaria infection could pose a risk of cerebral ischemia and infarction in patients with cerebrovascular disease. The onset may be gradual or sudden following a convulsion. The neurologic abnormalities that have been observed in association with cerebral involvement include disturbance of consciousness ranging from somnolence to coma, acute organic brain syndromes with altered intellectual function, behavioral changes, or hallucinations, major motor seizures, meningismus, and, rarely, focal neurologic signs, such as Babinski reflexes or hemiparesis, or movement disorders, such as tremors, myoclonus, and choreiform movements. Lumbar puncture is not diagnostic; an increased opening pressure due to cerebral edema and a normal cerebrospinal fluid (CSF) profile may be found. Rarely, an increased CSF protein concentration and lowgrade pleocytosis have been reported. In patients with cerebral malaria whose neurologic defects are predominantly focal, or in those who have increased erythrocytes or leukocytes in the CSF, evaluation should be undertaken to exclude other pathologic processes. It may be impossible to distinguish febrile convulsions from cerebral malaria in children with *P. falciparum* infection. Worsening cerebral dysfunction in patients with falciparum malaria, even during therapy, may be a sign of hypoglycemia. An important and common complication of severe malaria, hypoglycemia is associated with a poor prognosis and is particularly problematic in children and pregnant women. Hypoglycemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the

consumption of glucose by both host and parasite.

Malaria can be transmitted by blood transfusion, needle-stick injury, sharing of needles by infected drug addicts, or organ transplantation. The incubation period in these settings is often short because there is no preerythrocytic stage of development. The clinical features and management of these cases are the same as for naturally acquired infections, although falciparum malaria tends to be especially severe in drug addicts. Radical chemotherapy with primaquine is unnecessary for *P. vivax* and *P. ovale* infections.

Diagnosis. The ability of malaria to masquerade as other diseases is well known and frequently results in delays in establishing the correct diagnosis. The diagnosis of malaria rests on the demonstration of parasites in stained peripheral blood smears subjected to Romanovsky-Giemsa staining. A diagnosis of malaria can only be excluded by obtaining negative blood smears on several successive days. Once parasites are detected, thin smears should be examined in an effort to make a species diagnosis. Although enzyme-linked immunosorbent assay (ELISA) and indirect hemagglutination (IHA) are available. Serologic tests in malaria are useful in epidemiologic surveys and in identifying infected donors in cases of transfusion malaria.

Differential diagnosis includes cerebro-spinal meningitis, leptospirosis, typhus, amoebic hepatitis and abscess of liver, dengue fever, kala-azar relapsing fever, trypanosomiasis, tuberculous infection, endocarditis, etc.

Treatment. The choice of drug depends on the likely sensitivity of the infecting parasites. Despite recent evidence of chloroquine resistance in *P. vivax* from Oceania, uncomplicated malaria Infections due to *P. vivax*, *P. malariae*, *P. ovale*, and known sensitive strains of *P. falciparum* should be treated with oral chloroquine. If there is any doubt about the resistance status of the infecting organism, then quinine or quinidine should be given. In Africa, chloroquine-resistant strains are usually sensitive to sulfadoxine-pyrimethamine. Where there is resistance to the latter combination as well, quinine plus tetracycline/doxycycline or mefloquine should be used; tetracycline and doxycycline cannot be given to pregnant women or to children 8 years of age. Mefloquine (if available) or quinine in combination with a tetracycline is recommended for antifolate (fansidar)-resistant falciparum malaria. Significant resistance to mefloquine has been documented in Thailand, Burma, Vietnam, and Cambodia. In some areas, the Chinese drugs derived from artemisinin (artemether and artesunate) have become first-line treatments for severe malaria. These agents are rapidly effective against multidrug-resistant falciparum malaria.

Patients with severe malaria or those unable to take oral drugs should receive parenteral antimalarial therapy.

Primaquine should be given daily for 14 days to patients with *P. vivax* or *P.ovale* infections.

Malaria treatment

Chloroquine-sensetive malaria	Chloroquine-resistant *P. falciparum*- and *P.vivax*- malaria
Oral Chloroquine phosphate (Delagil) 600 mg base (1 g), then 300 mg base (500 mg) at 6h, 24h, and 48 h ***Followed by (for P. vivax and P. ovale only) for radical cure:*** Primaquine phosphate 15 mg base (26.3 mg)/d for 14 days or 45 mg base (79 mg)/wk for 8 weeks	**Oral** 1. Quinine sulfate 650 mg tid for 7 days ***plus one of the following:*** Pyrimethamine-sulfadoxine (Fansidar) 3 tablets at once on last day of quinine, Doxicycline 100 mg bid for 7 days, Tetracycline 250 mg qid for 7 days, Clindamycin 900 mg tid for 3 days 2. Mefloquine (Lariam) 750 mg followed by 500 mg 6-12 h later. Total dose 1.250 mg 3. Halofantrine 500 mg q6h for 3 doses, repeated in 1 week
Parenteral Quinidine gluconate 10 mg/kg loading dose (max 600 mg) over 1 h followed by continuous infusion of 0.02 mg/kg/min for 3 days maximum	**Parenteral** Quinidine gluconate as above

Prevention. In most of the tropics, the eradication of malaria is not feasible because of the widespread distribution of Anopheles breeding sites, the great number of infected persons, and inadequacies in resources, infrastructure, and control programs. Where possible, the disease is contained by judicious use of insecticides to kill the mosquito vector, rapid diagnosis and appropriate patient management, and administration of chemoprophylaxis to high-risk groups. Despite massive investment in efforts to develop a malaria vaccine, no safe, effective, long-lasting vaccine is likely to be available for general use in the near future.

Simple measures to reduce the frequency of mosquito bites in malarious areas are very important. These measures include the avoidance of exposure to mosquitoes at their peak feeding times (usually dusk and dawn) and the use of insect repellents, suitable clothing, and insecticide-impregnated bed nets. Widespread use of bed nets, particularly those treated with permethrin (a residual pyrethroid), often reduces the incidence of malaria and has recently been shown to reduce mortality in western and eastern Africa.

Few areas of therapeutics are as controversial as antimalarial drug prophylaxis. Recommendations for prophylaxis depend on knowledge of local patterns of plasmodial drug sensitivity and the likelihood of acquiring malarial infection. Chemoprophylaxis is never entirely reliable, and malaria should always be considered in the differential diagnosis of fever in patients who have traveled to endemic areas, even if they are taking prophylactic antimalarial drugs.

All pregnant women at risk should receive prophylaxis. In addition, antimalarial prophylaxis should be considered for children between the ages of 3 months and 4 years in areas where malaria causes high childhood mortality. However, such prophylaxis may not be logistically feasible in many countries. Children born to nonimmune mothers in endemic areas (usually expatriates moving to these areas) should receive prophylaxis from birth.

Travelers should start taking antimalarial drugs at least 1 week before departure so that any untoward reactions can be detected and therapeutic antimalarial blood concentrations will be present when needed. Antimalarial prophylaxis should continue for 4 weeks after the traveler has left the endemic area. Mefloquine has become the antimalarial prophylactic agent of choice for much of the tropics because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well tolerated. Nausea, dizziness, muzziness, disturbed sleep patterns, and dysphoria are relatively common. Approximately 1 in every 10,000 recipients develops an acute reversible neuropsychiatric reaction manifest by confusion, psychosis, convulsions, or encephalopathy. In recent studies in Africa, mefloquine prophylaxis was found to be effective and safe during pregnancy. Daily administration of doxycycline is an effective alternative to mefloquine that also exhibits some causal (preerythrocytic) prophylactic activity. It is generally well tolerated but may cause vulvovaginal thrush, diarrhea, and photosensitivity and cannot be used by children less than 8 years old or by pregnant women. Recent studies indicate that daily primaquine is effective for prophylaxis of *P. falciparum* and *P. vivax* malaria; further confirmatory studies are needed.

Chloroquine remains the drug of choice for the prevention of infection with drug-sensitive *P. falciparum* and with the other human malarial species (although chloroquine resistance in *P. vivax* has been reported recently from parts of eastern Asia and Oceania). This agent is generally well tolerated, although some patients are unable to take the drug because of dysphoria, headache, or in dark-skinned patients pruritus (a concomitant filarial infection may provoke or aggravate chloroquine-induced pruritus). Chloroquine is considered safe in pregnancy. With chronic administration over more than 5 years, a characteristic dose-related retinopathy may develop, but this condition is rare at the doses used for antimalarial prophylaxis. Idiosyncratic or allergic reactions are likewise rare. Skeletal and cardiac myopathy are rare and much more likely at the high doses used in the treatment of rheumatoid arthritis. Neuropsychiatric reactions and skin rashes are unusual. Amodiaquine, a related aminoquinoline, is associated with a high risk of agranulocytosis (approximately 1:2000) and is not recommended.

In the past, the dihydrofolate reductase inhibitors pyrimethamine and proguanil (chloroguanide) have been administered widely, but resistant strains of both *P.falciparum* and *P. vivax* have limited their use. Whereas antimalarial quinolines

such as chloroquine act on the erythrocyte stage of parasitic development, the dihydrofolate reductase inhibitors also inhibit preerythrocytic growth in the liver and development in the mosquito. Proguanil is safe and well tolerated, although mouth ulceration occurs in 8% of persons using this drug; it is considered the safest agent for antimalarial prophylaxis in pregnancy. The prophylactic use of the combination of pyrimethamine and sulfadoxine is not recommended because of an unacceptable incidence of severe toxicity, principally exfoliative dermatitis and other skin rashes, agranulocytosis, hepatitis, and pulmonary eosinophilia. The combination of pyrimethamine with dapsone (0.2/1.5 mg/kg weekly; 25/200 mg maximum) is a second-line drug available in some countries and can be used in areas with chloroquine-resistant *P. falciparum*. This combination is generally well tolerated; however, resistance is increasing, and dapsone may cause methemoglobinemia and allergic reactions and (at higher doses) may pose a significant risk of agranulocytosis.

Because of the increasing spread and intensity of plasmodial resistance to chloroquine in Africa and other areas of the world a weekly dose of mefloquine for all travelers recommends.

Malaria prophylaxis

Chloroquine-sensitive areas	***Chloroquine-resistant areas***
Chloroquine phosphate 300 mg base (500 mg salt) given PO once a week beginning 1 week before and continuing for 4 weeks after last exposure	1. Mefloquine 250 mg given PO once a week and continuing for 4 weeks after last exposure 2. Doxycycline 100 mg/d during exposure and for 4 weeks afterward 3. Chloroquine phosphate as in chloroquine-sensitive areas ***plus*** pyrimethamine-sulfadoxine for presumptive treatment ***or plus*** proguanil 200 mg/d in sub-Saharan Africa during exposure and for 4 weeks afterward

LEISHMANIASIS

Definition. The term “leishmaniases” refers collectively to various clinical syndromes that are caused by obligate intracellular protozoa of the genus *Leishmania* (order *Kinetoplastida*). Leishmaniasis is endemic in diverse ecologic settings in the tropics and subtropics, ranging from deserts to rain forests and from rural to periurban areas. It typically is a vector-borne zoonosis, with rodents, small mammals, and canines as common reservoir hosts and humans as incidental hosts. In humans, visceral, cutaneous, and mucosal leishmaniases result from infection of macrophages throughout the mononuclear-phagocyte system, in the skin, and in the naso-

oropharyngeal mucosae, respectively. The age range of infected persons depends on such factors as the duration of leishmaniasis endemicity in the specific geographic area, sandfly behavior (e.g., whether the sandfly species typically is intra- or extradomiciliary), and host behavior and immunity. Current challenges in this field include the emergence of leishmaniasis in new geographic areas and host populations [e.g., visceral leishmaniasis in civil war-affected southern Sudan and in persons infected with human immunodeficiency virus (HIV)] and the need for field-applicable, rapid diagnostic tests; efficacious, safe, inexpensive, and short-course oral treatment regimens; and effective and affordable control measures and immunoprophylactic agents.

Etiology. Visceral leishmaniasis is typically but not exclusively caused by organisms of the *Leishmania donovani* complex; Old World cutaneous leishmaniasis by *Leishmania tropica*, *Leishmania major*, and *Leishmania aethiopica*; New World (or American) cutaneous leishmaniasis by organisms of the *Leishmania mexicana* complex and the species now commonly placed in the subgenus *Viannia* (*Leishmania braziliensis*, *Leishmania guyanensis*, *Leishmania panamensis*, and *Leishmania peruviana*); and mucosal leishmaniasis by some organisms in the latter group.

Because all of the leishmanial parasites associated with human disease are morphologically similar, their identification and classification can be challenging. Information on factors such as setting of acquisition (epidemiologic and geographic) and clinical manifestations is valuable; however, this information does not serve to classify the organisms taxonomically since these factors are quite variable. Thus, data on the intrinsic characteristics of the parasites are needed. To this end, the biochemical characteristics of *Leishmania* have been studied by techniques such as isoenzyme analysis, the genetic characteristics by methods including kinetoplast-DNA hybridization, and the immunologic characteristics by approaches such as monoclonal antibody specificity determination and excreted-factor serotyping.

Epidemiology. Leishmaniasis is transmitted by the bite of female phlebotomine sandflies [genus *Phlebotomus* (Old World) or *Lutzomyia* (New World)]. As the flies attempt to feed, they regurgitate the parasite's flagellated promastigote stage into the skin of mammalian hosts. The saliva of *Lutzomyia longipalpis* sandflies, which transmit *Leishmania chagasi* infection, contains an erythema-producing peptide (maxadilan) that may enhance the infectivity of promastigotes and influence the course of infection. Promastigotes attach to receptors on macrophages, are phagocytized, and transform within phagolysosomes into the nonflagellated amastigote stage, which multiplies by binary fission. After rupture of infected macrophages, amastigotes are phagocytized by other macrophages. If ingested by feeding sandflies, amastigotes transform back into promastigotes, which require at least 7 days to become infective.

Pathogenesis. Advances in the understanding of the immunology of

leishmaniasis have made this parasitic disease the paradigm for studies of the T cell subsets and cytokines that govern resistance and susceptibility to intracellular pathogens. The paradigm is best demonstrated in murine leishmaniasis. In inbred mice, the nature of the T cell response determines the outcome of *L. major* infection: T helper type 1 (Th1) cells, which produce interferon g and interleukin (IL) 2, are involved in cell-mediated immunity and resistance (the healing phenotype), whereas T helper type 2 (Th2) cells, which produce IL-4, IL-5, and IL-10, confer susceptibility (the nonhealing phenotype).

Not all aspects of leishmaniasis in mice, whose susceptibility to leishmanial infection is genetically determined, apply to human infection, for which the genetic determinants have yet to be identified. However, a consistent principle is that healing and resistance to reinfection are associated with expanding numbers of *Leishmania*-specific Th1 cells, production of interferon g, and activation of macrophages to kill intracellular amastigotes. Whereas IL-12 promotes the development of Th1 responses, factors such as IL-4 and transforming growth factor b (murine leishmaniasis) and IL-10 (human visceral leishmaniasis) suppress their development. In murine macrophages, nitrogen oxides mediate intracellular killing, which occurs by nonoxidative mechanisms.

Diagnosis. Definitive diagnosis of leishmaniasis has historically required demonstration of the parasite. To identify amastigotes by light-microscopic examination, the specimen obtained from an infected site (e.g., thin smear, histologic section) should be stained with Giemsa or another Romanovsky stain and presumptive amastigotes (2 to 4 um in diameter) examined under oil immersion for the presence of a nucleus and a rod-shaped kinetoplast; the latter is a specialized mitochondrial structure that contains extranuclear DNA. Other means of parasitologic confirmation include in vitro culture (e.g., on Novy-MacNeal-Nicolle medium), inoculation into animals (e.g., golden hamsters, BALB/c mice), and use of molecular techniques (e.g., polymerase chain reaction). The parasites can be identified to the species level by isoenzyme analysis of cultured promastigotes or by use of monoclonal antibodies or DNA probes.

Indirect immunologic methods for diagnosis include serologic assays (e.g., indirect immunofluorescence antibody testing) and tests for *Leishmania*-specific cell-mediated immunity (e.g., skin testing for delayed-type hypersensitivity reactions). The usefulness of such methods depends on the clinical syndrome (see, for example, the section on diagnosis of visceral leishmaniasis). However, traditional serologic assays do not reliably distinguish past from current infection.

Treatment. For decades, the pentavalent antimonial (Sbv) compounds sodium stibogluconate (Pentostam; 100 mg of Sbv/mL) and meglumine antimonate (Glucantime; 85 mg of Sbv/mL) have been the mainstay of therapy for leishmaniasis. The CDC generally recommends a daily parenteral (either intravenous or

intramuscular) dose of 20 mg of Sbv/kg, with a duration of therapy of 20 consecutive days for cutaneous leishmaniasis and 28 consecutive days for visceral and mucosal leishmaniasis. Alternative Sbv regimens (e.g., longer or shorter courses) may have merit in some circumstances. Toxicity (manifested, for example, as myalgia, arthralgia, fatigue, hepatotoxicity, chemical pancreatitis, or electrocardiographic abnormalities) becomes increasingly common as the course of treatment progresses but usually does not limit therapy and is reversible.

Amphotericin B and pentamidine are the traditional parenteral alternatives to Sbv but are generally considered more toxic. Amphotericin B elicits reactions such as fever, chills, hypotension, nephrotoxicity, hypokalemia, and anemia, while pentamidine can cause hypotension, hypoglycemia, diabetes, vomiting, and pain at the injection site. Many other agents have been advocated as alternatives or adjuncts to Sbv, often on the basis of suboptimal data; even the results of well-conducted clinical trials may not be generalizable to the treatment of patients in other settings, particularly patients infected with other leishmanial species or strains. Even in the absence of a consensus about if, when, or how to use other agents, it is important to consider whether the patient's illness could result in substantial morbidity or in death and therefore requires expeditious treatment with a regimen that usually is highly effective.

Prevention. The transmission of *Leishmania* species is typically focal, with local "hot spots." This pattern is due in part to the characteristics of sandflies, whose flight is noiseless and limited in range; because of their short, hopping flight style, they usually remain within a few hundred meters of their breeding site. They rest in dark, moist places and are found in habitats ranging from deserts to rain forests; peridomestic sandflies rest in debris or rubble near buildings.

Personal protective measures include the avoidance of outdoor activities when sandflies are most active (dusk to dawn); the use of mechanical barriers such as screens and bed-nets that keep out sandflies, which are about one-third the size of mosquitoes; the wearing of protective clothing; and the application of insect repellent to exposed skin. Impregnation of clothing, bed-nets, and screens with permethrin may also be useful, as may spraying of dwellings with residual-action insecticide. Vaccine strategies are being investigated. Treatment of human cases is an effective control measure only where humans are the primary reservoirs of infection. Vector control and elimination of reservoir hosts (e.g., domestic dogs) may be useful in some settingssfor example, where transmission is intra- or peridomiciliary.

VISCERAL LEISHMANIASIS

Visceral leishmaniasis, which has been reported in 47 countries and continues to be epidemic in eastern India, has emerged in new geographic areas (e.g., southern Sudan, where persons of all ages have been affected), in new settings (e.g., suburban areas in northeastern Brazil, where most cases have occurred in children <10 years of

age), and among new host populations (e.g., HIV-infected persons). The causative leishmanial species typically are species of the *L. donovani* complex; *Leishmania amazonensis* in Latin America and *L. tropica* in the Old World also can cause visceral infection. The organisms can be transmitted not only by sandflies but also congenitally and parenterally (e.g., via blood transfusion or sharing of needles). Infection begins in macrophages at the inoculation site (e.g., in dermal macrophages at the site of a sandfly bite) and disseminates throughout the mononuclear-phagocyte system in the context of both specific (i.e., to leishmanial antigens) and nonspecific (e.g., to tuberculin) anergy.

Clinical manifestations. Visceral infection can remain subclinical or can become symptomatic, with an acute, subacute, or chronic course. In some settings, inapparent infections far outnumber clinically apparent ones; malnutrition is a risk factor for the development of disease. The incubation period usually ranges from weeks to months but can be as long as years. Whereas the general term *visceral leishmaniasis* covers a broad spectrum of severity and manifestations, the term *kala-azar* (Hindi for "black fever," indicating that the skin can turn gray) generally conjures up the classic image of profoundly cachectic, febrile patients who are heavily parasitized and have life-threatening disease. Splenomegaly (with the spleen most often soft and nontender) typically is more impressive than hepatomegaly, and the spleen can in fact be massive; both splenomegaly and hepatomegaly in visceral leishmaniasis result from reticuloendothelial cell hyperplasia. Peripheral lymphadenopathy is common in some geographic areas, including Sudan.

The abnormal laboratory findings associated with advanced disease include pancytopeniasanemia, leukopenia (neutropenia, marked eosinopenia, relative lymphocytosis and monocytosis), and thrombocytopeniasas well as hypergammaglobulinemia (chiefly involving IgG, from polyclonal B cell activation) and hypoalbuminemia. Causes of anemia can include bone-marrow infiltration, hypersplenism, autoimmune hemolysis, and bleeding.

Some patients develop post-kala-azar dermal leishmaniasis. This syndrome is manifested by skin lesions (including pigmented or depigmented macules, papules, nodules, and patches) that typically are most prominent on the face. These lesions can develop during or within a few months after therapy (e.g., in East Africa) or years after therapy (e.g., in India). Visceral infection can relapse. Persons with persistent skin lesions can serve as reservoirs of infection.

So-called viscerotropic leishmaniasis caused by *L. tropica*, which typically is dermotropic, has been recognized among U.S. soldiers who participated in Operation Desert Storm in the Persian Gulf. The affected persons have had light parasite burdens and either no symptoms or nonspecific symptoms such as fatigue, fever, and gastrointestinal problems.

Diagnosis. Parasitologic diagnosis of visceral leishmaniasis is accomplished by

demonstration of the parasite on stained slides or in cultures of a tissue aspirate or a biopsy specimen (e.g., of spleen, liver, bone marrow, or lymph node). The diagnostic yield is highest for splenic aspiration (specifically, as high as 98% for splenic aspirates vs. < 90% for other specimens), but this procedure can cause hemorrhage. Patients who have kala-azar typically carry a relatively heavy parasite burden; develop high titers of antibody to *Leishmania* (diagnostically useful but not protective); and have undetectable *Leishmania*-specific cell-mediated immunity (with leishmanin skin-test reactivity as well as lymphocyte proliferation and interferon g responses to leishmanial antigens noted only after recovery). In contrast, viscerotropic leishmaniasis can be difficult to diagnose because of a light parasite burden and a minimal antibody response.

A noninvasive method for diagnosing kala-azar based on antibody testing with *Leishmania* K39 antigen-impregnated nitrocellulose paper strips has recently been described. This method, which is estimated to be 100% sensitive and 98% specific, offers promise for rapid, accurate field diagnosis of visceral leishmaniasis, but requires confirmation under actual field conditions.

The differential diagnosis of visceral leishmaniasis includes other tropical infectious diseases that cause fever or organomegaly (e.g., typhoid fever, miliary tuberculosis, brucellosis, malaria with tropical splenomegaly syndrome, and schistosomiasis) as well as diseases such as leukemia and lymphoma. Post-kala-azar dermal leishmaniasis should be differentiated from syphilis, yaws, and leprosy.

Treatment. Because classic cases of kala-azar generally are fatal if not appropriately treated, highly effective therapy is essential, as is close monitoring for bleeding and intercurrent infectious conditions such as pneumonia and diarrhea. In general, use of a pentavalent antimonial agent (i.e., 20 mg of Sbv/kg given intravenously or intramuscularly once daily for 28 consecutive days) still constitutes first-line therapy. However, parasite-related factors such as apparent primary drug resistance and host characteristics such as coinfection with HIV can complicate treatment so that prolonged Sbv administration or use of an alternative or adjunctive agent may be indicated (see below).

Typically, patients feel better and become afebrile during the first week of treatment. Abnormal laboratory findings and splenomegaly improve during therapy but may take weeks or months to resolve; the reappearance of eosinophils in the leukocyte differential count is a good sign. The best indicator of permanent cure is freedom from clinical relapse during at least 6 months of follow-up. Repeat tissue sampling is indicated if the patient's status is in question. The results of repeat tissue sampling must be interpreted with caution: the persistence of some parasites is not necessarily a poor prognostic indicator, whereas the apparent absence of parasites does not ensure that the patient will not relapse. The possibility of HIV coinfection should be considered if the patient does not respond to therapy or repeatedly relapses.

In India, where unresponsiveness to Sbv therapy is becoming increasingly problematic, amphotericin B (0.5 to 1.0 mg/kg daily or every other day, given intravenously for a total dose of 7 to 20 mg/kg) has been found to be a highly effective, though potentially toxic, alternative. Pentamidine (2 to 4 mg/kg daily or every other day, given intravenously or intramuscularly for at least 15 doses) is reasonably effective but may need to be administered in prolonged courses that are associated with toxicity. Formulations of liposomal amphotericin B may prove highly effective and less toxic: liposomes passively target amphotericin away from the kidneys to macrophage-rich organs.

Various parenteral agents have been advocated as adjuncts to accelerate or improve the response to Sbv therapy. The aminoglycoside aminosidine (12 to 15 mg/kg per day, intravenously or intramuscularly), which is the chemical equivalent of paromomycin, is an effective adjunct. Cytokine immunotherapy with subcutaneous injections of recombinant interferon g or granulocyte macrophage colony-stimulating factor, both of which activate macrophages, also shows promise as an adjunctive measure. The oral agents allopurinol and ketoconazole have been used as adjuncts, but, because of the highly variable results obtained, their use cannot be generally recommended.

Visceral leishmaniasis in HIV-infected persons. Visceral leishmaniasis is becoming an important opportunistic infection among persons infected with HIV-1 in geographic areas in which both infections are endemic. To date, most coinfections have been reported from southern Europe, where *Leishmania infantum* is endemic and visceral leishmaniasis is no longer primarily a disease of young children. In HIV-infected patients, even relatively avirulent leishmanial strains can disseminate to the viscera. Clinical leishmaniasis in patients with HIV infection can represent newly acquired or reactivated infection; most coinfected patients who have clinically evident leishmaniasis have fewer than 200 CD4 lymphocytes per microliter. A better understanding of the interaction of these two infections is needed.

A diagnosis of visceral leishmaniasis should be considered for HIV-infected patients who have ever been in leishmaniasis-endemic areas and who have such manifestations as unexplained fever, organomegaly, anemia, or pancytopenia. Coinfected patients can develop unusual manifestations of visceral leishmaniasis, in part because of atypical localization of the parasite (e.g., in the gastrointestinal tract).

The diagnostic sensitivity of classic serologic methods is lower in coinfected than in immunocompetent patients (about 50% vs. >90%). On the other hand, parasitologic diagnosis by noninvasive means is easier in the case of coinfected patients; parasites are more commonly found in the circulating blood monocytes of these patients, and sensitivities are about 50% for a Giemsa-stained peripheral-blood smear and 70 to 75% for a stained or cultured buffy-coat preparation. Invasive methods of parasitologic diagnosis (e.g., microscopic examination or culture of a

bone-marrow aspirate) typically are highly sensitive, especially for previously untreated patients, who commonly have heavy parasite burdens.

Coinfected patients may initially respond well to antileishmanial therapy, albeit with more drug toxicity than is experienced by most immunocompetent persons. However, coinfected patients commonly have a chronic or relapsing course, seemingly irrespective of the drug regimens used for induction and suppression therapy. Comparative clinical trials of candidate drug regimens are urgently needed.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis, which has been reported from 61 countries, has traditionally been classified as New World (American) or Old World. Local names for New World disease include *chiclero ulcer*, *pian bois* (bush yaws), and *uta*; those for Old World disease include *oriental sore*, *bouton d'orient*, *Aleppo boil,* and *Baghdad sore*. In the Americas, the leishmaniasis-endemic area extends from southern Texas to northern Argentina; in many affected regions, most cases occur in men who have forest-related occupational exposures. The etiologic agents typically are those of the *L. mexicana* complex and the *Viannia* group but also include *L. major*-like organisms and *L. chagasi*. Old World cutaneous leishmaniasis is caused by *L. tropica*, *L. major*, and *L. aethiopica* as well as by *L. infantum* and *L. donovani*.

Clinical manifestations. Although the incubation period for clinically evident disease typically ranges from weeks to months, local trauma can activate latent infection. The first clinical manifestation is usually a papule at the site of the sandfly bite but is sometimes regional lymphadenopathy (sometimes bubonic) in *L. (V.) braziliensis* infection. Most skin lesions evolve from papular to nodular to ulcerative, with a central depression (which can be several centimeters in diameter) surrounded by a raised indurated border; some lesions persist as nodules or plaques. Multiple primary lesions, satellite lesions, regional adenopathy, sporotrichosis-like subcutaneous nodules, lesion pain or pruritus, and secondary bacterial infection are variably present. The infecting species, the location of the lesion, and the host's immune response are major determinants of the clinical manifestations and chronicity of untreated lesions. For example, in the New World, lesions caused by *L. mexicana* tend to be smaller and less chronic than those caused by *L. (V.) braziliensis*; in the Old World, *L. major* tends to cause "wet" exudative lesions that are less chronic than the "dry" lesions with central crusting that are caused by *L. tropica*. The spontaneous resolution of lesions, which may require weeks, months, or even years, does not preclude reactivation or reinfection.

The polyparasitic and oligoparasitic ends of the spectrum of cutaneous leishmaniasis are respectively represented by the rare syndromes of diffuse cutaneous leishmaniasis (DCL) and leishmaniasis recidivans, both of which are notoriously difficult to treat. DCL, caused by *L. aethiopica* (Old World) or by the *L. mexicana* complex (New World), develops in the context of *Leishmania*-specific anergy and is

manifested by chronic, nonulcerative skin lesions; on histopathologic examination of samples of these lesions, abundant parasites but few lymphocytes are noted. Leishmaniasis recidivans, a hyperergic variant with scarce parasites, is usually caused by *L. tropica* and manifested by a chronic solitary lesion on the cheek that expands slowly despite central healing.

Diagnosis. Dermal scrapings of debrided ulcerative lesions are useful for histologic examination, aspirates of skin lesions and lymph nodes for in vitro culture, and biopsy specimens for both examination and culture. Although examination of histologic sections of biopsy specimens can help exclude other diagnoses, amastigotes appear larger and are more easily recognizable on Giemsa-stained thin smears (e.g., smears of dermal scrapings, touch preparations of biopsy specimens). As lesions age, amastigotes become more scarce and parasitologic confirmation becomes more difficult. Serologic testing is an insensitive means for diagnosing cutaneous leishmaniasis; antibody titers are at most minimally elevated except in patients who have DCL. In contrast, leishmanin skin-test reactivity usually is evident or develops in persons who have simple cutaneous or recidivans leishmaniasis but not in those who have DCL.

Cutaneous leishmaniasis is frequently confused with tropical, traumatic, and venous-stasis ulcers; foreign-body reactions; superinfected insect bites; impetigo; fungal infections (e.g., sporotrichosis); mycobacterial infections; and other diseases (e.g., sarcoidosis, neoplasms). DCL and leishmaniasis recidivans must be differentiated from lepromatous leprosy and lupus vulgaris, respectively.

Treatment. In decisions about whether and how to treat cutaneous leishmaniasis, the possibility of mucosal dissemination should be considered, as should lesion location (the cosmetic implications), number, size, evolution, and chronicity. When optimal efficacy is important, Sbv therapy is recommended. In general, a regimen of 20 mg of Sbv/kg (intravenous or intramuscular) should be given once daily for 20 consecutive days; lower daily doses or shorter courses may have merit in some situations. The clinical response begins with lesion flattening and continues after the end of therapy, whereas relapse typically is manifested by clinical reactivation at the margin of the lesion.

Pentamidine (3 mg/kg intramuscularly, every other day for four doses) is an effective parenteral alternative to Sbv. The oral agents that are currently availablesmost notably, the imidazoles ketoconazole (adult dosage, 600 mg/d for 28 days) and itraconazole (adult dosage, 200 mg twice daily for 28 days); allopurinol; and dapsonesprobably are modestly active at best and are effective only against some leishmanial species/strains. Adjunctive immunotherapy remains highly experimental but may be useful in DCL.

Unless used in an adjunctive role, local or topical therapy should be considered only for the treatment of infection that does not have the potential for dissemination

(e.g., for relatively benign lesions caused by *L. mexicana* or *L. major*). Examples of local approaches include the application of an ointment containing paromomycin and methylbenzethonium chloride, the intralesional administration of Sbv (not an approved use of drug obtained through the CDC), heat therapy, and cryotherapy. Excisional biopsy poses a substantial risk for relapse and is not recommended.

MUCOSAL LEISHMANIASIS

Leishmanial infection of the naso-oropharyngeal mucosae is a relatively rare but potentially disfiguring metastatic complication of cutaneous leishmaniasis. Mucosal disease develops despite antileishmanial cell-mediated immunity and most commonly is caused by organisms of the *Viannia* group [typically *L. (V.) braziliensis* but also *L. (V.) panamensis* and *L. (V.) guyanensis*]. Although mucosal disease usually becomes clinically evident within several years after the healing of the original cutaneous lesions, cutaneous and mucosal lesions can exist simultaneously or can appear decades apart. Typically, the original cutaneous lesions in these cases were not treated or were inadequately treated.

Mucosal involvement generally is manifested first by persistent unusual nasal symptoms (e.g., epistaxis), with erythema and edema of the nasal mucosae, and then by progressive, ulcerative, naso-oropharyngeal destruction. Supportive laboratory data (e.g., a positive serologic test) are useful, but the scarcity of amastigotes makes parasitologic confirmation difficult. The differential diagnosis includes sarcoidosis, neoplasms, midline granuloma, rhinoscleroma, paracoccidioidomycosis, histoplasmosis, syphilis, and tertiary yaws.

Pentavalent antimonial therapy (20 mg of Sbv/kg per day, given intravenously or intramuscularly for 28 days) is moderately effective for mild mucosal disease, whereas advanced disease may not respond to such therapy or may relapse repeatedly. Therapy with amphotericin B is the best alternative currently available. Patients who develop signs of respiratory compromise during therapy may benefit from concomitant steroid treatment.

TRYPANOSOMIASIS

AMERICAN TRYPANOSOMIASIS

Definition. American trypanosomiasis, or Chagas' disease, is a zoonosis caused by the protozoan parasite *Trypanosoma cruzi*. Acute Chagas' disease is usually a mild febrile illness that results from initial infection with the organism. After spontaneous resolution of the acute illness, most infected persons remain for life in the indeterminate phase of chronic Chagas' disease, which is characterized by subpatent parasitemia, easily detectable antibodies to *T. cruzi*, and an absence of symptoms. In a minority of chronically infected patients, cardiac and gastrointestinal lesions develop that can result in serious morbidity and even death.

Epidemiology. *T. cruzi* is transmitted among its mammalian hosts by

hematophagous triatomine insects, or reduviid bugs. The insects become infected by sucking blood from animals or humans who have circulating parasites. Ingested organisms multiply in the gut of the reduviids, and infective forms are discharged with the feces at the time of subsequent blood meals. Transmission to a second vertebrate host occurs when breaks in the skin, mucous membranes, or conjunctivae become contaminated with bug feces that contain infective parasites. The presence of *T. cruzi* carriers creates a substantial risk of transmission by blood transfusion. *T. cruzi* also can be transmitted from mother to fetus, and in laboratory accidents.

T. cruzi is found only in the Americas. Wild and domestic mammals harboring *T. cruzi* and infected reduviids are found in spotty distributions from the southern United States to southern Argentina. Humans become involved in the cycle of transmission when infected vectors take up residence in the primitive wood, adobe, and stone houses common in much of Latin America. Thus, human *T. cruzi* infection is a health problem primarily among the poor in rural areas of Central and South America. Most new *T. cruzi* infections in rural settings occur in children, but the incidence is unknown because most cases go undiagnosed. Thousands of individuals also become infected every year through blood transfusions in urban areas. Currently, it is estimated that 16 to 18 million people, more than a third of whom live in Brazil, are chronically infected with *T. cruzi*. Chronic Chagas' disease is a major cause of morbidity and mortality in many Latin American countries, including Mexico, since many chronically infected persons eventually develop symptomatic cardiac lesions or gastrointestinal disease.

Pathogenesis. An indurated inflammatory lesion called a *chagoma* often appears at the site of the parasite's entry. Local histologic changes include the presence of parasites within leukocytes and cells of subcutaneous tissues and the development of interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. After dissemination of the organisms through the lymphatics and the bloodstream, muscles (including the myocardium) may become heavily parasitized. The characteristic pseudocysts seen in sections of infected tissues are intracellular aggregates of multiplying parasites.

The pathogenesis of chronic Chagas' disease is poorly understood. The heart is the organ most commonly affected, and changes include biventricular enlargement, thinning of the ventricular walls, apical aneurysms, and mural thrombi. Widespread lymphocytic infiltration, diffuse interstitial fibrosis, and atrophy of myocardial cells are often demonstrated, but parasites are rarely seen in myocardial tissue. Conduction-system involvement often affects the right branch and the left anterior branch of the bundle of His. In chronic Chagas' disease of the gastrointestinal tract (megadisease), the esophagus and colon may exhibit varying degrees of dilatation. On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen, and the number of neurons in the myenteric plexus may be

markedly reduced.

Clinical manifestations. The first signs of acute Chagas' disease develop at least 1 week after invasion by the parasites. When the organisms have entered through a break in the skin, an indurated area of erythema and swelling (the chagoma), accompanied by local lymphadenopathy, may appear. Romana's sign the classic finding in acute Chagas' disease, which consists of unilateral painless edema of the palpebrae and periocular tissues can result when the conjunctiva is the portal of entry. These initial local signs are followed by malaise, fever, anorexia, and edema of the face and lower extremities. Generalized lymphadenopathy and mild hepatosplenomegaly may appear. Severe myocarditis develops rarely; most deaths in acute Chagas' disease are due to heart failure. Neurologic signs are not common, but meningoencephalitis has been reported. The acute symptoms resolve spontaneously in virtually all patients, who then enter the asymptomatic or indeterminate phase of chronic *T. cruzi* infection.

Symptomatic chronic Chagas' disease becomes apparent years or even decades after the initial infection. The heart is commonly involved, and symptoms are caused by rhythm disturbances, cardiomyopathy, and thromboembolism. Right bundle-branch block is the most common electrocardiographic abnormality, but other types of atrioventricular block, premature ventricular contractions, and tachy- and bradyarrhythmias are seen frequently. Cardiomyopathy often results in right-sided or biventricular heart failure. Embolization of mural thrombi to the brain or other areas may take place. Patients with megaesophagus suffer from dysphagia, odynophagia, chest pain, and regurgitation. Aspiration can occur, especially during sleep, and repeated episodes of aspiration pneumonitis are common. Weight loss, cachexia, and pulmonary infection can result in death. Patients with megacolon are plagued by abdominal pain and chronic constipation, and advanced megacolon can cause obstruction, volvulus, septicemia, and death.

Diagnosis. The diagnosis of acute Chagas' disease requires the detection of parasites. Microscopic examination of fresh anticoagulated blood or of the buffy coat is the simplest way to see the motile organisms. Parasites also can be seen in Giemsa-stained thin and thick blood smears. When repeated attempts to visualize the organisms are unsuccessful, mouse inoculation and culture of blood in specialized media should be performed. As a last resort, xenodiagnosis should be attempted. In this technique, uninfected reduviid bugs are allowed to feed on the patient's blood. Approximately 30 days after the blood meal, the intestinal contents of the bugs are examined for parasites. When done properly, this method is positive in virtually all cases of acute Chagas' disease and in approximately half of chronic infections. Since early treatment of acute Chagas' disease is extremely important, however, the decision to initiate therapy for *T. cruzi* infection despite negative wet preparations and smears must be made on clinical and epidemiologic grounds before the results of

these indirect methods become available. Serologic testing is of limited usefulness in diagnosing acute Chagas' disease.

The diagnosis of chronic Chagas' disease is made by the detection of antibodies that bind to *T. cruzi* antigens. Demonstration of the parasite is not of primary importance. Several highly sensitive serologic tests for the detection of antibodies to *T. cruzi* are used widely in Latin America, including complement-fixation and immunofluorescence tests and ELISA. However, a persistent problem with these conventional assays is the occurrence of false-positive reactions, typically with sera from patients who have other parasitic infections or autoimmune diseases. For this reason, it is generally recommended that positivity in one assay be confirmed by two other tests and that well-characterized positive and negative comparison sera be included in each run. A highly sensitive and specific method for detecting antibodies to *T. cruzi* employs immunoprecipitation of radiolabeled *T. cruzi* antigens and electrophoresis. Serodiagnostic assays that employ recombinant *T. cruzi* proteins as target antigens are being developed, as are tests based on the amplification of *T. cruzi* DNA sequences by polymerase chain reaction. However, these tests are not yet available for general use.

Treatment. Therapy for Chagas' disease is unsatisfactory. In acute Chagas' disease, nifurtimox markedly reduces the duration of symptoms and parasitemia and decreases mortality. Nevertheless, its efficacy at eradicating parasites is low. Limited studies have shown that only approximately 50% of acute infections are cured parasitologically by a full course of treatment. Despite its limitations, nifurtimox treatment should be initiated as early as possible in acute Chagas' disease. Moreover, when laboratory accidents occur in which it appears likely that *T. cruzi* infection could become established, nifurtimox therapy should be initiated without waiting for clinical or parasitologic indications of infection.

The usefulness of nifurtimox in individuals with indeterminate-phase or symptomatic chronic Chagas' disease has not been established. No evidence suggests that patients in the indeterminate phase are less likely to develop symptomatic disease after treatment with nifurtimox, nor has this agent been shown to have any effect on symptomatic chronic disease. Moreover, posttreatment xenodiagnoses are positive in a large proportion of chronically infected patients given this drug. Hence there is no indication for nifurtimox treatment of chronic *T. cruzi* infections.

Common adverse effects of nifurtimox include abdominal pain, anorexia, nausea, vomiting, and weight loss. Neurologic reactions to the drug may include restlessness, disorientation, insomnia, twitching, paresthesia, polyneuritis, and seizures. These symptoms usually disappear when the dosage is reduced or treatment is discontinued. The recommended daily dosage is 8 to 10 mg/kg for adults, 12.5 to 15 mg/kg for adolescents, and 15 to 20 mg/kg for children 1 to 10 years of age. The drug should be given orally in four divided doses each day, and therapy should be

continued for 90 to 120 days.

Benznidazole is a second agent used to treat Chagas' disease. Its efficacy is similar to that of nifurtimox, and its adverse effects include peripheral neuropathy, rash, and granulocytopenia. The recommended oral dosage is 5 mg/kg per day for 60 days. It has not been shown, however, that treatment in the indeterminate phase of the illness with benznidazole reduces the likelihood of symptomatic disease.

Allopurinol is not useful for the treatment of chronic *T. cruzi* infections. Studies in mice have shown that recombinant interferon decreases the duration and severity of acute *T. cruzi* infection; however, its usefulness in persons with acute Chagas' disease has not been evaluated systematically. Patients who develop cardiac and/or gastrointestinal disease in association with *T. cruzi* infection should be referred to appropriate subspecialists for further evaluation and treatment.

Prevention. Since drug therapy is unsatisfactory and vaccines are not available, the control of *T. cruzi* transmission in endemic countries must depend on reduction of domiciliary vector populations by spraying of insecticides and improvement of housing. In addition, in endemic areas, programs for the screening of donated blood for *T. cruzi* need to be expanded and improved to reduce rates of transmission by transfusion. Tourists traveling in endemic areas should avoid sleeping in dilapidated houses outside urban areas. Mosquito nets and insect repellent will provide additional protection.

Blood donations should not be accepted from immigrants from regions in which Chagas' disease is endemic, unless serologic assays indicate that the donor is not infected with *T. cruzi*. Moreover, all immigrants from endemic regions should be screened for serologic evidence of infection with the parasite. Identification of infected individuals in this group is important not only in preventing transmission by blood transfusion but also in prompting physicians who care for these patients to undertake appropriate diagnostic monitoring and supportive therapy when indicated. Laboratory personnel should wear gloves and eye protection when working with *T. cruzi* and infected vectors. Patients with end-stage chagasic cardiopathies should not undergo cardiac transplantation because the immunosuppression required after surgery often leads to reactivation of *T. cruzi* infection, with serious consequences and even death.

AFRICAN TRYPANOSOMIASIS

Definition. African trypanosomiasis, or Sleeping sickness, is caused by flagellated protozoan parasites that belong to the *Trypanosoma brucei* complex and are transmitted to humans by tsetse flies. In untreated patients, the trypanosomes first cause a febrile illness that is followed months or years later by progressive neurologic impairment and death.

Etiology. The East African (rhodesiense) and the West African (gambiense) forms of sleeping sickness are caused, respectively, by two trypanosome subspecies:

T. brucei rhodesiense and *T. brucei gambiense*. These subspecies are morphologically indistinguishable but cause illnesses that are epidemiologically and clinically distinct. The parasites are transmitted by blood-sucking tsetse flies of the genus *Glossina*. The insects acquire the infection when they ingest blood from infected mammalian hosts. After many cycles of multiplication in the midgut of the vector, the parasites migrate to the salivary glands. Their transmission takes place when they are inoculated during a subsequent blood meal. The injected trypanosomes multiply in the blood and other extracellular spaces and evade immune destruction in mammalian hosts for long periods by undergoing antigenic variation, a process by which the antigenic structure of their surface coat of glycoproteins changes periodically.

Epidemiology. The trypanosomes that cause sleeping sickness are found only in Africa. Approximately 20,000 new cases are reported each year, but this number is surely an underestimate of the true incidence. Humans are the only reservoir of *T. b. gambiense*, which occurs in widely distributed foci in tropical rain forests of Central and West Africa. Gambiense trypanosomiasis is primarily a problem in rural populations; tourists rarely become infected. Trypanotolerant antelope species in savanna and woodland areas of Central and East Africa are the principal reservoir of *T. b. rhodesiense*. Cattle also can become infected but generally succumb to the parasite. Since risk results for the most part from contact with tsetse flies that feed on wild animals, humans acquire *T. b. rhodesiense* infection only incidentally, usually while working in areas where infected game and vectors are present. In addition, occasional cases occur among visitors to game parks in East Africa.

Pathogenesis. A self-limited inflammatory lesion (trypanosomal chancre) may appear a week or so after the bite of an infected tsetse fly. A systemic febrile illness then evolves as the parasites are disseminated through the lymphatics and bloodstream. Systemic African trypanosomiasis without central nervous system (CNS) involvement is generally referred to as *stage I disease*. In this stage, widespread lymphadenopathy and splenomegaly reflect marked lymphocytic and histiocytic proliferation and invasion of morular cells, which are plasmacytes that may be involved in the production of IgM. Endarteritis, with perivascular infiltration of both parasites and lymphocytes, may develop in lymph nodes and spleen. Myocarditis develops frequently in patients with stage I disease and is especially common in *T. b. rhodesiense* infections.

Hematologic manifestations that accompany stage I trypanosomiasis include moderate leukocytosis, thrombocytopenia, and anemia. High levels of immunoglobulins, consisting primarily of polyclonal IgM, are a constant feature, and heterophile antibodies, antibodies to DNA, and rheumatoid factor are often detected. High levels of antigen-antibody complexes may play a role in the tissue damage and increased vascular permeability that facilitate dissemination of the parasites.

Stage II trypanosomiasis involves invasion of the CNS. The presence of trypanosomes in perivascular areas is accompanied by intense infiltration of mononuclear cells. Abnormalities in cerebrospinal fluid (CSF) include increased pressure, elevated total protein concentration, and pleocytosis. In addition, trypanosomes are frequently found in CSF.

Clinical manifestations. A painful trypanosomal chancre appears in some patients at the site of inoculation of the parasite. Hematogenous and lymphatic dissemination (stage I disease) is marked by the onset of fever. Typically, bouts of high temperatures lasting several days are separated by afebrile periods. Lymphadenopathy is prominent in *T. b. gambiense* trypanosomiasis. The nodes are discrete, movable, rubbery, and nontender. Cervical nodes are often visible, and enlargement of the nodes of the posterior cervical triangle, or Winterbottom's sign, is a classic finding. Pruritus is frequent, and a circinate rash is often present. Inconstant findings include malaise, headache, arthralgias, weight loss, edema, hepatosplenomegaly, and tachycardia.

CNS invasion (stage II disease) is characterized by the insidious development of protean neurologic manifestations that are accompanied by progressive abnormalities in the CSF. A picture of progressive indifference and daytime somnolence develops (hence the designation "sleeping sickness"), sometimes alternating with restlessness and insomnia at night. A listless gaze accompanies a loss of spontaneity, and speech may become halting and indistinct. Extrapyramidal signs may include choreiform movements, tremors, and fasciculations. Ataxia is frequent, and the patient may appear to have Parkinson's disease, with a shuffling gait, hypertonia, and tremors. In the final phase, progressive neurologic impairment ends in coma and death.

The most striking difference between the West African and East African trypanosomiases is that the latter illness tends to follow a more acute course. Typically, in tourists, systemic signs of infection, such as fever, malaise, and headache, appear before the end of the trip or shortly after the return home. Persistent tachycardia unrelated to fever is common early in the course of *T. b. rhodesiense* trypanosomiasis, and death may result from arrhythmias and congestive heart failure before CNS disease develops. In general, untreated East African trypanosomiasis leads to death in a matter of weeks to months, often without a clear distinction between the hemolymphatic and CNS stages.

Diagnosis. A definitive diagnosis of African trypanosomiasis requires detection of the parasite. If a chancre is present, fluid should be expressed and examined directly by light microscopy for the highly motile trypanosomes. The fluid also should be fixed and stained with Giemsa stain. Material obtained by needle aspiration of lymph nodes early in the course of the illness should be examined similarly. Examination of wet preparations and Giemsa-stained thin and thick films

of serial blood samples is also useful. If parasites are not found by these methods, the buffy coat from 10 to 15 mL of anticoagulated blood or the pellet obtained by centrifugation of the eluate from 25 to 50 mL of blood passed through a DEAE-cellulose column should be examined. Trypanosomes may be seen in material aspirated from the bone marrow; the aspirate can be inoculated into liquid culture medium, as can blood, buffy coat, lymph node aspirates, and CSF. Finally, *T. b. rhodesiense* infection can be detected by inoculation of these specimens into mice or rats, which results in patent parasitemia in a week or two. Although this method is highly sensitive for the detection of *T. b. rhodesiense*, it unfortunately does not detect *T. b. gambiense* because of host specificity.

It is essential to examine CSF from all patients in whom African trypanosomiasis is suspected. An increase in the CSF cell count is the first abnormality to be detected; increases in opening pressure and in levels of total protein and IgM develop later. Trypanosomes may be seen in the sediment of centrifuged CSF. Any CSF abnormality in a patient in whom trypanosomes have been found at other sites must be viewed as pathognomonic for CNS involvement and thus must prompt specific treatment for CNS disease. A number of serologic assays are available to aid in the diagnosis of African trypanosomiasis, but their variable sensitivity and specificity mandate that decisions about treatment be based on demonstration of the parasite. These tests are of value for epidemiologic surveys.

Treatment. The drugs traditionally used for treatment of African trypanosomiasis are suramin, pentamidine, and organic arsenicals. An addition to this list is eflornithine (difluoromethylornithine). Therapy for African trypanosomiasis must be individualized on the basis of the infecting organism (*T. b. gambiense* or *T. b. rhodesiense*), the presence or absence of CNS disease, adverse reactions, and (occasionally) drug resistance. The choices of drugs for the treatment of African trypanosomiasis are summarized as follows.

Stage I (normal CSF) West African trypanosomiasis (*T. b. gambiense*) should be treated with either suramin or eflornithine. Pentamidine can be used as an alternative drug. Stage II West African trypanosomiasis (abnormal CSF) should be treated with eflornithine.

Stage I East African trypanosomiasis (*T. b. rhodesiense*) should be treated with suramin, and pentamidine can be used as an alternative drug. Since suramin and pentamidine do not penetrate the CNS well and since eflornithine has variable efficacy against *T. b. rhodesiense*, stage II East African trypanosomiasis should be treated with melarsoprol. Patients who cannot tolerate the latter drug should be treated with tryparsamide plus suramin.

Suramin is highly effective against stage I disease. However, it can cause serious adverse effects and must be administered under the close supervision of a physician. A 100- to 200-mg intravenous test dose should be administered to detect

hypersensitivity. The dosage for adults is 1 g intravenously on days 1, 3, 7, 14, and 21. The regimen for children is 20 mg/kg (maximum, 1 g) intravenously on days 1, 3, 7, 14, and 21. The drug is given by slow intravenous infusion of a freshly prepared 10% aqueous solution. Approximately 1 patient in 20,000 has an immediate, severe, and potentially fatal reaction to the drug, developing nausea, vomiting, shock, and seizures. Less severe reactions include fever, photophobia, pruritus, arthralgias, and skin eruptions. Renal damage is the most common important adverse effect of suramin. Transient proteinuria often appears during treatment. A urinalysis should be undertaken before each dose, and treatment should be discontinued if proteinuria increases or if casts and red cells appear in the sediment. Suramin should not be given to patients with renal insufficiency.

Eflornithine is highly effective for treatment of both stages of West African trypanosomiasis. In the trials on which the Food and Drug Administration based its approval, this agent cured more than 90% of 600 patients with stage II disease. The recommended treatment schedule is 400 mg/kg per day intravenously in four divided doses for 2 weeks followed by 300 mg/kg per day orally for 3 to 4 weeks. Adverse reactions include diarrhea, anemia, thrombocytopenia, seizures, and hearing loss. The efficacy of eflornithine in *T. b. rhodesiense* infection has not been determined. The high dosage and long duration of therapy required are disadvantages that may make widespread use of eflornithine difficult.

Pentamidine is the alternative drug for patients with stage I African trypanosomiasis, although some *T. b. rhodesiense* infections are unresponsive to this agent. The dose for both adults and children is 4 mg/kg per day intramuscularly or intravenously for 10 days. Frequent, immediate adverse reactions include nausea, vomiting, tachycardia, and hypotension. These reactions are usually transient and do not warrant cessation of therapy. Other adverse reactions include nephrotoxicity, abnormal liver function tests, neutropenia, rashes, hypoglycemia, and sterile abscesses.

The arsenical melarsoprol is the drug of choice for the treatment of East African trypanosomiasis with CNS involvement. Melarsoprol cures both stages of the disease and therefore is also indicated for the treatment of stage I disease in patients who fail to respond to or cannot tolerate suramin and/or pentamidine. However, because of its relatively high toxicity, melarsoprol is never the first choice for the treatment of stage I disease. The drug should be given to adults in three courses of 3 days each. The dosage is 2 to 3.6 mg/kg per day intravenously in three divided doses for 3 days followed 1 week later by 3.6 mg/kg per day, also in three divided doses and for 3 days. The latter course is repeated 10 to 21 days later. In debilitated patients, suramin is administered for 2 to 4 days before therapy with melarsoprol is initiated. An 18-mg initial dose of the latter drug, followed by progressive increases to the standard dose, has been recommended. For children, a total of 18 to 25 mg/kg

should be given over 1 month. A starting dose of 0.36 mg/kg intravenously should be increased gradually to a maximum of 3.6 mg/kg at 1- to 5-day intervals, for a total of 9 or 10 doses.

Melarsoprol is highly toxic and should be administered with great care. The incidence of reactive encephalopathy has been reported to be as high as 18% in some series. Clinical manifestations of reactive encephalopathy include high fever, headache, tremor, impaired speech, seizures, and even coma and death. Treatment with melarsoprol should be discontinued at the first sign of encephalopathy but may be restarted cautiously at small doses a few days after signs have resolved. Extravasation of the drug results in intense local reactions. Vomiting, abdominal pain, nephrotoxicity, and myocardial damage can occur.

The treatment of patients with stage II East African disease who cannot tolerate melarsoprol is problematic. The combination of the arsenical tryparsamide and suramin is one possible approach, but its efficacy is limited because suramin does not penetrate the CNS well and tryparsamide is much less effective against *T. b. rhodesiense* than it is against *T. b. gambiense*. The schedule for tryparsamide therapy is 30 mg/kg (maximum 2 g) in a single intravenous dose every 5 days for a total of 12 doses; that for suramin treatment is 10 mg/kg intravenously every 5 days, also for a total of 12 injections. Tryparsamide can cause encephalopathy, fever, vomiting, abdominal pain, rash, tinnitus, and a variety of ocular symptoms. Alternatively, eflornithine can be administered as outlined above to patients who cannot tolerate melarsoprol, but, as noted, its effectiveness against *T. b. rhodesiense* is variable.

Prevention. The trypanosomiases pose complex public-health and epizootic problems in Africa. Considerable progress has been made in some areas through control programs that focus on eradication of vectors and drug treatment of infected humans, but there is no consensus on the best approach to solving the overall problem. Individuals can reduce their risk of acquiring trypanosomiasis by avoiding areas known to harbor infected insects, by wearing protective clothing, and by using insect repellent. Chemoprophylaxis is not recommended, and no vaccine is available to prevent transmission of the parasites.

AMEBIASIS

Defenition. Diarrheal protozoal disease cased by *Entamoeba histolytica* and characterizes by colitis and in some cases extraintestinal lesions.

Epidemiology. The main sourse of invasion is patient with asymptomatic deseases. The most important routs of transmission are contaminated water or food and direct contact from patient to patient. Amebiasis is spreaded worldwide, with higher incidence of amebiasis in developing countries. About 10% of the world's population is infected with *Entamoeba histolytica*; amebiasis is the third most common cause of death from parasitic disease (after schistosomiasis and malaria).

Areas of highest incidence (due to inadequate sanitation and crowding) include most developing countries in the tropics, particularly Mexico, India, and nations of Central and South America, tropical Asia, and Africa. In industrialized countries, risk groups include male homosexuals, travelers and recent immigrants, and institutionalized populations.

Bacillary dysentery is most commonly caused by microorganisms belonging to the genus shigella, whereas amebic dysentery is caused by the protozoan parasite *E. histolytica*. Several protozoan species in the genus *Entamoeba* infect humans, but not all of them are associated with disease. *E. histolytica* is well recognized as a pathogenic ameba, associated with intestinal and extraintestinal infections. Amebic infections lead to significant morbidity while causing variable mortality as described below. Mortality rate in patients with uncomplicated amebic liver abscess is less than 1%. Fulminant amebic colitis has a mortality rate of more than 50%. Pleuropulmonary amebiasis has a mortality rate of 15-20%. Amebic pericarditis has a case fatality rate of 40%. Cerebral amebiasis is highly fatal, with a 90% death rate. Increased severity of amebiasis is noted in children (especially neonates), women who are pregnant or postpartum, individuals who use corticosteroids, individuals with malignancy, and malnourished individuals

All *E. histolytica* trophozoites and cysts are morphologically identical, but the wide spectrum of clinical disease is caused in part by infection with two different species of *Entamoeba*. Isolates of *E. histolytica* from patients with invasive amebiasis have unique isoenzymes, surface antigens, DNA markers, and virulence properties and now are classified as a separate species from the noninvasive species *Entamoeba dispar*.

Most asymptomatic carriers, including homosexual men and HIV-infected patients, harbor nonpathogenic strains and have self-limited infections. These findings suggest that nonpathogenic strains (i.e., *E. dispar*) are incapable of causing invasive disease, since *Cryptosporidium* and *Isospora belli*, which also cause only self-limited illnesses in immunocompetent people, cause devastating diarrhea in HIV-infected patients. However, host factors play a role as well: Some patients infected with strains shown (by isoenzyme patterns) to be pathogenic do not develop invasive amebiasis but rather remain asymptomatic. In one study, 10% of asymptomatic patients who were colonized with pathogenic strains went on to develop amebic colitis, while the rest remained asymptomatic and cleared the infection within 1 year.

Pathogenesis. Cysts and trophozoites are passed in feces. Cysts are typically found in formed stool, whereas trophozoites are typically found in diarrheal stool. Infection by *Entamoeba histolytica* occurs by ingestion of mature cysts in fecally contaminated food, water, or hands. Ingestion of the quadrinucleate cyst of *E. histolytica* from fecally contaminated food or water initiates infection. This is a daily occurrence among the poor in developing countries and is a threat to inhabitants of

developed countries, as the epidemic linked to contaminated municipal water supplies. Excystation occurs in the small intestine and trophozoites are released, which migrate to the large intestine.

Trophozoites adhere to colonic mucins and thereby colonize the large intestine. The reproduction of trophozoites has no sexual cycle, and the overall population of *E. histolytica* appears to be clonal. In most infections the trophozoites aggregate in the intestinal mucin layer and form new cysts, resulting in a self-limited and asymptomatic infection. The trophozoites multiply by binary fission and produce cysts, and both stages are passed in the feces. Because of the protection conferred by their walls, the cysts can survive days to weeks in the external environment and are responsible for transmission. Cysts excreted in stool perpetuate the life cycle by further fecal-oral spread. Trophozoites passed in the stool are rapidly destroyed once outside the body, and if ingested would not survive exposure to the gastric environment.

In some cases, however, adherence to and lysis of the colonic epithelium, mediated by the galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc) – specific lectin, initiates invasion of the colon by trophozoites. Neutrophils responding to the invasion contribute to cellular damage at the site of invasion. The trophozoites invade the intestinal mucosa (intestinal disease), or, through the bloodstream, extraintestinal sites such as the liver, brain, and lungs (extraintestinal disease), with resultant pathologic manifestations. It has been established that the invasive and noninvasive forms represent two separate species, respectively *E. histolytica* and *E. dispar*. Once the intestinal epithelium is invaded, extraintestinal spread to the peritoneum, liver, and other sites may follow. Factors controlling invasion, as opposed to encystation, most likely include parasite "quorum sensing" signaled by the Gal/GalNAc-specific lectin, interactions of amebae with the bacterial flora of the intestine, and innate and acquired immune responses of the host. These two species are morphologically indistinguishable unless *E. histolytica* is observed with ingested red blood cells (erythrophagocystosis).

Colitis results when the trophozoite penetrates the intestinal mucous layer, which otherwise acts as a barrier to invasion by inhibiting amebic adherence to the underlying epithelium and by slowing trophozoite motility. Invasion is mediated by the killing of epithelial cells, neutrophils, and lymphocytes by trophozoites. Interaction of the parasite with the intestinal epithelium causes an inflammatory response marked by the activation of nuclear factor B and the secretion of lymphokines. The development of this epithelial response may depend on trophozoite virulence factors such as cysteine proteinase and leads to intestinal abnormalities through neutrophil-mediated damage. Neutrophils can also be protective, however, in that activation of neutrophils or macrophages by tumor necrosis factor or interferon kills amebae in vitro and limits the size of amebic liver abscesses. In contrast to the

intense inflammatory response typical of early invasive amebiasis, inflammation surrounding well-established colonic ulcers and liver abscesses is minimal, given the degree of tissue damage.

Immunity to infection with *E. histolytica* is associated with a mucosal IgA response against the carbohydrate-recognition domain of the Gal/GalNAc lectin. Cell-mediated responses have been described in patients with amebic liver abscess, characterized by lymphocyte proliferation and lymphokine secretion that is amebicidal in vitro. HIV pandemic has not led to increases in invasive amebiasis, although asymptomatic intestinal colonization is undoubtedly common.

Clinical manifestations. Infection with *E. histolytica* may be asymptomatic or may cause dysentery or extraintestinal disease. The most common type of amebic infection is asymptomatic cyst passage. The invasive amebiasis is characterized by clinical forms of diseases, presence of trofozoites-hematophages in patient's feces, typical lission in intestine wall, appearence of specific antibody in serum. "Uninvasive" amebiasis is called amoeba-carriage. Asymptomatic infection, absence of trofozoites-hematophages in the feces and negative serological test are tipical for carriage stages.

Symptomatic amebic colitis develops 2 to 6 weeks after the ingestion of infectious cysts. Lower cramping abdominal pain and mild diarrhea develop gradually and are followed by malaise, weight loss, and diffuse lower abdominal or back pain. Cecal involvement may mimic acute appendicitis with severe pain. Patients with full-blown dysentery may pass 10 to 12 stools per day. Virtually all patients have heme-positive stools. The stools contain little fecal material and consist mainly of blood and mucus and looks like "raspberry jelly". In contrast to those with bacterial diarrhea, fewer than 40% of patients with amebic dysentery are febrile. The differential diagnosis of a diarrheal illness with occult or grossly bloody stools should include infection with shigella, salmonella, campylobacter, and enteroinvasive and enterohemorrhagic *Escherichia coli*. Noninfectious causes include inflammatory bowel disease, ischemic colitis, diverticulitis, and arteriovenous malformation.

More fulminant intestinal infection, with severe abdominal pain, high fever, and profuse diarrhea, is rare and occurs predominantly in children. Patients may develop toxic megacolon, in which there is severe bowel dilation with intramural air. Patients receiving glucocorticoids are at risk for severe amebiasis. Uncommonly, patients develop a chronic form of amebic colitis, which can be confused with inflammatory bowel disease. The positive association between severe amebiasis complications and steroid therapy emphasizes the importance of excluding amebiasis in any case in which inflammatory bowel disease is suspected. Amebomas are inflammatory mass lesions that develop owing to chronic intestinal forms of amebiasis. An occasional patient presents only with an asymptomatic or tender abdominal mass caused by an ameboma, which is easily confused with cancer on

barium studies. A positive serologic test or biopsy can prevent unnecessary surgery in this setting. The syndrome of postamebic colitis persistent diarrhea following documented cure of amebic colitis is controversial; no evidence of recurrent amebic infection can be found, and re-treatment usually has no effect.

Unusual manifestations of amebic colitis include acute necrotizing colitis, toxic megacolon, ameboma, and perianal ulceration with potential formation of a fistula. Acute necrotizing colitis is rare (occurring in less than 0.5% of cases) and is associated with a mortality rate of more than 40%. Patients with acute necrotizing colitis typically appear very ill, with fever, bloody mucoid diarrhea, abdominal pain with rebound tenderness, and signs of peritoneal irritation. Surgical intervention is indicated if there is bowel perforation or if the patient has no response to antiamebic therapy. Toxic megacolon is rare (occurring in approximately 0.5% of cases) and is typically associated with the use of corticosteroids. Early recognition and surgical intervention are important, since patients with toxic megacolon usually have no response to antiamebic therapy alone. Ameboma results from the formation of annular colonic granulation tissue at a single site or multiple sites, usually in the cecum or ascending colon. An ameboma may mimic carcinoma of the colon.

A number of complications can occur in intestinal amebiasis: bowel perforation (in often cases the place of caecum more, lesser in rectosigmoid area, which can lead to peritonitis and abscess of abdominal cavity); amebiac appendicitis; massive intestine bleeding (due to alteration of large artery); ameboma (tumour overgrowth in colon, mainly cases in ascending part of colon, caecum and rectum; consists of fibroblasts, collagen and celluar elements, and contains comparatively small amount of amoebas); amebic bowel stricture (is formed by granulation tissue; usually strictures are single and locates in place of caecum or rectum; contains amoebas; promotes development of constipations and partial intestinal obstruction), amebic liver abscess.

Amebic liver abscess is 10 times as common in men as in women and is a rare disease in children. Approximately 80% of patients with amebic liver abscess present with symptoms that develop relatively quickly (typically within two to four weeks), including fever, cough, and a constant, dull, aching abdominal pain in the right upper quadrant or epigastrium. Involvement of the diaphragmatic surface of the liver may lead to right-sided pleural pain or referred shoulder pain. Associated gastrointestinal symptoms, which occur in 10 to 35% of patients, include nausea, vomiting, abdominal cramping, abdominal distention, diarrhea, and constipation. Hepatomegaly with point tenderness over the liver, below the ribs, or in the intercostal spaces is a typical finding.

Routine hematology and chemistry tests are usually not very helpful in the diagnosis of invasive amebiasis. Laboratory studies may reveal a mild-to-moderate leukocytosis and anemia. Anemia, if present, is usually multifactorial. About three-

fourths of patients with an amebic liver abscess have leukocytosis (10,000 cells per microliter); this condition is particularly likely if symptoms are acute or complications have developed. Invasive amebiasis does not elicit eosinophilia. Patients with acute amebic liver abscess tend to have a normal alkaline phosphatase level and an elevated alanine aminotransferase level; the opposite is true of patients with chronic disease. Ultrasonography, abdominal computed tomography (CT), and magnetic resonance imaging (MRI) are all excellent for detecting liver lesions (usually single lesions in the right lobe) but are not specific for amebic liver abscess.

The differential diagnosis of a liver mass should include pyogenic liver abscess, necrotic hepatoma, and echinococcal cyst (usually an incidental finding that is not the cause of fever and abdominal pain). Patients with amebic liver abscess are more likely than patients with pyogenic liver abscess to be male, to be younger than 50 years of age, to have immigrated from or traveled to a country where the disease is endemic, and not to have jaundice, biliary disease, or diabetes mellitus. Less than half of patients with amebic liver abscess have parasites detected in their stool by antigen detection. Helpful clues to the diagnosis include the presence of epidemiologic risk factors for amebiasis and the presence of serum antiamebic antibodies (present in 70 to 80% of patients at the time of presentation). Preliminary studies indicate that the detection of serum amebic antigens is a sensitive, noninvasive means of diagnosis. Occasionally, aspiration of the abscess is required to rule out a pyogenic abscess. Amebae are visualized in the abscess fluid in a minority of patients with amebic liver abscess.

Complications of amebic liver abscess may arise from rupture of the abscess with extension into the peritoneum, pleural cavity, or pericardium. Extrahepatic amebic abscesses have occasionally been described in the lung, brain, and skin and presumably result from hematogenous spread.

Pleuropulmonary involvement, which is reported in 20 to 30% of patients, is the most frequent complication of amebic liver abscess. Manifestations include sterile effusions, contiguous spread from the liver, and rupture into the pleural space. Sterile effusions and contiguous spread usually resolve with medical therapy, but frank rupture into the pleural space requires drainage. A hepatobronchial fistula may cause cough productive of large amounts of necrotic material that may contain amebas. This dramatic complication carries a good prognosis. Abscesses that rupture into the peritoneum may present as an indolent leak or an acute abdomen and require both percutaneous catheter drainage and medical therapy. Rupture into the pericardium, usually from abscesses of the left lobe of the liver, carries the gravest prognosis; it can occur during medical therapy and requires surgical drainage.

The genitourinary tract may become involved by direct extension of amebiasis from the colon or by hematogenous spread of the infection. Painful genital ulcers, characterized by a punched-out appearance and profuse discharge, may develop

secondary to extension from either the intestine or the liver. Both these conditions respond well to medical therapy. Cerebral involvement has been reported in less than 0.1% of patients in large clinical series. Symptoms and prognosis depend on the size and location of the lesion.

Diagnosis. Entamoeba histolytica must be differentiated from other intestinal protozoa including: *E. coli, E. hartmanni, E. gingivalis, Endolimax nana*, and *Iodamoeba buetschlii* (the nonpathogenic amebas); *Dientamoeba fragilis* (which is a flagellate not an ameba); and the possibly pathogenic *Entamoeba polecki*. Differentiation is possible, but not always easy, based on morphologic characteristics of the cysts and trophozoites. The nonpathogenic Entamoeba dispar, however, is morphologically identical to *E. histolytica*, and differentiation must be based on isoenzymatic or immunologic analysis. Molecular methods are also useful in distinguishing between *E. histolytica* and *E. dispar* and can also be used to identify *E. polecki*. Microscopic identification of cysts and trophozoites in the stool is the common method for diagnosing *E. histolytica*. This can be accomplished using:

- Fresh stool: wet mounts and permanently stained preparations (e.g., trichrome).
- Concentrates from fresh stool: wet mounts, with or without iodine stain, and permanently stained preparations (e.g., trichrome). Concentration procedures, however, are not useful for demonstrating trophozoites.
- In addition, *E. histolytica* trophozoites can also be identified in aspirates or biopsy samples obtained during colonoscopy or surgery.

Examination of colonic mucosal biopsy specimens and exudates can reveal a wide range of histopathological findings associated with amebic colitis, including diffuse, nonspecific mucosal thickening with or without ulceration and, in rare cases, the presence of amebae in the mucinous exudate; focal ulcerations with or without amebae in a diffusely inflamed mucosal layer; classic flask-shaped lesions with ulceration extending through the mucosa and muscularis mucosa into the submucosa; and necrosis and perforation of the intestinal wall. Staining with periodic acid - Schiff or immunoperoxidase and antilectin antibodies aids in the visualization of amebae.

In developing countries, intestinal amebiasis is most commonly diagnosed by identifying cysts or motile trophozoites on a saline wet mount of a stool specimen. The drawbacks of this method include its low sensitivity and false positive results owing to the presence of *E. dispar* or *E. moshkovskii* infection.

Enzyme immunoassay (EIA) for *Entomoeba histolytica* antibody detection as well as for antigen detection are available. Antibody detection is most useful in patients with extraintestinal disease (i.e., amebic liver abscess) when organisms are not generally found on stool examination. Antigen detection may be useful as an adjunct to microscopic diagnosis in detecting parasites and can distinguish between pathogenic and nonpathogenic infections. The IHA test has been replaced by commercially available EIA test kits for routine serodiagnosis of amebiasis. Antigen

consists of a crude soluble extract of axenically cultured organisms. The EIA test detects antibody specific for *E. histolytica* in approximately 95% of patients with extraintestinal amebiasis, 70% of patients with active intestinal infection, and 10% of asymptomatic persons who are passing cysts of *E. histolytica*. If antibodies are not detectable in patients with an acute presentation of suspected amebic liver abscess, a second specimen should be drawn 7-10 days later. If the second specimen does not show seroconversion, other agents should be considered. Detectable *E. histolytica*-specific antibodies may persist for years after successful treatment, so the presence of antibodies does not necessarily indicate acute or current infection. Specificity is 95% or higher: false-positive reactions rarely occur. Although the immunodiffusion test is as specific, it is slightly less sensitive than the IHA and EIA and requires a minimum of 24 hours to obtain a result, in contrast to 2 hours required for the IHA or EIA tests. However, the simplicity of the procedure makes it ideal for the laboratory that has only an occasional specimen to test. The IHA and EIA tests are more suitable for laboratories that have frequent requests for amebiasis serology. Although detection of IgM antibodies specific for *E. Histolytica* has been reported, sensitivity is only about 64% in patients with current invasive disease. A drawback of current serologic tests is that patients remain positive for years after infection, making it difficult to distinguish new from past infection in regions of the world where the seroprevalence is high.

The diagnosis should ideally be based on the detection in stool of *E. histolytica* – specific antigen or DNA and by the presence of antiamebic antibodies in serum. Field studies that directly compared polymerase chain reaction (PCR) with stool culture or antigen-detection tests for the diagnosis of *E. histolytica* infection suggest that these three methods perform equally well. An important aid to antigen-detection and PCR-based tests is the detection of serum antibodies against amebae, which are present in 70 to more than 90% of patients with symptomatic *E. histolytica* infection. Antigen detection may be useful as an adjunct to microscopic diagnosis in detecting parasites and to distinguish between pathogenic and nonpathogenic infections. Recent studies indicate improved sensitivity and specificity of fecal antigen assays with the use of monoclonal antibodies which can distinguish between *E. histolytica* and *E. Dispar* infections. At least one commercial kit is available which detects only pathogenic *E. histolytica* infection in stool; several kits are available which detect *E. histolytica* antigens in stool but do not exclude *E. dispar* infections.

Radiographic barium studies are potentially dangerous in acute amebic colitis. Amebomas are usually identified first by a barium enema, but biopsy is necessary for differentiation from carcinoma. Newer radiographic techniques have improved the detection of amebic liver abscesses. Liver scans, ultrasonography, CT, and MRI are all useful for detection of the round or oval hypoechoic cyst. More than 80% of patients who have had symptoms for more than 10 days have a single abscess of the right lobe of the liver. Approximately 50% of patients who have had symptoms for

less than 10 days have multiple abscesses. Findings associated with complications include large abscesses (10 cm) in the superior part of the right lobe, which may rupture into the pleural space; multiple lesions, which must be differentiated from pyogenic abscesses; and lesions of the left lobe, which may rupture into the pericardium. Because abscesses resolve slowly and may increase in size in patients who are responding clinically to therapy, frequent follow-up ultrasonography may prove confusing. Complete resolution of a liver abscess within 6 months can be anticipated in two-thirds of patients, but 10% may have persistent abnormalities for a year.

Differential diagnosis of intestinal amebiasis includes bacterial diarrheas caused by *Campylobacter*; enteroinvasive *Escherichia coli*; and *Shigella*, *Salmonella*, and *Vibrio* species. Although the typical patient with amebic colitis has less prominent fever than in these conditions and heme-positive stools with few neutrophils, correct diagnosis requires bacterial cultures, microscopic examination of stools, and amebic serologic testing. As has already been mentioned, amebiasis must be ruled out in any patient thought to have inflammatory bowel disease.

Because of the variety of presenting signs and symptoms, amebic liver abscess can easily be confused with pulmonary or gallbladder disease or with any febrile illness with few localizing signs, such as malaria or typhoid fever. The diagnosis should be considered in members of high-risk groups who have recently traveled to endemic areas and in inmates of institutions. Once radiographic studies have identified an abscess in the liver, the most important differential diagnosis is between amebic and pyogenic abscess. Patients with pyogenic abscess typically are older and have a history of underlying bowel disease or recent surgery. Amebic serology is helpful, but aspiration of the abscess, with Gram staining and culture of the material, may be required for differentiation of the two diseases

Treatment. The drugs used to treat amebiasis can be classified according to their primary site of action. Luminal amebicides are poorly absorbed and reach high concentrations in the bowel, but their activity is limited to cysts and trophozoites close to the mucosa. Indications for the use of luminal agents include eradication of cysts in patients with colitis or a liver abscess and treatment of asymptomatic carriers. Until probes are available for differentiating nonpathogenic from pathogenic cysts, it is prudent to treat asymptomatic individuals who pass cysts.

Noninvasive infections may be treated with paromomycin. Nitroimidazoles, particularly metronidazole, are the mainstay of therapy for invasive amebiasis. Nitroimidazoles with longer half-lives (namely, tinidazole, secnidazole, and ornidazole) are better tolerated and allow shorter periods of treatment. Approximately 90% of patients who present with mild-to-moderate amebic dysentery have a response to nitroimidazole therapy. In the rare case of fulminant amebic colitis, it is prudent to add broad-spectrum antibiotics to treat intestinal bacteria that may spill into

the peritoneum; surgical intervention is occasionally required for acute abdomen, gastrointestinal bleeding, or toxic megacolon. Parasites persist in the intestine in as many as 40 to 60% of patients who receive nitroimidazole. Therefore, nitroimidazole treatment should be followed with paromomycin or the second-line agent diloxanide furoate to cure luminal infection. Metronidazole and paromomycin should not be given at the same time, since the diarrhea that is a common side effect of paromomycin may make it difficult to assess the patient's response to therapy.

Tissue amebicides reach high concentrations in the blood and tissue after oral or parenteral administration. The development of nitroimidazole compounds, especially metronidazole, was a major advance in the treatment of invasive amebiasis. Patients with amebic colitis should be treated with intravenous or oral metronidazole (750 mg three times daily for 10 days). Side effects include nausea, vomiting, abdominal discomfort, and a disulfiram-like reaction. Other imidazole compounds, such as tinidazole and ornidazole, are as effective. All patients should also receive a full course of therapy with a luminal agent, since metronidazole does not eradicate cysts. Resistance to metronidazole has not been identified. Relapses are not uncommon and probably represent reinfection or failure to eradicate amebas from the bowel because of an inadequate dosage or duration of therapy.

Therapy for invasive infection differs from therapy for noninvasive infection. In cases of amebic liver abscess metronidazole is the drug of choice for amebic liver abscess. The usefulness of nitroimidazoles in single-dose or abbreviated regimens is important in endemic areas where access to hospitalization is limited. With early diagnosis and therapy, mortality from uncomplicated amebic liver abscess is less than 1%. The second-line therapeutic agents emetine and chloroquine should be avoided if possible because of the potential cardiovascular and gastrointestinal side effects of the former and the higher relapse rates with the latter. There is no evidence that combined therapy with two drugs is more effective than the single-drug regimen. Studies of South Africans with liver abscesses demonstrated that 72% of patients without intestinal symptoms were colonized asymptomatically with pathogenic strains; thus, all treatment regimens should include a luminal agent to eradicate cysts and prevent further transmission. Amebic liver abscess recurs rarely.

Therapeutic aspiration of an amebic liver abscess is occasionally required as an adjunct to antiparasitic therapy. Drainage of the abscess should be considered in patients who have no clinical response to drug therapy within five to seven days or those with a high risk of abscess rupture, as defined by a cavity with a diameter of more than 5 cm or by the presence of lesions in the left lobe. Bacterial coinfection of amebic liver abscess has occasionally been observed (both before and as a complication of drainage), and it is reasonable to add antibiotics, drainage, or both to the treatment regimen in the absence of a prompt response to nitroimidazole therapy. Imaging-guided percutaneous treatment (needle aspiration or catheter drainage) has

replaced surgical intervention as the procedure of choice for reducing the size of an abscess. More than 90% of patients respond dramatically to metronidazole therapy with decreases in both pain and fever within 72 h. Indications for aspiration of liver abscesses are: need to rule out a pyogenic abscess, particularly in patients with multiple lesions; failure to respond clinically in 3 to 5 days; threat of imminent rupture; prevention of left-lobe abscesses rupture into the pericardium.

There is no evidence that aspiration, even of large abscesses (up to 10 cm), accelerates healing. Percutaneous drainage may be successful even if the liver abscess has already ruptured. Surgery should be reserved for instances of bowel perforation and rupture into the pericardium.

Amebiasis treatment

Treatment of Choice	Alternative Regimen
Intestical amebiasis (Acute colitis)	
Metronidazole 750 mg PO or IV tid for 7-10 days	
Tinidazole 2 g/id PO for 3 days	Tinidazole 2 g/d ***followed by*** Iodoquinol as above
Ornidazol 2 g/day PO or IV for 3 days	Tinidazole 600 mg bid or 800 mg tid for 5 days ***followed by*** Iodoquinol as above
Seknidazol 2 g/id PO for 3 days	
Asymptomatic carrier (luminal agents)	
Diloxanide furoate 500 mg tid for 7-10 days	Iodoquinol 650 mg tid for 20 days, ***or*** Paromomycin 25-30 mg/kg/d in 3 doses for 7 days
Amebic liver abscess	
Metronidazole 750 mg PO or IV tid for 5 to 10 days	Tinidazole 600 mg bid ***or*** 800 mg tid for 5 days ***followed by*** Iodoquinol as above
Tinidazole 800 mg PO tid for 5 days	
Ornidazole 2 g PO plus	
Diloxanide furoate 500 mg PO tid for 10 days	
Paromomycin 25-25 mg/kg/day in divited 3 doses tid for 7 days	

Prevention. Amebic infection is spread by ingestion of food or water contaminated with cysts. Since an asymptomatic carrier may excrete up to 15 million cysts per day, prevention of infection requires adequate sanitation and eradication of cyst carriage. In high-risk areas, infection can be minimized by the avoidance of unpeeled fruits and vegetables and the use of bottled water. Because cysts are resistant to readily attainable levels of chlorine, disinfection by iodination (tetraglycine hydroperiodide) is recommended. There is no effective prophylaxis.

BALANTIDIASIS

Definition. Balantidiasis is a protozoal disease caused by a large ciliated parasite *Balantidium coli* and characterized by a spectrum of intestinal disease

analogous to amebiasis.

Etyology. Trophozoite has a large size (approximately 50-100 mm in length and 40-70 mm in width), a short ciliary covering, and spiraling motility. It frequently is observed under low power. On stained preparations, the trophozoite characteristically shows 2 nuclei: the macronucleus, which is kidney-shaped, and the micronucleus, which is spherical and lies close to the macronucleus. Cysts may be spherical or ellipsoid and range from about 50-70 mm long. Newly encysted organisms observed on unstained specimens may still have cilia, but cilia disappear after a longer period of encystment. Observation of a macronucleus and a micronucleus is diagnostic if observed in a cyst on a stained specimen.

Epidemiology. *B. coli* have a worldwide distribution with an estimated prevalence of 1%. Pigs are the reservoir of infection, rodents may be important carriers. Infection tends to be more common among humans who handle pigs. It is reported most commonly in Latin America; Southeast Asia; and Papua, New Guinea. Infective cysts can be transmitted from person to person and through water, but many cases are due to the ingestion of cysts derived from porcine feces in association with slaughtering, with use of pig feces for fertilizer, or with contamination of water supplies by pig feces. Poor nutrition, achlorhydria, and immunosuppression can be contributing factors.

Pathogenesis. Humans ingest infective cysts, which then migrate to the large intestine, cecum, and terminal ileum. Ingested cysts liberate trophozoites, which reside and replicate in the large bowel. The trophozoites replicate by binary fission and conjugation, and they subsist on bacteria. The organisms primarily dwell in the lumen, but they also can penetrate the mucosa and submucosa, causing ulceration and infiltration with polymorphonuclear cells, lymphocytes, and eosinophils. Hyaluronidase is produced by this organism, which may enhance its ability to invade the mucosa. In symptomatic individuals, the pathology in the bowel both gross and microscopic is similar to that seen in amebiasis, with varying degrees of mucosal invasion, focal necrosis, and ulceration. Balantidiasis, unlike amebiasis, does not spread hematogenously to other organs.

Clinical manifestations. Most infections in immunocompetent individuals are asymptomatic. But some patients have persisting intermittent diarrhea, and a few develop more fulminant dysentery. Patients may develop watery, bloody or mucoid diarrhea, nausea, vomiting, abdominal pain, anorexia, weight loss, headache, mild colitis. Patients may present with abdominal tenderness and, in cases with prolonged diarrhea, signs of dehydration. Intestinal perforation and extraintestinal spread to liver and mesenteric lymph nodes are rare. Pulmonary involvement has been reported and appears to be more common in patients with underlying illnesses such as diabetes, cancer, or impaired lymphocyte function and has not always been associated with direct contact with pigs.

Diagnosis. The diagnosis is usually made by detection of the trophozoite stage in stool or sampled colonic tissue. *B. coli* does not stain well on permanent stained smears, making diagnosis more difficult; however, diagnosis can be made by examining wet smears of stool specimens or scrapings from the invading edge of ulcers or at the periphery of submucosal abscesses during an endoscopic examination. Chest radiography is necessary method of investigation and can show pulmonary parenchymal involvement. Bronchoalveolar lavage can identify organisms on wet mount of bronchial secretions. Pulmonary parenchymal and lymph node involvement, as well as involvement of other organ systems, may be seen on CT scan study.

Treatment. Tetracycline (500 mg qid for 10 days) is an effective therapeutic agent. Ensure that the patient has a follow-up visit after treatment to document the resolution of symptoms. Also, obtain a stool specimen and a wet smear to check for organisms. A clean water supply and hygienic living conditions can prevent this disorder. Avoiding contact with pigs and fertilizer that is contaminated with pig excrement can decrease the risk.

GIARDIASIS

Definition. Giardiasis is one of the most common parasitic diseases worldwide caused by *Giardia lamblia* and characterized by both endemic and epidemic intestinal disease and diarrhea.

Etyology. Cysts are oval, measure 8 to 12 um 7 to 10 um, and characteristically contain four nuclei. Trophozoites are pear-shaped, dorsally convex, flattened parasites with two nuclei and four pairs of flagella.

Epidemiology. Giardiasis is common in both developed and developing countries. In developing countries, *Giardia* infections can be extremely common, with cumulative rates close to 100% by 2 years of age and prevalences of 20 to 30% or higher among adults. Because cysts are infectious when excreted or shortly thereafter, person-to-person transmission occurs where fecal hygiene is poor and during homosexual contacts. If food is contaminated with *Giardia* cysts after cooking or preparation, food-borne transmission can occur. Waterborne transmission accounts for episodic infections (e.g., in travelers) and for massive epidemics in metropolitan areas. Surface water, ranging from mountain streams to large municipal reservoirs, can become contaminated with fecally derived *Giardia* cysts; outmoded water systems are subject to cross-contamination from leaking sewer lines. The efficacy of water as a means of transmission is enhanced by the small infectious inoculum of *Giardia*, the prolonged survival of cysts in cold water, and the resistance of cysts to killing by routine chlorination methods that are adequate for controlling bacteria. Viable cysts can be eradicated from water by either boiling or filtration. The importance of animal reservoirs as sources of infection for humans is unclear. *Giardia* parasites morphologically similar to those in humans are found in a large

number of mammals, including beavers from reservoirs implicated in epidemics, dogs, cats, and ruminants. Although the high degree of isolate heterogeneity noted in humans is consistent with infections originating from different animal sources, animals have not been directly established as sources of human infection.

Pathogenesis. Ingestion of as few as 10 cysts is sufficient to cause infection in humans. Infection follows the ingestion of the environmentally hardy cysts, which excyst in the small intestine, releasing trophozoites that multiply by binary fission, occasionally to enormous numbers. *Giardia* remains a pathogen of the proximal small bowel and does not disseminate hematogenously. Trophozoites remain free in the lumen or attach to the mucosal epithelium by means of a ventral sucking disk. As a trophozoite encounters altered conditions, it forms a morphologically distinct cyst, which is the stage of the parasite usually found in the feces. Trophozoites may be present and even predominate in loose or watery stools, but it is the resistant cyst that survives outside the body and is responsible for transmission. Cysts do not tolerate heating, desiccation, or continued exposure to feces but do remain viable for months in cold fresh water. The number of cysts excreted varies widely but can approach 107 per gram of stool.

The reasons why some, but not all, infected patients develop clinical manifestations and the mechanisms by which *Giardia* causes alterations in small-bowel function are largely unknown. While trophozoites adhere to the epithelium, they do not cause invasive or locally destructive alterations. The development of lactose intolerance and significant malabsorption in a minority of infected adults and children are clinical signs of the loss of brush border enzyme activities. In most infections the morphology of the bowel is unaltered, but in a few usually in chronically infected, symptomatic patients the histopathologic findings (including flattened villi) and the clinical manifestations resemble those of tropical sprue and gluten-sensitive enteropathy. The pathogenesis of diarrhea in giardiasis is not known.

Parasite as well as host factors may be important in determining the course of infection and disease. Both cellular and humoral responses develop in human infections, but their precise roles in the control of infection and/or disease are unknown. Because patients with hypogammaglobulinemia commonly suffer from prolonged, severe infections that are poorly responsive to treatment, humoral immune responses appear to be important. The greater susceptibility of the young than of the old and of newly exposed persons than of chronically exposed populations also suggests that at least partial protective immunity may develop. The marked biochemical and biological differences among some *Giardia* isolates may help account for the different courses of infection noted in experimentally infected humans and animals. The surface of trophozoites is covered by a family of related cysteine-rich proteins that undergo surface antigenic variation and may contribute to prolonged and/or repeated infections.

Clinical manifestations. Disease manifestations of giardiasis may be aborted, transient, recurrent, or chronic. Most infected persons are asymptomatic, but in epidemics the proportion of symptomatic cases may be higher. Symptoms may develop suddenly or gradually. In persons with acute giardiasis, symptoms develop after an incubation period that lasts at least 5 to 6 days and usually 1 to 3 weeks. Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting. Although diarrhea is common, upper intestinal manifestations such as nausea, vomiting, bloating, and abdominal pain may predominate. The duration of acute giardiasis is usually in excess of 1 week, although diarrhea often subsides. Individuals with chronic giardiasis may present with or without having experienced an antecedent acute symptomatic episode. Diarrhea is not necessarily prominent, but increased flatus, loose stools, sulfurous burping, and (in some instances) weight loss occur. Symptoms may be continual or episodic and can persist for years. Some persons who have relatively mild symptoms for long periods recognize the extent of their discomfort only in retrospect. Fever, the presence of blood and/or mucus in the stools, and other signs and symptoms of colitis are uncommon and suggest a different diagnosis or a concomitant illness. Symptoms tend to be intermittent yet recurring and gradually debilitating, in contrast with the acute disabling symptoms associated with many enteric bacterial infections. Because of the less severe illness and the propensity for chronic infections, patients may seek medical advice late in the course of the illness; however, disease can be severe, resulting in malabsorption, weight loss, growth retardation, dehydration, and (in rare cases) death. A number of extraintestinal manifestations have been described, such as urticaria, anterior uveitis, and arthritis; whether these are caused by giardiasis or concomitant processes is unclear. Giardiasis can be life-threatening in patients with hypogammaglobulinemia and is typically difficult to treat and eradicate. *Giardia* infections can complicate other preexisting intestinal diseases, such as cystic fibrosis. Although *Giardia* can cause enteric illness in patients with AIDS, neither the course of infection nor the response to treatment differs for patients with and without AIDS.

Diagnosis. Giardiasis is diagnosed by the identification of cysts in the feces or of trophozoites in the feces or small intestines. The diagnosis is sometimes difficult to establish. Direct examination of fresh or properly preserved stools as well as concentration methods should be used. Because cyst excretion is variable and may be undetectable at times, repeated examination of stool, sampling of duodenal fluid, and biopsy of the small intestine may be required to detect the parasite. Tests for parasitic antigen in stool, now commercially available, are as sensitive and specific as good microscopic examinations and easier to perform. All of these methods occasionally yield false-negative results.

Treatment. Cure rates with metronidazole (250 mg tid for 5 days) are usually higher than 80%; those with furazolidone (100 mg qid for 7 to 10 days) are

somewhat lower. The latter agent is frequently used to treat children because it is available as a palatable elixir that is not bitter. Patients in whom initial treatment fails can be re-treated with a longer course. Almost all patients respond to therapy and are cured, although some with chronic giardiasis experience delayed resolution of symptoms after eradication of *Giardia*. Those who remain infected after repeated treatments should be evaluated for reinfection through family members, close personal contacts, and environmental sources as well as for hypogammaglobulinemia. In cases refractory to multiple treatment courses, prolonged therapy with metronidazole (750 mg tid for 21 days) has been successful. Tinidazole is considered more effective than metronidazole or quinacrine. When children attending day-care centers infect an entire family, treatment of all infected family members, including asymptomatic carriers, may be required to prevent reinfection. Paromomycin, an oral aminoglycoside that is not well absorbed, can be given to symptomatic pregnant women, although the experience accumulated thus far is not a sufficient basis on which to judge how often this agent either eradicates infection or ameliorates symptoms.

Prevention. Although *Giardia* is extremely infectious, disease can be prevented by the exclusive consumption of noncontaminated food and water. Cooking food adequately and boiling or filtering potentially contaminated water prevent infection.

INFECTIONS CAUSED BY ARTHROPOD- AND RODENT-BORNE VIRUSES

Zoonotic viruses from at least seven virus families (*Flaviviridae, Togaviridae, Reoviridae, Rhabdoviridae, Bunyaviridae, Arenaviridae* and *Filoviridaea*) act as significant human pathogens. Most of these viruses either are maintained by arthropods (arboviruses) or chronically infected rodents.

Etiology. The virus families differ fundamentally from one another in terms of morphology, replication mechanisms, and genetics. The *Flaviviridae* are enveloped positive-sense, single-stranded RNA viruses that form particles of 40 to 65 nm in the endoplasmic reticulum. The flaviviruses from the genus *Flavivirus* make up two phylogenetically and antigenically distinct divisions transmitted among vertebrates by mosquitoes and ticks, respectively. The *Togaviridae* have a single positive strand RNA genome and bud particles of approximately 60 to 70 nm from the plasma membrane. The togaviruses of the genus *Alphavirus* are divided phylogenetically into two groups: one seems to have developed in the new world, and the other is associated primarily with the old world.

The *Reoviridae* are double-stranded RNA viruses with multisegmented genomes. The virus particles are spherical in appearance and have icosahedral symmetry. An outer and an inner capsid layer surround the genome. These 70-80 nm

particles do not have a lipid envelope and thus are insensitive to detergents. The *Rhabdoviridae* contain a negative-sense single-stranded RNA and are very stable to drying. Viruses of the genus *Vesiculovirus* (Vesicular stomatitis virus - VSV) can infect insects and mammals and are bullet-shaped. Two distinct serotypes of VSV, New Jersey and Indiana, have been recognized. Enveloped spherical viruses from the family *Bunyaviridae* have three single-stranded negative-senses RNA segments exist in a helical formation within the virion. Virions contain no matrix proteins, maturing into 90-120 nm particles in the cytoplasm. Mature virions bud from the Golgi apparatus into vesicles which are transported to the cell surface.

The *Arenaviridae* are spherical, 110-130 nm particles that are enveloped in a lipid membrane and utilize ambisense RNA genomes with two segments for replication. Ambisense means that some of the proteins on the RNA strand are negative sense. Virions are created by budding from the surface of their hosts' cells. Viewed in cross-section, they show grainy particles that are ribosomes acquired from their host cells. There are two main phylogenetic branches of *Arenaviridae*: the old world viruses, such as Lassa fever and lymphocytic choriomeningitis viruses, and the new world viruses, including those causing the South American hemorrhagic fevers (HF).

The viruses from the family *Filoviridae* are negative-sense single-stranded RNA particles with a helical nucleocapsid. There are two antigenically distinct genera: the *Ebola virus* (with four species) and the *Marburg virus*. The *virions* are characteristically shaped as long, cylindrical, filamentous particles which may be straight, curved, coiled, or found in a "6" or "U" shaped configuration. They are occasionally branched and the particles vary greatly in length but the diameter (about 80 nm) is consistent. They are produced by budding from an infected cell, and consist of the viral RNA strand and proteins encapsulated in a lipid membrane formed from the host cell's plasma membrane. The viruses are stable and remain infectious for prolonged periods at room temperature. They are destroyed by heat (60°C, 30 min) and lipid solvents. Both viruses are biosafety level IV pathogens and require maximal biologic containment facilities.

Epidemiology. The distribution of arthropod- and rodent-borne viruses is restricted by the areas inhabited by their reservoir and vectors. Most of diseases are acquired in a rural setting; a few have urban vectors (Seoul, sandfly fever, and Oropouche viruses, yellow fever, dengue, and chikungunya viruses).

Arthropod-borne viruses infect their vectors after the ingestion of a blood meal from a viremic vertebrate. The vectors then develop chronic, systemic infection as the viruses penetrate the gut and spread throughout the body. The viruses eventually reach the salivary glands during a period that is referred to as extrinsic incubation. At this point an arthropod is competent to continue the chain of transmission by infecting another vertebrate when a subsequent blood meal is taken. The arthropod

generally is unharmed by the infection, and the natural vertebrate partner usually has only transient viremia with no overt disease. An alternative mechanism for virus maintenance in its arthropod host is transovarial and transstadial transmission. Although the great majority of arbovirus infections of man follow exposure to the bite of an arthropod, infection may exceptionally follow ingestion off infected cows' or goats' milk, inhalation of infected secretions or accidentally produced aerosols, or close contact with infected secretions or blood. Distribution and seasonal activity may be variable and often depend largely on ecologic conditions such as rainfall and temperature, which in turn affect the density of vectors and reservoirs and the development of infection therein.

Rodent-borne viruses such as the hantaviruses and arenaviruses are maintained in nature by chronic infection transmitted between rodents. As in arthropod-borne virus cycles, there is usually a high degree of rodent-virus specificity, and there is generally no overt disease in the reservoir.

The flaviviruses are transmitted among vertebrates by mosquito or tick bites. The togaviruses of the genus *Alphavirus* are transmitted by mosquitoes in their natural cycle. Members of the *Reoviridae* family: orbiviruses (Orungo, Kemerovo viruses) and coltiviruses (Colorado tick fever virus) can infect and replicate within arthropods and vertebrate hosts (occasionally humans). There is no evidence of natural person-to-person transmission. However, rare cases of transmission from blood transfusions have been reported (Colorado tick fever virus may stay in the blood for as long as four months after onset of the illness).

Rhabdoviruses are transmitted to hosts by sandflies and mosquitoes. It has particular importance to farmers in certain regions of the world where it can infect cattle. Vesicular stomatitis is a viral illness of animals that affects chiefly domestic cattle, horses, swine, wild deer, raccoons, skunks, bobcats and occasionally affects humans. With the exception of hantaviruses, bunyaviruses are also vector-borne. Transmission occurs via an arthropod vector (mosquitos, tick, or sandfly). Sandflies or mosquitoes are the vectors for the genus *Phlebovirus*, while ticks serve as vectors for the genus *Nairovirus*. Viruses of both of these genera are also associated with transovarially transmission in the arthropod host and with horizontal spread through viremic vertebrate hosts. Incidence of infection is closely linked to vector activity. The genus *Hantavirus* is unique among the *Bunyaviridae* in that it is not transmitted by arthropods but is maintained in nature by rodent hosts that chronically shed virus. The hantaviruses usually display striking virus-rodent species specificity. As far as is known, however, the hantaviruses do not cause chronic viremia in their rodent host and are transmitted only horizontally from rodent to rodent.

Some arenaviruses are zoonotic pathogens and are generally associated with rodent-transmitted disease in humans. Each virus usually is associated with a particular rodent host species in which it is maintained. Arenaviruses persist in nature

by chronically infecting rodents with a striking one-virus-one-rodent species relationship. These rodent infections result in long-term virus excretion and perhaps in lifelong viremia; vertical infection is common with some arenaviruses. Humans become infected through the inhalation of aerosols containing arenaviruses, which are then deposited in the terminal air passages, and probably also through close contact with rodents and their excreta, which results in the contamination of mucous membranes or breaks in the skin. Person-to-person spread is reported for Lassa fever in community and in hospital settings, but is apparently rare with the other pathogen arenaviruses.

The mechanisms through which filoviruses spread are not fully understood. The natural reservoir of both the *Marburg virus* and the *Ebola virus* appears to be zoonotic, which means that the virus is transmitted to humans from other animals. Despite numerous attempts to find the source, neither has been found. Bats, though, have been suspected because they can replicate filoviridae-like viruses. The route of transmission from animals to humans is unknown. Person-to-person transmission occurs primarily through physical contact with infected bodily fluids. Most of secondary cases appeared to be related to accidental needle sticks or abrasions, a few one through sexual intercourse. Contact with patients' perspiration may have facilitated the spread of the agent.

Pathogenesis. The pathogenesis of arthropod- and rodent-borne virus-infections is poorly understood and varies among the viruses. The acute phase in most cases of them is associated with ongoing virus replication and viremia. Exceptions are the dengue HF, hantavirus and arenavirus diseases, in which the immune response plays a major pathogenic role.

Clinical manifestations. Human infection caused by arthropod- and rodent-borne viruses range from subclinical through febrile fever and myalgia, arthritis and rash, to aseptic meningitis and encephalitis, and hemorrhagic fever. The spectrum of possible responses to infection is wide, and our knowledge of the outcome of most of these infections is limited.

Diagnosis. One of the major diagnostic clues is travel to an endemic area within the incubation period. Except for virus infections, which have urban vectors, travel to a rural setting is especially suggestive of a diagnosis. A history of mosquito bite has little diagnostic significance in the individual; a history of tick-bite is more diagnostically specific. Rodent exposure is often reported by persons infected with an arenavirus or a hantavirus but again has little specificity. Indeed, aerosols may infect persons who have no recollection of having even seen rodents.

Laboratory diagnosis is required in any given case, although epidemics occasionally provide clinical and epidemiologic clues. For most arthropod- and rodent-borne viruses, acute-phase serum samples (collected within 3 or 4 days of onset) have yielded isolates, and paired sera have been used to demonstrate rising

antibody titers by a variety of tests. Intensive efforts to develop rapid tests for HF have resulted in an antigen-detection ELISA and an IgM-capture ELISA that can provide a diagnosis based on a single serum sample within a few hours and are particularly useful in severe cases. More sensitive reverse transcription PCR (RT-PCR) tests may yield diagnoses based on samples without detectable antigen and may also provide useful genetic information about the virus.

At the time of diagnosis, patients with encephalitis generally are no longer viremic or antigenemic and usually do not have virus in CSF. In this situation, the value of serologic methods is being validated. IgM capture is increasingly being used for the testing of serum and CSF. IgG ELISA or classic serology is useful in the evaluation of past exposure to the viruses, many of which circulate in areas with a minimal medical infrastructure and sometimes cause mild or subclinical infection.

HAEMORRHAGIC FEVERS

Definition. Hemorrhagic fevers are a group of acute endemic diseases, caused by five distinct families of viruses and characterized by development of a general-purpose capillary toxicosis, hemorrhagic syndrome on a background of the expressed intoxication and fever.

Etiology. Each of these virus families (*Flaviviridae, Togaviridae, Bunyaviridae, Arenaviridae* and *Filoviridaea*) share a number of features: they are all RNA viruses, and all are enveloped, in a lipid coating; their survival is dependent on an natural reservoir (animal or insect host); the viruses are geographically restricted to the areas where their host species live; humans are not the natural reservoir for any of these viruses (humans are infected when they come into contact with infected hosts, however, with some viruses, after the accidental transmission from the host, humans can transmit the virus to one another);. human cases or outbreaks of HF caused by these viruses occur sporadically and irregularly (the occurrence of outbreaks cannot be easily predicted).

Epidemiology. The viruses associated with arthropod vectors are spread most often when the vector mosquito or tick bites a human, or when a human crushes a tick. However, some of these vectors may spread virus to animals, livestock, for example. Humans then become infected when they care for or slaughter the animals. The viruses carried in rodent reservoirs are transmitted when humans have contact with urine, fecal matter, saliva, or other body excretions from infected rodents. Some viruses that cause hemorrhagic fever can spread from one person to another, once an initial person has become infected. Ebola, Marburg, Lassa and Crimean-Congo hemorrhagic fever viruses are examples. This type of secondary transmission of the virus can occur directly, through close contact with infected people or their body fluids. It can also occur indirectly, through contact with objects contaminated with infected body fluids (contaminated syringes and needles).

Pathogenesis. The diversity of clinical features seen among the HF probably originates from varying mechanisms of pathogenesis. The reasons for variation among patients infected with the same virus are unknown but stem from a complex system of virus-host interactions. Hemodynamic pathogenesis is based on a massive acute capillary leak syndrome of uncertain specific etiology. In some cases direct damage to the vascular system or even to parenchymal cells of target organs is important, whereas in others soluble mediators are thought to play the major role. An immunopathogenic mechanism, for example, has been identified for dengue HF, which usually occurs among patients previously infected with a heterologous dengue serotype. An influential theory explaining this phenomenon is called "antibody-dependent enhancement." In most HF, however, the etiology of the coagulopathy is most likely multifactorial (e.g., hepatic damage, consumptive coagulopathy, primary marrow dysfunction, etc.).

An assault, direct or indirect, on the microvasculature leads to increased permeability and to actual disruption and local hemorrhage. Blood pressure is decreased, and in severe cases shock supervenes. Cutaneous flushing and conjunctival suffusion are examples of common, observable abnormalities in the control of local circulation. The hemorrhage is inconstant and is thought in most cases to be an indication of widespread vascular damage rather than a life-threatening loss of blood volume. Disseminated intravascular coagulation is occasionally found in any severely ill patient with HF but is thought to occur regularly only in the early phases of HF with renal syndrome, in Crimean Congo HF, Marburg and Ebola fevers. In some viral HF syndromes, specific organs may be particularly impaired, such as the kidney in HF with renal syndrome, the lung in hantavirus pulmonary syndrome, or the liver in yellow fever, but in all these diseases the generalized circulatory disturbance is critically important.

Clinical manifestations. While some of HF viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening disease. Specific signs and symptoms vary by the type of HF, but initial signs and symptoms often include marked fever, fatigue, dizziness, variable sore throat and headache, arthralgia and myalgia usually of abrupt onset. Within a few days the patient presents for medical attention because of increasing prostration that is often accompanied by severe headache, dizziness, photophobia, hyperesthesia, abdominal or chest pain, anorexia, nausea or vomiting, and other gastrointestinal disturbances. Initial examination often reveals only an acutely ill patient with conjunctival suffusion, tenderness to palpation of muscles or abdomen, and borderline hypotension or postural hypotension, perhaps with tachycardia. Multiorgan damage is common, with evidence of liver dysfunction, bone marrow depression, renal impairment and evidence of widespread tissue damage (falling sodium levels, elevation of transaminases, falling blood pressure, encephalopathy and extreme lassitude). These problems may be accompanied by

specific features such as rash, diarrhoea or renal failure. Petechiae (often best visualized in the axillae), flushing of the head and thorax, periorbital edema, and proteinuria are common. Haemorrhage is usually due to platelet deficiency or dysfunction, and evidence of significant disseminated intravascular coagulation is uncommon. Hemoconcentration from vascular leakage, which is usually evident, is most marked in hantavirus diseases and in dengue HF. The seriously ill patient progresses to more severe symptoms and develops shock and other findings typical of the causative virus. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, and convulsions) are all poor prognostic signs.

Diagnosis depends on clinical and epidemiological suspicion. Except for Seoul, Dengue, and Yellow fever virus infections, which have urban vectors, travel to a rural setting is especially suggestive of a diagnosis of HF. Haemorrhagic conditions that should be considered before a diagnosis of viral haemorrhagic fever is assumed include malignant malaria, meningococcal infection, severe rickettsial infections, leptospirosis and Gram-negative septicaemia with disseminated intravascular coagulation. Most infections are retrospective diagnosed on the basis of serological tests, which include the classic neutralization, complement fixation and haemagglutination inhibition tests. Paired sera have been used to demonstrate rising antibody titres. Antibodies detectable by these tests generally appear within 10-14 days of onset. Viruses may be detected by using monoclonal antibodies and the immunofluorescence technique. The diagnosis can be rapidly and specifically achieved by demonstrating IgM or IgG antibodies by an antigen-detection ELISA and radioimmunoassays, which can provide a diagnosis based on a single serum sample within a few hours and are particularly useful in severe cases. More sensitive RT-PCR and molecular hybridization tests may yield diagnoses based on samples without detectable antigen and may also provide useful genetic information about the virus. Diagnosis by isolation of virus from the blood or of tissues obtained postmortem, in suckling mice, adult hamsters or tissue culture, is possible in the first days of illness. Because of the aerosol hazard to laboratory personnel, however, attempts to isolate agent should be restricted to facilities with maximum containment.

Treatment. Medical management of HF patients may require intensive supportive care, including prompt, atraumatic hospitalization; judicious fluid therapy that takes into account the patient's increased capillary permeability; use of pressors to maintain blood pressure at levels that will support renal perfusion; treatment of the relatively common secondary bacterial infections; replacement of clotting factors and platelets as indicated; and the usual precautionary measures used in the treatment of patients with hemorrhagic diatheses. Disseminated intravascular coagulation should be treated only if clear laboratory evidence of its existence is found and if laboratory monitoring of therapy is feasible; there is no proven benefit of such therapy. The available evidence suggests that HF patients have a decreased cardiac output and will

respond poorly to fluid loading as it is often practiced in the treatment of shock associated with bacterial sepsis. Specific antiviral therapy with ribavirin is available for *Bunyaviridae* and *Arenaviridae* infections (specifically Lassa fever, Rift Valley fever, Congo-Crimean HF, HF with renal syndrome and Hantavirus pulmonary syndrome). Orally ribavirin is used in dosage 500 mg every six hours for seven to ten days and intravenously (infusion over 15 to 20 minutes) – 30 mg per kg of body weight loading dose, then 16 mg per kg of body weight every six hours for four days, then 8 mg per kg of body weight every eight hours for six more days. Convalescent plasma may be effective in Argentine or Bolivian HF.

Prevention. With the exception of Yellow fever and Argentine HF, for which vaccines have been developed, no vaccines exist that can protect against these diseases. Therefore, prevention efforts must concentrate on avoiding contact with host species; controlling rodent populations; discouraging rodents from entering or living in homes or workplaces; encouraging safe cleanup of rodent nests and droppings; community-wide insect and arthropod control; encouraging to use insect repellant, proper clothing, bednets, window screens, and other insect barriers. If prevention methods fail and a case of HF do occur, efforts should focus on preventing further transmission from person to person. All HF patients (with the exception of HF with renal syndrome, yellow fever, Rift Valley fever, and dengue patients) should be cared for using strict contact precautions, including hand hygiene, double gloves, gowns, shoe and leg coverings, and faceshield or goggles. Lassa, Congo-Crimean HF, Ebola, and Marburg viruses may be particularly prone to nosocomial spread. Airborne precautions should be utilized including, at a minimum, a fit-tested, HEPA filter-equipped respirator (such as an N-95 mask), a battery-powered, air-purifying respirator, or a positive pressure supplied air respirator to be worn by personnel coming within six feet of a HF patient. Multiple patients should be cohorted to a separate building or a ward with an isolated air-handling system. Prophylactic ribavirin may be effective for some *Bunyaviridae* and *Arenaviridae* infections. Environmental decontamination is typically accomplished with hypochlorite or phenolic disinfectants.

YELLOW FEVER

The yellow fever virus (flavivirus) is maintained in nature by mosquito-borne transmission between nonhuman primates. Transmission by mosquitoes from one human to another occurs during epidemics of "urban yellow fever." The disease occurs only in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic. In Africa, where most cases are reported, a variety of vectors are responsible for transmitting the virus (most often *Aedes* spp. mosquitoes). The case-fatality rate is >20%, and infants and children are at greatest risk for infection. In South America, cases occur most frequently in young men who have occupational exposure to forest-dwelling mosquito vectors (*Haemagogus* spp.

mosquitoes) in forested or transitional areas of Bolivia, Brazil, Colombia, Ecuador, Venezuela, Guyana, French Guiana, and Peru. The incidence of yellow fever in South America is lower than that in Africa because the mosquitoes that transmit the virus between monkeys in the forest canopy do not often come in contact with humans and because immunity in the indigenous human population is high. Urban epidemic transmission has not occurred in South America for many years, although the risk of introduction of the virus into towns and cities is ever present. For travelers, the risks of illness and death due to yellow fever are probably 10 times greater in rural West Africa than in South America; these risks vary greatly according to specific location and season. In West Africa, the most dangerous time of year is during the late rainy and early dry seasons (July-October). Virus transmission is highest during the rainy season (January-March) in Brazil.

Yellow fever ranges in severity from an influenza-like syndrome to HF accompanied by prominent hepatic necrosis. A period of viremia, typically lasting 3 or 4 days, is followed by a period of "intoxication." During the latter phase in severe cases, the characteristic jaundice, hemorrhages, black vomit, anuria, and terminal delirium occur, perhaps related in part to extensive hepatic involvement. Blood leukocyte counts may be normal or reduced and are often high in terminal stages. Albuminuria is usually noted and may be marked; as renal function fails in terminal or severe cases, the level of blood urea nitrogen rises proportionately. Abnormalities detected in liver function tests range from modest elevations of AST levels in mild cases to severe derangement.

The continuing sylvatic cycle requires vaccination of all visitors to areas of potential transmission. Reactions to vaccine are minimal; immunity is provided within 10 days and lasts for at least 10 years. An egg allergy dictates caution in vaccine administration. Although there are no documented harmful effects of the vaccine on the fetus, pregnant women should be immunized only if they are definitely at risk of yellow fever exposure. Since vaccination has been associated with several cases of encephalitis in children under 6 months of age, it should be delayed until after 12 months of age unless the risk of exposure is very high.

DENGUE HF

Dengue HF is a severe form of dengue infection in which there is haemorrhage and a tendency to develop fatal shock (dengue shock syndrome). A syndrome of HF associated with dengue virus (mosquito-borne flavivirus) infections, particularly those occurring against a background of previous exposure to another serotype. The transient heterotypic protection after dengue virus infection is replaced within several weeks by the potential for heterotypic infection resulting in typical dengue fever (see below) or-uncommonly-for enhanced disease (secondary Dengue HF). In rare instances, primary dengue infections lead to an HF syndrome, but much less is known about pathogenesis in this situation. *A. aegypti* has progressively reinvaded Latin

America and other areas, and frequent travel by infected individuals has introduced multiple strains of dengue virus from many geographic areas. Thus the pattern of hyperendemic transmission of multiple dengue serotypes has now been established in the Americas and the Caribbean and has led to the emergence of Dengue HF as a major problem there as well. Millions of dengue infections, including many thousands of cases of Dengue HF, occur annually.

The induction of vascular permeability and shock depends on multiple factors, including the following:

1. Presence of enhancing and nonneutralizing antibodies-transplacental maternal antibody may be present in infants 9 months old, or antibody elicited by previous heterologous dengue infection may be present in older individuals.
2. Age – susceptibility to Dengue HF drops considerably after 12 years of age.
3. Sex – females are more often affected than males.
4. Race – caucasians are more often affected than blacks.
5. Nutritional status – malnutrition is protective.
6. Sequence of infection – for example, serotype 1 followed by serotype 2 is more dangerous than serotype 4 followed by serotype 2.
7. Infecting serotype – type 2 is apparently more dangerous than other serotypes.

Dengue HF is identified by the detection of bleeding tendencies (tourniquet test, petechiae) or overt bleeding in the absence of underlying causes such as preexisting gastrointestinal lesions. Dengue shock syndrome, usually accompanied by hemorrhagic signs, is much more serious and results from increased vascular permeability leading to shock. In mild Dengue HF, restlessness, lethargy, thrombocytopenia (100,000/uL), and hemoconcentration are detected 2 to 5 days after the onset of typical dengue fever, often at the time of defervescence. The maculopapular rash that often develops in dengue fever may also appear in Dengue HF. In more severe cases, frank shock is apparent, with low pulse pressure, cyanosis, hepatomegaly, pleural effusions, ascites, and in some cases severe ecchymoses and gastrointestinal bleeding. The period of shock lasts only 1 or 2 days, and most patients respond promptly to close monitoring, oxygen administration, and infusion of crystalloid or-in severe cases-colloid. The mortality rates reported vary greatly with case ascertainment and the quality of treatment; however, most Dengue HF patients respond well to supportive therapy, and overall mortality in an experienced center in the tropics is probably as low as 1%.

A virologic diagnosis can be made by the usual means, although multiple flavivirus infections lead to a broad immune response to several members of the group, and this situation may result in a lack of virus specificity of the IgM and IgG immune responses. A secondary antibody response can be sought with tests against several flavivirus antigens to demonstrate the characteristic wide spectrum of reactivity.

The key to control of both dengue fever and Dengue HF is the control of *A. aegypti*, which also reduces the risk of urban yellow fever and chikungunya virus circulation. Control efforts have been handicapped by the presence of nondegradable tires and long-lived plastic containers in trash repositories, insecticide resistance, urban poverty, and an inability of the public health community to mobilize the populace to respond to the need to eliminate mosquito breeding sites.

KYASANUR FOREST DISEASE

Kyasanur Forest virus is a tick-borne flavivirus that cause a syndrome of viral HF during a wave of viremia and that may also enter the CNS to cause subsequent viral encephalitis. Kyasanur Forest disease has a limited geographical distribution in evergreen rain forests interspersed with deciduous patches and clearings for rice cultivation and human habitations in Karnataka State, India. The virus is amplified by transmission between immature ixodid ticks (*Haemaphysalis spinigera*) and small mammals (rodents, porcupines), passes to the adult tick stage during moulting, and is spread to man and wild monkeys by the bite of adult ticks. Forest workers are particularly at risk. As many as 1,000 human cases occur each year. Most cases occur during the dry season (January-May), when nymphal activity is maximal. Such a zoonosis is a good example of deforestation and agricultural development leading to human habitat expansion into natural foci of a viral infection.

The clinical illness appears after an incubation period of 2 to 7 days with abrupt onset of fever, chills, severe headache and myalgia, abdominal pain, nausea, vomiting, and diarrhoea. Patients often present markedly dehydrated. Haemorrhage (purpura, epistaxis, menorrhagia, gastrointestinal bleeding) occurs in a minority of patients after about 72 h. Hypotension is frequently noted towards the end of the acute stage. Fatal cases develop signs of circulatory failure, pulmonary oedema, and acute respiratory distress. During the acute phase of illness, physical examination reveals relative bradycardia, cervical lymphadenopathy, conjunctival injection, and papulovesicular lesions on the soft palate. A biphasic illness is not uncommon, with resolution of the first phase in about 5 to 12 days, and return of fever and signs of meningoencephalitis after an interval of 1 to 3 weeks. Convalescence is prolonged. Laboratory abnormalities include leucopenia, thrombocytopenia, and elevated serum transaminases during the acute phase of illness. Mortality rate is of 10 to 15%. Inactivated vaccine has been used in India.

OMSK HF

Omsk HF is caused by Omsk HF virus, a member of the virus family *Flaviviridae*. Infection occurs in the western Siberia regions of Omsk, Novosibirsk, Kurgan and Tyumen. The main host for the virus is rodents, principally the water vole (*Arvicola terrestris*), but the virus also infects the non-native muskrat (*Ondatra zibethica*). Virus is transmitted to the rodents from the bite of an infected tick (*Dermacentor reticulatus*, *Dermacentor marginatus*, *Ixodes persulcatus*). Humans

usually get the disease from a tick bite. However, humans can contract Omsk HF through contact with the blood, feces, or urine of an infected sick or dead muskrat. Experimental evidence shows that other rodents, i.e. narrow-skulled voles (*Microtus gregalis*) suffer similarly to muskrats; therefore, contact with these animals may also cause disease in humans. Virus can be transmitted through the milk of infected goats or sheep and isolated from aquatic animals and water. This suggests that the virus is extremely stable in the environment.

After an incubation period of 3-8 days, the symptoms of Omsk HF begin suddenly with fever, headache, severe muscle pain, cough, dehydration, gastrointestinal symptoms and bleeding problems. Patients may experience abnormally low blood pressure, and low platelet, red blood cell, and white blood cell counts. After 1-2 weeks of symptoms, some patients recover without complication. However, in most patients, the illness is biphasic and the patient begins experiencing a second wave of symptoms at the beginning of the third week. These symptoms include fever and signs of encephalitis. Omsk HF frequently causes hearing loss, hair loss, and behavioral or psychological difficulties associated with neurological conditions. The case fatality rate of Omsk HF is 0.5% to 3%. The diagnosis is made by virus isolation from blood or by serologic testing using ELISA. There is no vaccine currently available for Omsk HF, but vaccines for other tick-borne encephalitis diseases have shown to confer immunity and may be used for high-risk groups. Additionally, utilizing insect repellents and wearing protective clothing in areas where ticks are endemic is recommended.

CHIKUNGUNYA

Chikungunya virus (mosquito-borne togavirus) is transmitted in Africa by *Aedes africanus* and *Ae. aegypti* among nonhuman primates, whereas *Ae. aegypti* transmits the disease in urban centres of India and South-East Asia, where it poses a prominent health problem. The disease is endemic in rural areas of Africa, and intermittent epidemics take place in towns and cities of Africa and Asia. No vertebrate host other than man has confirmed, although evidence has been found that monkeys might be a maintenance host in Africa.

Chikungunya ("that which bends up") is most common among adults, in whom the clinical picture may be dramatic. After an incubation period of 2-12 days there is a sudden onset of fever and crippling arthralgia, which may incapacitate the patient within a few minutes to a few hours of onset. The pain in the limbs and spine is as severe as to cause patients to be doubled up and immobile. There are chills and constitutional symptoms such as mild headache, anorexia, nausea, constipation, abdominal pain photophobia and conjunctival injection but no retro-orbital or eye pain. Migratory polyarthritis mainly affects the small joints of the hands, wrists, ankles, and feet, with lesser involvement of the larger joints. The disease has a biphasic course: after 1-6 days of lever the temperature returns to normal for 1-3 days

and then there is a second period of fever for a few days during which 80% of patients develop a maculopapular pruritic rash on the trunk and extensor surfaces of the limbs. It may desquamate. Petechiae are occasionally seen, and epistaxis, haematemesis and melaena is not uncommon, but this virus is not a regular cause of the HF syndrome, even in children. No haemorrhagic complications in Chikungunya infections have ever been reported in Africa. It is not severe enough to cause shock. A few patients develop leukopenia. Elevated levels of aspartate aminotransferase and C-reactive protein have been described, as have mildly decreased platelet counts. Recovery may require weeks. Some older patients continue to suffer from stiffness, joint pain, and recurrent effusions for several years. A live attenuated investigational vaccine has been developed but requires further testing.

RIFT VALLEY FEVER

This mosquito-borne bunyavirus primarily affects livestock and can cause disease in a large number of domestic animals (sheep, cattle, goats etc.). It is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes and presumably in a vertebrate amplifier. Epizootics and epidemics occur when sheep or cattle become infected during particularly heavy rains; developing high-level viremia, these animals infect many different species of mosquitoes. Remote sensing via satellite can detect the ecologic changes associated with high rainfall that predict the likelihood of Rift Valley fever transmission; it can also detect the special depressions from which the floodwater mosquito vectors (*Aedes*, *Culex*, *Eratmopodites*, and *Culicoides*) emerge. In addition, the virus is infectious when transmitted by contact with the blood, body fluids, or tissues of infected animals (e.g., exposure through veterinary or obstetric procedures or direct exposure during slaughter). The natural range of Rift Valley fever virus is confined to sub-Saharan Africa, but the virus has also occurred in Egypt, the Arabian Peninsula, and Madagascar. Neither person-to-person nor nosocomial transmission has been documented.

Rift Valley fever virus is unusual in that it causes at least four different clinical syndromes. Most infections are manifested as the febrile-myalgic syndrome. A small proportion results in HF with especially prominent liver involvement. Perhaps 10% of otherwise mild infections lead to retinal vasculitis; funduscopic examination reveals edema, hemorrhages, and infarction, and some patients permanently lose partial vision. A small proportion of cases (1 in 200) are followed by typical viral encephalitis. One of the complicated syndromes does not appear to predispose to another.

There is no proven therapy for any of the syndromes. The sensitivity of animal models of Rift Valley fever to antibody or ribavirin therapy suggests that either could be given intravenously to persons with HF. Both retinal disease and encephalitis occur after the acute febrile syndrome has ended and serum neutralizing antibody has

developed-events suggesting that only supportive care need be given. Epidemic disease is best prevented by vaccination of livestock. The established ability of this virus to propagate after an introduction into Egypt suggests that other potentially receptive areas should have a response ready to use in such an eventuality. It seems likely that this disease, like Venezuelan equine encephalitis, can be controlled only with adequate stocks of an effective live attenuated vaccine, and there are no such global stocks. A formalin-inactivated vaccine confers immunity on humans, but quantities are limited and three injections are required; this vaccine is recommended for exposed laboratory workers and for veterinarians working in sub-Saharan Africa.

CRIMEAN CONGO HF

This severe HF syndrome has a wide geographic distribution, potentially being found wherever ticks of the genus *Hyalomma* occur. The propensity of these ticks to feed on domestic livestock and certain wild mammals means that veterinary serosurveys are the most effective mechanism for the surveillance of virus circulation in a region. Human infection is acquired via a tick bite or during the crushing of infected ticks. Domestic animals do not become ill but do develop viremia; thus there is danger of infection at the time of slaughter and for a brief interval thereafter (through contact with hides or carcasses). A recent epidemic was associated with slaughter of tick-infested ostriches in South Africa. Nosocomial epidemics are common and are usually related to extensive blood exposure or needle sticks.

Following an incubation period of 2-9 days after exposure to infection, patients had a sudden onset of disease with fever, nausea, severe headache, and myalgia. Petechial rash and hemorrhagic signs such as epistaxis, hematemesis, and melena supervened on days 3-6 of illness. Although generally similar to other HF syndromes, Crimean Congo HF causes extensive liver damage, resulting in jaundice in some cases. Deaths occurred on days 5-14 of illness. Patients with fatal cases generally have more marked changes even in the early days of illness: leukocytosis rather than leucopenia, thrombocytopenia and markedly elevated levels of serum aspartate and alanine aminotransaminases, gamma-glutamyltransferase, lactic dehydrogenase, creatine kinase, bilirubin, creatinine, and urea. Total protein, albumin, fibrinogen, and hemoglobin levels were depressed. Values for prothrombin ratio, activated partial thromboplastin time, thrombin time, and fibrin degradation products were grossly elevated, findings that indicate the occurrence of disseminated intravascular coagulopathy. Many of the clinical pathologic changes were evident at an early stage of the disease and had a highly predictive value for fatal outcome of infection. Changes were present but less marked in nonfatal infections.

No controlled trials have been performed with intravenous ribavirin, but clinical experience and retrospective comparison of patients with ominous clinical laboratory values suggest that ribavirin is efficacious and should be given. No human or veterinary vaccines are recommended.

HF WITH RENAL SYNDROME

This disease is widely distributed over Europe and Asia; the major causative viruses (hantaviruses) and their rodent reservoirs on these two continents are Puumala virus (bank vole, *Clethrionomys glareolus*) and Hantaan virus (striped field mouse, *Apodemus agrarius*), respectively. Other potential causative viruses exist, including Dobrava virus (yellow-necked field mouse, *Apodemus flavicollus*), which causes severe HF with renal syndrome in the Balkans. Seoul virus is associated with the Norway or sewer rat, *Rattus norvegicus*, and has a worldwide distribution through the migration of the rodent; it is associated with mild or moderate HF with renal syndrome in Asia, but in many areas of the world the human disease has been difficult to identify. Most cases occur in rural residents or vacationers; the exception is Seoul virus disease, which may be acquired in an urban or rural setting or from contaminated laboratory rat colonies. Classic Hantaan disease in Korea (Korean HF) and in rural China (epidemic HF) is most common in spring and fall and is related to rodent density and agricultural practices. Human infection is acquired primarily through aerosols of rodent urine, although virus is also present in saliva and feces. Patients with hantavirus diseases are not infectious. HF with renal syndrome is the most important form of HF today, with more than 100,000 cases of severe disease in Asia annually and milder Puumala infections numbering in the thousands as well.

Severe cases of HF with renal syndrome caused by Hantaan virus evolve in identifiable stages: the febrile stage with myalgia, lasting 3 to 4 days; the hypotensive stage, often associated with shock and lasting from a few hours to 48 h; the oliguric stage with renal failure, lasting 3 to 10 days; and the polyuric stage with diuresis and hyposthenuria.

The febrile period is initiated by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the V area of the neck, and the back are characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Laboratory evidence of mild to moderate disseminated intravascular coagulation is present. Other laboratory findings include proteinuria and an active urinary sediment.

The hypotensive phase is ushered in by falling blood pressure and sometimes by shock. The relative bradycardia typical of the febrile phase is replaced by tachycardia. Kinin activation is marked. The rising hematocrit reflects increasing vascular leakage. Leukocytosis with a left shift develops, and thrombocytopenia continues. Atypical lymphocytes-which in fact are activated CD8+ and to a lesser extent CD4+ T cells-circulate. Proteinuria is marked, and the urine's specific gravity

falls to 1.010. The renal circulation is congested and compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria.

During the oliguric phase, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. The oliguria persists for 3 to 10 days before renal function returns and marks the onset of the polyuric stage, which carries the danger of dehydration and electrolyte abnormalities.

Mild cases of HF with renal syndrome may be much less stereotyped. The presentation may include only fever, gastrointestinal abnormalities, and transient oliguria followed by hyposthenuria.

HF with renal syndrome should be suspected in patients with rural exposure in an endemic area. Prompt recognition of the disease will permit rapid hospitalization and expectant management of shock and renal failure. Useful clinical laboratory parameters include leukocytosis, which may be leukemoid and is associated with a left shift; thrombocytopenia; and proteinuria. Mainstays of therapy are the management of shock, reliance on pressors, modest crystalloid infusion, intravenous use of human serum albumin, and treatment of renal failure with prompt dialysis for the usual indications. Hydration may result in pulmonary edema, and hypertension should be avoided because of the possibility of intracranial hemorrhage. Use of intravenous ribavirin has reduced mortality and morbidity in severe cases provided treatment is begun within the first 4 days of illness. The case-mortality rate may be as high as 15% among unrecognized cases but with proper therapy should be 5%. Sequelae have not been definitely established, but there is a correlation between chronic hypertensive renal failure and the presence of antibodies to Seoul virus.

Infections with Puumala virus, the most common cause of HF with renal syndrome in Europe, result in a much attenuated picture but the same general presentation. The syndrome may be referred to by its former name, nephropathia epidemica. Bleeding manifestations are found in only 10% of cases, hypotension rather than shock is usually seen, and oliguria is present in only about half of patients. The dominant features may be fever, abdominal pain, proteinuria, mild oliguria, and sometimes blurred vision or glaucoma followed by polyuria and hyposthenuria in recovery. Mortality is 1%.

The diagnosis is readily made by IgM-capture ELISA, which should be positive at admission or within 24 to 48 h thereafter. The isolation of virus is difficult, but RT-PCR of a blood clot collected early in the clinical course or of tissues obtained postmortem will give positive results. Such testing is undertaken only if definitive identification of the infecting viral species is required.

HANTAVIRUS PULMONARY SYNDROME

Hantavirus pulmonary syndrome is a severe respiratory distress syndrome with a short incubation and fulminant course endemic throughout the Americas. The

causative viruses are hantaviruses of a distinct phylogenetic lineage that is associated with the rodent subfamily *Sigmodontinae*. Sin Nombre virus chronically infects the deer mouse (*Peromyscus maniculatus*) and is the most important virus causing hantavirus pulmonary syndrome in the United States. In the southern states, the disease is also caused by a Sin Nombre virus variant from the white-footed mouse (*Peromyscus leucopus*), by Black Creek Canal virus (*Sigmodon hispidus*, the cotton rat), and by Bayou virus (*Oryzomys palustris*, the rice rat). Viruses such as Andes virus are responsible for cases of hantavirus pulmonary syndrome in Argentina, Brazil, Chile, and Paraguay. The disease is linked to rodent exposure and particularly affects rural residents living in dwellings permeable to rodent entry or working at occupations that pose a risk of rodent exposure. Each rodent species has its own particular habits; in the case of the deer mouse, these behaviors include living in and around human habitation.

The disease begins with a prodrome of about 3 to 4 days (range, 1 to 11 days) comprising fever, myalgia, malaise, and often gastrointestinal disturbances such as nausea, vomiting, and abdominal pain. Dizziness is common and vertigo occasional. Severe prodromal symptoms sometimes bring some individuals to medical attention, but patients more commonly present as the pulmonary phase begins. Typically, there is slightly lowered blood pressure, tachycardia, tachypnea, mild hypoxemia, and early radiographic signs of pulmonary edema. Physical findings in the chest are often surprisingly scant. The conjunctival and cutaneous signs of vascular involvement seen in other types of HF are absent. During the next few hours, decompensation may progress rapidly to severe hypoxemia and respiratory failure. Most patients surviving the first 48 h of hospitalization are extubated and discharged within a few days, with no apparent residua.

Management during the first few hours after presentation is critical. The goal is to prevent severe hypoxemia by oxygen therapy and, if needed, intubation and intensive respiratory management. During this period, hypotension and shock with increasing hematocrit invite aggressive fluid administration, but this intervention should be undertaken with great caution. Because of low cardiac output and increased pulmonary vascular permeability, shock should be managed expectantly with pressors and modest infusion of fluid guided by the pulmonary capillary wedge pressure. Mild cases can be managed by frequent monitoring and oxygen administration without intubation. Many patients require intubation to manage hypoxemia and also develop shock. Mortality remains at about 40% with good management. The antiviral drug ribavirin inhibits the virus in vitro and is undergoing clinical trials for efficacy but did not have a marked effect on patients treated in an open-label study.

During the prodrome, the differential diagnosis of hantavirus pulmonary infection is difficult, but by the time of presentation or within 24 h thereafter, a

number of helpful clinical features become apparent. Cough is not usually present at the outset but may develop later. Interstitial edema is evident on the chest X-ray. Later, bilateral alveolar edema with a central distribution develops in the setting of a normal-sized heart; occasionally, the edema is initially unilateral. Pleural effusions are often visualized. Thrombocytopenia, circulating atypical lymphocytes, and a left shift (often with leukocytosis) are almost always evident. Hemoconcentration, proteinuria, and hypoalbuminemia should also be sought. Although thrombocytopenia virtually always develops and prolongation of the partial thromboplastin time is the rule, clinical evidence for coagulopathy or laboratory indications of disseminated intravascular coagulation are found in only a minority of cases, usually in severely ill patients. These patients also have acidosis and elevated serum levels of lactate. Mildly increased values in renal function tests are common, but patients with severe cases often have markedly elevated concentrations of serum creatinine; some of the viruses other than Sin Nombre virus (Bayou, Andes and Black Creek Canyon virus) have been associated with renal failure. The differential diagnosis includes abdominal surgical conditions and pyelonephritis as well as rickettsial disease, sepsis, meningococcemia, plague, tularemia, influenza, and relapsing fever. The case fatality rate is 40% or more, due to respiratory failure.

A specific diagnosis is best made by IgM testing of acute-phase serum, which has yielded a positive result even in the prodrome. Tests using a Sin Nombre virus antigen detect the related hantaviruses causing the pulmonary syndrome in the Americas. Occasionally, heterologous viruses will react only in the IgG ELISA, but this finding is highly suspicious given the very low seroprevalence of these viruses in normal populations. RT-PCR is usually positive when used to test blood clots obtained in the first 7 to 9 days of illness as well as tissues; this test is useful in identifying the infecting virus in areas outside the home range of the deer mouse and in atypical cases.

SOUTH AMERICAN HF (ARGENTINE, BOLIVIAN, VENEZUELAN, BRAZILIAN AND WHITEWATER ARROYO)

The causative agents of South American HF: Junin (Argentine HF), Machupo (Bolivian HF), Guanarito (Venezuelan HF), Sabia (Brazilian HF) and Whitewater Arroyo (Whitewater Arroyo HF) viruses belong to a New World arenaviruses. These diseases are similar to one another clinically, but their epidemiology differs with the habits of their rodent reservoirs and the interactions of these animals with humans.

Transmission of Junin and Machupo virus is via rodents (*Calomys musculinus* and *Calomys callosus* respectively). Female rodents infected neonatally with Junin or Machupo virus are subfertile. Infection is via inhalation of swirling dust containing dried rodent urine (aerogenic transmission). Infection with Junin virus is seasonal and shows a peak during the harvest in autumn. *Calomys musculinus* has a preference for linear habitats, e.g. hedges and roadsides. *Calomys callosus* prefers to live in open

fields. The Guanarito virus has *Zygodontomys brevicauda* as its reservoir. The role of *Sigmodon alstoni* is as yet unclear. Various species of *Neotoma* spp. woodrats form the reservoir for Whitewater Arroyo virus in New Mexico and California. Person-to-person or nosocomial transmission is rare but has occurred.

Characteristic features of South American HF are rather slow onset of aspecific malaise and fever, headache, arthralgia, muscle pain, conjunctivitis, pharyngitis, nausea, vomiting and sometimes diarrhoea and photophobia. Other features include cough, chest or abdominal pain, convulsions and haemorrhagic manifestations. Enlarged lymph nodes and pronounced erythema of the face, neck and thorax are common. Unlike Lassa fever, pharyngitis is not pronounced; thrombocytopenia (often marked) is the rule, and bleeding is quite common. The clinical laboratory is helpful in diagnosis since thrombocytopenia, leukopenia, and proteinuria are generally present. Chest X-ray is usually normal. Machupo and Guanarito virus infections often cause neurological symptoms. CNS dysfunction is often manifest by marked confusion, tremors of the arms and tongue, and cerebellar signs. Haemorrhage and shock herald a poor prognosis. Whitewater Arroyo virus causes high fever, acute respiratory distress syndrome liver failure, internal haemorrhage and in a three known cases death. Only a few cases of Sabia virus infection have been documented.

Good results have been described with convalescent plasma from survivors, especially if this is administered within the first 8 days of illness. In the absence of passive antibody therapy, intravenous ribavirin is likely to be effective in all the South American HF. The penetration of ribavirin into the cerebrospinal fluid is very low. Salicylates and intramuscular injections should be avoided. Thrombocytes should be transfused if in case of severe thrombocytopenia. In view of the heightened vascular permeability, caution is advised with intravenous fluid (risk of pulmonary oedema). In better centres monitoring via a Swan-Ganz catheter can be performed. A safe, effective, live attenuated vaccine exists for Argentine HF. In experimental animals, this vaccine is cross-protective against the Bolivian HF virus. Sometimes high-risk persons are given ribavirin preventively for two weeks (1.2 g daily PO). The transmission of the disease from men convalescing from Argentine HF to their wives suggests the need for counseling of arenavirus HF patients concerning the avoidance of intimate contacts for several weeks after recovery.

LASSA FEVER

Lassa virus is known to cause disease in Nigeria, Sierra Leone, Guinea, and Liberia, but probably exists in other West African countries as well. Like other arenaviruses, Lassa virus is spread to humans by small-particle aerosols from chronically infected rodents and may be acquired during the capture or eating of these animals; it can also be transmitted by person-to-person contact. The virus is often present in urine during convalescence and is suspected to be present in seminal fluid early in recovery. Nosocomial spread has occurred but is uncommon if proper sterile

parenteral techniques are used. People of all ages and both sexes are affected; the incidence of disease is highest in the dry season, but transmission takes place year-round. In countries where Lassa virus is endemic, Lassa fever can be a prominent cause of febrile disease.

The average case has a gradual onset (among the HF agents, only the arenaviruses are typically associated with a gradual onset) that gives way to more severe constitutional symptoms and prostration. Shaking chills, fever, malaise, myalgia, arthralgia, headache/retroorbital pain, facial/cervical/epiglottal edema, conjunctival injection, sore throat, nausea, vomiting, diarrhea, epigastric/right upper quadrant tenderness, dysphagia, cough, dyspnea, pleuritic chest pain, adult respiratory distress syndrome, abdominal pain/cramps, lymphadenopathy, hypotension and weight loss are the symptoms of the disease. The best predictors of Lassa fever is the combination of fever, vomiting, pharyngitis, retrosternal pain, and proteinuria. A maculopapular rash is often noted in light-skinned Lassa patients. Bleeding is seen in only about 15 to 30% of cases. Pleural (3%) or pericardial (2%) effusion may develop later. Array of acute and chronic neurologic and neuropsychiatric complications, including auditory or vestibular dysfunction (tinnitus, autophony, hearing loss, dizziness, vertigo, nystagmus, and ataxia), left-sided facial weakness, right-sided Babinski reflex, paresthesias, syncope, dysmorphopsias, fatigue, insomnia, asthenia, multiple somatic complaints, psychosis, hallucinations, personality disorders, severe adjustment reactions, dementia, mania, and depression have been reported. The fetal death rate is 92% in the last trimester, when maternal mortality is also increased from the usual 15% to 30%; these figures suggest that interruption of the pregnancy of infected women should be considered. White blood cell counts are normal or slightly elevated, and platelet counts are normal or somewhat low. Deafness coincides with clinical improvement in about 20% of cases and is permanent and bilateral in some. Reinfection may occur but has not been associated with severe disease.

High-level viremia or a high serum concentration of AST predicts a fatal outcome. Thus patients with an AST level of 150 IU/mL should be treated with intravenous ribavirin. This antiviral nucleoside analogue appears to be effective in reducing mortality from rates among retrospective controls, and its only major side effect is reversible anemia that usually does not require transfusion. The drug should be given by slow intravenous infusion in a dose of 32 mg/kg; this dose should be followed by 16 mg/kg q 6 h for 4 days and then by 8 mg/kg q 8 h for 6 days.

MARBURG AND EBOLA FEVERS

Both Marburg virus and Ebola virus cause an acute systemic febrile illness associated with high mortality. This illness is characterized by the abrupt onset of headache, myalgias, pharyngitis, rash, and hemorrhagic manifestations. Person-to-person and nosocomial contact may lead to secondary cases and intermittent

outbreaks of infection. Both Marburg virus and Ebola virus appear to be "pantropic"; viral replication takes place in almost all organs, including lymphoid tissue, liver, spleen, pancreas, adrenals, thyroid, kidneys, testes, skin, and brain. The lungs may exhibit interstitial pneumonitis as well as vascular lesions indicative of endarteritis in small arterioles. Neuropathologic changes consist of multiple small hemorrhagic infarcts with glial proliferation.

After an incubation period of 3 to 9 days, patients develop frontal and temporal headache, malaise, myalgias (especially in the lumbar area), nausea, and vomiting. Fever with temperatures of 39.4 to 40°C is characteristic, and about half of all patients have conjunctivitis. Between 1 and 3 days after onset, watery diarrhea (often severe), lethargy, and a change in mentation are noted. An enanthem of the palate and tonsils and cervical lymphadenopathy also may become apparent during the first week of illness. The most reliable clinical feature is the appearance of a nonpruritic maculopapular rash, which begins on the fifth to seventh day on the face and neck and spreads centrifugally to the extremities. A fine desquamation of the affected skin, especially on the palms and soles, appears 4 to 5 days later. Hemorrhagic manifestations, including gastrointestinal, renal, vaginal, and/or conjunctival hemorrhages, generally develop between days 5 and 7 of disease.

During the first week, the temperature remains around 40°C, falling by lysis during the second week only to increase again between days 12 and 14. Other clinical signs apparent in the second week of disease include splenomegaly, hepatomegaly, facial edema, and scrotal or labial reddening. Complications include orchitis, which may lead to testicular atrophy; myocarditis, with irregular pulse and electrocardiographic abnormalities; and pancreatitis. Patients who die usually do so on the eighth to sixteenth days of illness. Recovery is often protracted over a 3- to 4-week period, during which loss of hair, intermittent abdominal pain, poor appetite, and prolonged psychotic disturbances have been noted. Late sequelae, including transverse myelitis and uveitis, have been reported. Marburg virus has been isolated from the anterior eye chamber and semen nearly 3 months after onset of disease.

Abnormalities in granulocyte function are found in filovirus infection. Leukopenia is detected as early as the first day, with leukocyte counts as low as 1000/uL and neutrophilia by the fourth day. Subsequently, atypical lymphocytes as well as neutrophils exhibiting the Pelger-Huet anomaly may appear. Thrombocytopenia develops early and is most marked (often with fewer than 10,000 cells/uL) between days 6 and 12. Fatal cases may include evidence of disseminated intravascular coagulation. Hypoproteinemia, proteinuria, and azotemia may develop. Elevations in aspartate and alanine aminotransferases are usual. Lumbar puncture may yield normal findings or reveal minimal pleocytosis. The erythrocyte sedimentation rate is usually low. Specific diagnosis requires isolation of the virus or detection of serologic evidence of infection in paired serum samples. In fatal filovirus

infections, there is high-titer viremia and little evidence of a host immune response. Virus has been isolated from tissue as well as from urine, semen, and throat and rectal swabs. Attempts to isolate virus must be made only in specialized high-security laboratories. Specimens should be sent to the Centers for Disease Control and Prevention, Atlanta, Georgia; the Central Public Health Laboratory, Colindale, London, England; or the National Institute of Virology, Sandringham, Republic of South Africa. Since person-to-person transmission is the means by which outbreaks are propagated, all patients should be managed under conditions of strict barrier isolation, and all specimens should be handled and shipped with extreme care. RT-PCR has been useful when conducted in specialized laboratories. Gamma irradiation is the most common way to inactivate virus.

Other than supportive care, no definitive treatment for filovirus infection is available. The administration of convalescent-phase serum from recovered patients has been proposed but has not been systematically evaluated. In any event, such serum is rarely available. In vitro, neither Marburg virus nor Ebola virus is inhibited by ribavirin.

ARBOVIRAL ENCEPHALITISES

Definition. Arboviral encephalitises are a group of endemic seasonal diseases, commonly occurring in the warmer months. Its incidence varies markedly with time and place, depending on ecologic factors.

Etyology. The causative viruses differ markedly in terms of case-infection ratio (i.e., the ratio of clinical to subclinical infection), mortality, and residua. Humans are not an important amplifier of these viruses.

Pathogenesis. All the viral encephalitises discussed below have a similar pathogenesis as far as is known. An infected arthropod ingests a blood meal from a human and infects the host. The initial period of viremia is thought to originate most commonly from the lymphoid system. Viremia leads to CNS invasion, presumably through infection of olfactory neuroepithelium with passage through the cribiform plate or through infection of brain capillaries and multifocal entry into the CNS. During the viremic phase, there may be little or no recognized disease except in the case of tick-borne flaviviral encephalitis, in which there may be a clearly delineated phase of fever and systemic illness. The disease process in the CNS arises partly from direct neuronal infection and subsequent damage and partly from edema, inflammation, and other indirect effects. The usual pathologic picture is one of focal necrosis of neurons, inflammatory glial nodules, and perivascular lymphoid cuffing; the severity and distribution of these abnormalities vary with the infecting virus. Involved areas display the "luxury perfusion" phenomenon, with normal or increased total blood flow and low oxygen extraction.

Clinical manifestations. The typical patient presents with a prodrome of nonspecific constitutional symptoms, including fever, abdominal pain, vertigo, sore

throat, and respiratory symptoms. Headache, meningeal signs, photophobia, and vomiting follow quickly. Involvement of deeper structures may be signaled by lethargy, somnolence, and intellectual deficit (as disclosed by the mental status examination); more severely affected patients will be obviously disoriented and may be comatose. Tremors, loss of abdominal reflexes, cranial nerve palsies, hemiparesis, monoparesis, difficulty in swallowing, and frontal lobe signs are all common. Convulsions and focal signs may be evident early or may appear during the course of the disease. Some patients present with an abrupt onset of fever, convulsions, and other signs of CNS involvement. The results of human infection range from no significant symptoms through febrile headache to aseptic meningitis and finally to full-blown encephalitis; the proportions and severity of these manifestations vary with the infecting virus.

The acute encephalitis usually lasts from a few days to as long as 2 to 3 weeks, but recovery may be slow, with weeks or months required for the return of maximal recoupable function. Common complaints during recovery include difficulty concentrating, fatigability, tremors, and personality changes.

Diagnosis. The diagnosis of arboviral encephalitis depends on the careful evaluation of a febrile patient with CNS disease, with rapid identification of treatable herpes simplex encephalitis, ruling out of brain abscess, exclusion of bacterial meningitis by serial CSF examination, and performance of laboratory studies to define the viral etiology. Leptospirosis and neurosyphilis should also be considered. The CSF examination usually shows a modest cell count-in the tens or hundreds or perhaps a few thousand. Early in the process, a significant proportion of these cells may be polymorphonuclear leukocytes, but usually there is a mononuclear cell predominance. CSF glucose levels are usually normal. There are exceptions to this pattern of findings. In eastern equine encephalitis, for example, polymorphonuclear leukocytes may predominate during the first 72 h of disease and hypoglycorrhachia may be detected. In LCM, lymphocyte counts may be in the thousands, and the glucose concentration may be diminished. Experience with imaging studies is still evolving; clearly, however, both CT and MRI may be normal except for evidence of preexisting conditions or sometimes may suggest diffuse edema. Several patients with eastern equine encephalitis have had focal abnormalities, and individuals with severe Japanese encephalitis have presented with bilateral thalamic lesions that have often been hemorrhagic. Electroencephalography usually shows diffuse abnormalities and is not directly helpful.

A humoral immune response is usually detectable at or near the onset of disease. Both serum and CSF should be examined for IgM antibodies. Virus generally cannot be isolated from blood or CSF, although Japanese encephalitis virus has been recovered from CSF in severe cases. Virus can be obtained from and viral antigen is present in brain tissue, although its distribution may be focal.

Treatment. The acute illness requires management of a comatose patient who may have intracranial pressure elevations, inappropriate secretion of antidiuretic hormone, respiratory failure, and convulsions. There is no specific therapy for these viral encephalitides.

Prevention. The only practical preventive measures are vector management and personal protection against the arthropod transmitting the virus; for Japanese encephalitis or tick-borne encephalitis, vaccination should be considered in certain circumstances (see relevant sections below).

CALIFORNIA, LA CROSSE AND JAMESTOWN CANYON ENCEPHALITISES

The isolation of California encephalitis virus established the California serogroup of bunyaviruses as a cause of encephalitis. Serologically related La Crosse virus is the major cause of encephalitis among viruses in the California serogroup. "California encephalitis" due to La Crosse virus infection is most commonly reported from the upper Midwest but is also found in other areas of the central and eastern United States, most often in West Virginia, North Carolina, and Georgia. The serogroup includes 13 other viruses, some of which may also be involved in human disease that is misattributed because of the complexity of the group's serology; these viruses include the Jamestown Canyon, snowshoe hare, Inkoo, and Trivittatus viruses, all of which have *Aedes* mosquitoes as their vector and all of which have a strong element of transovarial transmission in their natural cycles.

The mosquito vector of La Crosse virus is *Aedes triseriatus*. In addition to a prominent transovarial component of transmission, a mosquito can also become infected through feeding on viremic chipmunks and other mammals as well as through venereal transmission from another mosquito. The mosquito breeds in sites such as tree holes and abandoned tires and bites during daylight hours; these findings correlate with the risk factors for cases: recreation in forested areas, residence at the forest's edge, and the presence of abandoned tires around the home. Intensive environmental modification based on these findings has reduced the incidence of disease in a highly endemic area in the Midwest. Most cases occur from July through September. The Asian tiger mosquito, *Aedes albopictus*, efficiently transmits the virus to mice and also transmits the agent transovarially in the laboratory; the possible impact of this aggressive anthropophilic mosquito, which has the capacity to urbanize, on transmission to humans is of concern.

An antibody prevalence of 20% in endemic areas indicates that infection is common, but CNS disease has been recognized primarily in children 15 years of age. The illness varies from a picture of aseptic meningitis accompanied by confusion to severe and occasionally fatal encephalitis. Although there may be prodromal symptoms, the onset of CNS disease is sudden, with fever, headache, and lethargy often joined by nausea and vomiting, convulsions (in one-half of patients), and coma (in one-third of patients). Focal seizures, hemiparesis, tremor, aphasia, chorea,

Babinski's sign, and other evidence of significant neurologic dysfunction are common, but residua are not. Perhaps 10% of patients have recurrent seizures in the succeeding months. Other serious sequelae are rare, although a decrease in scholastic standing has been reported and mild personality change has occasionally been suggested. Treatment is supportive over a 1- to 2-week acute phase during which status epilepticus, cerebral edema, and inappropriate secretion of antidiuretic hormone are important concerns.

The blood leukocyte count is commonly elevated, sometimes reaching levels of 20,000/uL, and there is usually a left shift. CSF cell counts are typically 30 to 500/uL with a mononuclear cell predominance (although 25 to 90% of cells are polymorphonuclear in some cases). The protein level is normal or slightly increased, and the glucose level is normal. Specific virologic diagnosis based on IgM-capture assays of serum and CSF is efficient. The only human anatomic site from which virus has been isolated is the brain.

Jamestown Canyon virus has been implicated in several cases of encephalitis in adults; in these cases the disease was usually associated with a significant respiratory illness at onset. Human infection with this virus has been documented in New York, Wisconsin, Ohio, Michigan, Ontario, and other areas of North America where the vector mosquito, *Aedes stimulans*, feeds on its main host, the white-tailed deer.

ST. LOUIS ENCEPHALITIS

St. Louis encephalitis virus is transmitted between *Culex* mosquitoes and birds. This virus causes low-level endemic infection among rural residents of the western and central United States, where *Culex tarsalis* is the vector, but the more urbanized mosquito species *Culex pipiens* and *Culex quinquefasciatus* have been responsible for epidemics resulting in hundreds or even thousands of cases in cities of the central and eastern United States. Most cases occur in June through October. The urban mosquitoes breed in accumulations of stagnant water and sewage with high organic content and readily bite humans in and around houses. The elimination of open sewers and trash-filled drainage systems is expensive and may not be possible, but screening of houses and implementation of personal protective measures against the dusk-biting vectors may be an effective approach for individuals. The rural vector is most active at dusk and outdoors; its bites can be avoided by modification of activities and use of repellents.

Disease severity increases with age: infections that result in aseptic meningitis or mild encephalitis are concentrated in children and young adults, while severe and fatal cases primarily affect the elderly. Infection rates are similar in all age groups; thus the greater susceptibility of older persons to disease is a biologic consequence of aging. The disease has an abrupt onset, sometimes following a prodrome, and begins with fever, lethargy, confusion, and headache. In addition, nuchal rigidity, hypotonia, hyperreflexia, myoclonus, and tremor are common. Severe cases can include cranial

nerve palsies, hemiparesis, and convulsions. Patients often complain of dysuria and may have viral antigen in urine as well as pyuria. The overall mortality is generally around 7% but may reach 20% among patients over the age of 60. Recovery is slow. Emotional lability, difficulties in concentration and memory, asthenia, and tremor are commonly prolonged in older patients.

The CSF of patients infected with St. Louis encephalitis virus usually contains tens to hundreds of cells, with a lymphocytic predominance and a normal glucose level. Leukocytosis with a left shift is often documented.

JAPANESE ENCEPHALITIS

Japanese encephalitis virus is found throughout Asia, including far eastern Russia, Japan, China, India, Pakistan, and Southeast Asia, and causes occasional epidemics on western Pacific islands. This flavivirus is particularly common in areas where irrigated rice fields attract the natural avian vertebrate hosts and provide abundant breeding sites for mosquitoes such as *Culex tritaeniorhyncus*, which transmit the virus to humans. Additional amplification by pigs, which suffer abortion, and horses, which develop encephalitis, may be significant as well. Vaccination of these additional amplifying hosts can reduce the transmission of the virus. An effective, formalin-inactivated vaccine purified from mouse brain is produced in Japan. It is given on days 0, 7, and 30 or-with some sacrifice in serum neutralizing titer-on days 0, 7, and 14. Vaccination is indicated for summer travelers to rural Asia, where the risk of clinical disease may be 0.05 to 2.1/10,000 per week. The severe and often fatal disease reported in expatriates must be balanced against the 0.1 to 1% chance of a late systemic or cutaneous allergic reaction. These reactions are rarely fatal but may be severe and have been known to begin 1 to 9 days after vaccination, with associated pruritus, urticaria, and angioedema. Live attenuated vaccines are being used in China.

WEST NILE ENCEPHALITIS

West Nile virus is transmitted among wild birds by *Culex* mosquitoes in Africa, the Middle East, southern Europe, and Asia. It is a frequent cause of febrile disease without CNS involvement, but it occasionally causes aseptic meningitis and severe encephalitis; these serious infections are particularly common among children and the elderly. In 1996, West Nile or a closely related virus caused more than 300 cases of CNS disease, with 10% mortality, in the Danube flood plains, including Bucharest. The febrile-myalgic syndrome caused by West Nile virus is distinguished from other such syndromes by the frequent appearance of a maculopapular rash concentrated on the trunk and lymphadenopathy. Headache, ocular pain, sore throat, nausea and vomiting, and arthralgia (but not arthritis) are common accompaniments. In addition, the virus has been implicated in severe and fatal hepatic necrosis in Central Africa.

West Nile virus falls into the same phylogenetic group of flaviviruses as St.

Louis and Japanese encephalitis viruses, as do Murray Valley and Rocio viruses. The latter two viruses are both maintained in mosquitoes and birds and produce a clinical picture resembling that of Japanese encephalitis. Murray Valley virus has caused occasional epidemics and sporadic cases in Australia. Rocio virus caused recurrent epidemics in a focal area of Brazil in 1975 to 1977 and then virtually disappeared.

CENTRAL EUROPEAN TICK-BORNE AND RUSSIAN SPRING-SUMMER ENCEPHALITISES

A spectrum of tick-borne flaviviruses has been identified across the Eurasian land mass. Many are known mainly as agricultural pathogens. From Scandinavia to the Urals, central European tick-borne encephalitis is transmitted by *Ixodes ricinus*. Human cases occur between April and October, with a peak in June and July. A related and more virulent virus is that of Russian spring-summer encephalitis, which is associated with *Ixodes persulcatus* and is distributed from Europe across the Urals to the Pacific Ocean. The ticks transmit the disease primarily in the spring and early summer, with a lower rate of transmission later in summer. Small mammals are the vertebrate amplifiers for both viruses. The risk varies by geographic area and can be highly localized within a given area; human cases usually follow outdoor activities or consumption of raw milk from infected goats or other infected animals.

After an incubation period of 7 to 14 days or perhaps longer, the central European viruses classically result in a febrile-myalgic phase that lasts for 2 to 4 days and is thought to correlate with viremia. A subsequent remission for several days is followed by the recurrence of fever and the onset of meningeal signs. The CNS phase varies from mild aseptic meningitis, which is more common among younger patients, to severe encephalitis with coma, convulsions, tremors, and motor signs lasting for 7 to 10 days before improvement begin. Spinal and medullary involvement can lead to typical limb-girdle paralysis and to respiratory paralysis. Most patients recover, only a minority with significant deficits. Infections with the far eastern viruses generally run a more abrupt course. The encephalitic syndrome caused by these viruses sometimes begins without a remission and has more severe manifestations than the central European syndrome. Mortality is high, and major sequelae-most notably, lower motor neuron paralyses of the proximal muscles of the extremities, trunk, and neck-are common.

In the early stage of the illness, virus may be isolated from the blood. In the CNS phase, IgM antibodies are detectable in serum and/or CSF. Thrombocytopenia sometimes develops during the initial febrile illness, which resembles the early hemorrhagic phase of some other tick-borne flaviviral infections, such as Kyasanur Forest disease. Other tick-borne flaviviruses are less common causes of encephalitis, including louping ill virus in the United Kingdom and Powassan virus.

There is no specific therapy for infection with these viruses. However, effective alum-adjuvanted, formalin-inactivated vaccines are produced in Austria, Germany, and Russia. Two doses of the Austrian vaccine separated by an interval of

1 to 3 months appear to be effective in the field, and antibody responses are similar when vaccine is given on days 0 and 14. Other vaccines have elicited similar neutralizing antibody titers. Since rare cases of postvaccination Guillain-Barre syndrome have been reported, vaccination should be reserved for persons likely to experience rural exposure in an endemic area during the season of transmission. Cross-neutralization for the central European and far eastern strains has been established, but there are no published field studies on cross-protection of formalin-inactivated vaccines. Because 0.2 to 4% of ticks in endemic areas may be infected, tick bites raise the issue of immunoglobulin prophylaxis. Prompt administration of high-titered specific preparations should probably be undertaken, although no controlled data are available to prove the efficacy of this measure. Immunoglobulin should not be administered late because of the risk of antibody-mediated enhancement.

POWASSAN ENCEPHALITIS

Powassan virus is a member of the tick-borne encephalitis virus complex and is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States, where it has been responsible for 20 recognized cases of human disease. Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes dammini*, a competent vector in the laboratory, may become involved as it becomes more prominent in the United States. Patients with Powassan encephalitis-often children-present in May through December after outdoor exposure and an incubation period thought to be about 1 week. Powassan encephalitis is severe, and sequelae are common.

EASTERN EQUINE ENCEPHALITIS

Eastern equine encephalitis is found primarily within endemic swampy foci along the eastern coast of the United States, with a few inland foci as far removed as Michigan. Human cases present from June through October, when the bird-*Culiseta* mosquito cycle spills over into other mosquito species such as *Aedes sollicitans*, or *Aedes vexans*, which are more likely to bite mammals. There is concern over the potential role of the introduced anthropophilic mosquito species *A. albopictus*, which has been found to be naturally infected and is an effective vector in the laboratory. Horses are a common target for the virus; if not vaccinated, they serve as a harbinger of human disease but probably do not play a significant role in amplification of the virus.

Eastern equine encephalitis is one of the most destructive of the arboviral conditions, with a brusque onset, rapid progression, high mortality, and frequent residua. This severity is reflected in the extensive necrotic lesions and polymorphonuclear infiltrates found at postmortem examination of the brain and the acute polymorphonuclear CSF pleocytosis often occurring during the first 1 to 3 days of disease. In addition, leukocytosis with a left shift is a common feature. A formalin-

inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

WESTERN EQUINE ENCEPHALITIS

The primary maintenance cycle for western equine encephalitis virus in the United States is between *C. tarsalis* and birds, principally sparrows and finches. Equines and humans become infected, and both species suffer encephalitis without amplifying the virus in nature. St. Louis encephalitis is transmitted in a similar cycle in the same region but causes human disease about a month earlier than the period (July through October) in which western equine encephalitis virus is active. In recent years the disease has been uncommon. Decline in incidence may reflect in part the integrated approach to mosquito management that has been employed in irrigation projects and the increasing use of agricultural pesticides; it almost certainly reflects the increased tendency for humans to be indoors behind closed windows at dusk, the peak period of biting by the major vector.

Western equine encephalitis virus causes typical diffuse viral encephalitis with an increased attack rate and increased morbidity in the young, particularly children under 2 years of age. In addition, mortality is high among the young and the very elderly. One-third of individuals who have convulsions during the acute illness have subsequent seizure activity. Infants under 1 year of age-particularly those in the first months of life-are at serious risk of motor and intellectual damage. Twice as many males as females develop clinical encephalitis after 5 to 9 years of age; this difference may be related to greater outdoor exposure of boys to the vector but is also likely to be due in part to biologic differences. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

VENEZUELAN EQUINE ENCEPHALITIS

There are six known types of virus in the Venezuelan equine encephalitis complex. An important distinction is between the "epizootic" viruses (subtypes IAB and IC) and the "enzootic" viruses (subtypes ID to IF and types II to VI). The epizootic viruses have an unknown natural cycle but periodically cause extensive epidemics in equines and humans in the Americas. These epidemics rely on the high-level viremia in horses and mules that result in the infection of several species of mosquitoes, which in turn infect humans and perpetuate virus transmission. Humans also have high-level viremia but probably are not important in virus transmission. Enzootic viruses are found primarily in humid tropical forest habitats and are maintained between *Culex* mosquitoes and rodents; these viruses cause human disease but are not pathogenic for horses and do not cause epizootics.

Epizootics of Venezuelan equine encephalitis occurred repeatedly in Venezuela, Colombia, Ecuador, Peru, and other South American countries at intervals of 10 years or less from the 1930s until 1969, when a massive epizootic spread throughout Central America and Mexico, reaching southern Texas in 1972.

Genetic sequencing of the virus from the 1969 to 1972 outbreak suggested that it originated from residual "un-inactivated" virus in veterinary vaccines. The outbreak was terminated in Texas with the use of a live attenuated vaccine (TC-83) originally developed for human use by the U.S. Army; this virus was then used for further production of inactivated veterinary vaccines. No further epizootic disease was definitely identified until 1993 to 1995, when additional epizootics took place in Mexico, Colombia, and Venezuela. The viruses involved in these epizootics as well as previously epizootic subtype IC viruses have been shown to be close phylogenetic relatives of known enzootic subtype ID viruses. This finding suggests that active evolution and selection of epizootic viruses are under way in northern South America.

During epizootics, extensive human infection is the rule, with clinical disease in 10 to 60% of infected individuals. Most infections result in notable acute febrile disease, while relatively few result in encephalitis. A low rate of CNS invasion is supported by the absence of encephalitis among the many infections resulting from exposure to aerosols in the laboratory or from vaccine accidents. The most recent epizootic of Venezuelan equine encephalitis occurred in Colombia and Venezuela in 1995; of the more than 85,000 clinical cases, 4% (with a higher proportion among children than adults) included neurologic symptoms and 300 ended in death.

Enzootic strains of Venezuelan equine encephalitis virus are common causes of acute febrile disease, particularly in areas such as the Florida Everglades and the humid Atlantic coast of Central America. Encephalitis has been documented only in the Florida infections; the three cases were caused by type II enzootic virus, also called *Everglades virus*. All three patients had preexisting cerebral disease. Extrapolation from the rate of genetic change suggests that Everglades virus was introduced into Florida less than 200 years ago and that it is most closely related to the ID subtypes that appear to have given evolutionary rise to the epizootic strains active in South America.

The prevention of epizootic Venezuelan equine encephalitis depends on vaccination of horses with the attenuated TC-83 vaccine or with an inactivated vaccine prepared from that strain. Humans can be protected with similar vaccines, but the use of such products is restricted to laboratory personnel because of reactogenicity and limited availability. In addition, wild-type vaccine and perhaps TC-83 vaccine are thought to have some degree of fetal pathogenicity. Enzootic viruses are antigenically somewhat different from epizootic viruses, and protection against the former with vaccines prepared from the latter is relatively ineffective.

OTHER ARBO- AND RODENT-BORNE VIRUS INFECTIONS

DENGUE FEVER

All four distinct dengue viruses (mosquito-borne flaviviruses) have *A. aegypti*

as their principal vector, and all cause a similar clinical syndrome. In rare cases, second infection with a serotype of dengue virus different from that involved in the primary infection leads to dengue HF with severe shock. Sporadic cases are seen in the settings of endemic transmission and epidemic disease. Year-round transmission between latitudes 25 N and 25 S has been established. With increasing spread of the vector mosquito throughout the tropics and subtropics, large areas of the world have become vulnerable to the introduction of dengue viruses, particularly through air travel by infected humans, and both dengue fever and the related dengue HF are becoming increasingly common. *A. aegypti*, which also is an efficient vector of the yellow fever and chikungunya viruses, typically breeds near human habitation, using relatively fresh water from sources such as water jars, vases, discarded containers, coconut husks, and old tires. *A. aegypti* usually inhabits dwellings and bites during the day.

After an incubation period of 2 to 7 days, the typical patient experiences the sudden onset of fever, headache, retroorbital pain, and back pain along with the severe myalgia that gave rise to the colloquial designation "break-bone fever." There is often a macular rash on the first day as well as adenopathy, palatal vesicles, and scleral injection. The illness may last a week, with additional symptoms usually including anorexia, nausea or vomiting, marked cutaneous hypersensitivity, and-near the time of defervescence-a maculopapular rash beginning on the trunk and spreading to the extremities and the face. Epistaxis and scattered petechiae are often noted in uncomplicated dengue, and preexisting gastrointestinal lesions may bleed during the acute illness. Laboratory findings include leukopenia, thrombocytopenia, and, in many cases, serum aminotransferase elevations. The diagnosis is made by IgM ELISA or paired serology during recovery or by antigen-detection ELISA or RT-PCR during the acute phase. Virus is readily isolated from blood in the acute phase if mosquito inoculation or mosquito cell culture is used.

SINDBIS VIRUS INFECTION

Sindbis virus (alphavirus from *Togaviridae* family) is transmitted among birds by mosquitoes. Infections with the northern European strains of this virus (which cause, for example, Pogosta disease in Finland, Karelian fever in Russia, and Okelbo disease in Sweden) and with the genetically related southern African strains are particularly likely to result in the arthritis-rash syndrome. Exposure to a rural environment is commonly associated with this infection, which has an incubation period of less than 1 week. The disease begins with rash and arthralgia. Constitutional symptoms are not marked, and fever is modest or lacking altogether. The rash, which lasts about a week, begins on the trunk, spreads to the extremities, and evolves from macules to papules that often vesiculate. The arthritis of this condition is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days. Wrists, ankles, phalangeal joints, knees, elbows, and-to a much lesser

extent-proximal and axial joints are involved. Persistence of joint pains and occasionally of arthritis is a major problem and may go on for months or even years despite a lack of deformity.

O'NYONG-NYONG VIRUS INFECTION

O'nyong-nyong virus caused a major epidemic of arthritis and rash involving at least 2 million people as it moved across eastern and central Africa in the 1960s. After its mysterious emergence, the virus virtually disappeared, leaving only occasional evidence of its persistence in Kenya until a resurgence of activity in 1997.

MAYARO FEVER

Mayaro virus is maintained in the forests of the Americas by *Haemagogus* mosquitoes and nonhuman primates. It causes a frequent endemic and sometimes epidemic infection of humans and appears to cause a syndrome resembling chikungunya.

ROSS RIVER VIRUS INFECTION

Ross River virus (alphavirus from *Togaviridae* family) has caused epidemics of distinctive clinical disease in Australia, New Guinea and eastern Pacific Islands. The virus is transmitted by *Aedes vigilax, A. polynesiensis*, *A. aegypti* and other mosquitoes, and its persistence is thought to involve transovarial transmission. No definitive vertebrate host has been identified, but several mammalian species, including wallabies, have been suggested.

The incubation period is 7 to 11 days long, and the onset of illness is sudden, with joint pain usually ushering in the disease. The rash generally develops coincidentally or follows shortly but in some cases precedes joint pains by several days. Constitutional symptoms such as low-grade fever, asthenia, myalgia, headache, and nausea are not prominent and indeed are absent in many cases. Most patients are incapacitated for considerable periods by joint involvement, which interferes with sleeping, walking, and grasping. Wrist, ankle, metacarpophalangeal, interphalangeal, and knee joints are the most commonly involved, although toes, shoulders, and elbows may be affected with some frequency. Periarticular swelling and tenosynovitis are common, and one-third of patients have true arthritis. Only half of all arthritis patients can resume normal activities within 4 weeks, and 10% still must limit their activity at 3 months. Occasional patients are symptomatic for 1 to 3 years but without progressive arthropathy. Aspirin and nonsteroidal anti-inflammatory drugs are effective for the treatment of symptoms.

Clinical laboratory values are normal or variable in Ross River virus infection. Tests for rheumatoid factor and antinuclear antibodies are negative, and the erythrocyte sedimentation rate is acutely elevated. Joint fluid contains 1000 to 60,000 mononuclear cells per microliter, and Ross River virus antigen is demonstrable in macrophages. IgM antibodies are particularly valuable in the diagnosis of this infection. The isolation of the virus from blood by mosquito inoculation or mosquito

cell culture is possible early in the illness. Because of the great economic importance of annual epidemics in Australia, an inactivated vaccine is being developed and has been found to be protective in mice.

Other arthritogenic arboviruses have been identified in Australia, including Gan Gan virus, a member of the family Bunyaviridae; Kokobera virus, a flavivirus; and Barmah Forest virus, an alphavirus. The last virus is a common cause of infection and must be differentiated from Ross River virus by specific testing.

COLORADO TICK FEVER

Several hundred cases of Colorado tick fever virus (coltivirus of *Reoviridae* family) infection are reported annually in the United States. The infection is acquired between March and November through the bite of an infected *Dermacentor andersoni* tick in mountainous western regions at altitudes of 1200 to 3000 m (4000 to 10,000 ft). Small mammals serve as the amplifying host. The most common presentation consists of fever and myalgia; meningoencephalitis is not uncommon, and hemorrhagic disease, pericarditis, myocarditis, orchitis, and pulmonary presentations are also reported. Rash develops in a substantial minority of cases. The disease usually lasts 7 to 10 days and is often biphasic. The most important differential diagnostic considerations have been Rocky Mountain spotted fever and tularemia.

Infection of erythroblasts and other marrow cells by Colorado tick fever virus results in the appearance and persistence (for several weeks) of erythrocytes containing the virus. This feature, detected in smears stained by immunofluorescence, can be diagnostically helpful. The clinical laboratory detects leukopenia and thrombocytopenia.

ORBIVIRUS INFECTION

The orbiviruses (*Reoviridae* family) encompass many human and veterinary pathogens. For example, Orungo virus is widely transmitted by mosquitoes in tropical Africa and causes febrile disease in humans. The Kemerovo complex includes the Kemerovo, Lipovnik, and Tribec viruses of Russia and central Europe; these viruses are transmitted by ticks and are associated with febrile and neurologic disease.

VESICULAR STOMATITIS

In animals, vesicular stomatitis virus (vesiculovirus from *Rhabdoviridae* family) infection is characterized by the development of vesicles on the oral mucosa, particularly the tongue; the udders; and the heels. The mode of spread is probably by direct contact; however, epidemics tend to occur in warm weather, and isolation of the virus from *Phlebotomus sandflies* in Panama and *Aedes* species in New Mexico suggests that these insects may be vectors. Vesicular stomatitis is most common among laboratory workers. In one report, three-fourths of laboratory personnel handling experimentally infected animals or manipulating the virus developed neutralizing antibodies. The disease is also transmissible, however, under natural

conditions among workers having direct contact with infected animals, especially cattle.

An incubation period ranging from 1 to 6 days is followed by the sudden onset of fever (with temperatures of up to 40°C), chills, profuse sweating, myalgias, malaise, headache, and pain on ocular movement. One-third to one-half of patients have a sore throat and cervical and/or submandibular adenopathy. Small raised vesicular lesions may appear on the buccal mucosa. Conjunctivitis and coryza are evident in about 20% of cases. Occasionally, small subcorneal, intraepithelial vesicles appear on the fingers, usually in association with direct inoculation of the virus. Symptoms generally last 3 to 4 days, but occasionally the course is diphasic. Inapparent infection is common: among laboratory workers with serologic evidence of infection, only about one-half reported symptoms. In some areas of Panama, 17 to 35% of the population has neutralizing antibodies to vesicular stomatitis virus.

The differential diagnosis includes hand-foot-and-mouth disease, herpangina, primary herpetic pharyngitis and other mucocutaneous syndromes, and influenza. The virus is not commonly isolated from patients. However, a rise in titer of complement-fixation and/or neutralizing antibody to vesicular stomatitis virus between acute- and convalescent-phase sera helps to confirm the diagnosis. Treatment is nonspecific.

BUNYAMWERA VIRUS INFECTION

The mosquito-transmitted Bunyamwera serogroup of bunyaviruses are found on every continent except Australia and Antarctica. Bunyamwera virus and its close relative Ilesha virus commonly cause febrile disease in Africa. Other related viruses are implicated in such disease in Southeast Asia (Batai virus), Europe (Calovo virus), and South America (Wyeomyia virus). In North America, Cache Valley virus has been implicated in febrile human disease and in rare instances of more serious systemic illness; the presence of serum antibodies to this virus may be associated with congenital malformations. In Central America, the closely related Fort Sherman virus causes the fever-myalgia syndrome.

GROUP C VIRUS INFECTION

The group C viruses (*Bunyaviridae* family) include at least 11 agents transmitted by mosquitoes in neotropical forests. These agents are among the most common causes of arboviral infection in humans entering American jungles and cause acute febrile disease with myalgia.

TAHYNA VIRUS INFECTION

This California-serogroup virus from bunyaviruses family occurs in central and western Europe, and related viruses are emerging in Russia. The significance of Tahyna virus in human health has been well studied only in the Czech and Slovak Republics; there, the virus was found to be a prominent cause of febrile disease, in some cases causing pharyngitis, pulmonary syndromes, and aseptic meningitis. The potential for arboviruses to be unexpectedly involved in such cases in areas of high

mosquito prevalence needs to be kept in mind.

OROPOUCHE FEVER

Oropouche bunyavirus is transmitted in Central and South America by a biting midge, *Culicoides paraensis*, which often breeds to high density in cacao husks and other vegetable detritus found in towns and cities. Explosive epidemics involving thousands of cases have been reported from several towns in Brazil and Peru. Rash and aseptic meningitis have been detected in a number of cases.

SANDFLY FEVER

The sandfly *Phlebotomus papatasi* transmits sandfly fever. Female sandflies may be infected by the oral route as they take a blood meal and may transmit the virus to offspring when they lay their eggs after a second blood meal. This prominent transovarial pattern was the first to be recognized among dipterans and complicates virus control. The former designation for sandfly fever, "3-day fever," instructively describes the brief, debilitating course associated with this essentially benign infection. There is neither a rash nor CNS involvement, and complete recovery is the rule.

Sandfly fever is found in the circum-Mediterranean area, extending to the east through the Balkans into China as well as into the Middle East and southwestern Asia. The vector is found in both rural and urban settings and is known for its small size, which enables it to penetrate standard mosquito screens and netting, and for its short flight range. Epidemics have been described in the wake of natural disasters and wars. In parts of Europe, sandfly populations and virus transmission were greatly reduced by the extensive residual spraying conducted after World War II to control malaria, and the prevalence continues to decline. A common pattern of disease in endemic areas consists of high attack rates among travelers and military personnel with little or no disease in the local population, who are protected after childhood infection. In addition to the two well-characterized, non-cross-protective Sicilian and Naples virus species, more than 30 related phleboviruses are transmitted by sandflies and mosquitoes, but most are of unknown significance in terms of human health.

TOSCANA VIRUS INFECTION

Toscana virus is a *Phlebovirus* (family *Bunyaviridae*) transmitted primarily by the circum-Mediterranean sandfly *Phlebotomus perniciosus*. The vertebrate amplifying host, if one exists, is unknown. Toscana virus infection is common during the summer among rural residents and vacationers; a number of cases have been identified in travelers returning to Germany and Scandinavia. The disease may manifest as an uncomplicated febrile illness but is often associated with aseptic meningitis, with virus isolated from the CSF.

PUNTA TORO VIRUS INFECTION

Of the several phleboviruses that are associated with new world sandflies and infect humans, Punta Toro virus is the best known. The disease caused by this virus is

clinically similar to but epidemiologically different from that caused by the Naples or Sicilian sandfly fever viruses. Punta Toro virus infections are sporadic and are acquired in the tropical forest, where the vectors rest on tree buttresses. Epidemics have not been reported, but antibody prevalences among inhabitants of villages in the endemic areas indicate a cumulative lifetime exposure rate of more than 50%.

LYMPHOCYTIC CHORIOMENINGITIS

Lymphocytic choriomeningitis virus is transmitted from the common house mouse (*Mus musculus*) to humans by aerosols of excreta and secreta. Arenavirus, is maintained in the mouse mainly by vertical transmission from infected dams. The vertically infected mouse remains viremic for life, with high concentrations of virus in all tissues. Infected colonies of pet hamsters have also served as a link to humans. Virus is widely used in immunology laboratories as a model of T cell function and can silently infect cell cultures and passaged tumor lines, resulting in infections among scientists and animal caretakers. Patients with lymphocytic choriomeningitis may have a history of residence in rodent-infested housing or other exposure to rodents. An antibody prevalence of about 5 to 10% has been reported in the United States, Argentina, and endemic areas of Germany.

Lymphocytic choriomeningitis virus infection onset is gradual. Among the conditions occasionally associated with this infection are orchitis, transient alopecia, arthritis, pharyngitis, cough, and maculopapular rash. An estimated one-fourth of patients or fewer suffer a febrile phase of 3 to 6 days and then, after a brief remission, develop renewed fever accompanied by severe headache, nausea and vomiting, and meningeal signs lasting for about a week. These patients virtually always recover fully, as do the uncommon patients with clear-cut signs of encephalitis. Recovery may be delayed by transient hydrocephalus.

During the initial febrile phase, leukopenia and thrombocytopenia are common and virus can usually be isolated from blood. During the CNS phase of the illness, virus may be found in the CSF, but antibodies are present in blood. The pathogenesis of lymphocytic choriomeningitis is thought to resemble that following direct intracranial inoculation of the virus into adult mice; the onset of the immune response leads to T cell-mediated immunopathologic meningitis. During the meningeal phase, CSF mononuclear-cell counts range from the hundreds to the low thousands per microliter, and hypoglycorrhachia is found in one-third of cases. The IgM-capture ELISA of serum and CSF is usually positive; recently, RT-PCR assays have been developed for application to CSF.

Infection with lymphocytic choriomeningitis virus should be suspected in acutely ill febrile patients with marked leukopenia and thrombocytopenia. In cases of aseptic meningitis, the well-marked febrile prodrome, adult age, autumn seasonality, low CSF glucose levels, or mononuclear cell counts exceeding 1000/uL all should raise a suspicion of this viral infection. In pregnant women, lymphocytic

choriomeningitis virus infection may lead to fetal invasion with consequent congenital hydrocephalus and chorioretinitis. Since the maternal infection may be mild, consisting of only a short febrile illness, antibodies to the virus should be sought in both the mother and the fetus in suspicious circumstances.

HELMINTHIC INFECTIONS

At present about 250 species of human helminthes are known. According to their organization all helminthes are divided into 3 classes: Nematodes (roundworm), Cestodes (tapeworm) and Trematodes (flukes). According to the type of parasitizing and life cycle all helminthes are divided into geohelminths (one of their life-cycle stages take place in the soil) and biohelminths (all life-cycle stages take place in different living organisms – humans, animals, fish, snails etc.).

PATHOGENESIS OF HELMINTHIASES

1. ***Parasitic existence***. The Nematodes have a complete digestive system that is well adapted for active ingestion of the host's gut contents including vitamins, cells, blood, or cellular breakdown products. In case of Trematodes and Cestodes, glucose and other simple predigested nutrients are absorbed directly from the host's gut through millions of submicroscopic hair-like extensions, or microtriches, which interdigitate with the host's microvilli. Such parasitic existence can cause malnutrition with loss of the host's body weight, sometimes even up to cachexy, development of hypovitaminosis and anemia. The host's appetite is increased at first and then it is suppressed.
2. ***Chronic poisoning with helminthes toxins***. Products of helminthes life activity acts on the host's organism like poisons. The clinical features, associated with intoxication present: weakness, headache, decreasing of appetite or mental and physical activity etc.
3. ***Allergic effect***. Numerous products of helminthes life activity and especially their cuticle, which is changed 4 times during helminthes life, act similar to strong allergens. Allergic effect is more expressed in the migrant stage. The clinical features develop urticarial or serpiginous eruption («running larvae»), itching, eosinophylia, eosinophylic infiltrates in the lungs, and even anaphylactic shock.
4. ***Immune and immunopathologic response***. Persisting of helminthes in the human organism produce specific immune response. Detection of specific antibodies is an important method of laboratory investigations. Immunopathologic response usually develops in case of long-lasting helminthiasis, and leads to chronic autoimmune inflammation (e.g. development of elephantiasis — morbid gross enlargement of the limbs, breasts and genitalia in case of filarial infection). Immunopathologic reactions can be presented also as immunosuppression, which is especially severe in case of massive and prolonged infection. Infectious diseases in patients with helminthiasis usually tend to development of severe or chronic

forms of diseases.

5. ***Mechanical effect***. Many of helminthes have special organization of the mouth for taking of food (e.g. blood, or lymph) from the host's organism (*Trichuris trichiura, Ancylostoma duodenale* or *Necator americanus*). «Teeth» or oral plates of different hooks and suckers can traumatize the mucous membranes of the intestines and cause ulceration. Cysticercs of *Taenia solium*, or large hydatid cysts of *Echinococcus multilocularis* can press on the tissue of the organs (skin, eye, brain, lungs, liver) and lead to their failure. Accumulating of helminthes in the host's gut can cause intussusceptions or volvulus. Some helminthes have strong muscles and can penetrate the mucous membrane of the gut causing peritonitis (*Ascariasis*).
6. ***Malignant transformation***. Long persisting of helminthes in organs can cause chronic perifocal inflammation followed by malignant transformations of the tissue cells (e. g. *Shistosomiasis* can produce cancer of the colon or the urine bladder).
7. ***Neuro-reflex effect***. Moving of helminthes along the gastrointestinal tract or bronchi can irritate the endings of nerves and cause spastic pain in the abdomen or bronchospastic syndrome.

NEMATODOSES

More than a billion people worldwide are infected with one or more species of intestinal nematodes. These parasites are most common in regions with poor fecal sanitation, particularly in developing countries in the tropics and subtropics. Although nematode infections are not usually fatal, they contribute to malnutrition and diminished work capacity.

Nematodes are elongated, symmetric roundworms, which have an anterior mouth and posterior anus and constitute one of the largest phyla in the animal kingdom. Parasitic nematodes of medical significance may be broadly classified as intestinal or tissue nematodes, but such classification system is imprecise. All nematodes hatch from eggs as first stage larvae (L1) and metamorphose by molting through second-, third-and fourth-stage larvae (L2, L3, L4) to become adult warms. Life cycles range from simple (e.g., ingestion of the eggs is followed by development from eggs of adult warms in the intestine) to complex (e.g., involving tissue migration or stage of development in intermediate hosts or vectors). Some species, including *Strongyloides stercoralis* and *Enterobius vermicularis*, can be transmitted directly from person to person, while others, such as *Ascaris lumbricoides*, *Necator americanus*, and *Ancylostoma duodenale*, require a soil phase for development; so there are biohelminths and geohelminths. All species are diecious but some can reproduce by parthenogenesis.

TRICHINOSIS

Etyology. *Trichinella* species are small, roundworms. Males and females are 1

mm and 2.5 mm long. Five species of *Trichinella* are now recognized as causes of infection in humans. The most important role belongs to *Trichinella spiralis*, which is found in a great variety of carnivorous and omnivorous animals.

After the consumption of trichinous meat by the host, encysted larvae are liberated by digestive acid and pepsin. The larvae invade the small-bowel mucous membrane and mature rapidly into adult worms. After about 1 week, female worms release newborn larvae that migrate via the circulation to striated muscle. The larvae then encyst by inducing a radical transformation in the muscle cell architecture. After 17 days, larvae are full-grown and a capsule has formed over each parasitized myocyte (the «nurse cell»). Muscle larvae remain dormant for as long as 5-10 years, when they die and the capsules become calcified. When a new host ingests meat containing infective larvae, the larvae are released from their capsules and life cycle may be repeated. Although host immune responses may help to expel the adult worms, they have little effect on the muscle-dwelling larvae.

Epidemiology. Human trichinosis is most often caused by the ingestion of infected pork products (or meat from wild carnivores) and thus can occur in almost any location where the undercooked meat of domestic or wild swine is eaten. Human trichinosis also may be acquired from the meat of other animals, including dogs (in parts of Asia and Africa), and bears and walruses (in northern regions). About 50 to 100 cases of trichinosis are reported annually in this country, but most mild cases probably remain undiagnosed.

Pathogenesis. Worms are mature 5 days post infection and live for 2-3 weeks in the intestine before being expelled by the host immune response (intestinal stage). Intestinal pathology includes villous atrophy and inflammation and is characterized with neuro-reflex, toxic and slight allergic effect. Migratory stage lasts 1-4 weeks. Migrating larvae cause intensive allergic, toxic effect and development of immune inflammation in different tissues, where larvae migrate trough Larvae can cause pneumonitis, neurologic symptoms, conjunctivitis, splinter hemorrhages. Muscle stage starts approximately 3 weeks after infection and lasts up to several months. Growth and encystment of the larvae causes inflammation around the infected muscle cells and produces symptoms of muscle tenderness, spasm, and edema. Hypersensitivity reactions may occur, so eosinophylia and increased levels of IgE are pronounced during the migratory and muscle stages. Larvae only encyst in striated muscle, including myocardium. Usually well-oxygenated muscles are involved in process (e.g., the tongue, diaphragm, intercostals, orbital and others muscles).

Clinical manifestations. While most infections are mild and asymptomatic, heavy infections can cause severe enteritis, periorbital edema, myositis, and (infrequently) death. Most light infections (those with fewer than 10 larvae per gram of muscle) are asymptomatic, whereas heavy infections (which can involve more than 50 larvae per gram of muscle) can be life threatening. Invasion of the gut by large

numbers of parasites occasionally provokes diarrhea during the first week after infection. Abdominal pain, constipation, nausea, or vomiting also may be prominent. Symptoms due to larval migration and muscle invasion begin to appear on the second week after infection. The migrating *Trichinella* larvae provoke a marked local and systemic hypersensitivity reaction, with fever and hypereosinophylia. Periorbital and facial edema is common as well as hemorrhages in the subconjunctivae, retina, and nail beds ("splinter" hemorrhages). A maculopapular rash, headache, cough, dyspnea, or dysphagia sometimes develops. Myocarditis with tachyarrhythmias or heart failure and, less commonly, encephalitis or pneumonitis may develop and account for most deaths of patients with trichinosis. Upon onset of larval encystment in muscle 2 to 3 weeks after infection, symptoms of myositis with myalgias, muscle edema, and weakness develop, usually overlapping with the inflammatory reactions to migrating larvae. The most commonly involved muscle groups include the periorbital muscles; the biceps; and the muscles of the jaw, neck, lower back, and diaphragm. Peaking about 3 weeks after infection, symptoms subside only gradually during a prolonged convalescence.

Diagnosis. Trichinosis usually affects groups of people who have shared the same food source, so epidemiological data are important for diagnosis. Cyclic clinical cause with alternating stages of disease and specific symptoms is very characteristic. A presumptive clinical diagnosis can be based on fevers, eosinophilia, periorbital edema, and myalgias after a suspect meal.

Blood eosinophylia develops in more than 90% of patients with symptomatic trichinosis and may peak at a level of greater than 50% between 2 and 4 weeks after infection. Serum levels of IgE and muscle enzymes, including creatine phosphokinase, lactate dehydrogenase, and aspartate aminotransferase, are elevated in most symptomatic patients. Arise in the titer of parasite-specific antibody (assayed by the bentonite flocculation test or enzyme immunoassay – EIA), which usually does not occur until after the third week of infection, confirms the diagnosis. Alternatively, a definitive diagnosis requires surgical biopsy of at least 1 g of involved muscle where *Trichinella* may be revealed; the yields are highest near tendon insertions. Gluteus or triceps muscle are usually preferred.

Treatment. Current anthelminthic drugs are ineffective against *Trichinella* larvae in muscle. Fortunately, most lightly infected patients recover uneventfully with bed rest, antipyretics, and analgesics. All patients with severe and moderate forms of invasion must be hospitalized in hospitals where there are departments or wards of intensive care. Treatment is individual, according to period of disease, clinical manifestation and severity of patient’s condition. Mebendazole (Vermox), like thiabendazole, appears to be active against enteric stages of the parasite, but its efficacy against encysted larvae has not been conclusively demonstrated. Mebendazole kills larvae and sterilizes female warms. So the most effective period

for the treatment is incubation period and first two weeks after onset of disease. It is used after meal in doze 100 mg trice a day for 5-7 days. Daily doze for children is 5 mg/kg. Further when muscle larvae predominate in organism Mebendazole cause their massive killing that leads to exacerbation of allergic reactions, formation of inflammatory infiltrates in muscles and development of chronic myositis. Glucocorticoids like prednisone (1 mg/kg daily for 5 days) should be used to reduce the intense inflammatory response in the muscles (for severe myositis and myocarditis). Albendazole (Vormil) acts effectively against all stages of the parasite. It is used for patients with moderate and severe forms of disease after meal twice a day for 7-14 days. Daily doze for adults is 10 mg/kg (in average 800 mg) and for children - 5 mg/kg.

Prevention. Larvae may be killed by cooking pork until it is no longer pink or by freezing it at 15C for 3 weeks.

ASCARIASIS

Etyology. *Ascaris lumbricoides* is the largest intestinal nematode parasite of humans, reaching up to 40 cm in length. Usually females are 300×5 mm in size; males, 200×4 mm.

The life cycle is indirect: adult worms in the small intestine release embryonated (L2) eggs (each producing up to 240,000 eggs a day), which are passed in the feces and mature in moist soil in 10-21 days. Ascarid eggs are remarkably resistant to environmental stresses and can remain infective for years. After infective eggs are swallowed, larvae hatched in the intestine, invade the mucosa, enter the circulatory or lymph system, migrate via the liver and heart to the lungs, break into the alveoli, ascend the bronchial tree, and return via swallowing to the small intestine, where they develop into adult worms. Between 2 and 3 months elapse between initial infection and egg production. The adult worms live for approximately 1 to 2 years.

Epidemiology. Ascariasis is widely distributed in tropical and subtropical regions as well as in other humid areas and causes approximately 1 billion infections per year worldwide. Transmission typically occurs via feces contaminated with soil and is due either to a lack of sanitary facilities or to the use of human manure ("night soil") as fertilizer. Younger children in impoverished rural areas are most affected. Infection outside endemic areas can occur via eggs borne on transported vegetables.

Pathogenesis. Migratory stage is associated with toxic and allergic effects. Migration via the lungs can cause allergic inflammation (also known as Loeffler's syndrom or eosinophylic pneumonia). Neuro-reflectory action of larvae, which pass along the bronchi, can cause bronchoobstructive syndrome. Adult *Ascaris* resist digestion in the small intestine by secreting a trypsin inhibitor. Worms can enter into the bile or pancreatic ducts and penetrate the wall of intestine. Such mechanical action leads to dangerous consequences. In case of intensive invasion deficit of nutrition took place. Neuro-reflectory effect results in spastic pain in abdomen and

diarrhea.

Clinical manifestations. Most infected individuals have low worm burdens and are asymptomatic. Clinical disease arises from pulmonary hypersensitivity and intestinal complications. During the lung phase of larval migration, about 9 to 12 days after eggs ingestion, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing on deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever is usually reported, with temperatures sometimes exceeding 38.5°C. Eosinophylia develops during this symptomatic phase and subsides slowly over weeks. Chest X-rays may reveal evidence round or oval infiltrates a few millimeters to several centimeters in size. These infiltrates usually are accompanied with high eosinophylia (eosinophylic pneumonitis – Loeffler's syndrome), may be transient and intermittent, clearing after several weeks. Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophylia may develop in previously infected and sensitized hosts. Hypersensitive patients may experience urticaria and asthma.

Adult worms in the small intestine usually cause no symptoms, but may cause nausea and vomiting. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction, sometimes complicated by perforation, intussusceptions, or volvulus. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, and (rarely) intrahepatic abscesses. Migration of an adult worm up the esophagus can provoke coughing and oral expulsion of the worm. In highly endemic areas, intestinal and biliary ascariasis can rival acute appendicitis and gallstones as causes of surgical acute abdomen. Heavy infection can exacerbate malnutrition and contribute to vitamin A and C deficiency. Death occurs in 0.02% of cases and is usually associated with obstruction or with hypersensitivity reactions.

Diagnosis. Most patients usually present eosinophylia, more intensive in migratory stage. Intestinal infection in asymptomatic patients may only be recognized after adult worms are passed or vomited. Most cases of Ascariasis can be diagnosed by the microscopic detection of characteristic *Ascaris* eggs (65 by 45 μm) in fecal samples. During the early transpulmonary migratory phase, when eosinophylic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool. The large adult worms may be revealed on contrast X-ray studies of the gastrointestinal tract. A plain abdominal film may reveal masses of worms in gas-filled loops of bowel in patients with intestinal obstruction. Pancreaticobiliary worms can be detected by ultrasound and endoscopic retrograde cholangiopancreatography; the latter method also has been used to extract biliary *Ascaris* worms.

Treatment. Ascariasis should always be treated to prevent potentially serious

complications. Mebendazole (100 mg for adults, 5-7 mg/1 year of life for children once a day through 1 hour after meal) or albendazole (400 mg for adults and 300 mg for children once a day) is effective. These benzimidazoles are contraindicated in pregnancy and in heavy infections, in which they may provoke ectopic migration. Pyrantel pamoate (250 mg trice a day for 1-3 days) and piperazine citrate (1,5-2 g twice a day for 2 days) are safe in pregnancy. Pyrantel, albendazole and mebendasole are 90-100% effective. Anaphylactic shock, resulting from the death of a large number of worms, is a risk of therapy. To prevent such complications high enema is recommended after treatment for quick evacuation of warms from intestine. Severe complications (intestinal obstruction) require immediate surgical intervention. Supportive therapy (e.g., administration of glucocorticoids, or bronchodilators) may be advisable during the pulmonary stage of infection.

Prevention. Ascariasis is associated with poor sanitation and hygiene. Proper treatment and disposal of sewage and filtering of drinking water reduces incidence. Vegetable and hands should be washed well before meals.

HOOKWORM

Etyology. The two species of hookworms are differentiated by their dentition. *Necator americanus* has two broad plates in the buccal cavity, while *Ancylostoma duodenale* has two pair of sharp teeth. The mouth and teeth are used to attach to the mucosal surface. Adult worms are creamy-white, approximately 10 mm long, and live mostly in the jejunum. In heavy infections they are usually found in the cecum.

The adult hookworms produce thousands of eggs daily. The eggs are deposited with feces in soil, where rhabditiform larvae (L1) hatch and develop over a 1-week period (by molting twice) into infectious filariform larvae (L3). These larvae survive 2-5 weeks in warm, moist soil. Infective larvae penetrate the skin and reach the lungs by way of the bloodstream, invade alveoli and ascend the airways before being swallowed and reaching the small intestine. The prepatent period from skin invasion to appearance of eggs in the feces is about 6 to 8 weeks, but it may be longer with *A. duodenale*. Larvae of *A. duodenale*, if swallowed, can survive and develop directly in the intestinal mucosa. Adult hookworms may survive over a decade but usually live about 6 to 8 years for *A. duodenale* and 2 to 5 years for *N. americanus*.

Epidemiology. One-fourth of the world's population is infected with one of the two hookworm species (approximately 600 million infections worldwide). Hookworms are distributed throughout the tropics and subtropics, particularly Southeast Asia. Transmission is by larval penetration of skin, usually through the feet. In most areas, older children have the greatest incidence and intensity of hookworm infection. In rural areas where fields are fertilized with “night soil”, older working adults also may be heavily affected.

Pathogenesis. Hookworm disease develops from a combination of factors: a

heavy worm burden, a prolonged duration of infection, and an inadequate iron intake; and results in iron-deficiency anemia and, on occasion, hypoproteinemia. Penetrating by larvae the skin and migratory stage are characterized by allergic effect. Adult worms use their teeth to attach to the mucosal surface, and for sucking blood (intestinal stage). One worm receive approximately 150-200 microliter of the blood per day in the case of *A. duodenale* and 40 microliter per day – in the case of *N. americanus*. Worms frequently change their attachment sites and traumate the mucosal membrane. Considerable blood loss can lead to a chronic hypochromic and microcytic anemia secondary to iron deficiency. Chronic erosive duodenitis and enteritis usually develop. Severity of symptoms depends on worm burden.

Clinical manifestations. Most hookworm infections are asymptomatic. Infective larvae may provoke pruritic maculopapular dermatitis ("ground itch") at the site of skin penetration as well as serpiginous tracts of subcutaneous migration (similar to cutaneous larva migrans) in previously sensitized hosts. Larvae migrating through the lungs occasionally cause mild transient pneumonitis (Loeffler's syndrom), but this condition develops less frequently in hookworm infection than in ascariasis. In the early intestinal phase, infected persons may develop epigastric pain, inflammatory diarrhea, or other abdominal symptoms accompanied by eosinophylia. The major consequence of chronic hookworm infection is iron deficiency. Symptoms are minimal if iron intake is adequate, but marginally nourished individuals develop symptoms of progressive iron-deficiency anemia and hypoproteinemia, including weakness, shortness of breath, and skin depigmentation. Intercurrent infections may precipitate frank cardiac failure. Changes in the intestinal mucosa are minimal, and malabsorption is uncommon.

Diagnosis. Hypochromic microcytic anemia, occasionally with eosinophylia or hypoalbuminemia, accompanied by the finding of blood in the feces is characteristic of hookworm disease. Diagnosis is established by the finding of characteristic 40- by 60-μm oval hookworm eggs in the feces. Eggs of the two species are indistinguishable. In a stool sample that is not fresh, the eggs may have hatched to release rhabditiform larvae, which need to be differentiated from those of *S. stercoralis*.

Treatment. Hookworms can be eradicated with several safe and highly effective antihelmintic drugs, including mebendazole (100 mg for adults, 5-7 mg/1 year of life for children once a day through 1 hour after meal; it is 60-90% effective), albendazole (400 mg for adults and 300 mg for children once a day for 3 days; it is 85-90% effective), naphthamon (5 g with 50 ml sugar sirope once a day in 2-3 h before breakfast for 2-3 days; it is 60-70% effective) and pyrantel pamoate (250 mg trice a day for 3 days; it is 70-100% effective). Mild iron-deficiency anemia often can be treated with oral iron alone. Severe hookworm disease with protein loss and malabsorption necessitates nutritional support and oral iron replacement along with

deworming.

Prevention. Proper disposal and treatment of sewage is necessary to avoid contamination of soil. Patients should be advised to wear shoes. Reinfection is extremely common in endemic areas.

STRONGYLOIDIASIS

Etyology. *Strogyloides stercoralis* is distinguished by a capacity, unusual among helminthes, to replicate in the human host. After penetration of skin or mucous membranes larvae travel through the bloodstream to the lungs, where they break into the alveolar spaces, ascend the bronchial tree, are swallowed, and thereby reach the small intestine. There the larvae mature into adult worms that penetrate the mucosa of the proximal small bowel. Parasitic adult female worms (2-mm long) reproduce by parthenogenesis; parasitic adult males do not exist. Eggs hatch locally in the intestinal mucosa, releasing rhabditiform larvae that migrate to the lumen and pass with the feces into soil. Rhabditiform larvae in soil transform into infectious filariform larvae, which are ready for contamination of humans. Alternatively, rhabditiform larvae in the bowel can develop directly into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to repeat the migration that establishes ongoing internal reinfection. This autoinfection cycle allows strongyloidiasis to persist for decades after the host has left an endemic area (without further exposure of the host to exogenous infective larvae).

Epidemiology. *S. stercoralis* is a cosmopolitan parasite found throughout the tropics and subtropics and is particularly common in Southeast Asia, sub-Saharan Africa, and Brazil. This infection may persist sometimes in moderate climate. Humans acquire strongyloidiasis when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes.

Clinical manifestations. In immunocompetent patients up to 50% of cases are asymptomatic or have mild cutaneous and/or abdominal symptoms. Recurrent urticaria, often involving the buttocks and wrists, is the most common cutaneous manifestation. Migrating larvae can elicit a pathognomonic serpiginous eruption, *larva currents* ("running larva") – a pruritic, raised, erythematous lesion that advances as rapidly as 10 cm/h along the course of larval migration. Adult parasites burrow into the duodenojejunal mucosa and can cause abdominal (usually epigastric) pain, which resembles peptic ulcer pain except that it is aggravated by food ingestion. Nausea, watery diarrhea, gastrointestinal bleeding, mild chronic colitis, and weight loss can occur. Pulmonary symptoms are rare in uncomplicated strongyloidiasis. Eosinophylia is common, with levels fluctuating over time.

In immunocompromised patients ongoing autoinfection cycle of strongyloidiasis is characteristic with the generation of large numbers of filariform larvae. Colitis, enteritis, or malabsorption may develop. In disseminated strongyloidiasis, larvae may invade not only gastrointestinal tissues and the lungs but

also the CNS, peritoneum, liver, and kidney. Moreover, bacteremia may develop due to the entry of enteric flora through disrupted mucosal barriers. Gram-negative sepsis, pneumonia, or meningitis may complicate or dominate the clinical course. Eosinophylia is often absent in severely infected patients. Disseminated strongyloidiasis, particularly in patients with unsuspected infection who are given immunosuppressive drugs, can be fatal. Strongyloidiasis is a frequent complication of infection with human T-cell lymphotropic virus type I, but disseminated strongyloidiasis is not common among patients infected with human immunodeficiency virus.

Diagnosis. In uncomplicated strongyloidiasis, the finding of rhabditiform larvae in feces is diagnostic. The eggs are almost never detectable because they hatch in the intestine. Eggs are similar to those of hookworms. The Harada-Mori test, which entails incubation of feces to allow the larvae to hatch and develop, allows differentiation of Strongyloides infection from hookworms infection based on identification of the tail of filariform larvae. Rhabditiform larvae are 200 to 250 μm long, with a short buccal cavity that distinguishes them from hookworm rhabditiform larvae. Single stool examinations will detect only about one-third of uncomplicated infections. Serial examinations or use of the Baermann concentration method improves the sensitivity of stool diagnosis. If the result of stool examination is negative, duodenal contents may be examined for *S. stercoralis* larvae as well or the Enterotest string method may be used. An enzyme-linked immunosorbent assay for antibodies to antigens of *Strongyloides* is a sensitive method of diagnosing uncomplicated infections. In disseminated strongyloidiasis, filariform larvae (550 μm long) should be sought in stool as well as in samples obtained from sites of potential larval migration, including sputum, bronchoalveolar lavage fluid, CSF or surgical drainage fluid.

Treatment. Strongyloidiasis must be treated because of the potential for fatal hyperinfection. Thiabendazole (25 mg/kg bid) is generally administered for 2 days, but in disseminated strongyloidiasis, treatment should be extended for at least 5 to 7 days or until the parasites are eradicated. It is 80-95% effective. Common adverse effects of thiabendazole include nausea, vomiting, diarrhea, dizziness, and neuropsychiatric disturbances. Because thiabendazole is not uniformly effective, stool examinations, eosinophil counts, and monitoring of clinical symptoms should be continued after treatment. Albendazole (400 mg once a day after meal for 3 days; it is 99-100% effective) and ivermectin (200 mg/kg/day for 2-3 days) are newer drugs effective in the treatment of intestinal disease, but, to date, efficacy in disseminated strongyloidiasis has been demonstrated only for thiabendazole.

Prevention. Proper disposal and treatment of sewage and wearing of shoes help to control the incidence of disease.

TRICHURIASIS (WHIPWORM)

Etyology. *Trichuris trichiura* is a roundworm that lives in the colon – the thinner anterior halves of their bodies are embedded in the mucosa and the thicker posterior ends extend into the lumen. Such appearance gives the *T. trichiura* whip-like shape. Adult females are approximately 50 mm long. Males are 35 mm long with a coiled tail. The worm has a direct life cycle. Thousands of eggs laid daily by adult female worms pass via the feces and mature in the soil (eggs require at least 2 weeks' incubation). After ingestion, infective eggs hatch in the duodenum, releasing larvae that mature before migrating to the large bowel. The entire cycle takes about 3 months, and adult worms may live for several years.

Epidemiology. Like the other soil-transmitted helminthes, whipworm is distributed globally. Prevalence and intensity of Trichuriasis is higher in the tropics and subtropics. Approximately 800 to 1000 million cases occur worldwide. Transmission occurs through ingestion of eggs, usually on contaminated vegetables or in soil.

Pathogenesis. Mechanical traumatic action, anemia, neuro-reflecting and allergic effects are the principal features of Trichuriasis. Secondary bacterial infection of intestine may be associated with this disease.

Clinical manifestations. Most infected individuals have no symptoms or eosinophilia. Heavy infections may result in abdominal pain, anorexia, and bloody or mucoid diarrhea resembling inflammatory bowel disease. Rectal prolapse can result from massive infections in children, who often suffer from malnourishment and other diarrheal illnesses. Moderately heavy whipworm burdens also contribute to growth retardation. Extremely heavy infections may result in death (e.g., because of microperforations and followed peritonitis), but this is rare.

Diagnosis. Identifying eggs in feces make diagnosis. Eggs are oval, barrel-shaped and have distinctive protruding polar plugs. The eggs measure approximately 50/20-μm. Adult worms occasionally can be seen on proctoscopy.

Treatment. Mebendazole (100 mg once a day for 4-6 days), albendazole (400 mg once a day for 2-3 days), medamine (daily doze is 10 mg/kg for 3 days) and naphthamone (5 g once a day) are safe and effective for treatment

ENTEROBIASIS (PINWORM)

Etyology. *Enterobius vermicularis* is a small, white roundworm. Females average 10 mm in length, males - 3 mm. The worm has a direct life cycle. The gravid female worm migrates nocturnally out into the perianal region and releases up to 10,000 immature eggs. The eggs become infective within hours and are transmitted via hand-to-mouth passage. The larvae hatch and mature entirely within the intestine. This life cycle takes about 1 month, and adult worms survive for about 2 months. Self-infection results from perianal scratching and transport of infective eggs on the hands or under the nails to the mouth.

Epidemiology. *E. vermicularis* is more common in temperate countries than in the tropics More than 1 billion cases occur worldwide. Peak prevalence is in the 5 to 6-year-old age group. Owing to the ease of person-to-person spread, pinworm infections are common among family members and institutionalized populations. Adults are more refractory, indicating that resistance may occur with age (possibly with acquired immunity). Eggs are deposited in sticky secretion on the perianal skin by nocturnally wondering female worms. Eggs also contaminated bed making. Infection occurs via ingestion or inhalation of eggs.

Pathogenesis. The most common features of it are neuro-reflectoring action and secondary inflammation.

Clinical manifestations. Most pinworm infections are asymptomatic. Perianal pruritus is the cardinal symptom. The itching is often worse at night owing to the nocturnal migration of the female worms, and it may lead to excoriation and bacterial superinfection. Heavy infections have been claimed to cause abdominal pain, which is produced with necrosis of mucosal surface, and weight loss. Pinworms often occur in the appendix and may be associated with appendicitis. On rare occasions, worms may migrate to ectopic sites, invading the female genital tract and causing vulvovaginitis and pelvic or peritoneal granulomas. Eosinophilia or elevated levels of serum IgE are rare.

Diagnosis. Since pinworm eggs are not usually released in the bowel, looking for eggs in the feces cannot make the diagnosis. Instead, eggs deposited in the perianal region are detected by the application of clear cellulose acetate tape to the perianal region in the morning (Cellophane tape test). After the tape is transferred to a microscope slide, low-power examination will reveal the characteristic pinworm eggs, which are oval, measure 55 by 25 μm, and are flattened along one side and they contain a larva. Specimens should be collected prior to bathing or using of the toilet. Four to six consecutive negative pinworm tape preparations are required to rule out infection. In patients with heavy worm burdens adult female worms may be seen in stool samples.

Treatment. Single dose of mebendazole, albendazole, naphthamone, decaris or pyrantel pamoate are highly effective. Because ongoing reinfection routinely occurs treatment should be repeated after 10 to 14 days to kill the newly acquired developing adult worms. Treatment of household members is also advocated.

Prevention. Treating the patient's entire family is recommended to eliminate asymptomatic reservoirs of potential reinfection. Bed linens and towels should be washed.

LYMPHATIC FILARIASIS

Etyology. Lymphatic filariasis is caused by *Wuchereria. bancrofti*, *Brugia malayi*, or *Brugia timori*. Adult female worms measure 100×0.25 mm, while males measure 40×0.1 mm. Adult worms can live in the mammalian host lymphatic system

for up to 17 years, where they viviparously produce blood-dwelling, microfilariae (pre-L1). The microfilariae are ingested by mosquitoes, penetrate the stomach wall, grow, and metamorphose through stage L2 and L3 within the thoracic flight muscle. After approximately 10 days, the L3 migrate to the mosquito's salivary glands, proboscis, and associated structures, from which they are injected into the next host. In humans, the L3 migrates through the deep tissues, molting into an L4 and then an adult in approximately 10 days. The adult penetrates the lymphatics after 4-12 months.

Epidemiology. The most widely distributed human filarial parasite *W.bancrofti*, affects an estimated 80 million people and is found throughout the tropics and subtropics, including Asia and the Pacific Islands, Africa, areas of South America, and the Caribbean basin. *B. malayi* occurs primarily in China, India, Indonesia, Korea, Japan, Malaysia, and the Philippines *B. timori* exists only on islands of the Indonesian archipelago. Generally, the subperiodic form is found only in the Pacific Islands; elsewhere, *W. bancrofti* is nocturnally periodic. (Nocturnally periodic forms of microfilariae are scarce in peripheral blood by day and increase at night, whereas subperiodic forms are present in peripheral blood at all times and reach maximal levels in the afternoon). Brugian filariasis due to *B. malayi* also has two forms distinguished by the periodicity of microfilaremia. The more common nocturnal form is transmitted in areas of coastal rice fields, while the subperiodic form is found in forests. Together, these parasites account for over 90 million cases of lymphatic filariasis.

Humans are the only definitive host for the parasite. *B. malayi* naturally infects cats as well as humans. Dogs, cats, monkeys, wild carnivores ad rodents serve as reservoirs for *B. malayi. W. bancrofti* and *B. malayi* are transmitted by mosquitoes of several genera, particularly *Culex fatigans* mosquitoes in urban settings and anopheline or aedean mosquitoes in rural areas.

Pathogenesis. Pathogenesis of lymphatic filariasis is associated with mechanical action of worms in lymphatic channels, toxic, allergic effects and development of immune and immunopathologic reactions. The principal pathologic changes result from inflammatory damage to the lymphatics, which are caused by adult worms. The presence of masses of adult worms (not of microfilariae) causes lymph nodes and ducts dilation, leading to lymph retention in the areas drained by the affected nodes and vessels. The infiltration of plasma cells, eosinophyls, and macrophages in and around the infected vessels, along with endothelial and connective tissue proliferation, leads to thickening of the vessel walls and tortuosity of the lymphatics and damaged or incompetent lymph valves. Lymphedema and chronic-stasis changes with hard or brawny edema develop in the overlying skin.

These consequences of filariasis are due both to direct effects of the worms and to the immune response of the host to the parasite. These immune responses are

believed to cause the granulomatous and proliferative processes that precede total lymphatic obstruction. It is thought that the vessel remains patent as long as the worm remains viable, and that death of the worm leads to enhanced granulomatous reaction and fibrosis. Lymphatic obstruction results, and, despite collateralization of the lymphatics, lymphatic function is compromised. Secondary infection plays an important role in the development of complications of this disease.

Clinical manifestations. Many cases remain to be clinically asymptomatic for years. Patients experience lymphangitis, headache, nausea, and urticaria during the early, acute stages of disease. Asymptomatic microfilaremia is found in most infected individuals who are clinically well. Infected males frequently develop disease in the scrotum primarily because of the presence of adult worms in the lymphatics of the spermatic cord. Hydrocele may develop and, in advanced stages, may evolve into scrotal elephantiasis. Acute lymphangitis and lymphadenitis with high fever ("filarial fevers") are often accompanied by shaking chills and transient local edema. Episodes can recur frequently and usually abate spontaneously after 7 to 10 days. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can develop. In brugian filariasis, a local abscess may form over a lymphatic tract and rupture. Lymphadenitis and lymphangitis involve both the upper and the lower extremities in bancroftian and brugian filariasis, but genital lymphatic involvement develops almost exclusively in relation to *W. bancrofti* infection. Genital involvement can be manifested by funiculitis, epididymitis, and scrotal pain and tenderness

If lymphatic damage progresses to lymphatic obstruction, the permanent changes associated with elephantiasis may ensue. Brawny edema follows early pitting edema. With thickening of subcutaneous tissues come hyperkeratosis, fissuring of the skin, and hyperplastic changes. Bacterial superinfection of the poorly vascularized tissues is common. In bancroftian filariasis, scrotal lymphedema can develop. If the retroperitoneal lymphatics become obstructed, increased pressure leads to the rupture of renal lymphatics and the development of chyluria, which is usually intermittent and most prominent in the morning.

The clinical manifestations of filarial infections in travelers or transmigrants, which have recently entered an endemic region, are distinctive. Given a sufficient number of bites by infected vectors, usually over a 3-to 6-month period, recently exposed patients can develop acute lymphatic or scrotal inflammation with or without urticaria and localized angioedema. Lymphadenitis of epitrochlear, axillary, femoral, or inguinal lymph nodes is often followed by retrogradely evolving lymphangitis. Acute attacks are short-lived and, in contrast to filarial fevers in patients native to endemic areas, are usually not accompanied by fever. With prolonged exposure to infected mosquitoes, these attacks, if untreated, become more severe and lead to permanent lymphatic inflammation and obstruction. Tropical pulmonary eosinophylia

occurs in a subgroup of patients. These patients do not have circulating microfilariae and respond well on therapy.

Diagnosis. In acute episodes, lymphatic filariasis must be distinguished from thrombophlebitis, infection, and trauma. Retrogradely evolving lymphangitis is a characteristic feature that helps distinguish filarial lymphangitis from typically ascending bacterial lymphangitis. Chronic filarial lymphedema must be distinguished from the lymphedema of malignancy, postoperative scarring, trauma, chronic edematous states, and congenital lymphatic-system abnormalities. Adult worms localized in lymphatic vessels or nodes are largely inaccessible.

Demonstrating of microfilariae in a thick blood smear makes definitive diagnosis. Microfilariae can be found also in hydrocele fluid, or (occasionally) in other body fluids. Blood and such fluids can be examined microscopically, either directly or for greater sensitivity after concentration of the parasites by the passage of fluid through a polycarbonate cylindrical pore filter (pore size 3 nm) or by the centrifugation of fluid fixed in 2% formalin (Knott's concentration technique). The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved. A Giemsa-stained thin blood smear is used to differentiate *W Bancrofti* microfilariae, which have not nuclei in the tip of tail, from those of *B. malayi,* which have two prominent nuclei at the tip of tail. Many infected individuals do not have microfilaremia, and definitive diagnosis in such cases can be difficult; in some instances, the diagnosis must be made on clinical grounds.

Eosinophilia and elevations of serum concentrations of IgE and antifilarial antibody support the diagnosis of lymphatic filariasis. There is, however, extensive cross-reactivity between filarial antigens and antigens of other helminthes, including the common intestinal roundworms; thus, interpretations of serologic findings can be difficult. In addition, residents of endemic areas can become sensitized to filarial antigens through exposure to infected mosquitoes without having patent filarial infections. Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. Polymerase chain reaction-based assays for DNA of *W. bancrofti* and *B. malayi* in blood have also been developed.

Evaluation of lymphatic function with lymphoscintigraphy can provide useful information in cases of lymphatic filariasis. The procedure involves the intradermal or subcutaneous injection of 99Tc-labeled albumin or 99Tc-labeled dextran and subsequent sequential imaging with a gamma camera. In males with suspected lymphatic filariasis, examination of the scrotum by ultrasonography may reveal nodules or lymphatic dilatation. The use of Doppler techniques may reveal motile worms within the scrotal lymphatics.

Treatment. Diethylcarbamazine (DEC) is the drug of choice, because it kills

microfilariae as well as adult worms (slowly). It is used at 6 mg/kg per day in either single or divided doses for 2 to 3 weeks. If at least some adult parasites survive, as is often the case, microfilaremia along with clinical symptoms can recur within months after therapy. There is some evidence that several courses of DEC or chronic administration of low-dose DEC may affect a cure. Ivermectin kill microfilariae, but not adults. It has been used in a single dose; it appears to be as effective as DEC at clearing microfilariae. Side effects of treatment with DEC (or ivermectin) include fever, chills, arthralgia, headaches, nausea, and vomiting. These side effects can be avoided either by the initial use of a small dose of DEC, with an increase to a full dose over a few days, or by premedication of the patient with glucocorticoids.

Treatment of chronic lymphatic obstruction is difficult but may be helpful. Antibiotic soaps and topical creams can be used to reduce the elephantiasis. Elevation of the infected limb, use of elastic stockings, and local foot care eliminate some of the associated symptoms. Surgical decompression with a nodovenous shunt may provide relief for severely affected limbs. Hydroceles can be drained or managed surgically. The management of filarial chyluria is unsatisfactory; neither surgical intervention nor sclerosis of infected lymphatics is effective.

Prevention. Avoidance of mosquito bites usually is not feasible for residents of endemic areas, but visitors should use insect repellent and mosquito nets. DEC can kill developing filarial larvae and is useful as a prophylactic agent, although the optimal regimen for prophylaxis has not been ascertained. Mass treatment with DEC may reduce community levels of microfilariae so as to interrupt vector-borne transmission among humans.

ONCHOCERCIASIS

Etyology. Onchocerciasis ("river blindness") is caused by the filarial nematode *Onchocerca volvulus*, which infects an estimated 13 million individuals.

Infection in humans begins with the deposition of infective larvae on the skin by the bite of an infected black fly. The larvae develop into adults, which are typically found in subcutaneous nodules. About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodule and throughout the tissues, concentrating in the dermis. Infection is transmitted to other persons when a female fly ingests microfilariae from the host's skin and these microfilariae then develop into infective larvae. Adult *O. volvulus* females and males are about 40 to 60 cm and 3 to 6 cm in length, respectively. The life span of adults can be as long as 18 years, with an average of approximately 9 years.

Epidemiology. The majority of individuals infected with *O. volvulus* live in the equatorial region of Africa, and infection is focal in Yemen, Saudi Arabia and Central and South America. Onchocerciasis is the second leading cause of infectious blindness worldwide.

Black flies of the genus *Simulium* are the insect vectors of the disease. Because

the black fly breeds along free-flowing rivers and streams (particularly in rapids) and generally restricts its flight to an area within several kilometers of these breeding sites, disease transmission is most intense in these locations.

Pathogenesis. The principal role in pathogenesis of onchocerciasis belongs to chronic immunopathologic inflammation on dying microfilariae and atrophic processes caused by it. Onchocerciasis affects primarily the skin, eyes and lymph nodes. The damage in onchocerciasis is elicited by microfilariae and not by adults. In the skin, there are mild but chronic inflammatory changes that can result in loss of elastic fibers, atrophy, and fibrosis. The subcutaneous nodules, or onchocercomata, consist primarily of fibrous tissues surrounding the adult worm, often with a peripheral ring of inflammatory cells. In the eye, neovascularization and corneal scarring lead to corneal opacities and blindness. Inflammation in the anterior and posterior chambers frequently results in anterior uveitis, chorioretinitis, and optic atrophy. Although punctate opacities are due to an inflammatory reaction surrounding dead or dying microfilariae, the pathogenesis of most manifestations of onchocerciasis is still unclear.

Clinical manifestations. Pruritus and rash are the most frequent manifestations of onchocerciasis. The pruritus can be incapacitating; the rash is typically a papular eruption that is generalized rather than localized to a particular region of the body. Long-term infection results in exaggerated and premature wrinkling of the skin, loss of elastic fibers, and epidermal atrophy that can lead to loose, redundant skin and hypo- or hyperpigmentation. Localized eczematoid dermatitis can cause hyperkeratosis, scaling, and pigmentary changes. Such lesions are often seen in the lower extremities but can be distributed more extensively.

Onchocercomata – subcutaneous nodules, which can be palpable and/or visible, contain the adult worm. In African patients, they are common over the coccyx and sacrum, the trochanter of the femur, the lateral anterior crest, and other bony prominences; in Latin American patients, they tend to develop preferentially in the upper part of the body, particularly on the head, neck, and shoulders. Nodules vary in size and characteristically are firm and not tender. It has been estimated that, for every palpable nodule, there are four deeper nonpalpable ones.

Visual impairment is the most serious complication of onchocerciasis and usually affects only those persons with moderate or heavy infections. Lesions may develop in all parts of the eye. The most common early finding is conjunctivitis with photophobia. In the cornea, punctate keratitis consisting of acute inflammatory reactions surrounding dying microfilariae manifested as "snowflake" opacities,which are frequent in younger patients and resolves without apparent complications. Sclerosing keratitis occurs in approximately 5% of persons infected with savannah strains and 1% of those infected with forest strains and is the leading cause of onchocercal blindness in Africa. Anterior uveitis and iridocyclitis develop in about

5% of infected persons in Africa. In Latin America, complications of the anterior uveal tract (pupillary deformity) may cause secondary glaucoma. Characteristic chorioretinal lesions develop as a result of atrophy and hyperpigmentation of the retinal pigment epithelium and the choriopapillaris. Constriction of the visual field and frank optic atrophy may occur. Mild to moderate lymphadenopathy is frequent, particularly in the inguinal and femoral areas, where the enlarged nodes may hang down in response to gravity ("hanging groin"), sometimes predisposing to inguinal and femoral hernias. Some heavily infected individuals develop cachexia with loss of adipose tissue and muscle mass. Among adults who become blind, there is a three- to fourfold increase in the mortality rate.

Diagnosis. The presence of palpable subcutaneous nodules, skin lesions, or ocular changes in an endemic area is characteristic. Slit lamp examination of the eye will reveal microfilariae in the aqueous humor.

Definitive diagnosis depends on the detection of an adult worm in an excised nodule or, more commonly, of microfilariae in a skin snip. Skin snips are obtained with a corneal-scleral punch, which collects a blood-free skin biopsy sample extending to just below the epidermis, or by lifting of the skin with the tip of a needle and excision of a small (1- to 3-mm) piece with a sterile scalpel blade. The biopsy tissue is incubated in tissue culture medium or in saline on a glass slide or flat-bottomed microtiter plate. After incubation for 2 to 4 h (or occasionally overnight in light infections), microfilariae emergent from the skin can be visualized by low-power microscopy.

Treatment. The main goals of therapy are to prevent the development of irreversible lesions and to alleviate symptoms. *Noduleectomy* to remove adult worms is recommended for head modules (because of the proximity of microfilaria-producing adult worms to the eye), but is largely cosmetic in other parts of the body.

Chemotherapy is the mainstay of management. Ivermectin, a semisynthetic macrocyclic lactone active against microfilariae, is the first-line agent for the treatment of onchocerciasis. It is given orally in a single dose of 150 mg/kg, either yearly or semiannually. After treatment, most individuals have few or no reactions. Pruritus, cutaneous edema, and/or maculopapular rash occurs in approximately 1 to 10% of treated individuals. Contraindications to treatment include pregnancy, breast feeding, CNS disorders that may increase the penetration of ivermectin into the CNS (e.g., meningitis), and an age of less than 5 years. Although ivermectin treatment results in a marked drop in microfilarial density, its effect may last for only 6 months. Suramin, a potent but potentially toxic macrofilaricidal agent, is recommended only if total cure is necessary. Because of the drug's nephrotoxicity, renal function must be monitored closely during treatment.

Prevention. Insecticides have been successful in reducing fly populations and preventing disease as part of the onchocerciasis control program implemented in

West Africa. Vector control has been beneficial in highly endemic areas in which breeding sites are vulnerable to insecticide spraying, but most areas endemic for onchocerciasis are not suited to this type of control. Because insecticide resistance is becoming significant, control is moving toward mass therapy with ivermectin. Persons working in fly-infested areas can minimize the number of bites they sustain by wearing protective garments

LOIASIS

Etyology. Loiasis is caused by *Loa loa* (the African eye worm). Adult parasites (females, 50 to 70 mm long and 0.5 mm wide; males, 25 to 35 mm long and 0.25 mm wide) live in subcutaneous tissues; microfilariae circulate in the blood with a diurnal periodicity that peaks between 12:00 noon and 2:00 P.M.

Epidemiology. *L. loa* is found in the rain forests of West and Central Africa. *Loa loa* is transmitted by large tabanid flies similar to horse's ones or deer flies, which acquire the worm by sucking blood from infected individuals and latter depositing larvae in the skin of uninfected subjects.

Pathogenesis. The pathogenesis of the manifestations of loiasis is poorly understood. Calabar swellings are thought to result from a hypersensitivity reaction to the adult worm. Mechanical effect and toxic reactions are characteristic too.

Clinical manifestations. Manifestations of loiasis in natives of endemic areas may differ from those in temporary residents or visitors. Among the indigenous population, loiasis is often an asymptomatic infection with microfilaremia. Infection may be recognized only after subconjunctival migration of an adult worm or may be manifested by episodic Calabar swellings. Calabar swelling (a mild, transient, inflammatory swelling, which is accompanied by eosinophylia) to be appear as evanescent localized areas of angioedema and erythema developing on the extremities and less frequently at other sites. Patients may experience intense itching and pruritus accompanied by fever. In chronic infections, in rare cases the worms may migrate into deeper tissues and may cause nephropathy, encephalopathy, and cardiomyopathy. In patients who are not residents of endemic areas, allergic symptoms predominate, episodes of Calabar swelling tend to be more frequent and debilitating, microfilaremia is rare, and eosinophylia, fever and increased levels of antifilarial antibodies are characteristic.

Diagnosis. The fugitive swelling with eosinophylia and patient history is clinically suggestive. Definitive diagnosis of loiasis requires the detection of microfilariae in the peripheral blood or the isolation of the adult worm from the eye or from a subcutaneous biopsy specimen from a site of swelling developing after treatment. Elevated levels of antifilarial antibodies are usually present, particularly in travelers to the endemic region, who are usually amicrofilaremic. Other clinical findings in the latter individuals include hypergammaglobulinemia, elevated levels of serum IgE, and elevated leukocyte and eosinophil counts.

Treatment. DEC (8 to 10 mg/kg per day for 21 days) is effective against both the adult and the microfilarial forms of *L. loa*, but multiple courses are frequently necessary before the disease resolves completely. In cases of heavy microfilaremia, allergic or other inflammatory reactions can take place during treatment, including CNS involvement with coma and encephalitis. Heavy infections are treated initially with low doses of DEC (0.5 mg/kg per day) and glucocorticoids (40 to 60 mg of prednisone per day). If antifilarial treatment has no adverse effects, the prednisone dose can be rapidly tapered and the dose of DEC gradually increased to 8 to 10 mg/kg per day. Albendazole and ivermectin have been shown to be effective in reducing microfilarial loads.

Prevention. DEC (300 mg weekly) is an effective prophylactic regimen for loiasis.

TREMATODOSES

Four major groups of trematodes affect humans: blood, liver, lung, and intestinal flukes.The trematodes (flukes) that commonly infect humans live in the intestines, biliary tract, lungs, and venules of the intestines or genitourinary tract. Except in the case of the intestinal schistosomes, which cause a unique type of liver fibrosis, disease is limited primarily to the organs where the parasites reside.

The trematodes are typically leaf-shaped. They have an oral and a ventral sucker used for attachment and movement. The gut usually lacks an anus, and digested food is regurgitated through the oral opening. The trematodes are hermaphroditic, except schistosoma species (blood flukes), which are diecious.

The life cycles of all human trematodes are similar. After eggs reach fresh water, they either hatch immediately or mature before releasing a free-swimming ciliated miracidium larva, which seeks out the appropriate intermediate snail host or is ingested by the snail. After a number of cycles of multiplication in the snail, free-swimming cercariae are released and, depending on the species, can (1) infect the definitive host (schistosome); (2) seek out a second intermediate host, such as a fish or crustacean (Clonorchis species); or (3) encyst on vegetation (Fasciola hepatica). The encysted cercaria, or metacercaria, is a dormant, relatively resistant form that infects the host following ingestion.

OPISTORCHIASIS

Etyology. Opistorchosis is a human liver fluke infection**,** which is caused by *Clonorchis* (*Opistorchis felineus, Opistorchis sinensis, Opistorchis viverrini)*. Worms are 7 to 20 mm by 1.5 to 3 mm (depending on the species), with similar morphology and life cycles and may live for 20 to 25 years (*C. sinensis*).

Epidemiology. *C. sinensis* occur in Japan, Korea, China, and Vietnam. *O.viverrini* is found predominantly in Thailand, and Laos. *O. felineus* is found in Kazakhstan, Russia, Ukraine, Turkey, Latvia, and Poland.

Eggs are passed in feces and are eaten by fresh-water snails of specific species.

The eggs hatch within the snail's gut, where the first asexual reproductive phase takes place to produce redia, which migrate into the snail's digestive gland. Cercariae shed from infected snails penetrate the skin of fresh-water fish, where they encyst as metacercariae in the subcutaneous tissues and muscles. Ingestion of metacercariae in raw or poorly cooked, pickled, or smoked infected fish transmits the disease to its definitive hosts, which include humans and fish-eating mammals (particularly cats and dogs).

Pathogenesis. The metacercariae excyst in the small intestine of definitive hosts, and migrate through the ampulla of Vater into the bile duct, gallbladder, and pancreatic duct, where they mature in 3 to 4 weeks. Flukes reside mostly in small to medium-sized biliary ducts but at times are also found in the larger biliary ducts as well as the gallbladder. They do not invade the parenchyma of the liver, and most disease manifestations reflect direct or indirect effects of the adult trematodes on the biliary ducts. The warms feed on the duct epithelium and cause biliary hyperplasia, fibrosis, cirrhosis, and cholangitis. Diffuse and localized dilation of ducts due to obstruction by worms, stones, or strictures is frequently found. Intercurrent bacterial infection via the damaged bile duct epithelium may be fatal. Allergic and mechanical effect with development of mechanical (obstructive) jaundice is characteristic. Chronic inflammation may lead to malignant transformation.

Clinical manifestations. Acute infections are infrequently recognized and are characterized by fever, eosinophilia, and hepatomegaly. In endemic areas, almost the entire population may be infected; however, most are lightly infected and asymptomatic. Heavy worm burdens (100-1000) lead to symptoms of hepatomegaly, diarrhea, anorexia and epigastric pain. The liver may be enlarged and tender. Ascending cholangitis is a serious complication. Jaundice may periodically occur. Clonorchis infection is also associated with the development of cholangiocarcinoma of the bile ducts. Ultrasonography reveals varying degrees of peripheral dilation of the biliary ducts without proximal obstruction. Biliary stones and flukes also may be noted ultrasonographically. Endoscopic cholangiopancreatography reveals ductal dilation, proliferation, irregularities, and blunting of the terminal branches in a majority of cases. Adult worms are visualized as multiple filling defects.

Diagnosis. Diagnosis is based on the clinical presentation and the detection of the characteristic ova in the feces or bile (30 μm by 15 μm, oval, operculated eggs). Worms can be visualized by a number of techniques and are frequently noted at surgery. Serologic tests may be available in endemic areas or research laboratories.

Treatment. Praziquantel is the drug of choice (25 mg/kg tid for 1 day).

Prevention. Control on cocking of fish products and sanitary education of population is important.

FASCIOLIASIS

Etyology. Adults of *Fasciola hepatica* are relatively large, measuring 30×13

mm. The ova of *F. hepatica* are immature in the feces, measure 130-150 × 90 μm, and are indistinguishable from those of *Fasciolopsis buski*

Metacercariae excyst in the duodenum, pass through the intestine into the peritoneum, invade the liver through Glisson's capsule, and eventually reside in the biliary ducts. In humans, the flukes require at least 3 to 4 months to mature, but eggs may not be detected in stool.

Epidemiology. *Fasciola* species are cosmopolitan, found in all sheep-rearing and cattle-rearing areas, including Europe, Australia, and other developed countries. The definitive hosts are sheep, cattle, and other domestic and wild herbivores. Transmission occurs by ingestion of metacercariae on grass or vegetables, principally watercress and lettuce for humans.

Pathogenesis. The severity of infection depends on its intensity and duration and the responses of the host. Early manifestations are due to migration of the flukes through the tissues. The metacercariae penetrate the liver, and eat their way through the parenchyma to the bile ducts. Punctate hemorrhages, tracts, and nodules are seen on the surface of the liver and constitute points of entry, migration routes, and areas of encapsulated eosinophilic abscesses, respectively. Granulomatous reactions also occur around eggs themselves. In chronic infections, worms reside in the biliary system, and the anatomic changes caused by the worms generally resemble those caused by other liver flukes. However, intermittent obstruction of the biliary passages by worms appears more common in fascioliasis and leads to periods of jaundice.

Clinical manifestations. Acute manifestations consist of a combination of systemic symptoms and signs and manifestations directly referable to invasion of the liver. Chronic disease has many features indistinguishable from those caused by the other liver flukes.

Fever, hepatomegaly and/or abdominal pain, and eosinophilia are the hallmarks of acute fascioliasis, which usually begins within 2 to 3 months following ingestion. Nausea, vomiting, diarrhea, cough, fever, pruritus, urticaria and occasionally, anemia are characteristic. Elevation of liver function values is inconstant, eosinophylia is found and the erythrocyte sedimentation rate is commonly elevated. Untreated, the disease lasts from months to years, but the manifestations change and with time more closely resemble those of other liver fluke infections, including intermittent obstruction, gallbladder and biliary duct thickening, cholecystitis, lithiasis, and the development of strictures. In serious cases, biliary stasis, liver atrophy, and periportal cirrhosis may ensue. Ectopic localization of flukes is also relatively common and leads to findings related to the invaded tissue. In contrast to the other liver flukes, *F. hepatica* has no apparent association with cholangiocarcinoma. CT scans show multiple, hypodense, irregular lesions in the liver; ultrasonography sometimes fails to detect these lesions but is helpful in detecting resulting biliary duct pathology.

Diagnosis. An association with sheep- or cattle-rearing and a history of

consumption of homegrown raw watercress or vegetables, together with fever, eosinophilia, and hepatomegaly or liver pain and elevated serum transaminase levels is highly suggestive. Definitive diagnosis is established by the detection of ova in the feces and/or by serologic tests. Ova may not be detected in the feces because the disease becomes manifest before potency, because the ova are unable to pass into the biliary system, or because the worms are in an ectopic location or there is a low level of excretion of ova. Therefore, stool concentration methods should be employed.

Treatment. Bithionol at 30 to 50 mg/kg on alternate days for 10 to 15 doses is the treatment of choice. Infections also have been treated successfully with the triclabendazole and albendazole.

Prevention. Control on cocking or proper washing of vegetables and sanitary education of population is important.

SCHISTOSOMIASIS

Etyology. Three major schistosome species *Schistosoma mansoni*, *S. haematobium*, and *Schistosoma japonicum* and a number of less prevalent species infect humans. Adult worms are about 1 to 2 cm long. Adult schistosomes can survive for 20 years or more in the human host but usually live for 5 to 8 years.

The ova of *S. mansoni* are 114 to 175 μm in length and 45 to 68 μm in width and have a prominent lateral spine. The eggs of *S. japanicum* are oval in shape, measure 70 to 100 μm by 50 to 65 μm, and have a vestigial spine. The eggs of *S. mekongi* are similar to those of *S. japonicum* but are slightly smaller (about 56 by 64 μm) and round. The eggs of *S. haematobium* measure 112 to 170 μm by 40 to 70 μm, have a prominent terminal spine. The eggs of *S. intercalatum* are about140 to 240 μm by 50 to 85 μm and have a terminal spine.

Humans become infected after contact with water containing the infective stage of the parasite, which is called a cercaria; this microscopic form possesses a forked tail, used for swimming, and a head. With the help of secreted enzymes, cercariae penetrate the unbroken skin, shed their tail to become schistosomules, and enzymatically and mechanically burrow through the skin and into a capillary. After 2 to 3 days, the schistosomules migrate to the lungs and then via the cardiopulmonary circulation to the hepatic artery and liver. Here they cross from hepatic arterial system to the portal venous system and back-migrate into the mesenteric blood vessels. In the portal vein, the maturing male and female schistosomes pair up and eggs are laid in the blood vessels wall. To complete the cycle, eggs must pass through the blood vessel wall, intestinal musculature, and mucosa to reach the lumen (in the case of *S. mansoni* and *S. japonicum)* or from the vessels of the bladder and vesicle plexus into the genitourinary tract (in case of *S. hematobium)*. The time spent in migration and maturation differs. *S. mansoni* and *S. japonicum* begin depositing eggs around 4 to 5 weeks after infection, while egg deposition begins after 2 to 3 months for *S. haematobium*. Adult worms migrate in the blood vessels without eliciting a

local inflammatory reaction. Some of the mature schistosome ova are extruded into the lumen of the intestines, bladder, or ureters. After contact with water they hatch, releasing a miracidium. This free-swimming ciliated stage seeks out the proper intermediate snail vector and burrows into its soft tissues. After 1 to 2 months (depending on the species), the miracidium begins releasing cercariae into the surrounding water. One miracidium produces many cercariae. Thousands of cercariae can be released daily from each infected snail. This arrangement amplifies the number of infective parasites and the risk of infection.

Epidemiology. *S. mansoni* is found in parts of South America (Brazil, Venezuela, and Surinam), some Caribbean islands, Africa, and the Middle East, while infections with *S. japonicum* occur in the Far East, mostly in China and the Philippines. Infections with *S. haematobium* occur in Africa and the Middle East. Of lesser importance are *S. mekongi*, a parasite related to *S. japonicum* that is found along the Mekong River in Indochina, and *S. intercalatum*, a species found in certain areas of West Africa. Worldwide, as many as 200 million persons may be infected with schistosomes, and infection of entire communities is common.

Each species of schistosomes uses a different species of aquatic snails as an intermediate host. Humans are essentially the reservoirs of disease, except in the case of *S. japonicum*, where rodents, ungulates, and other wild mammals can maintain infection. Transmission is via penetration of the dermis by cercariae. Schistosomiasis is associated with activities that involve contact with fresh water (e.g., fishing, washing, irrigating, recreating). Unlike most parasitic diseases this disease has become more widespread as a result of economic improvements (e.g., dams, irrigation schemes).

Pathogenesis. A number of factors govern the disease manifestations of schistosomiasis. These include the duration and intensity of infection, the location of egg deposition, host genetics, concurrent infections, and other still undefined factors.

Both *S. mansoni* and *S. japonicum* adults reside in the venules of the intestine, and the major disease manifestations of these parasites are hepatic. *S. haematobium* adults are found mostly in the venules of the urinary tract and cause lesions primarily of the ureters and bladder. In individuals from endemic areas, initial infection goes unnoticed. In contrast, in visitors to endemic areas, initial infection with schistosomes commonly results in an acute febrile illness (Katayama fever, or acute schistosomiasis), which most likely is a manifestation of the immune response to the developing schistosomes and eggs. Patients develop elevated levels of eosinophils and immune complexes; and they display a marked reaction to schistosome antigens. The exudative acute granulomatous response to schistosome eggs, which contain miracidia is also modulated. The host becomes sensitized to the egg proteins by a T cell-mediated mechanism that induces a larger granuloma. Eggs, which lodge in the different tissues, become to be encapsulated in granulomata.

Periintestinal granulomata are «ejected» through the gut wall into the lumen. Hepatic granulomata cannot be expelled from the liver. The eggs die and become to be fibrosed and calcified. Hepatomegaly is characteristic, as the liver tries to regenerate. The portal pressure increases, and end-stage fibrotic lesions, mainly portal fibrosis (Symmers' fibrosis); esophageal varices and splenomegaly develop (mainly in case of *S. mansoni*, *S. japonicum*, and *S. mekongi* infections). Host genetic factors have been found to influence the development of Symmers' fibrosis.

The passage of eggs across the ureters and bladder (in case of *S. hematobium)* causes injury and hematuria. With time fibrosis and calcification of the walls of the bladder and ureters develops, blocking urine flow and leading to enlargement of the ureters and kidneys. A major factor in the development of disease in humans is the worm burden of the host, which determines the number of eggs produced. The inflammatory and fibrotic response to these eggs accounts for most of the morbidity and mortality associated with schistosomiasis.

In human schistosome infections, protective immunity is thought to develop, because reinfection rates are reduced in previously treated adults despite continuing water contact. In the first few days after infection, the schistosomule is relatively susceptible to immune attack. However, as the schistosomules mature, they become refractory to these immune responses. In addition, schistosomes coat their tegument with host proteins and evade recognition by the host.

Clinical manifestation. When cercariae penetrate the skin, they may provoke a reaction known as schistosome dermatitis. In previously unexposed persons, the initial invasion causes transient itching and occasionally urticaria followed by the development of macules within 24 h and papules after 24 h. Following repeated exposures, the signs and symptoms increase dramatically and occur earlier. Large, pruritic, erythematous papules and (uncommonly) vesicles develop within 24 h. The lesions are most intense 2 to 3 days following exposure and subside after a few days. These lesions represent a delayed hypersensitivity reaction to the invading schistosome.

From 2 to 6 weeks or longer after exposure, the patient may complain of a variety of symptoms, including fever (Katayama fever), chills, headache, hives or angioedema, weakness, weight loss, nonproductive cough, abdominal pain, and diarrhea (acute stage of schistosomiasis). These symptoms gradually diminish but may last as long as 2 to 3 months. Other newly infected individuals may be asymptomatic or have only minimal symptoms. More severe symptoms occur with heavier infections, but light infections may cause severe illness. CNS lesions may develop during acute schistosome infection.. Clinically, acute schistosomiasis is frequently misdiagnosed as typhoid fever; in fact, it can be confused with any prolonged febrile illness.

The most important complication of intestinal schistosome infection is the

development of periportal or Symmers' fibrosis and portal hypertension. This finding is pathognomonic in *S. mansoni*, *S. japonicum*, and *S. mekongi* infections, but it has been studied best in *S. mansoni* infections, where it normally develops after 10 to 15 years of prolonged exposure and infection. The liver may be enlarged, although in many cases it is small, firm, and nodular, and the left lobe is characteristically prominent. Microscopic examination shows finger-sized bands of fibrosis ("pipe-stem" fibrosis) encompassing the large portal tracts. The portal venous tracts are replaced with fibrous tissue; this situation sometimes leads to presinusoidal blockage, portal hypertension, splenomegaly, and esophageal and gastric varices. The intrahepatic pressure is normal. Hepatic function is generally well preserved, and patients commonly present with hematemesis and/or signs and symptoms of splenomegaly. Ascites, hepatic coma, edema, spider angiomas, gynecomastia, and other signs of liver failure occur less frequently than in alcoholic and postnecrotic cirrhosis. Despite repeated episodes of hematemesis, patients may do reasonably well. Mortality among patients with portal fibrosis has not been well studied, but in one group the rate was 8.2% after 3-6 years. Patients with periportal fibrosis may not have schistosome eggs in the feces because of previous treatment and/or attrition of adult worms without subsequent reinfection. Since schistosome infections are practically universal in many populations, the mere presence of schistosome eggs in the feces does not establish the diagnosis of schistosomal periportal fibrosis; other liver diseases may be present.

Glomerulonephritis and pulmonary hypertension develop almost exclusively in patients with periportal fibrosis and portal hypertension. Pulmonary hypertension appears to be due to obliteration of pulmonary arterioles by granulomatous inflammation induced by shunted and embolized schistosome eggs. This condition is most frequently recognized with *S. mansoni* and *S. japonicum* infections but is also seen with *S. haematobium*. Renal complication is manifested clinically as proteinuria and/or renal failure. Schistosome-specific antibodies and antigens have been detected in the glomeruli of infected patients.

Focal dense deposits of eggs of *S. mansoni* in the large intestine (and less commonly of *S. haematobium* and probably of *S. japonicum*) insight an exudative granulomatous response resulting in the formation of inflammatory polyps. Histological study reveals that these polyps consist of masses of eggs, inflammatory cells, and fibrotic tissue. The major clinical presentation is bloody diarrhea, sometimes associated with protein-losing enteropathy and anemia. This type of involvement of the bowel is recognized primarily in Egypt and the Sudan. Granulomatous masses involving the bowel wall may mimic carcinoma of the bowel. With regard to CNS involvement, *S. mansoni* and *S. haematobium* show a predilection for the spinal cord, while the brain is involved more commonly in *S. japonicum* infections.

Patients infected with the three major species of schistosomes and subsequently infected with *Salmonella* may develop a prolonged intermittent febrile illness. In *S. haematobium* infections, prolonged excretion of *Salmonella* in the urine is common. In many cases, treatment of the *Salmonella* infection alone is not effective, and specific antischistosomal chemotherapy is also required. *Salmonella* may be protected from host immune responses by residence in the schistosome gut or by adherence to the surface of the schistosome.

Schistosomiasis caused by *S. intercolati* has a few symptoms and no cases of portal fibrosis have been reported.

Clinical features of schistosomiasis caused by S. hematobium. The signs and symptoms caused by the organism result from involvement of the ureters and bladder. In contrast to the asymptomatic period following initial infection with the intestinal schistosomes, dysuria and hematuria are frequently noted 2 to 3 months after *S. haematobium* infection. These findings may continue throughout the course of active infection. Cystoscopic examination may reveal friable masses extending into the bladder, ulceration, petechiae, and granulomas. These early lesions are reversible by antischistosomal chemotherapy. Eggs shed into the urine are usually easily demonstrable. As the infection progresses and fibrosis increases, disease cause anatomic and/or functional obstruction, hydroureter and hydronephrosis, and masses in the bladder or ureters. When the concentration of calcified eggs in the tissues is high enough, radiographic opacification of the affected areas of the urinary tract becomes evident. Fibrotic lesions that cause hydroureter and hydronephrosis are not reversible by antischistosomal chemotherapy. Renal failure occurs in a small proportion of infected individuals.

Portal fibrosis and clinically significant glomerulonephritis are not complications of this infection, but passage of eggs into the lungs may result in pulmonary hypertension.. Although eggs of *S. haematobium* are frequently detected in the feces in low numbers and are often found in rectal biopsy specimens, intestinal polyposis is uncommon. In Egypt, bladder cancer is the most common cancer and is directly linked to *S. hematobium*.

Diagnosis. Characteristic clinical features, epidemiological datas are very useful for diagnosis. Gross or microscopic hematuria (usually terminal hematuria) is common in endemic populations, and its presence always suggests the diagnosis in exposed individuals. The diagnosis of acute schistosomiasis is suggested by the clinical findings and the presence of eosinophilia, with values sometimes greater than 50%. Leukocytosis, increased levels of immune complexes, and elevated concentrations of IgM, IgG, and IgE are found commonly. The specific diagnosis can be established, even before the shedding of ova, by the detection of antibodies to adult schistosome gut antigens (by appropriate serologic testing) or, after egg excretion (5 to 6 weeks after exposure), by finding of eggs in the stool or a rectal

biopsy sample.

The diagnosis of *S. mansoni* infection is established by identification of ova in the feces or tissues. In light infections with fewer than 50 eggs per gram of feces, ova may not be detected in the stool without the use of techniques that sample large volumes. A 24-hour urine collection may be used if low levels of infection are suspected. Even in light infections, ova can usually be detected in rectal or bladder biopsy specimens and are best identified by squashing a small amount of tissue between two glass slides and viewing the tissue microscopically.

Serologic tests (EIA) may be helpful when no eggs are found (e.g., in cases where the adult worms locate in ectopic sites such as CNS, spinal vessels or orbital vessels). An immunofluorescent antibody test employing sections of adult schistosomes to assess the presence of antibodies to schistosome gut antigens has been extremely useful in identifying recently infected persons or those with acute schistosomiasis.

Old, calcified, dead eggs are commonly retained in the tissues for long periods and do not indicate active infection. CT shows a characteristic pattern of calcified eggs in the liver and intestine. Ultrasonographic or X-ray examinations reveal anatomic alteration of the genitourinary tract, calcification of bladder and ureters, hydronephrosis and hydroureters. Ultrasonograms of the liver show characteristic findings. The fibrotic bands appear as dense echogenic areas surrounding the portal vein and its tributaries. Studies comparing the effectiveness of wedge biopsy of the liver with ultrasonographic examination showed the latter technique to have both specificity and a sensitivity of 100%. Ultrasonography should replace invasive biopsies as the method of choice for the diagnosis of hepatic schistosomiasis.

Treatment. There are at least four drugs available that will treat all forms of schistosomiasis in a single dose without serious side effects. The drug of choice is praziquantel. Other drugs include mertifonate and niridasole for *S. haematobium,* oxamniquine and niridazole for *S. mansoni,* and oltipraz for *S. japonicum.* Most persons with active infections should be treated because even in light infections, there is the risk that complications will arise from ectopic location of the schistosome eggs (e.g., in the spinal cord). The effectiveness of treatment is evaluated by the cessation of egg excretion after 2 to 3 months. Successful treatment is associated with a reduction of organomegaly and of periportal fibrosis and/or inflammation in some patients. These patients tend to be young people with less severe involvement.

Prevention. Simple and effective health-education measures, such as the elimination of indiscriminate urination and defecation, are difficult to implement in endemic areas. The intermediate molluscan host can be eliminated by the use of molluscicides or the destruction of its habitat. Both methods require dedication of resources and personnel that often are not readily available. Mass chemotherapy of populations has been tried; the need for repeated treatments depends on the degree of

reinfection. The methods employed will depend on the nature of the endemic area and the resources available. Cercariae are most infectious immediately after shedding and are no longer viable 48 h after release, so storage of water for 48 h before contact prevents exposure and infection. A recombinant vaccine for *S. mansoni* based on the parasite's glutathione-S-transferase (GST) is currently entering limited clinical trials.

PARAGONIMIASIS

Etyology. More than 30 species of *Paragonimus* have been described, and a number of these infect humans. *P. westermani* is the most common species causing infection in humans. These adult flukes measure up to 11mm by 8 mm and occur in pairs within pulmonary cysts.

Metacercariae excyst in the duodenum and within 1 h pass through the intestinal wall into the peritoneal cavity. After 3 to 6 h they migrate into the abdominal wall and then through the diaphragm into the pleura and lung tissue, where they become encapsulated, usually in pairs or triplets. It takes 65 to 90 days for the flukes to develop fully, although symptoms may begin earlier. Eggs are shed around the worm and, with rupture of the contents of the encapsulated cyst into the bronchioles, are excreted in the sputum or swallowed and excreted in the feces. Adults may live for 20 years.

Epidemiology. *P. westermani* is distributed worldwide in foci, but is particularly prevalent in the coastal regions of the Far East, Africa, and South America. An estimated 1.6 million cases are reported in South Korea alone. Many wild carnivores, including mink, bobcats, foxes, cats, tigers, badgers, dogs, weasels, monkeys and muskrats have been reported and could act as reservoirs of infection

Several species of aquatic snails are potential intermediate hosts, followed by freshwater crustaceans (crayfish, shrimp, and crabs) as second intermediate hosts. Human's infections occur from ingestion of raw or undercooked infected freshwater crayfish, shrimp, and crabs.

Pathogenesis. Disease is caused by the inflammation and fibrosis elicited by the worms in the lungs or in ectopic locations. Manifestations depend on the duration of infection and probably on the intensity of infection. Flukes and eggs initially elicit an acute inflammatory response, mostly consisting of eosinophils, which is followed by the formation of a fibrous capsule. In the lung parenchyma, the cysts rupture into the bronchioles, extruding blood, eggs, and inflammatory exudate. Pleura-based lesions cause eosinophilic empyemas that can be confused clinically with tuberculosis. Lesions in long-standing infections exhibit increased fibrosis and decreased inflammatory responses, and some eventually calcify. Not uncommonly, flukes are found in abnormal locations, including the pleura, abdominal wall, viscera, and brain, where they elicit inflammation and fibrosis. Brain involvement is a particularly serious complication. Bacterial infections may be associated with paragonimiasis.

Clinical manifestations. Acute disease is noted infrequently and may include fever, hepatosplenomegaly, cough, eosinophilia, pleural effusions, pulmonary abnormalities, pneumothorax, and signs and symptoms referable to ectopic locations. The findings in chronic infections often include cough, expectoration of rusty or pigmented sputum, and hemoptysis. Dyspnea, chest pain, fever, and constitutional symptoms are found less frequently. Chest X-ray findings are varied, nondiagnostic, and often confused with those of tuberculosis. Localized or multisegmental infiltrates, usually poorly defined, are most common, but nodular, cystic, cavitary, ring shadow patterns are also found. Other findings include pleural effusions, empyemas, pleural thickening, and calcification of lesions. In contrast to the findings in tuberculosis, apical lesions do not predominate, cavities are smooth and regular, and infiltrates are less well defined. Morbidity and mortality are significant with ectopic lesions (brain and other lesions). Both acute and chronic forms of brain involvement are recognized (the former associated with the sudden onset of neurologic symptoms, usually in the presence of pulmonary disease, and the latter most often associated with seizures and long-term deficits). "Soap bubble" calcifications are a characteristic X-ray pattern in chronic neuroparagonimiasis.

Diagnosis. The diagnosis is established by detection of the characteristic ova in stool or sputum. The golden-brown eggs are unembryonated and measure 80 to 118 um by 48 to 60 um. Concentration techniques may be needed for the detection of eggs in lightly infected patients. Serologic tests are available and may be particularly useful in lightly infected individuals or those with suspected ectopic lesions or in acute disease when eggs may not be detected until 2 to 3 months after exposure.

Treatment. Praziquantel is the treatment of choice at 25 mg/kg three times a day for 2 days. Bithionol is also effective but is more toxic.

CESTODOSES

Cestodes, or tapeworms, are segmented worms. The adults reside in the gastrointestinal tract, but the larvae can be found in almost any organ. Human tapeworm infections can be divided into two major clinical groups. In one group, humans are the definitive hosts, and the adult tapeworms live in the gastrointestinal tract (*Taenia saginata*, *Diphyllobothrium*, *Hymenolepis*). In the other, humans are intermediate hosts, and larval-stage parasites are present in the tissues (echinococcosis, and others). For *Taenia solium*, the human may be either the definitive or the intermediate host.

The ribbon-shaped tapeworm attaches to the intestinal mucosa by means of sucking cups or grooves located on the head (scolex). Behind the scolex is a short, narrow neck from which proglottids (segments) form. As each proglottid matures, it is displaced further back from the neck by the formation of new, less mature segments. The progressively elongating chain of attached proglottids, called the

strobila, may consist of more than 1000 proglottids and may be several meters long. As each proglottid becomes gravid, eggs are released. Since eggs of the different *Taenia* species are morphologically identical, differences in the morphology of the scolex or proglottids provide the only basis for diagnostic identification to the species level. Most human tapeworms require at least one intermediate host for complete larval development. After ingestion by an intermediate host, an egg develops into a larval oncosphere capable of penetrating the intestinal mucosa. The oncosphere migrates to tissues and develops into an encysted form known as a *cysticercus* (single scolex), a *coenurus* (multiple scolices), or a *hydatid* (cyst with daughter cysts, each containing several scolices). Ingestion by the definitive host of tissues containing a cyst enables a scolex to develop into a tapeworm.

TAENIASIS SAGINATA

Etyology. Humans are the only definitive host for the adult stage of beef tapeworm *T. saginata*. This tapeworm, which can reach 3 to 8 m in length, inhabits the upper jejunum and has a scolex with four prominent suckers and 1000 to 2000 proglottids. Each gravid segment has 15 to 30 uterine branches (in contrast to 8 to 12 for *T. solium*). The eggs are indistinguishable from those of *T. solium*; each measures 30 to 40 um and has a thick brown striated shell containing a fully developed embryo.

Eggs deposited on vegetation can live for months to years until they become to be ingested by cattle or other herbivores. The embryo released after ingestion invades the intestinal wall and is carried to striated muscle (predominantly in the hind limbs, diaphragm, and tongue), where it transforms into a cysticercus. When ingested in raw or undercooked beef, this form can infect humans. After the cysticercus is ingested, it takes about 2 months for an adult worm to develop.

Epidemiology. *T. saginata* is globally distributed in all regions where beef are eaten. Infection occurs in all countries but is most prevalent in sub-Saharan African and Middle Eastern countries. Humans are the definitive hosts for this species; ingestion of cysts in raw or undercooked beef is the source of infection.

Pathogenesis. This giant adult tapeworm can cause different kinds of mechanical actions in the human's intestine: slight inflammative changes in the place of attachment; obstructive syndrome up to the development of ileus (especially in the case of intensive invasion). Their movement along the intestine cause neuro-reflecting effect and spastic pain in abdomen. *T. saginata* need in amount quantity of glucose and other simple predigested nutrients which they absorb directly from the host's gut. Such parasitic existence can cause loss of the host's body weight, and hypovitaminoses. This effect usually forced by toxic effect of this helminthes. Allergic effect and immune response usually develop.

Clinical manifestations. Patients become aware of the infection most commonly by noting passage of proglottids in their feces. They may experience perianal discomfort when proglottids are discharged. Discharging of proglottids is

active process, it takes place in the night or sometimes in the daytime, often after drinking or plenty food. Eggs may be passed in feces or laid in the perianal region. Although usually minimal or mild, abdominal pain or discomfort, nausea, diarrhea, change in appetite, weakness, and weight loss can occur with *T. saginata* infection.

Diagnosis. The diagnosis is made by the detection of eggs or proglottids in the stool as soon as about 3 months after infection. Eggs also may be present in the perianal area; thus, if proglottids or eggs are not found in the stool, the perianal region should be examined with use of a cellophane-tape swab (as in pinworm infection). The distinguishing of *T. saginata* from *T. solium* requires examination of mature proglottids or the scolex. Serologic tests are not helpful diagnostically. Eosinophilia and elevated levels of serum IgE may be detected.

Treatment. A single dose of praziquantel (5 to 10 mg/kg) is highly effective for therapy. Niclosamide is also highly effective.

Prevention. The major means of preventing infection is the adequate cooking of beef; exposure to temperatures as low as 56°C for 5 min will destroy cysticerci. Refrigeration or salting for long periods or freezing at 100°C for 9 days also kills cysticerci in beef. General preventive measures include inspection of beef and proper disposal of human feces.

TAENIASIS SOLIUM AND CYSTICERCOSIS

Etyology. The pork tapeworm *T. solium* can cause two distinct forms of infection: intestinal (caused with adult tapeworms) and cysticercosis (caused with larval forms).

Eggs are passed in feces and must be transported to pasture to reach the intermediate host. After the eggs hatches in the host's intestine, the onchosphere (embryo) emerges from the eggs and penetrates a blood vessel. The onchosphere migrates to, and penetrates, striated muscle, where it becomes a cysticercus surrounded by a fibrous capsule derived from the host. Cysticerci may lie dormant for many years. After ingestion by definitive host undercooked meat with these dormant forms scolex release from cysticerci and adult worm began grow. The tapeworm, usually about 3 meters in length, may have as many as 1000 proglottids, each of which produces up to 50,000 eggs. Groups of 3 to 5 proglottids generally are released and excreted into the feces, and the eggs in these proglottids are infective for both humans and animals. Eggs may survive in the environment for several months.

Epidemiology. *T. solium* exists worldwide but is most prevalent in Mexico, Africa, Southeast Asia, eastern Europe, and South America. Cysticercosis occurs in industrialized nations largely as a result of the immigration of infected persons from endemic areas. Humans are the definitive hosts for *T. solium.* Ingestion of cysts in raw or undercooked pork is the source of infection. Humans can also serve as an intermediate host. Autoinfection may occur if an individual with an egg-producing tapeworm ingests fresh eggs derived from his or her own feces or if eggs or

proglottids pass from the intestine into the stomach during vomiting.

Pathogenesis. The adult tapeworm generally resides in the upper jejunum. Its globular scolex attaches by both sucking disks and two rows of hooklets causing damaging of mucous. Slight inflammation in the place of attachment; obstructive syndrome up to the development of ileus may develop. Their movement along the intestine cause neuro-reflecting effect and pain in abdomen. Often only one adult worm is present, but that worm may live for up to 25 years. Such parasitic existence can cause loss of the host's body weight, and hypovitaminoses. This effect usually forced by toxic effect of this helminthes. Allergic effect and immune response usually develop. After ingestion by the intermediate host, eggs embryonate, penetrate the intestinal wall, and are carried to many tissues, with a predilection for striated muscle of the neck, tongue, and trunk. Within 60 to 90 days, the encysted larval stage develops.

Clinical manifestations. Intestinal infections with *T. solium* may be asymptomatic. Epigastric discomfort, nausea, a sensation of hunger, weight loss, hypovitaminoses and diarrhea are infrequent. Patients may note passage of proglottids in the feces. In cysticercosis, the clinical manifestations are entirely different. Since cysticerci can be found anywhere in the body (most commonly in the brain and the skeletal muscle), their location and size determine the clinical presentation. The manifestations of cysticercosis reflect two distinct processes: the local inflammatory response induced by the parasite and the local effect of the space-occupying lesions. Neurologic manifestations constitute the most common presentation. When inflammation surrounds lesions, seizures and focal neurologic deficits are frequent, and communicating and noncommunicating hydrocephalus and meningitis also can be seen. Generalized, focal, or Jacksonian seizures occur in most cases. Signs of increased intracranial pressure, including headache, nausea, vomiting, changes in vision, dizziness, ataxia, and confusion, often are present. Patients with hydrocephalus may develop papilledema and may experience alterations of mental status. Grapelike clusters of proliferating larval membranes characterize the unusual racemose form of cyticercosis. This form typically occurs at the base of the brain or in the subarachnoid space and causes chronic meningitis and arachnoiditis. Communicating or noncommunicating hydrocephalus is common. The clinical presentation of neurocysticercosis therefore depends on the number, form, and location of cysticerci, the extent of cyst-associated inflammatory responses, and the duration of disease.

Diagnosis. The diagnosis of intestinal *T. solium* infection is made by the detection of eggs or proglottids, as described for *T. saginata*. For cysticercosis, definitive diagnosis requires examination of the cysticercus in an involved tissue, but a diagnosis often can be based on clinical presentation in conjunction with compatible results in radiographic studies especially CT and MRI and serologic tests.

For soft tissue involvement, plain films may reveal multiple calcified "puffed-rice" lesions. For cerebral cysticercosis, CT studies demonstrate parenchymal lesions of varying number and size that are either cystic or solid and may exhibit contrast enhancement. Some or many of the lesions seen by CT and MRI may be calcified; thus, multiple punctate calcifications are common findings in neurocysticercosis. Ventricular dilation may be demonstrable, but the CT finding of multiple calcified or noncalcified cystic lesions is strongly suggestive of cerebral cysticercosis. Because CT is more sensitive in identifying calcified lesions and MRI is better at identifying small cystic lesions, both techniques are useful in evaluating neurocysticercosis.

Most patients with cerebral cysticercosis have CSF pleocytosis with a predominance of mononuclear cells. The glucose level is often decreased and the protein level elevated in CSF. Serologic tests of CSF and sera are helpful in establishing the diagnosis, but many of them have been complicated by cross-reactivity with other tapeworm, filarial, and echinococcal infections. An immunoblotting technique has improved specificity to 98%, with sensitivities reaching 91%. Even with this technique, however, patients with single intracranial neurocysticercotic lesions may be seronegative.

Treatment. Intestinal *T. solium* infection is treated with praziquantel, as specified for *T. saginata* infection. However, praziquantel can evoke an inflammatory response in the CNS if concomitant cryptic cysticercosis is present. The management of cysticercosis can involve chemotherapy, surgery, and supportive medical treatment. Asymptomatic patients with calcified soft tissue or neural lesions generally require no treatment. For symptomatic patients with neurocysticercosis, both praziquantel (50 mg/kg per day in three doses for 15 days) and albendazole (15 mg/kg per day in three doses for 8 to 28 days) are effective. Because both agents provoke inflammatory responses around dying cysticerci, patients receiving either drug should be hospitalized and given high doses of glucocorticoids during treatment. Radiographic imaging can monitor the efficacy of therapy. The size of active lesions should decrease within 3 to 6 months. For ocular and spinal lesions, drug-induced inflammation may cause irreversible damage; thus, these lesions as well as those within the ventricles are best managed by surgical resection. Ventricular obstruction may require ventriculostomy or ventriculoperitoneal shunting. Not all neurologic deficits resolve after therapy, and some patients may require continued anticonvulsive treatment.

Prevention. The major means of preventing infection is the adequate cooking of pork; exposure to temperatures as low as 56°C for 5 min will destroy cysticerci. Refrigeration or salting for long periods or freezing at 100°C for 9 days also kills cysticerci in pork. General preventive measures include inspection of pork and proper disposal of human feces. The prevention of cysticercosis involves minimizing the opportunities for ingestion of fecally derived eggs by means of good personal

hygiene, effective fecal disposal, and treatment and prevention of human intestinal infections.

HYMENOLEPIASIS

Etiology. *Hymenolepis nana*, the dwarf tapeworm, is the only cestode of humans that does not require an intermediate host. Both the larval and adult phases take place in the human. The adult, the smallest tapeworm parasitizing humans, is about 2 cm long and dwells in the proximal ileum. Proglottids, which are quite small and are rarely seen in the stool, release spherical eggs 30 to 44 um in diameter, each of which contains an oncosphere with six hooklets. The eggs are immediately infective and are unable to survive in the external environment for more than 10 days. *H. nana* also can be acquired by the ingestion of infected insects (especially larval meal-worms and larval fleas).

When the egg are ingested by a new host, the oncosphere is freed and penetrates the intestinal villi, becoming a cysticercoid larva. Larvae migrate back into the intestinal lumen, attach to the mucosa, and mature over 10 to 12 days into adult worms. Eggs also may hatch before passing into the stool, causing internal autoinfection with increasing numbers of intestinal worms. Although the life span of adult *H. nana* is only about 4 to 10 weeks, the autoinfection cycle perpetuates the infection.

Epidemiology. *H. nana* is endemic in both temperate and tropical regions of the world. Infection is spread by fecal/oral contamination and is common among institutionalized children.

Clinical manifestations. *H. nana* infection, even with many intestinal worms, is usually asymptomatic. When infection is intense, anorexia, abdominal pain, and diarrhea develop.

Diagnosis. Infection is diagnosed by the finding of eggs in the stool.

Treatment. Praziquantel (25 mg/kg once) is the treatment of choice, since it acts against both the adult worms and the cysticercoids in the intestinal villi.

Prevention. Good personal hygiene and improved sanitation can eradicate the disease. Epidemics have been controlled by mass chemotherapy coupled with improved hygiene.

DIPHYLLOBOTHRIASIS

Etiology. The adult worm *Diphyllobothrium latum*, the longest tapeworm (up to 25 m), attaches to the ileal and occasionally to the jejunal mucosa by its suckers, which are located on its elongated scolex. The adult worm has 3000 to 4000 proglottids, which release approximately 1 million eggs daily into the feces. If an egg reaches water, it hatches and releases a free-swimming embryo that can be eaten by small freshwater crustaceans (*Cyclops* or *Diaptomus* species). After a fish swallows an infected crustacean containing a developed procercoid, the larva migrates into the fish's flesh and grows into a plerocercoid. After ingesting infected raw fish, within 3

to 5 weeks, the tapeworm matures into an adult in the human intestine.

Epidemiology. *D. latum* and other *Diphyllobothrium* species are found in the lakes, rivers, and deltas of the northern hemisphere, Central Africa, and Chile. Humans acquire the infection by ingesting infected raw fish.

Clinical manifestations. Most *D. latum* infections are asymptomatic, although manifestations may include transient abdominal discomfort, diarrhea, vomiting, weakness, and weight loss. Occasionally, infection can cause acute abdominal pain and intestinal obstruction; in rare cases cholangitis or cholecystitis may be produced by migrating proglottids. Because the tapeworm absorbs large quantities of vitamin B_{12} and interferes with ileal B_{12} absorption, vitamin B_{12} deficiency can develop. Up to 2% of infected patients, especially the elderly have megaloblastic anemia resembling pernicious anemia and may exhibit neurologic sequel of B_{12} deficiency.

Diagnosis. The diagnosis is made readily by the detection of the proglottids or characteristic eggs in the stool. The eggs possess a single shell with an operculum at one end and a knob at the other. Mild to moderate eosinophilia and sometimes the signs of pernicious anemia may be detected.

Treatment. Praziquantel (5 to 10 mg/kg once) is highly effective. Parenteral vitamin B_{12} should be given if B_{12} deficiency is manifested.

Prevention. Infection can be prevented by heating fish to 54°C for 5 min or by freezing it ã18°C for 24 h. Placing fish in brine with a high salt concentration for long periods kills the eggs.

ECHINOCOCCOSIS

Etyology. Echinococcosis is an infection of humans caused by the larval stage of *Echinococcus granulosus*, *Echinococcus multilocularis*, or *Echinococcus vogeli*. *E. granulosus*, which produces unilocular cystic lesions. The small (5 mm long) adult *E. granulosus* worm, which lives for 5 to 20 months in the jejunum of dogs, has only three proglottids one immature, one mature, and one gravid. The gravid segment splits to release eggs that are morphologically indistinguishable from *Taenia* eggs and are extremely hardy.

After humans ingest the eggs, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to various organs, most commonly the liver and lungs. Larvae develop into fluid-filled unilocular hydatid cysts that consist of an external membrane and an inner germinal layer, surrounded in turn by thick cuticular and fibrous layer. Daughter cysts develop from the inner aspect of the germinal layer, as do germinating cystic structures called brood capsules. New larvae, called scolices, develop in large numbers within the brood capsule. Numerous brood capsules and protoscoleces bud off internally from the germinal layer; sediment in the cyst fluid is known as «hydatid sand». The cysts expand slowly over a period of years. The life cycle of *E. multilocularis* is similar. *E. multilocularis* cysts lack a thick cyst wall and external as well as internal budding

occurs, producing a multilobed cyst. Portion of the cyst may form metastatic secondary cysts in other locations. When a dog or rodents ingest beef or lamb containing cysts, the life cycle is completed.

Epidemiology. This tapeworm species is found in Australia, Argentina, Chile, Africa, Eastern Europe, the Middle East, New Zealand, and the Mediterranean region, particularly Lebanon and Greece. *E. multilocularis*, which causes multilocular alveolar lesions that are locally invasive, is found in sub-Arctic or Arctic regions, including Canada, the United States, and northern Europe and Asia.

The definitive hosts are dogs that pass eggs in their feces. Cysts develop in the intermediate hosts(sheep, cattle, humans, goats, camels, and horses for *E. granulosus* and mice and other rodents for *E. multilocularis)* after the ingestion of eggs. A domestic cycle of transmission of *E. granulosus* between cattle or sheep and domestic dogs occurs in most areas of the world where cattle and sheep are reared. A feral cycle of transmission involving wild canids and wild herbivores occurs as well. For *E. multilocularis* definitive hosts are predominantly foxes and small rodents. While eating contaminated meat infects dogs and definitive hosts, humans like the usual intermediate hosts, become infected following ingestion of eggs passed in dogs feces.

Pathogenesis. In humans *E. granulosus* hydatid *cysts* take several years to develop sufficiently to cause symptoms. The main pathogenic feature of *Ecchinococcosis* is mechanical action. Prolonged compression with cysts on surrounded tissues can lead to its necrosis and failure of infected organs. This effect depends on size of cysts and on their location. The compression of a bile duct or leakage of cyst fluid into the biliary tree may cause biliary obstruction, which can result in jaundice. The location of hydatid cyst in lungs can cause bronchial obstruction. Enlarged cysts can induce chronic inflammation of surrounded tissues, leading to their fibrosis. Secondary bacterial infection nay produce abscesses in cysts. Important role in pathogenesis of the disease belongs to allergic action. Rupture of or episodic leakage from a hydatid cyst may produce severe allergic symptoms up to fatal anaphylaxis.

Clinical manifestations. Slowly enlarging echinococcal cysts generally remain asymptomatic from 5 to 20 years. In this period cysts may be discovered incidentally on a routine X-ray or ultrasound study. Patients with hepatic echinococcosis who are symptomatic most often present with abdominal pain or a palpable mass in the right upper quadrant. The part of patients may mimic recurrent cholelithiasis with jaundice. Periodically patients produce fever, pruritus, urticaria, eosinophilia, associated with spontaneous rupture of hydatid cysts. Pulmonary hydatid cysts may rupture into the bronchial tree or peritoneal cavity and produce cough, chest pain, or hemoptysis. By spreading the multitudinous infectious scolices, the rupture of hydatid cysts leads to multifocal dissemination of new cyst-forming elements. Cysts may involve any organ. Other presentations are due to the involvement of bone (invasion of the

medullary cavity with slow bone erosion producing pathologic fractures), the CNS (space-occupying lesions), and the heart (conduction defects, pericarditis). Cysts in bones, the CNS, heart, and kidney carry a serious prognosis. Up to 10% of all diagnosed cases are fatal. Multilocular hydatids do not grow well in humans, may not contain protoscolices, and may become calcified early. The cysts of *E. multilocularis* characteristically present as a slowly growing hepatic tumor, with progressive destruction of the liver and extension into vital structures. Patients commonly complain of upper quadrant and epigastric pain, and obstructive jaundice may be apparent. A minority of patients experiences the metastasis of lesions to the lung and brain.

Diagnosis. Radiographic and related imaging studies are important in detecting and evaluating of echinococcal cysts. Plain films will define pulmonary cysts usually as rounded irregular masses of uniform density but may miss other cysts in other organs unless there is cyst wall calcification (as occurs in the liver).

MRI, CT and ultrasound reveal well-defined cysts with thick or thin walls. When older cysts contain a layer of hydatid sand that is rich in accumulated scolices, these imaging methods may detect this fluid layer of different density. However, the most pathognomonic finding, if demonstrable, is that of daughter cysts within the larger cyst. This finding, like eggshell or mural calcification on CT, is indicative of *E. granulosus* infection and helps to distinguish the cyst from carcinomas, bacterial or amebic liver abscesses, or hemangiomas. CT of alveolar hydatid cysts reveals indistinct solid masses with central necrosis and plaquelike calcifications.

A specific diagnosis can be made by the examination of aspirated fluids for scoliceal hooklets or biopsies of liver or lungs, sputum, or urine. But diagnostic aspiration is not conventionally recommended because of the risk of fluid leakage resulting in either dissemination of infection or anaphylactic reactions. Pretreatment with albendazole (a 1-month course) is believed to minimize biopsy complications.

Serodiagnostic assays can be useful, although a negative test does not exclude the diagnosis of echinococcosis. While cysts in the liver are more likely to elicit positive antibody responses than those in the lungs. Detection of antibody to specific echinococcal antigens by immunoblotting has the highest degree of specificity.

Treatment. Therapy for echinococcosis is based on considerations of the size, location, and manifestations of cysts and the overall health of the patient. Surgical removal of *E. granulosus* cysts or tissue containing *E. multilocularis* cysts may follow successful treatment. Risks at surgery from leakage of fluid include anaphylaxis and dissemination of infectious scolices. Albendazole, which has antiechinococcal activity, is the drug of choice. As medical therapy, albendazole, given at a dose of 400 mg twice a day for 12 weeks, is most efficacious against hepatic and pulmonary cysts, although multiple courses may be necessary. Response to treatment is best assessed by repeated evaluation of cysts by CT or MRI, with

particular attention to cyst size and consistency.

Prevention. In endemic areas, echinococcosis can be prevented by administering praziquantel to infected dogs and by denying dog's access to butchering sites and to the offal of infected animals. Limitation of the number of stray dogs is helpful in reducing the prevalence of infection among humans.

Helminthiases treatment

Etyology	Treatment of choice	Alternative regimen
Intestinal nematodoses		
Trchinosis	Mebendazole 0,1 twice a day for 3 days (for treatment of enteric stage)	
Ascariasis	Mebendazole 0,1 twice a day for 3 days; Decaris (Laevamizole) 150 mg, single doze; Pyrantel pamoate 1 tabl., single doze	Albendazole 400 mg, single doze; Ivermectin 12 μg/kg, single doze
Hookworm	Mebendazole 0,1 twice a day for 3 days; Pyrantel pamoate 1 tabl., single doze	
Strongyloidiasis	Mebendazole 25 mg/kg twice a day for 3-3 days, in disseminated cases - for 5-7 days; repeat after 2-3 weeks	Albendazole 400 mg twice a day for 3 days; Ivermectin 200 μg/kg/day for 1-2 days
Trichuriasis	Mebendazole 0,1 twice a day, for 3 days; (repeat after 2-3 weeks). Pyrantel pamoate 1 tabl. per day, for 3-5 days;	Albendazole 400 mg single doze; (in severe cases for 3 days, repeating courses are possible); Ivermectin 12 μg/kg single doze;
Enterobiasis	Mebendazole 0,1 single doze, repeat after 2 weeks; Pyrantel pamoate 1 tabl. single doze; Decaris 150 mg/day for 3-5 days	Albendazole 400 mg single doze; repeat after 2 weeks
Tissue nematodoses		
Lymphatic Filariasis	Diethylcarbamazine Day 1: 50 mg PO; Day 2: 50 mg tid; Day 3: 100 mg tid; Days 4-21: 6 mg/kg/d in 3 doses; repeated courses are necessary	Ivermectin 150 μg/kg, single doze

Etyology	Treatment of choice	Alternative regimen
Onchocerciasis	Ivermectin 150 μg/kg once, repeated every 3-12 months	
Loiasis	Diethylcarbamazine Day 1: 50 mg PO; Day 2: 50 mg tid; Day 3: 100 mg tid; Days 4-21: 6 mg/kg/d in 3 doses	
Trematodoses		
Opistorchiasis	Praziquantel 75 mg/kg/d in 3 doses for 1 day	
Fascioliasis	Bithionol 30-50 mg/kg on alternate days for 10-15 doses	
Schistosomiasis mansoni	Praziquantel 40 mg/kg/d in 2 doses for 1 day	Oxamniquine 15 mg/kg once; 30 mg/kg once in East Africa; 30 mg/kg once daily for 2 days in Egypt and South Africa
Schistosomiasis haematobium	Praziquantel 40 mg/kg/d in 2 doses for 1 day	
Schistosomiasis japonicum and mekongi	Praziquantel 60 mg/kg/d in 3 doses for 1 day	
Paragonimiasis	Praziquantel 75 mg/kg/d in 3 doses for 2 days	Bithionol 30-50 mg/kg on alternate days for 10-15 doses
Cestodoses		
Taeniasis	Praziquantel 10-20 mg/kg once	
Cysticercosis	praziquantel (50 mg/kg per day in three doses for 15 days)	Albendazole (15 mg/kg per day in three doses for 8 to 28 days)
Echinococcosis	Surgical excision if possible and albendazole 400 mg bid for 20 days, repeated as necessary	
Hymenolepiasis	Praziquantel 25 mg/kg once	
Diphyllobothriasis	Praziquantel 10-20 mg/kg once	

ECTOPARASITE INFESTATIONS

Ectoparasites are arthropods or helminths that infest the skin of other animals from which they derive sustenance. They may penetrate beneath the surface of the host or attach superficially by their mouthparts. These organisms damage their hosts by inflicting direct injury, by eliciting a hypersensitivity reaction, or by inoculating toxins or pathogens. The main medically important ectoparasites are arachnids

(including mites and ticks), insects (including lice, fleas, and flies), pentastomes (tongue worms), and leeches.

SCABIES

The human itch mite, *Sarcoptes scabiei,* which infests some 300 million persons each year, is one of the most common causes of itching dermatoses throughout the world. Gravid female mites measuring 0.3 to 0.4 mm in length burrow superficially beneath the stratum corneum for a month, depositing two or three eggs a day. Nymphs that hatch from these eggs mature in about 2 weeks through a series of molts and then emerge as adults to the surface of the skin, where they mate and subsequently reinvade the skin of the same or another host. Transfer of newly fertilized female mites from person to person occurs by intimate personal contact and is facilitated by crowding, uncleanliness, and sexual promiscuity. Medical practitioners are at particular risk of infestation. Transmission via sharing of contaminated bedding or clothing is infrequent because these mites cannot survive much more than a day without host contact. Outbreaks occur in nursing homes, mental institutions, and hospitals.

The itching and rash associated with scabies derive from a sensitization reaction directed against the excreta that the mite deposits in its burrow. For this reason, an initial infestation remains asymptomatic for 4 to 6 weeks, and a reinfestation produces a hypersensitivity reaction without delay. Scratching generally destroys the burrowing mite, but symptoms remain even in its absence. Burrows become surrounded by infiltrates of eosinophils, lymphocytes, and histiocytes, and a generalized hypersensitivity rash later develops in remote sites. By destroying these pathogens, immunity and associated scratching limit most infestations to fewer than 15 mites per person. Hyperinfestation with thousands or millions of mites, a condition known as *crusted* (or *Norwegian) scabies,* may result from glucocorticoid use, immunodeficiency diseases (including AIDS), and neurologic and psychiatric illnesses that interfere with itching and scratching.

Patients with scabies report intense itching that worsens at night and after a hot shower. Typical burrows may be difficult to find because they are few in number and may be obscured by excoriations. Burrows appear as dark wavy lines in the epidermis that measure 3 to 15 mm and end in a small pearly bleb that contains the female mite. Such lesions generally develop on the volar wrists, between the fingers, on the elbows, and on the penis. Small papules and vesicles, often accompanied by eczematous plaques, pustules, or nodules, are symmetrically distributed in these sites and in skin folds under the breasts and around the navel, axillae, belt line, buttocks, upper thighs, and scrotum. Except in infants, the face, scalp, neck, palms, and soles are spared. Burrows and other typical lesions may be sparse in persons who wash frequently, and topical glucocorticoid treatment and bacterial superinfection may alter the appearance of the rash. Superinfection with nephritogenic strains of

streptococci has led to acute glomerulonephritis. Crusted scabies resembles psoriasis in its typical widespread erythema, thick keratotic crusts, scaling, and dystrophic nails. Characteristic burrows are not seen in crusted scabies, and patients usually do not itch, although their infestations are highly contagious and have been responsible for outbreaks of classic scabies in hospitals. Bacteremia occurs frequently in HIV-infected patients with crusted scabies and prominent fissures. Persons with massive infestations occasionally present with diffuse pruritus and generalized papules or with minimal or no cutaneous signs.

A diagnosis of scabies should be considered in patients with pruritus and symmetric polymorphic skin lesions in characteristic locations, particularly if there is a history of household contact with a case. Burrows should be sought and unroofed with a sterile needle or scalpel blade, and the scrapings should be examined microscopically for the mite, its eggs, and its fecal pellets. A drop of mineral oil facilitates removal of the sample. Biopsies or scrapings of papulovesicular lesions also may be diagnostic. In the absence of identifiable mites or mite products, the diagnosis is based on clinical presentation and history. The possibility of other sexually transmitted diseases should be excluded in adults with scabies.

For the treatment of scabies, 5% permethrin cream is less toxic than the once commonly used 1% lindane preparations and is effective against lindane-tolerant infestations. Both scabicides are applied thinly but thoroughly behind the ears and from the neck down after bathing and are removed 8 h later with soap and water. Lindane is absorbed through the skin, and its overuse has led to seizures and aplastic anemia. It should not be applied to pregnant women or infants. Alternatives include topical crotamiton cream, benzyl benzoate, and sulfur ointments. Successful treatment of crusted scabies requires the application first of a keratolytic agent such as 6% salicylic acid (to improve the penetration of scabicides) and then of scabicides to the scalp, face, and ears (with care to avoid the eyes). Repeated treatments or the sequential use of several agents may be necessary. A single oral dose of ivermectin (200 ug/kg) effectively treats scabies in otherwise healthy persons. Patients with crusted scabies may require two or more doses of ivermectin. Although effectively treated scabies infestations become noninfectious within a day, itching and rash due to hypersensitivity frequently persist for weeks or months. Unnecessary retreatment of the affected patients may provoke contact dermatitis. Antihistamines, salicylates, and calamine lotion relieve itching during treatment, and topical glucocorticoids are useful for the pruritus that lingers after effective treatment. An oral antibiotic may be necessary for bacterial superinfections that fail to resolve with antiscabietic therapy. To prevent reinfestations, bedding and clothing should be washed in hot water, and close contacts, even if asymptomatic, should be treated simultaneously.

SARCOPTIC MANGE (ANIMAL SABIES)

Persons who have close contact with dogs may become transiently infested by

the mites responsible for zoonotic scabies; such infestation less often follows contact with cats and horses. Zoonotic mites are unable to propagate on the human host or to produce their elongate burrows, and the characteristic pruritic papulovesicular rash is self-limited.

CHIGGER AND OTHER MITE INFESTATIONS

Chiggers are the larvae of trombiculid (harvest) mites that normally feed on mice in grassy or brush-covered sites in the tropics, subtropics, and (less frequently) in temperate areas during warm months. They wait for hosts on low vegetation and attach themselves to passing animals or to people. The larva then pierces the skin of its host and deposits a tubelike structure in the dermis through which it imbibes lymph and tissue juices. This highly antigenic "stylostome" serves as the focus of an exceptionally pruritic papule that may be 2 cm in diameter and that develops within hours of attachment in persons previously sensitized to mite antigen. Scratching invariably destroys the body of a mite attached to a person. These lesions generally vesiculate and develop a hemorrhagic base. Itching and burning last for weeks. The rash is most common on the ankles or near tight-fitting clothes that obstruct the mites' movements. Repellents are useful for preventing chigger bites. Certain mesostigmatid mites that infest the nests of mice or birds feed on human beings when their usual hosts have been displaced. For example, intense episodes of itching dermatitis in humans may follow the removal of trash from a human residence or the departure of pigeons that have been nesting on a window air-conditioner. Other mites that infest grain, straw, cheese, or other animal products occasionally produce similar episodes. Mouse mites are the vectors of rickettsialpox in cities of the northeastern United States. Although sanitary measures effectively prevent rickettsialpox, removal of accumulated refuse may result in a transient period of elevated risk. Diagnosis of mite-induced dermatitides (including those caused by chiggers) relies heavily on a history of exposure to the source of the mite, since the tiny mite may escape notice or may already have fallen off or been scratched off the lesions. Antihistamines or topical steroids effectively reduce mite-induced pruritus. Species of *Demodex,* the follicle mite, live in hair follicles and sebaceous glands of the face and ears. The worm-like mites measure up to 0.4 mm in length and, if carefully sought, can be found on almost all persons. They appear not to cause disease, although their density is high in persons with rosacea. House dust mites of the genus *Dermatophagoides* infest houses throughout the world, living on furniture and rugs and feeding on shed human dander. Exposure to their allergens causes asthma, rhinitis, conjunctivitis, and eczema in persons with house dust allergies. Management includes immunotherapy with mite extracts and environmental interventions such as frequent vacuuming and removal of rugs from bedrooms to reduce mite density.

TICK INFESTATIONS AND PARALYSIS

Ticks attach and feed painlessly; blood is their only food. Their secretions,

however, produce local reactions, a febrile illness, or paralysis. Local reactions to tick bites vary from small pruritic papules to chronic nodules, or "tick granulomas," that reach several centimeters in diameter and may require surgical excision. Tick-induced fever, associated with headache, nausea, and malaise, usually resolves within 24 to 36 h after the tick is removed. Tick paralysis is an ascending flaccid paralysis believed to be caused by a toxin in tick saliva that causes neuromuscular block and decreased nerve conduction. Throughout the world, this rare complication has followed the bites of more than 40 kinds of ticks. Children, especially girls with long hair, are most often affected. Weakness begins in the lower extremities 5 to 6 days after the tick's attachment and ascends symmetrically over several days to result in complete paralysis of the extremities and cranial nerves. Deep tendon reflexes are diminished or lacking altogether, but sensory examination and findings on lumbar puncture are typically normal. Removal of the tick results in improvement within a few hours and usually in complete recovery after several days. Failure to remove the tick may lead to death from aspiration or respiratory paralysis. Diagnosis depends on finding the tick, which often is hidden beneath hair. An antiserum to the saliva of *Ixodes holocyclus*, the usual cause of tick paralysis in Australia, effectively reverses paralysis caused by these ticks. Ticks should be removed by firm traction with a forceps placed near their point of attachment. The site of attachment should be disinfected (e.g., with tincture of iodine). Removal of ticks during the first 48 h of attachment prevents transmission of the agents of Lyme disease and babesiosis. Gentle handling to avoid rupture of ticks and use of gloves may avert accidental contamination with tick fluids containing pathogens. Protective measures against ticks include avoidance of brushy vegetation, use of protective clothing sprayed with 0.5% permethrin, and application of a repellent containing N,N-diethyl-m-toluamide (DEET). The cuffs of trousers should be tucked inside the socks.

FLEA INFESTATIONS AND TUNGIASIS

Fleas are wingless insects 2 to 4 mm long that feed on the blood of human beings and other warm-bodied animals. Common human-biting fleas include the dog and cat fleas *(Ctenocephalides* species) and the rat flea *(Xenopsylla cheopis),* which inhabit the nests and resting sites of their hosts. Larval fleas feed on pellets of dried host blood that the adult fleas eject from their rectums while feeding. The high-jumping adults attack human beings or other available warm-bodied animals when the usual host abandons or is driven from its nest. The human flea *(Pulex irritans)* infests human bedding and furniture but mainly in relatively humid buildings that lack central heating. Sensitized persons develop erythematous pruritic papules, urticaria, and occasionally vesicles and bacterial superinfection at the site of the bite. Treatment consists of antihistamines and antipruritics. Fleas transmit plague, murine typhus, the rat and dog tapeworms, and possibly *Bartonella henselae.* Flea infestations are eliminated by frequent cleaning of the nesting sites and bedding of

the host or judicious dusting or spraying of insecticides such as pyrethrin, DDT, or malathion. Human infestations with *Tunga penetrans* (the chigoe flea, sand flea, or jigger) occur in tropical regions of Africa and the Americas. Adults live in sandy soil and burrow under the skin between toes, under nails, or on the soles of bare feet. The fleas engorge on blood and grow from pinpoint to pea size over a 2-week period. The lesions resemble a white pustule with a central black depression and may be pruritic or painful. Occasional complications include tetanus, bacterial infections, and autoamputation of toes. Tungiasis is treated by removal of the intact flea with a sterile needle or scalpel.

MYIASIS

Myiasis refers to infestations by maggots, mainly due to the larvae of metallic-colored screw-worm flies or botflies. Maggots invade living or necrotic tissue or body cavities and produce different clinical syndromes depending on the species of fly.

In forested parts of Central and South America, larvae of *Dermatobia hominis* (the human botfly) produce boil-like subcutaneous nodules 2 to 3 cm in diameter (furuncular myiasis). The adult female captures a mosquito or other bloodsucking insect and deposits her eggs beneath its abdomen. When the carrier insect attacks a human or bovine host several days later, the warmth and moisture of the host's surface stimulate the larvae to hatch and penetrate the skin. After 6 to 12 weeks, the larvae mature and drop to the ground, where they pupate. The African tumbu fly, *Cordylobia anthropophaga,* produces similar lesions. Dozens of eggs are deposited on sand or drying laundry that is contaminated with urine or sweat. Larvae hatch on contact with the body, penetrate the skin, and produce boils from which they emerge 8 or 9 days later. A diagnosis of furuncular myiasis is suggested by uncomfortable lesions with a central breathing pore that emits bubbles when submerged in water. Tumbu fly larvae can be removed by manual expression after the air pore is coated with petroleum to suffocate the larvae and induce them to emerge. *Dermatobia* larvae often require surgical excision.

Maggots of the horse botfly, *Gasterophilus intestinalis,* do not mature after penetrating human skin but migrate for weeks in the epidermis (creeping dermal myiasis). The resulting pruritic and serpiginous eruption resembles cutaneous larva migrans caused by *Ancylostoma braziliense.* Horseback riders become infested when eggs deposited on the flank of the horse hatch against their bare legs. The black spines of the larvae can be identified after mineral oil is smeared over the lesion. Larva are removed with a needle. The larvae of the cattle botfly *(Hypoderma* species) invade more deeply and produce boil-like swellings.

Certain flies are attracted to blood and pus, and their newly hatched larvae enter wounds or diseased skin. Larvae of species such as *Phaenicia sericata,* the green-bottle fly, remain superficial and confined to necrotic tissue and were used in

the past to debride purulent wounds. Other species, including the screw-worms *(Chrysomyia* bezziana in Asia and Africa and *Cochliomyia hominivorax* in Latin America) and the flesh fly (*Wohlfahrtia vigil* in northern North America), invade more deeply into viable tissue and produce large suppurating lesions. Larvae that infest wounds also may infest body cavities such as the mouth, nose, ears, sinuses, anus, vagina, and lower urinary tract. The consequences range from harmless colonization to destruction of the nose, meningitis, and deafness. Treatment involves removal of maggots and debridement of tissue.

The maggots responsible for furuncular and wound myiasis also may cause ophthalmomyiasis. Sequelae include nodules in the eyelid, retinal detachment, and destruction of the globe. In addition, the adult sheep botfly, *Oestrus ovis*, may deposit larvae in the eyes of persons tending sheep and goats, and the larvae may produce a conjunctival infestation and acute conjunctivitis. True intestinal myiasis occurs when eggs or larvae of the drone fly (*Eristalis tenax*) are ingested with contaminated food, mature in the gut, and cause enteritis. Most instances in which maggots are found in human feces are the result of larviposition by flesh flies on recently passed stools.

PEDICULOSIS (LOUSE INFESTATIONS)

All three species of human louse feed at least once a day on human blood. *Pediculus humanus* var. *capitis* infests the head, P. *humanus* var. *corporis* the clothing, and *Pthirus pubis* mainly the hair of the pubis. Females cement their eggs (nits) firmly to hair or clothing. The saliva of lice produces an intensely irritating maculopapular or urticarial rash in sensitized persons. Head lice are transmitted directly from person to person and occasionally by shared headgear and grooming implements. The prevalence is highest among school-aged girls who wear long hair; black children are less frequently infested than other children. Excoriations of pruritic lesions on the scalp, neck, and shoulders lead to oozing, crusting, matting of hair, bacterial infections, and regional lymphadenopathy. Body lice remain in clothing except when feeding and cannot survive more than a few hours away from the human host. It follows, therefore, that P. *humanus* var. *corporis* mainly infests disaster victims or indigent persons who do not change their clothes. Transmission by direct contact or by sharing of clothing and beds is enhanced under crowded conditions. The fact that the body louse leaves febrile persons or corpses as they become cold facilitates the transmission of typhus, louse-borne relapsing fever, and trench fever. Pruritic lesions are particularly common around the neckline. Chronic infestations result in the postinflammatory hyperpigmentation and thickening of skin known as *vagabonds' disease.* The cosmopolitan crab or pubic louse is transmitted mainly by sexual contact but can infest eyelashes, axillary hair, and hair in other sites as well as pubic hair. Intensely pruritic lesions and 2- to 3-mm blue macules (maculae ceruleae) develop at the site of bites. Blepharitis commonly accompanies infestations of the eyelashes.

A suspected diagnosis of pediculosis is confirmed by the finding of nits or adult lice on hairs or in clothing. The preferred treatment is 1% permethrin creme rinse, which kills both lice and eggs and is available without prescription. An alternative, 0.5% malathion, requires a prescription and may not be as effective. Other agents, such as the more toxic 1% lindane and pyrethrins with piperonyl butoxide, are not ovicidal and require a second application 1 week after the first to kill hatching nymphs. Dead or hatched nits, which remain attached to hair sheaths, may falsely suggest an active infection. Lindane-resistant head lice have been reported. After louse infestations have been treated with insecticide, the hair should be combed with a fine-toothed nit comb to remove nits. Combs and brushes should be disinfected in hot water at 65°C for 5 min or soaked in insecticide for 1 h. Body lice can be eliminated by bathing and application of topical pediculicides from head to foot. Clothes and bedding are deloused by heat sterilization in a dryer at 65°C for 30 min or by fumigation. Infestations with pubic lice are treated with topical pediculicides except for eyelid infestations (phthiriasis palpebrum), which respond to a coating of petroleum applied for 3 to 4 days or 1% yellow oxide of mercury ointment applied four times daily for 2 weeks.

PENTASTOMIASIS

Pentastomids, or tongue worms, are parasites with characteristics of both helminths and arthropods and are classified in a separate phylum. The wormlike adults inhabit the respiratory passages of reptiles and carnivorous mammals. Human infestation with *Linguatula serrata* is common in the Middle East and occurs in the Sudan following ingestion of encysted larval stages in raw liver or lymph nodes of sheep and goats, the intermediate hosts. The larvae migrate to the nasopharynx and produce an acute self-limiting syndrome known as halzoun (Marrara in the Sudan), which is characterized by pain and itching of the throat and ears, coughing, hoarseness, dysphagia, and dyspnea. Severe edema may cause obstruction and necessitate tracheostomy, and ocular invasion has been described. Diagnostic larvae measuring 5 to 10 mm in length are found in the copious nasal discharge or vomitus. Human beings become infected with *Armillifer armillatus* by ingesting eggs in contaminated food or drink or after handling the definitive host, the African python. Larvae encyst in various organs but rarely cause symptoms unless they compress vital structures or perforate an organ during migration. Cysts occasionally require surgical removal as they enlarge during molting, but they are usually encountered as an incidental finding at autopsy. There are reports of the cutaneous larva migrans syndrome due to other pentastomes *(Reighardia* and *Sebekia* species) in Southeast Asia and Central America.

LEECH INFESTATIONS

Medically important leeches are annelid worms that attach to their hosts with chitinous cutting jaws and draw blood with muscular suckers. The medicinal leech,

Hirudo medicinalis, is still used occasionally to reduce venous congestion in surgical flaps or replanted body parts. This practice has been complicated by wound infections, myonecrosis, and sepsis due to *Aeromonas hydrophila,* which colonizes the gullets of commercially available leeches. Ubiquitous aquatic leeches that parasitize fish, frogs, and turtles readily attach to the skin of human beings and avidly suck blood. More notorious are the land leeches *(Haemadipsa)* that live in moist vegetation of tropical rain forests. Attachment is usually painless. Hirudinin, a powerful anticoagulant secreted by the leech, causes continued bleeding after the leech has detached. Healing of the wound is slow, and bacterial infections are not uncommon. Several species of aquatic leeches in Africa, Asia, and southern Europe can enter through the mouth, nose, and genitourinary tract and attach to mucosal surfaces at sites as deep as the esophagus and trachea. Bleeding may be intense. Externally attached leeches are removed by steady gentle traction. Removal is hastened by application of alcohol, salt, vinegar, or a flame to the leech. Internally attached leeches may detach on exposure to gargled saline or may be removed by forceps.

DELUSIONAL INFESTATIONS

The groundless conviction that one is infested with arthropods or other parasites is an extremely difficult disorder to treat and unfortunately is not rare. Patients report infestations of their skin, clothing, or homes and describe sensations of something moving in or on their skin. Excoriations often accompany complaints of pruritus or insect bites. Patients bring in as evidence of infestation specimens that are identified microscopically as plant-feeding or peridomestic arthropods, pieces of skin, vegetable matter, or inanimate objects. In suspected cases, it is imperative to rule out true infestations and neuropathies, environmental irritants such as fragments of fiberglass, and other causes of tingling or prickling sensations. Pharmacotherapy with pimozide, which blocks dopamine receptors, has been more helpful than psychotherapy in treating this disorder.

ARTHROPOD BITES AND STINGS

Arthropods may also harm humans through brief encounters in which they take a blood meal or attempt to defend themselves by biting, stinging, or inoculating venoms. Various arachnids (spiders, scorpions), insects (including bees, hornets, wasps, ants, flies, bugs, caterpillars, and beetles), millipedes, and centipedes produce ill effects in this manner.

SPIDER BITES

Of the more than 30,000 recognized species of spider, only about 100 defend themselves aggressively and have fangs sufficiently long to penetrate human skin. The venom that spiders use to immobilize and digest their prey can cause necrosis of skin and systemic toxicity. While the bites of most spiders are painful but not

harmful, envenomations of the brown or fiddle spiders *(Loxosceles* species), widow spiders *(Latrodectus* species), and other species may be life-threatening. Identification of the offending spider should be attempted, since specific treatments exist for bites of widow and brown recluse spiders and since injuries attributed to spiders are frequently due to other causes.

Recluse spider bites and necrotic arachnidism. Severe necrosis of skin and subcutaneous tissue follows envenomation by *Loxosceles reclusa,* the brown recluse spider, and by other species of *Loxosceles*. Other spiders that produce necrotic ulceration include the hobo spider *(Tegenaria agrestis)*, the sac spiders *(Chiracanthium* species). All these spiders measure 7 to 15 mm in body length and 2 to 4 cm in leg span. Recluse spiders are brown and have a dark violin-shaped spot on their dorsal surface; hobo spiders are brown with gray markings; and sac spiders may be pale yellow, green, or brown.

These spiders are not aggressive toward human beings and bite only if threatened or pressed against the skin. They hide under rocks and logs or in caves and animal burrows, and they emerge at night to hunt other spiders and insects. They invade homes, particularly in the fall, and seek dark and undisturbed hiding spots in closets, in folds of clothing, or under furniture and rubbish in storage rooms, garages, and attics. Bites often occur while the victim is dressing and are sustained primarily to the arms, neck, and lower abdomen.

The clear viscous venoms of these spiders contain an esterase, alkaline phosphatase, protease, and other enzymes that produce tissue necrosis and hemolysis. Sphingomyelinase B, the most important dermonecrotic factor, binds cell membranes and promotes chemotaxis of neutrophils, leading to vascular thrombosis and an Arthus-like reaction. Initially, the bite is painless or produces a stinging sensation. Within the next few hours, the site becomes painful and pruritic, with central induration surrounded by a pale zone of ischemia and a zone of erythema. In most cases, the lesion resolves without treatment over 2 to 3 days. In severe cases, the erythema spreads, and the center of the lesion becomes hemorrhagic and necrotic with an overlying bulla. A black eschar forms and sloughs several weeks later, leaving an ulcer that may be >25 cm in diameter and eventually a depressed scar. Healing usually takes place within 3 to 6 months but may take as long as 3 years if adipose tissue is involved. Local complications include injury to nerves and secondary infection. Fever, chills, weakness, headache, nausea, vomiting, myalgia, arthralgia, maculopapular rash, and leukocytosis may develop within 72 h of the bite. In rare instances, acute complications such as hemolytic anemia, hemoglobinuria, and renal failure are fatal.

Initial management includes local cleansing, application of sterile dressings and cold compresses, and elevation and loose immobilization of the affected limb. Analgesics, antihistamines, antibiotics, and tetanus prophylaxis should be

administered if indicated. Within the first 48 to 72 h, the administration of dapsone, a leukocyte inhibitor, may halt the progression of lesions that are becoming necrotic. Dapsone is given in oral doses of 50 to 100 mg twice daily after glucose-6-phosphate dehydrogenase deficiency has been ruled out. The efficacy of locally or systemically administered glucocorticoids has not been demonstrated. Debridement and later skin grafting may be necessary after signs of acute inflammation have subsided, but immediate surgical excision of the wound is detrimental. Patients should be monitored closely for signs of hemolysis, renal failure, and other systemic complications.

Widow spider bites. The bite of the female widow spider is notorious for the effect of its potent neurotoxin. *Latrodectus mactans,* the black widow, measures up to 1 cm in body length and 5 cm in leg span, is shiny black, and has a red hourglass marking on the ventral abdomen. Other dangerous *Latrodectus* species include *L. geometricus* (the brown widow), *L bishopi* (the red widow), *L variolus,* and *L. hesperus,* and there are related species in other temperate and subtropical parts of the world.

Widow spiders spin their webs under stones, logs, plants, or rock piles or in dark spaces in barns, garages, and outhouses. Bites are most common in the summer and early autumn and occur when the web is disturbed or when the spider is trapped or provoked. The buttocks or genitals are sites of bites incurred by humans while sitting in an outdoor privy.

The initial bite goes unnoticed or is perceived as a sharp pinprick. Two small red marks, mild erythema, and edema develop at the fang entrance site. The oily yellow venom that is injected does not produce local necrosis, and some persons experience no other symptoms. However, alpha-latrotoxin, the most active component of the venom, binds irreversibly to nerves and causes release and eventual depletion of acetylcholine, norepinephrine, and other neurotransmitters from presynaptic terminals. Within 30 to 60 min, painful cramps spread from the bite site to large muscles of the extremities and the trunk. Extreme rigidity of the abdominal muscles and excruciating pain may suggest peritonitis, but the abdomen is not tender on palpation. Other features include salivation, diaphoresis, vomiting, hypertension, tachycardia, labored breathing, anxiety, headache, weakness, fasciculations, paresthesia, hyperreflexia, urinary retention, uterine contractions, and premature labor. Rhabdomyolysis and renal failure have been reported, and respiratory arrest, cerebral hemorrhage, or cardiac failure may end fatally, especially in very young, elderly, or debilitated persons. The pain begins to subside during the first 12 h but may recur during several days or weeks before resolving spontaneously.

Treatment consists of local cleansing, application of ice packs, and tetanus prophylaxis. Hypertension that does not respond to analgesics and antispasmodics, such as benzodiazepines or methocarbamol, requires specific antihypertensive

medication. Intravenous administration of one or two vials of a widely available equine antivenin rapidly relieves pain and can be life-saving. Because of the risk of anaphylaxis and serum sickness, antivenin should be reserved for severe cases involving respiratory arrest, uncontrollable hypertension, seizures, or pregnancy.

Envenomations by tarantulas and other spiders. Tarantulas are long-lived, hairy spiders. The tarantulas that have become popular household pets are usually imported species with bright colors and a leg span of up to 25 cm. Tarantulas bite only when threatened and cause no more harm than a bee sting, but the venom occasionally provokes deep pain and swelling. Several species are covered with urticating hairs that are launched in the thousands when a threatened spider rubs its hind legs across the dorsal abdomen. These hairs penetrate human skin and produce pruritic papules that last for weeks. Treatment of bites includes local washing and elevation of the bitten area, tetanus prophylaxis, and analgesic administration. Antihistamines and topical or systemic glucocorticoids are given for exposure to urticating hairs.

Atrax robustus, the Sydney funnel-web spider of Australia, and *Phoneutria* species, the South American banana spiders, are among the most dangerous spiders in the world because of their aggressive behavior and potent neurotoxins. Envenomation by *A. robustus* causes a rapidly progressive neuromotor syndrome that can be fatal within 2 h. The bite of the banana spiders causes severe local pain followed by profound systemic symptoms and respiratory paralysis that can lead to death within 2 to 6 h. Specific antivenins for envenomation by each of these spiders are available. *Lycosa* species (wolf spiders) are found throughout the world and may produce painful bites and transient local inflammation.

SCORPION STINGS

Scorpions are crablike arachnids that feed on ground-dwelling arthropods and small lizards, which they grasp with a pair of frontal pinchers and paralyze by injecting venom from a stinger on the tip of the tail. Painful but relatively harmless scorpion stings need to be distinguished from the potentially lethal envenomations that are produced by about 30 of the approximately 1000 known species and cause more than 5000 deaths worldwide each year. Scorpions feed at night and remain hidden during the day in crevices or burrows or underwood, loose bark, or rocks on the ground. They seek cool spots under buildings and often enter houses, where they get into shoes, clothing, or bedding or enter bathtubs and sinks in search of water. Scorpions sting human beings only when disturbed.

Only the bark scorpion *(Centruroides sculpturatus* or *Centruroides exilicauda)* produces a venom that can be lethal. Stings of the other species, such as the common striped scorpion *Centruroides vittatus* and the large *Hadrurus arizonensis,* cause immediate sharp local pain followed by edema, ecchymosis, and a burning sensation. Symptoms typically resolve within a few hours, and skin does not slough. Allergic

reactions to the venom sometimes develop.

The deadly *C. sculpturatus* of the southwestern United States and northern Mexico measures about 7 cm in length and is yellow-brown in color. Its venom contains neurotoxins that cause sodium channels to remain open and neurons to fire repetitively. In contrast to the stings of nonlethal species, *C. sculpturatus* envenomations are usually associated with little swelling, but prominent pain, paresthesia, and hyperesthesia can be accentuated by tapping on the affected area (the tap test). These symptoms soon spread to other locations; dysfunction of cranial nerves and hyperexcitability of skeletal muscles develop within hours. Patients present with restlessness, blurred vision, abnormal eye movements, profuse salivation, lacrimation, rhinorrhea, slurred speech, difficulty in handling secretions, diaphoresis, nausea, and vomiting. Muscle twitching, jerking, and shaking may be mistaken for a seizure. Complications include tachycardia, arrhythmias, hypertension, hyperthermia, rhabdomyolysis, and acidosis. Symptoms progress to maximal severity in about 5 h and subside within a day or two, although pain and paresthesia can last for weeks. Fatal respiratory arrest is most common among young children and the elderly.

Envenomations by *Leiurus quinquestriatus* in the Middle East and North Africa, by *Mesobuthus tamulus* in India, by *Androctonus* species along the Mediterranean littoral and in North Africa and the Middle East, and by *Tityus serrulatus* in Brazil cause massive release of endogenous catecholamines with hypertensive crises, arrhythmias, pulmonary edema, and myocardial damage. Acute pancreatitis occurs with stings of *Tityus trinitatis* in Trinidad, and central nervous toxicity complicates stings of *Parabuthus* and *Buthotus* scorpions of South Africa. Tissue necrosis and hemolysis may follow stings of the Iranian *Hemiscorpius lepturus.*

Identification of the offending scorpion aids in planning therapy. Stings of nonlethal species require at most ice packs, analgesics, or antihistamines. Because most victims of dangerous envenomations (such as those produced by *C. sculpturatus)* experience only local discomfort, they can be managed at home with instructions to return to the emergency department if signs of cranial-nerve or neuromuscular dysfunction develop. Aggressive supportive care and judicious use of antivenin can reduce or eliminate mortality from more severe envenomations. Keeping the patient calm and applying pressure dressings and cold packs to the sting site decrease the absorption of venom. Although narcotics and sedatives can control restlessness and hypertension, these agents interfere with protective airway reflexes and should not be given to patients with neuromuscular symptoms unless endotracheal intubation is planned. Hypertension and pulmonary edema respond to nifedipine, nitroprusside, hydralazine, or prazosin, and bradyarrhythmias can be controlled with atropine. Commercially prepared antivenins are available in several

countries for some of the most dangerous species. A caprine C. *sculpturatus* antivenini is available as an investigational drug only in Arizona. Because of the risk of anaphylaxis or serum sickness following administration of goat serum, use of the antivenin is controversial. Intravenous administration of antivenin rapidly reverses cranial-nerve dysfunction and muscular symptoms but does not affect pain and paresthesia.

In scorpion-infested areas, shoes, clothing, bedding, and towels should be shaken and inspected before being used. Removal of wood, stones, and debris from yards and campsites eliminates hiding places for scorpions, and household spraying of insecticides can deplete their source of food.

HYMENOPTERA STINGS

Insects that sting to defend their colonies or subdue their prey belong to the order *Hymenoptera*, which includes apids (bees and bumblebees), vespids (wasps, hornets, and yellow jackets), and ants. Their venoms contain a wide array of amines, peptides, and enzymes that are responsible for local and systemic reactions.

Bee and wasp stings. Bees lose their venom apparatus in the act of stinging and subsequently die, while vespids can sting numerous times in succession. The familiar honeybees *(Apis mellifera)* and bumblebees *(Bombus* and other genera) attack when a colony is disturbed, but the extremely aggressive Africanized honeybees respond to minimal intrusions rapidly and in large numbers. Vespids sting in defense of their nests, which they often build near human dwellings and suspend from eaves or shubbery, plaster onto walls, or burrow into wood or soil. Yellow jackets feed on sugary substances and decaying meat and are annoyingly abundant at recreation sites and around garbage, particularly in the late summer and fall.

Venom is produced in glands at the posterior end of the abdomen and is expelled rapidly by contraction of muscles of the venom sac, which has a capacity of up to 0.1 mL in large insects. The venoms of different species of hymenopterans are biochemically and immunologically distinct. Direct toxic effects are mediated by mixtures of low-molecular-weight compounds such as serotonin, histamine, and acetylcholine and several kinins. Polypeptide toxins in honeybee venom include mellitin, which damages cell membranes; mast cell-degranulating protein, which causes histamine release; apamin, a neurotoxin; and adolapin, which has anti-inflammatory action. Enzymes in venom include hyaluronidase, which allows the spread of other venom components, and phospholipases, which may be among the major venom allergens. There appears to be little cross-sensitization between honeybee and wasp venoms.

Uncomplicated stings cause immediate pain, a wheal-and-flare reaction, and local edema and swelling that subside in a few hours. Stings from accidentally swallowed insects may induce life-threatening edema of the upper airways. Multiple stings can lead to vomiting, diarrhea, generalized edema, dyspnea, hypotension, and

collapse. Rhabdomyolysis and intravascular hemolysis may cause renal failure. Death from the direct effects of venom has followed 300 to 500 honeybee stings.

Large local reactions that spread >10 cm around the sting site over 24 to 48 h are not uncommon. These reactions may resemble cellulitis but are caused by hypersensitivity rather than secondary infection. Such reactions tend to recur on subsequent exposure but seldom are accompanied by anaphylaxis and are not prevented by venom immunotherapy.

Persons who experience severe allergic reactions are likely to have similar reactions after subsequent stings; occasionally, adults who have had mild reactions later experience serious reactions. Mild anaphylactic reactions from insect stings, as from other causes, consist of nausea, abdominal cramping, generalized urticaria, flushing, and angioedema. Serious reactions, including upper airway edema, bronchospasm, hypotension, and shock, may be rapidly fatal. Severe reactions usually begin within 10 min of the sting and only rarely develop after 5 h. Unusual complications, including serum sickness, vasculitis, neuritis, and encephalitis, develop several days or weeks after a sting.

Stingers embedded in the skin should be scraped or brushed off with a blade or a fingernail but not removed with forceps, which may squeeze more venom out of the venom sac. The site should be cleansed and disinfected and ice packs used to slow the spread of venom. Elevation of the affected site and administration of analgesics, oral antihistamines, and topical calamine lotion relieve symptoms; application of meat tenderizer containing papain is of no proven value. Large local reactions may require a short course of oral therapy with glucocorticoids. Patients with numerous stings should be monitored for 24 h for evidence of renal failure or coagulopathy.

Anaphylaxis is treated with subcutaneous injection of 0.3 to 0.5 mL of epinephrine hydrochloride in a 1:1000 dilution; treatment is repeated every 20 to 30 min if necessary. Intravenous epinephrine (2 to 5 mL of a 1:10,000 solution administered by slow push) is indicated for profound shock. A tourniquet may slow the spread of venom. Parenteral antihistamines, fluid resuscitation, bronchodilators, oxygen, intubation, and vasopressors may be required. Patients should be observed for 24 h for recurrent anaphylaxis.

Persons with a history of allergy to insect stings should carry a sting kit with a preloaded syringe containing epinephrine for self-administration in case of a sting. These patients should seek medical attention immediately after using the kit. To avoid stings when outdoors, individuals can wear shoes and protective clothing and avoid attracting insects with sweet foods, bright-colored clothes, perfumes, or cosmetics.

Repeated injections of purified venom produce a blocking IgG antibody response to venom and reduce the incidence of recurrent anaphylaxis from between 50 and 60% to less than 5%. Honeybee, wasp, yellow jacket, and mixed vespid

venoms are commercially available for desensitization and for skin testing. Adults with a history of anaphylaxis should undergo desensitization. Results of skin tests and venom-specific radioallergosorbent tests aid in the selection of patients for immunotherapy and guide the design of such treatment. A 3- to 5-year course of immunotherapy usually eliminates the risk of anaphylaxis.

Stings of ants. All ants that are large enough can bite human beings, and some can secrete repugnant substances when handled. They excavate open fields and yards to build tall mounds that can harbor 200,000 worker ants. Slight disturbances of the mounds have provoked massive outpourings of ants and as many as 10,000 stings on a single person. Waterborne ants bite on contact during times of flooding.

Red-brown or brown-black fire ants attach to human skin with powerful mandibles and rotate their bodies around their heads while repeatedly injecting venom with posteriorly situated stingers. The alkaloid venom consists of cytotoxic and hemolytic piperidines and several proteins with enzymatic activity. The initial wheal-and-flare reaction, burning, and itching resolve in about 30 min, and a sterile pustule develops within 24 h. The pustule ulcerates over the next 48 h and then heals a week or 10 days later unless it becomes secondarily infected. Large areas of erythema and edema lasting several days are not uncommon and in extreme cases may compress nerves and blood vessels. Anaphylaxis occurs in about 1 to 2% of persons, and seizures and mononeuritis have been reported. Stings are treated with ice packs, topical glucocorticoids, and oral antihistamines. Covering pustules with bandages and antibiotic ointment may prevent bacterial infection. Epinephrine and supportive measures are indicated for anaphylactic reactions. Whole-body extracts are available for skin testing and immunotherapy, which appears to lower the rate of anaphylactic reactions.

The painful local reaction following harvester ant (*Pogonomyrmex* species) stings often extends to lymph nodes and may be accompanied by anaphylaxis. Large Australian bulldog ants and the aggressive South American *Paranopera* ants deliver extremely painful stings and may cause systemic symptoms. Velvet ants that inhabit sandy beaches in the United States and sting the bare feet of bathers are actually wingless female wasps of the genus *Dasymutilla.*

OTHER ARTHROPOD BITES AND ENVENOMATIONS

Dipteran (fly) bites. In the process of feeding on vertebrate blood, adults of certain fly species inflict painful bites, produce local allergic reactions, or transmit infectious diseases. Unlike insect stings, insect bites rarely cause anaphylaxis. Mosquitoes are ubiquitous pests and are the vectors of malaria, filariasis, yellow fever, dengue, and viral encephalitides. Their bite typically produces a wheal and later a pruritic papule. A similar reaction follows the bite of tiny but aggressive midges, which attack in swarms during warm months, or of other *Culicoides* species that transmit "nonpathogenic" filariae in tropical climates. The bite of the small

humpbacked blackfly of the genus *Simulium* leaves a large bleeding puncture and painful and pruritic sores that are slow to heal; regional lymphadenopathy, fever, or anaphylaxis occasionally ensues. Blackflies are vectors of onchocerciasis in Africa and Latin America. The widely distributed tabanids, including deerflies (*Chrysops* species) and horseflies (*Tabanus* species), are stout flies measuring 10 to 25 mm in length that attack during the day and produce large and painful bleeding punctures. Deerflies transmit loiasis in African equatorial rain forests and tularemia elsewhere. Tsetse flies of the genus *Glossina* transmit African trypanosomiasis in sub-Saharan Africa. Tiny phlebotomine sand flies are the vectors of leishmaniasis, bartonellosis (Carrion's disease), sand-fly fever, and other arboviral infections in warm climates. *Stomoxys calcitrans,* the stable fly, which resembles a large housefly, is a fierce biter of human beings and domestic animals and a major pest in seacoast areas. Treatment of fly bites is symptom-based. Topical application of antipruritic agents, glucocorticoids, or antiseptic lotions may relieve the itching and pain. Allergic reactions may require oral antihistamines. Antibiotics may be necessary for large bite wounds that become secondarily infected. Personal protection measures against biting flies include avoidance of infested areas, application of a DEET-containing repellent to exposed skin, and use of protective clothing and bed nets treated with permethrin.

Hemipteran (true bug) bites. Several true bugs of the family Reduviidae inflict bites that produce allergic reactions and are sometimes painful. The cosmopolitan bedbug (*Cimex* species) hides in mattresses, behind bedboards, and under loose wallpaper during the day and takes its blood meal at night. The bite is painless, but sensitized persons develop erythema, itching, and wheals around a central hemorrhagic punctum. The cone-nose bugs, so called because of their elongated-heads, include the assassin and wheel bugs, which feed on other insects and bite human beings only in self-defense, and the kissing bugs, which routinely feed on vertebrate blood. Assassin and wheel bugs inhabit many parts of the world. The bites of the nocturnally feeding kissing bugs are painless and occur commonly in groups on the face and other exposed parts of the body. Reactions to such bites depend on prior sensitization and include tender and pruritic papules, vesicular or bullous lesions, giant urticaria, fever, lymphadenopathy, and anaphylaxis. *Triatoma infestans* and other species of kissing bug are the vectors of *Trypanosoma cruzi* in South and Central America and Mexico. Bug bites are treated with topical antipruritics or oral antihistamines. Persons with anaphylactic reactions to reduviid bites should keep an epinephrine kit available.

Centipede bites and millipede dermatitis. The fangs of centipedes of the genus *Scolopendra* can penetrate human skin and deliver venom that produces intense burning pain, swelling, erythema, and lymphangitis. Dizziness, nausea, and anxiety are occasionally described, and rhabdomyolysis and renal failure have been

reported. Treatment includes washing of the site, application of cold dressings, oral analgesic administration or local lidocaine infiltration, and tetanus prophylaxis. Species of *Scolopendra,* measuring up to 25 cm, occur widely in areas with warm climates worldwide. The smaller house centipede *Scutigera coleopatrata* is harmless.

Millipedes, unlike centipedes, do not bite but rather secrete and in some cases eject defensive fluids that burn and discolor human skin. Affected skin turns brown overnight and may blister and exfoliate. Secretions in the eye cause intense pain and inflammation that may lead to corneal ulceration and blindness. Management includes irrigation with copious amounts of water or saline, use of analgesics, and local care of denuded skin. Millipedes are found throughout the world in leaf litter and under rocks.

Caterpillar stings and dermatitis. The surface of caterpillars of several moth species is covered with hairs or spines that produce mechanical irritation and may contain or be coated with venom. Contact with these caterpillars causes an immediate burning sensation followed by local swelling and erythema and occasionally by regional lymphadenopathy, nausea, vomiting, and headache; shock, seizures, and coagulopathy are rare complications. Stings are most often caused by io moth larvae and puss as well as saddleback and brown-tail moth caterpillars as they cling to leaves and branches. Contact with even detached hairs of other caterpillars, such as gypsy moth larvae (*Lymantria dispar*), can produce a pruritic urticarial or papular rash hours later. Spines may be deposited on tree trunks and drying laundry or may be airborne and cause irritation of the eyes and upper airways. Treatment of caterpillar stings consists of repeated application of adhesive or cellophane tape to remove the hairs, which can then be identified microscopically. Local ice packs, topical steroids, and oral antihistamines relieve symptoms.

Beetle vesication. When disturbed, blister beetles (*Epicauta* species) extrude cantharidin, a low-molecular-weight toxin that produces thin-walled blisters measuring up to 5 cm in diameter 2 to 5 h after contact with the beetle. The blisters are not painful or pruritic unless broken, and they resolve without treatment in a week to 10 days. Nephritis may follow unusually heavy cantharidin exposure. Contact occurs when people sit on the ground, work in the garden, or deliberately handle the beetles. In other countries, different species of beetle produce different vesicants. No treatment is necessary, although ruptured blisters should be kept clean and bandaged until healing is complete.

ABBREVIATION

AIDS	-	acquired immunodeficiency syndrome
CDC	-	Center for Disease Control and Prevention
CNS	-	central nervous system
CSF	-	cerebrospinal fluid
CT	-	computed tomography
DCL	-	diffuse cutaneous leishmaniasis
DEC	-	Diethylcarbamazine
EBV	-	Epstein-Barr virus
EIA	-	enzyme immunoassay
ELISA	-	enzyme-linked immunosorbent assay
HF	-	hemorrhagic fevers
HIV	-	human immunodeficiency virus
IHA	-	indirect hemagglutination
IL	-	interleukin
MRI	-	magnetic resonance imaging
RT-PCR	-	reverse transcription polymerase chain reaction
Th	-	T-helper
WHO	-	World Health Organization

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