Chapter 12

TROPICAL PARASITIC INFECTIONS

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INTRODUCTION

A *parasite* is an organism that lives on or within another organism. The organism on which or within which it lives is referred to as the *host*. While a parasite–host relationship may be one of mutual benefit (mutualism) or one in which the host derives no benefit but is not injured by the relationship (commensalism), the term parasitism is used in this chapter to mean that the parasite is afforded physical protection or nourishment to the detriment of its human host.

The life cycles of parasites may be complex. In a *definitive* host, the parasite becomes sexually mature and undergoes reproduction. *Reservoir* hosts are those in which parasites that are pathogenic to other animals or to humans reside. An animal reservoir confers a survival benefit to the parasite, for it is often difficult to track and eliminate the organism from the larger pool of animals in which it is carried. When humans intrude into the wild and interrupt the zoonotic life cycle, they may be incidentally infected and thus become *incidental* (or accidental) hosts. In an *intermediate* host, the parasite exists in larval or asexual forms pending transmission to a definitive host.[1]

Often, the means by which a parasite is transmitted to the host involves an agent (eg, arthropod, mollusk), which is referred to as the *vector* of disease transmission. In a biological vector, the parasite undergoes development or multiplication prior to transmission. On the other hand, a mechanical vector carries or transmits the organism without any biological modification of its life cycle.[1]

Because they are deployed worldwide, U.S. armed forces are often in tropical locales where parasitic organisms produce diseases that may be truly foreign to the clinical experience of many military physicians. Although the historical record suggests that bacterial and fungal infections and immersion syndromes produce the bulk of cutaneous disease, the record also shows that parasites can cause considerable morbidity in war.[2] Tropical parasitic diseases that manifest with distinctive cutaneous signs offer a unique opportunity for early diagnosis and treatment. To reduce morbidity and thus increase troop effectiveness and morale, medical officers must know the cutaneous signs, methods of diagnosis, epidemiology, and effective treatment of these diseases.

Furthermore, members of the local populace, in whom the incidence and prevalence of these diseases is much greater, are often treated at military medical treatment facilities. During peacetime humanitarian missions, this is expected; however, it also often occurs during wartime. During the Vietnam conflict, medical teams were sent to treat natives in nearby villages. The l8th Surgical Hospital (Mobile), located south of the border with North Vietnam at Quang Tri, Republic of Vietnam, had 20 to 30 beds added to its normal configuration to care for pediatric patients.[3] During Operation Desert Storm in Southwest Asia, physicians who were attached to hospitals that were deployed forward into Iraq, providing medical and surgical support to forces engaged in active combat, also provided medical and surgical care to civilians caught within the theater of operations. An understanding of the tropical parasitic diseases in the civilian populace, then, becomes important not only in delivering proper medical care but also in limiting the possibility of spread of disease from these civilians, who may also serve as disease reservoirs.[4]

Diseases common to the tropics are discussed in other chapters in this textbook. This chapter focuses on the characteristic cutaneous manifestations of protozoan and helminthic diseases that medical officers might expect to encounter during troop deployments.

PROTOZOAL INFECTIONS

Parasitic protozoa that are infectious to humans are generally unicellular organisms that have nuclear structures separated from the cytoplasm by a membrane. Because these organisms can replicate in human tissue, single exposures can result in massive infections.[1] Those most likely to be associated with cutaneous manifestations are to be found in subphylum Mastigophora (in which flagella are the characteristic means of locomotion) or in subphylum Sarcodina (in which pseudopodia [ie, creeping protoplasmic flow] are the basis of movement).[1,5]

Leishmaniasis

While reporting on a case of Delhi boil in 1885, British Surgeon-Major D. D. Cunningham is cred-

ited with making the first scientific observation of leishmanial organisms. Subsequently, Borovsky and Wright, working independently, concluded that the parasite was probably protozoan. In 1903, two British Army medical officers, Colonel W. B. Leishman (of the Royal Army Medical College) and Colonel C. Donovan (of the Indian Medical Service, working at Madras, India) discovered that the parasite is the cause of visceral leishmaniasis; henceforth, the organism has been referred to as a Leishman-Donovan body in tissue.[6]

Although in 1913 the British Army reported only 53 cases of "oriental sore," the numbers increased during World War I to an estimated 10,000 in its Mesopotamia Force.[7] During World War II, U.S. forces experienced 1,000 to 1,500 cases of cutaneous leishmaniasis, most of which originated in the Persian Gulf Command between October 1943 and August 1945. Because all these soldiers were treated as outpatients, manpower was little affected. Fifty to 75 cases of visceral leishmaniasis were estimated to have occurred in the Mediterranean Theater of Operations and India.[8]

To standardize therapy, the treatment of leishmaniasis in U.S. military personnel has been done on protocol at Walter Reed Army Medical Center, Washington, D. C. Between 1957 and 1981, approximately 288 patients diagnosed as having leishmaniasis were treated—most having contracted the disease in Central or South America. (Because the leishmanial species from this region have the potential to cause mucocutaneous disease, treatment takes on added importance.) By 1994, the total number of cases had increased to more than 440.[9] A number of patients (including several cases of systemic disease that were documented by bone marrow examination) were diagnosed following Operations Desert Shield and Desert Storm in 1990 and 1991.[10] Given the fact that the primary lesion of leishmaniasis from Southwest Asia tends to be of short duration and often is a self-limited disease, it is likely that a number of cases of cutaneous leishmaniasis have gone unreported or undiagnosed.

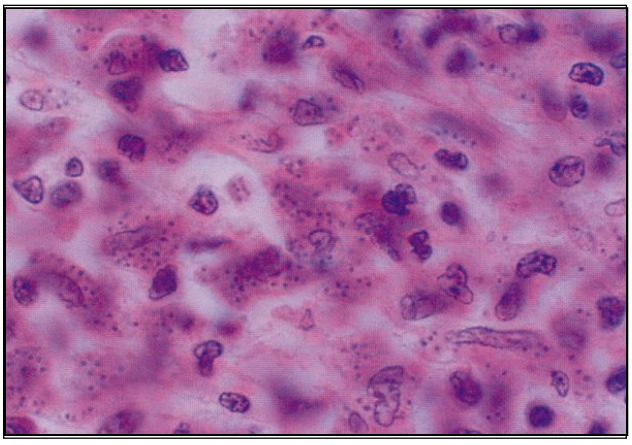


Fig. 12-1. Intracellular amastigotes of cutaneous leishmaniasis. Photograph: Courtesy of Lieutenant Colonel Martha L. McCollough, Medical Corps, U.S. Army, San Antonio, Tex.

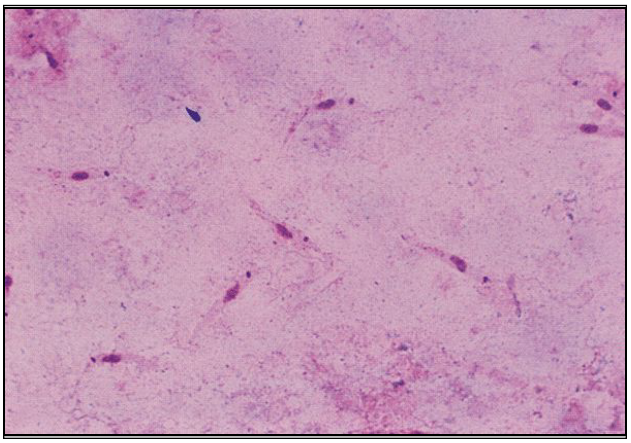


Fig. 12-2. Promastigotes of leishmaniasis obtained from an infected sandfly. The flagellum, large central nucleus, and kinetoplast are apparent.

The life cycle of leishmaniasis begins in nature with a variety of animals (eg, dogs, sloths, rodents), as well as humans, serving as reservoirs for infection.[11] Located within reticuloendothelial cells of infected tissues, leishmania exist in an *amastigote* (nonflagellate) form, which is round or oval in shape and approximately 2 to 5 μm in its greatest dimension (Figure 12-1). Feeding on a reservoir animal's infected tissues, female sandflies of the genera *Phlebotomus* or *Lutzomyia* ingest the parasitized cells. In the gut of the vector, the leishmania transform to the *promastigote* (or flagellate) form (Figure 12-2). The promastigote is a slender organism with a flagellum, undulating membrane, nucleus, and terminal kinetoplast; it can measure 28 μm (including the flagellum) in length. After replicating, the leishmania promastigotes migrate to the sandfly's proboscis, from which they are regurgitated into the next host as the sandfly feeds (Figure 12-3).

Although the adult sandfly lives only a few weeks, it is able to transmit disease within 7 to 10 days after feeding on an infected reservoir host.[11] In some cases, the number of promastigotes is so great that they may physically obstruct the proboscis and

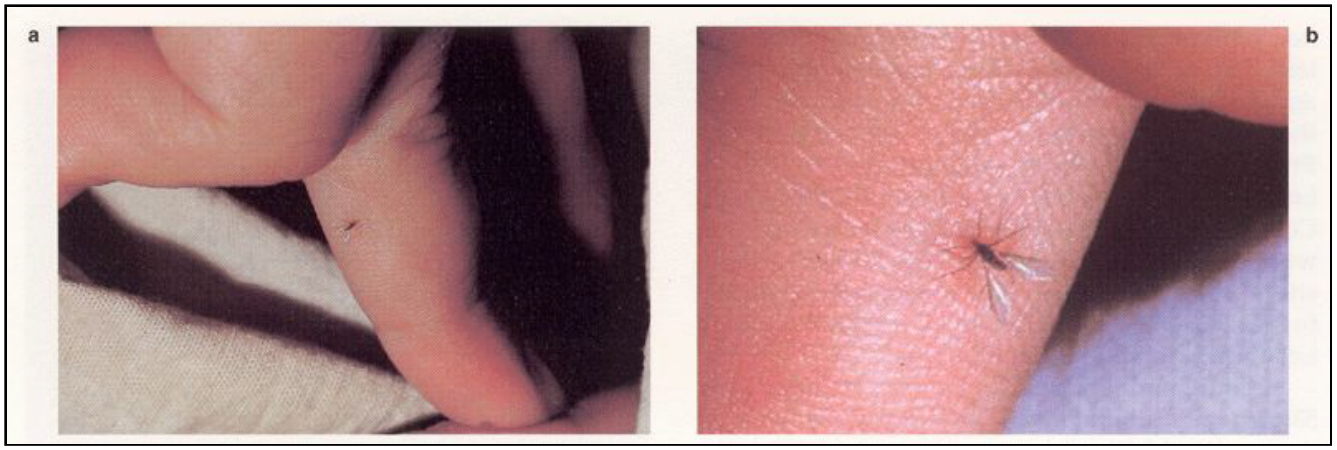


Fig. 12-3. (**a**) An adult sandfly, the vector of leishmaniasis. (**b**) The sandfly, seen in close-up. Photographs: Courtesy of Jorge Molina, M.D., Honduras, Central America.

prevent feeding.[12] Thus, the sandfly may make several attempts before successfully feeding. As a result, multiple primary inoculations, resulting in multiple primary lesions, can occur in a single human host; in other cases, single abortive feeding attempts on different persons may cause several individuals to become infected.

Once introduced into human skin, promastigotes activate complement, bind C3, and become internalized by means of complement receptors on mature macrophages.[13,14] Assuming the amastigote form, the leishmania replicate, causing the cell to rupture, which releases amastigotes that then infect other cells. Thus, infection (as defined by the presence of organisms) may be widespread, although the obvious manifestations of disease are limited.

Control of disease by eliminating the parasite is thought to be mediated by (*a*) a cellular oxidative burst or (*b*) lymphocyte-mediated cytotoxicity. When the cellular immune response is adequate, the parasite is eliminated and species-specific immunity results. Also, limited cross-immunity with other *Leishmania* species develops in some cases. Immunity, however, is not absolute, as reinfection with the same species of organism can occur.[13]

The taxonomy of the genus *Leishmania* has been complicated by the inclusion of complexes, subgenera, species, and subspecies identification based on a variety of clinical, biological, epidemiological, immunological, and biochemical criteria.[15] For a number of years, the standard procedure has been to classify organisms as members of complexes: *L mexicana* complex, *L braziliensis* complex, *L tropica* complex, or *L donovani* complex. A recently proposed change in the classification is that all mammalian leishmania that develop in the foregut or midgut of the vector be placed into subgenus *Leishmania,* and those with hindgut development into subgenus *Viannia*. Because a consensus has yet to be developed, many authorities have adopted the simplified nomenclature used in Table 12-1.[16,17]

Cutaneous Manifestations

Clinically, it is convenient (although immunologically simplistic) to think of leishmaniasis in three forms: cutaneous, mucocutaneous, and visceral. Because of clinical differences, the disease is often classified as Old World (Africa, the Mediterranean littoral, the Middle East, India, Southwest Asia, and Asia) or New World (Central America and South America) leishmaniasis. Old World leishmaniasis tends to produce either cutaneous or visceral disease, while New World leishmaniasis may be cutaneous, mucocutaneous, or visceral.

Morphologically, the initial cutaneous lesions of both Old World and New World disease are similar (Figures 12-4, 12-5, and 12-6).[13,18–23] In the Old World, these lesions are called Baghdad sore, Aleppo boil, Delhi boil, or oriental sore. Synonyms for cutaneous New World disease include American leishmaniasis, South American leishmaniasis, *uta, pian bois,* and Chiclero's ulcer. Generally occurring on exposed areas of the body (ie, face, ears, arms, legs), single or multiple erythematous papules develop weeks to months after the bite of an infected sandfly. The papules enlarge ($\geq$ 1–5 cm) to form indurated nodules or plaques. Satellite lesions are not uncommon. These lesions may have overlying scale or they may ulcerate, leaving a central crater. The extensive differential diagnosis includes pyoderma, kerion, deep fungal infection, tuberculosis, atypical

TABLE 12-1

NAMES, GEOGRAPHICAL DISTRIBUTION, AND DISEASE MANIFESTATION OF *LEISHMANIA* SPECIES THAT INFECT HUMANS

Table 12-1 is not shown because the copyright permission granted to the Borden Institute, TMM, does not allow the Borden Institute to grant permission to other users and/or does not include usage in electronic media. The current user must apply to the publisher named in the figure legend for permission to use this illustration in any type of publication media.

*rare manifestation
†taxa not recognized by all authorities
CL: cutaneous leishmaniasis
DCL: disseminated cutaneous leishmaniasis
MCL: mucocutaneous leishmaniasis
PKADL: post–kala-azar dermal leishmaniasis
VL: visceral leishmaniasis
Reprinted with permission from Walton BC. Leishmaniasis: A worldwide problem. *Int J Dermatol*. 1989;28:307.

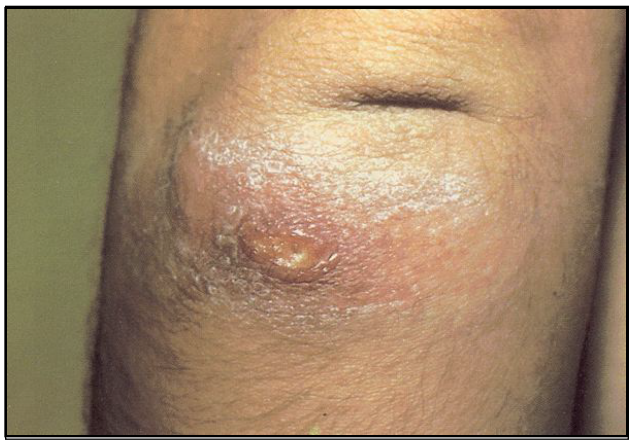


Fig. 12-4. An ulcerated nodule of cutaneous leishmaniasis in an active-duty soldier. The lesion appeared during Operation Desert Shield in Saudi Arabia. Clinical resolution occurred spontaneously after 6 to 7 months.

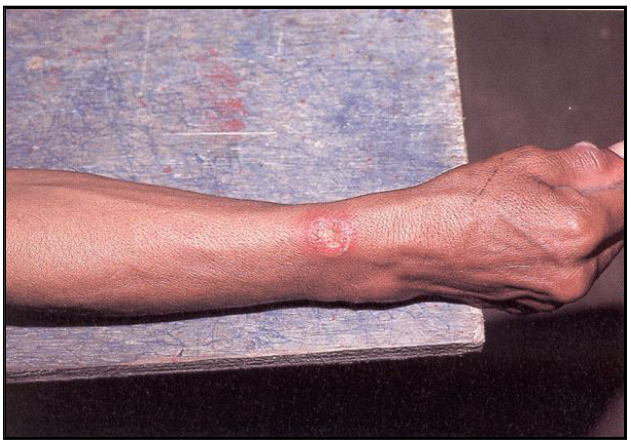


Fig. 12-5. An ulcerated nodule of leishmaniasis in a patient from Panama.

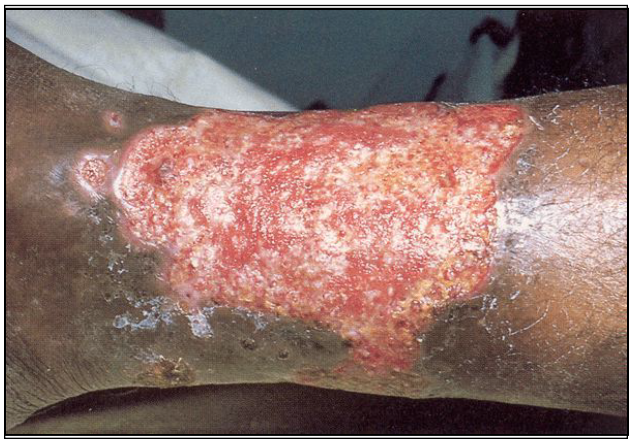


Fig. 12-6. A cutaneous ulcer of leishmaniasis. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

mycobacteria, sarcoidosis, foreign body reaction, squamous cell carcinoma, or granuloma faciale. Extension of disease may be manifest as subcutaneous nodules following the lymphatic drainage, which occurs in both Old World and New World disease (Figure 12-7).[24] Gradually the lesions begin to flatten and develop dermal fibrosis, leaving an irregular, sometimes disfiguring, scar. Disease due to *L tropica* or *L major* (Old World) generally resolves within a few months to a year. Leishmaniasis occurring in Central America or South America may produce cutaneous lesions that persist for much longer periods of time.[21]

A form of leishmaniasis associated with specific immunological unresponsiveness is disseminated anergic cutaneous leishmaniasis, often called diffuse cutaneous leishmaniasis.[18,19] In patients with this disease, hundreds of nonulcerating nodules and plaques develop and may become confluent. The facial involvement may become extensive and create the appearance of leonine facies. Macrophages within the lesions teem with amastigotes and the skin test reaction to leishmanial antigen is negative. Visceral involvement is thought not to occur.[19] The differential diagnosis includes lepromatous leprosy.

Mucocutaneous Manifestations

Seemingly unique to the spectrum of New World disease, espundia (mucocutaneous leishmaniasis) is caused by infection with *L braziliensis* or *L*

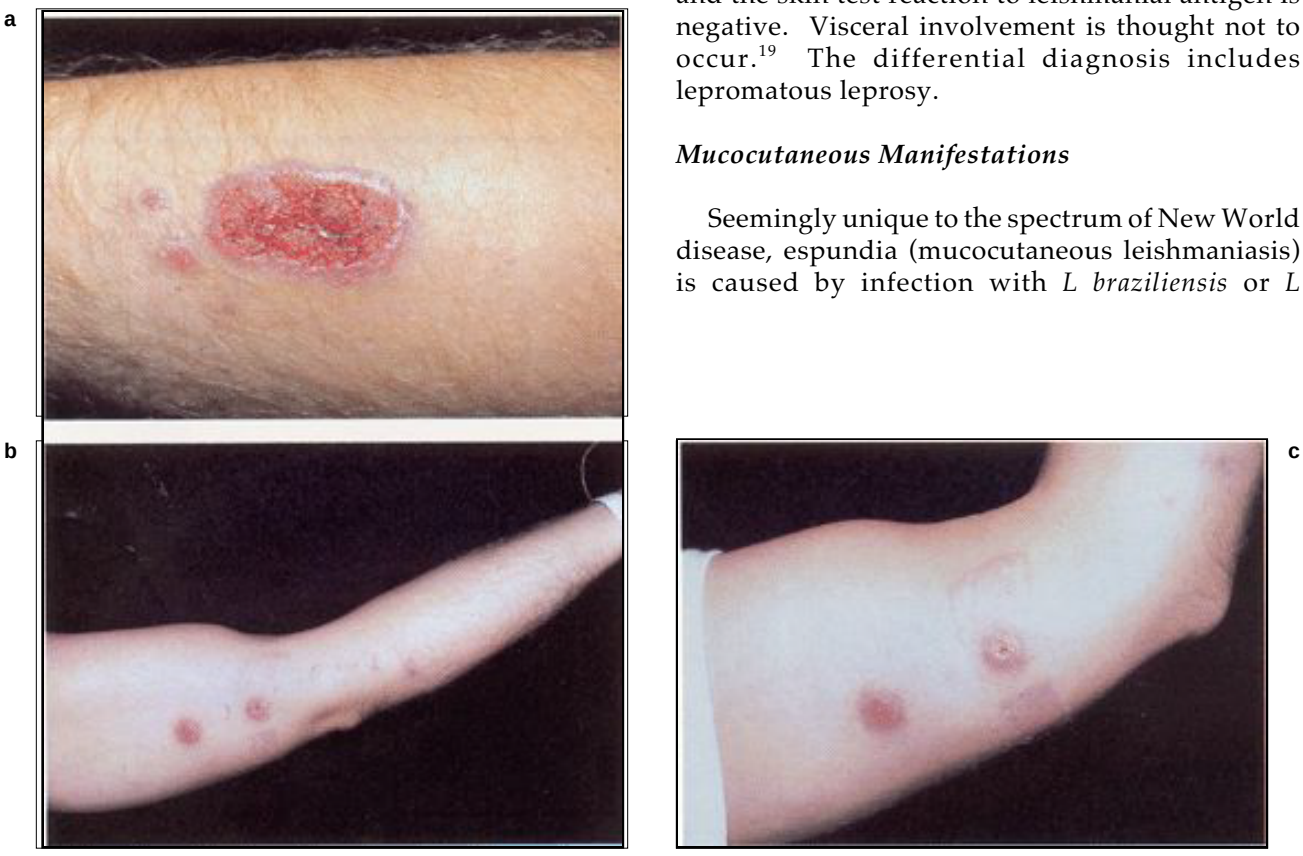
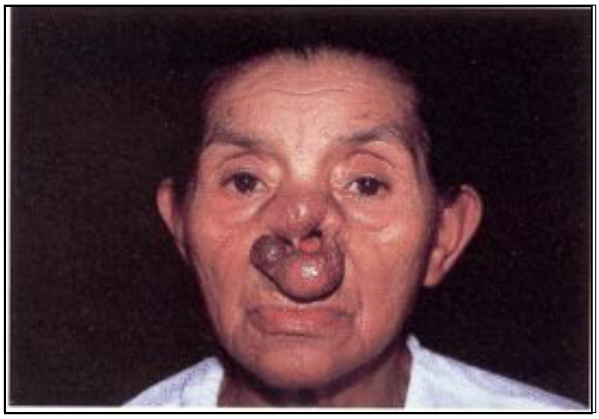


Fig. 12-7. (**a**) Plaque with satellite papules of *Leishmania panamensis* in a U.S. Army soldier on active duty in Panama, Central America. (**b**) The soldier's inner arm shows the array of papules and nodules occurring along lymphatic drainage that is known as sporotrichoid lymphatic involvement. (**c**) Close-up of the lesions along the pathway of lymphatic drainage.



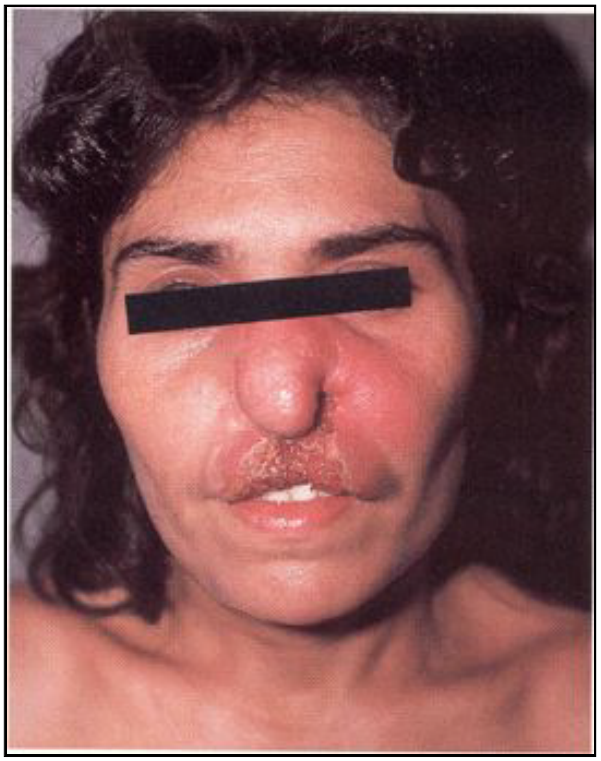


Fig. 12-8. Mucocutaneous leishmaniasis (espundia) of (**a**) the nose and (**b**) the nose, malar region, and upper lip in two patients from Central America. Photographs: Courtesy of Colonel Eric W. Kraus, Medical Corps, U.S. Army (ret).

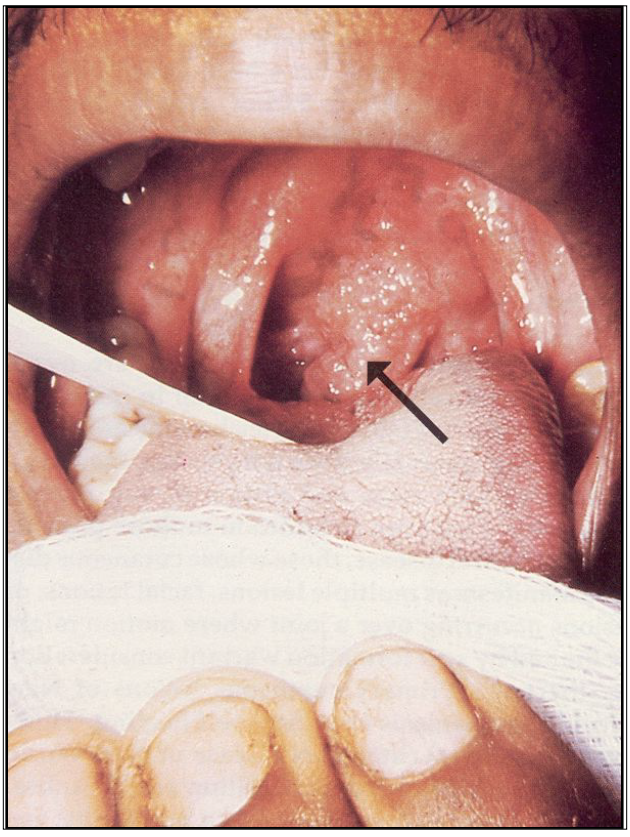


Fig. 12-9. Mucocutaneous leishmaniasis. A friable plaque (arrow) in the patient's posterior pharynx. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

panamensis.[17] Recurrent leishmaniasis involving the upper respiratory system may develop 3 to 10 years after the primary lesion—often at a distant site—has apparently healed.[21] Symptoms frequently begin with epistaxis or coryza, with subsequent extensive destruction of the nasal cartilage (Figure 12-8). The resulting overhanging nasal deformity coupled with infiltration is said to make the patient resemble a tapir.[19] Espundia's further progression to the palate, tongue, floor of the mouth, and pharynx may create an extensive midline facial defect (Figure 12-9). Untreated, inanition with aspiration pneumonia and death may occur (Figure 12-10). The differential diagnosis of espundia includes deep fungal infections, lethal midline granuloma, malignant tumors, rhinoscleroma, syphilis, tuberculosis, and leprosy.

Visceral Manifestations

Visceral leishmaniasis is caused by organisms of both the Old World and the New World (see Table 12-1). Viscerotropic species cause a systemic disease that may have fever, malaise, abdominal swelling, pain, anorexia, hepatosplenomegaly, and anemia. The earth-gray pigmentation of the face, hands, and feet gives this disease its common name, kala

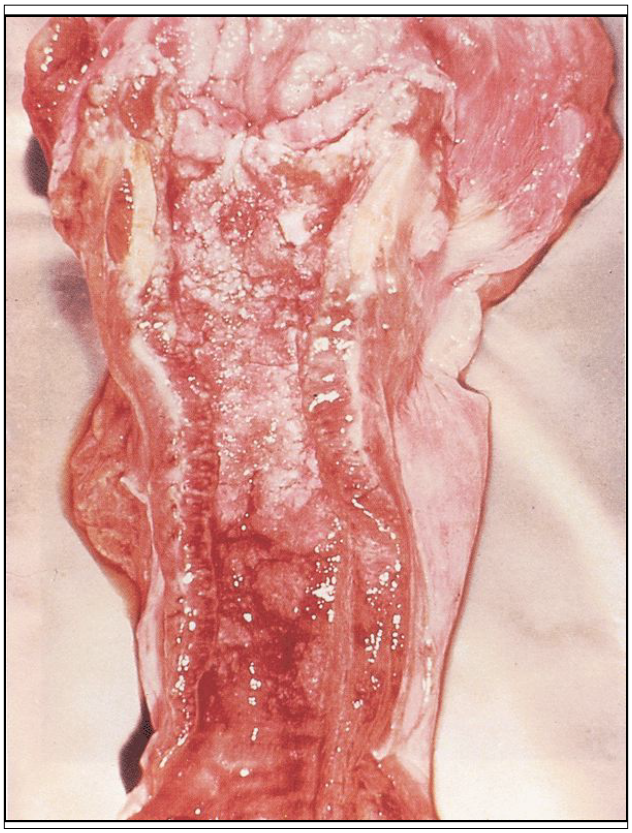


Fig. 12-10. Mucocutaneous leishmaniasis. Autopsy specimen showing tracheal involvement. The patient died after aspirating a portion of the plaque. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

azar (ie, black sickness).[25] No pigmentary changes were noted in the cases of visceral disease that occurred among U.S. military personnel during World War II.[26] Either during the course of treatment or years after their apparent cure, an eruption of hypopigmented macules, butterfly erythema, and diffuse nodules develop in some patients in Kenya and India with visceral leishmaniasis.[25,26] The disorder is known as post–kala azar dermal leishmaniasis.

Diagnosis

Diagnosis of leishmaniasis is generally accomplished by demonstrating the organism.[22,23,27,28] Methods of directly visualizing leishmania that are infecting tissue include the following:

- scraping of the primary lesion,
- a nonbloody slit smear of a nodule,
- needle aspiration at the elevated edge away from the scar, or
- biopsy and subsequent touch preparation.

All of these preparations are stained by Giemsa or Wright's stain and the investigator should look for the amastigote within the cell. Demonstrating organisms in tissue by this method is difficult, especially when numbers of parasites are low; thus, cultures of tissue specimens are often prepared. Results of cultures, however, are dependent on the numbers of organisms inoculated and the skill of the laboratory. The culture is usually grown on Novy-MacNeal medium, modified by Nicolle (ie, NNN medium), overlaid with Schneider's Drosophila medium and fetal bovine serum. Promastigotes are demonstrated in positive cultures. The Montenegro intradermal skin test is produced from promastigotes but is not commercially available in the United States.[28] This skin test is of limited usefulness in endemic areas because (*a*) a high percentage of the population may have been exposed to leishmania and (*b*) diffuse cutaneous disease tests negative. Serologic tests, in particular indirect fluorescent antibody tests and enzyme immunosorbent assays, have been developed but may be negative in 20% to 30% of cases.[23,28] Indirect immunofluorescent studies using monoclonal antibodies directed against leishmanial antigens are more sensitive than either Giemsa stains or culture and hold great promise in facilitating diagnosis.[10,29]

Therapy

Comprehensive reviews of therapy are available.[30,31] Medical officers must keep in mind that strictly cutaneous Old World leishmaniasis is often self-healing, generally does not presage the development of kala azar, and thus may not require treatment. However, in addition to those patients having visceral disease, those whose cutaneous disease manifests as multiple lesions, facial lesions, or lesions occurring over a joint where motion might be limited by scar formation warrant consideration for therapy. Primary cutaneous lesions of New World leishmaniasis also show self-healing. However, because (*a*) cutaneous disease of New World leishmaniasis has a longer duration and (*b*) subsequent mucocutaneous disease is a possibility, patients with New World leishmaniasis are treated. *L tropica*, *L major*, *L donovani*, *L mexicana*, and *L braziliensis* are treated with stibogluconate sodium (20 mg Sb [antimony, the active ingredient]/kg/d, administered intravenously or intramuscularly for

20–28 d) or meglumine antimonate (20 mg Sb/kg/d, for 20–28 d, route of administration not specified).[32] Adequate treatment of cutaneous disease due to *L braziliensis* may markedly diminish the risk of espundia.[33] Because pentavalent antimonials are not always effective and drug resistance has been documented, the quest for new therapies continues.[34,35] Investigational treatments include the use of amphotericin B, pentamidine isethionate, ketoconazole, recombinant human gamma interferon, and heat.[22,32]

South American Trypanosomiasis

Trypanosoma cruzi causes a disease encountered in Central America and South America known as South American trypanosomiasis or Chagas' disease. Over a period of years, the disease may evolve from an acute stage, which includes cutaneous manifestations, through a clinically silent latent stage, to a chronic phase characterized by cardiac and gastrointestinal disease.

The life cycle of the parasite causing human disease typically begins with a wide variety of domestic (eg, dogs, cats, pigs) and wild (eg, rodents, marsupials) animals, which serve as reservoirs for infection.[36–38] The trypomastigote form circulates in the blood stream as a slender, spindle-shaped form, 15 to 20 μm in length (in humans), having a nucleus, terminal kinetoplast, undulating membrane, and a long flagellum (Figure 12-11). While feeding on infected animals, true bugs (of the suborder Hemiptera) from the insect family Reduviidae (subfamily Triatomidae) ingest the trypomastigote. Dividing and transforming in the gut of the bug, the *T cruzi* appear in the hindgut as metacyclic trypomastigotes, which are infective to humans. Once infected, the bug remains so for life. Although many species of triatomid bugs exist, those that are adapted to living in human habitats serve as vectors of trypanosomiasis: *Rhodnius prolixus* in Central America, Colombia, and Venezuela (Figure 12-12); *Triatoma infestans* throughout much of South America; and *Panstrongylus megistus* in Brazil. Hiding within the cracks and crevices of mud and thatch homes during the day, the bug ventures out at night to feed on exposed skin (typically the face, hence the name "kissing bug") of sleeping humans. While feeding, the bug defecates, thus depositing the infective metacyclic trypomastigotes on the skin surface. Although the insect is undetected while feeding, a short time later the victim develops pruritus, which elicits a rubbing or scratching response, which then inoculates the organism from the fecal deposit into the victim's skin or mucous membrane. Invading tissue macrophages, the organisms transform to rounded, nonflagellate amastigote forms of approximately 3 μm in diameter.

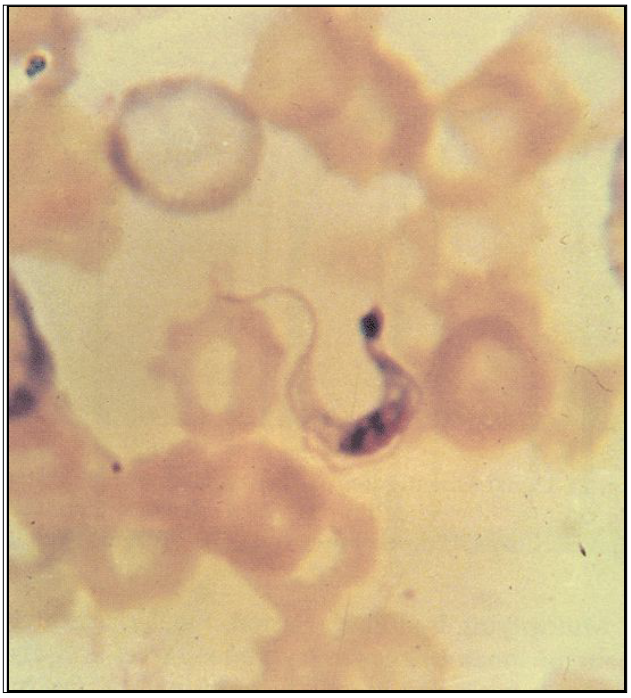


Fig. 12-11. A peripheral blood smear of *Trypanosoma cruzi.* The flagellum, undulating membrane, nucleus, and large terminal kinetoplast are obvious. The C-shape is characteristic. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 73-1150.

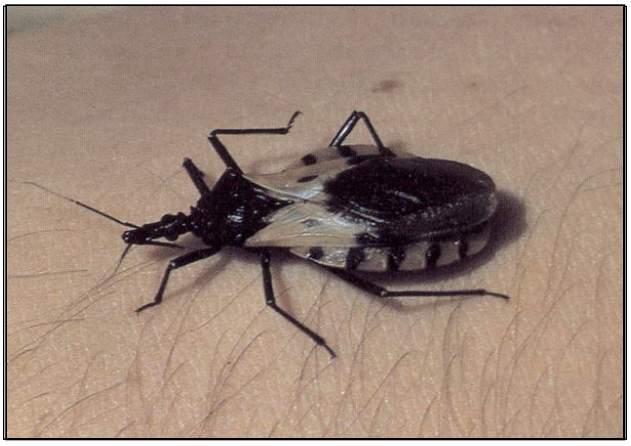


Fig. 12-12. A reduviid bug, the vector of South American trypanosomiasis. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

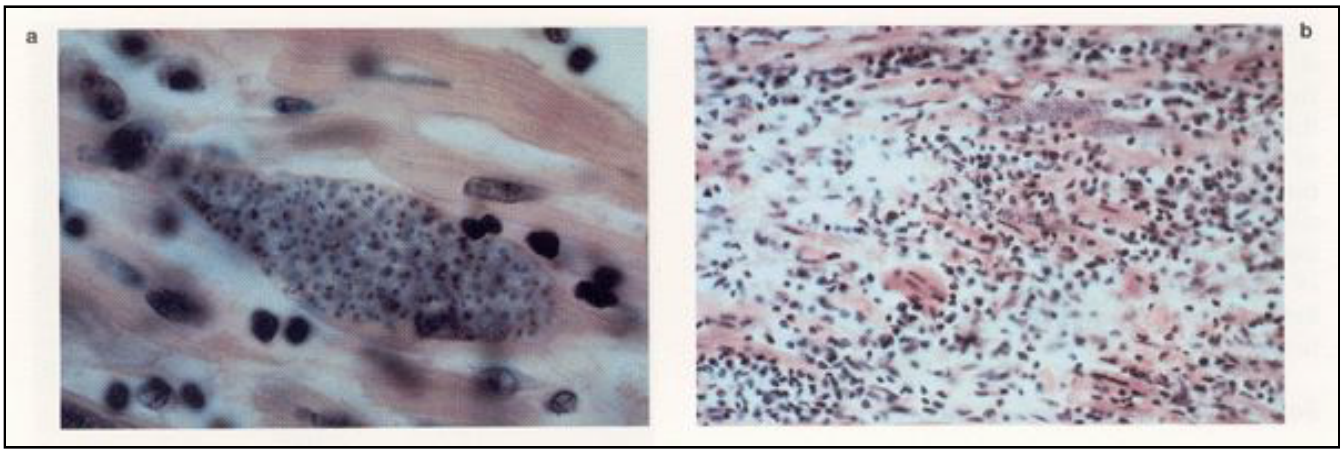


Fig. 12-13. (**a**) Amastigotes of *Trypanosoma cruzi* within a cardiac muscle fiber. (**b**) Inflammatory response elicited by the rupture of cardiac muscle fiber releasing trypanosomes. Photographs: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

Multiplying by binary fission, the *T cruzi* burst from the macrophages as trypomastigotes and disseminate widely to invade most human tissues including cardiac and skeletal muscle, parasympathetic ganglion cells, the central nervous system (CNS), and the reticuloendothelial system, where the cycle is repeated (Figure 12-13).[39,40] In addition to being vector-borne, the disease can also be transmitted transplacentally, by transfusion, transplantation, and in laboratory accidents.[41]

The circulating trypomastigotes produce a glycoprotein that may protect them from destruction by the alternate complement pathway.[38,40] Thus, parasites are relatively numerous initially and easily demonstrable on peripheral blood smear. With time, however, the human body produces neutralizing antibodies that permit complement-mediated destruction. Binding to fibronectin receptors on monocytes and macrophages, the *T cruzi* are internalized to the cytoplasm, where they are protected from the cellular oxidative burst as well as from the hostile extracellular milieu. This phase of immunologically diminished but, importantly, life-long parasitemia corresponds to latent and chronic phases of disease and creates a reservoir of disease. Although the parasite persists in the human body, an autoimmune response to the parasite may magnify the extent of parasite-induced disease—especially in the chronic stages.[42]

Clinical Manifestations

While infection may occur at any age, often only in children is clinical disease detected acutely.[39,40,43–45] Rupturing from infected macrophages about 5 days after infection, the *T cruzi* precipitate an inflammatory response at the site of inoculation. This produces an erythematous, edematous, indurated lesion, known as a *chagoma*, which is only minimally tender. A chagoma occurring on the eyelid and conjunctivae is known as Romana's sign and is often associated with bipalpebral edema and en-

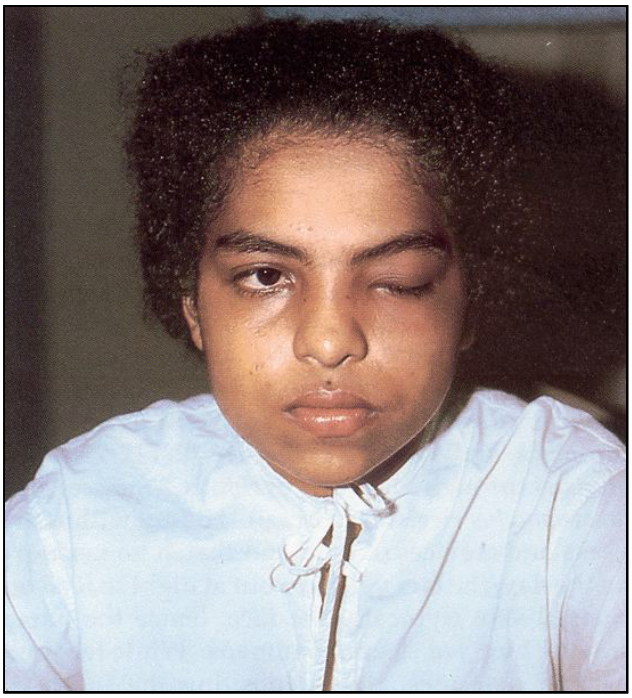


Fig. 12-14. A child manifesting Romana's sign of South American trypanosomiasis. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

larged preauricular nodes (Figure 12-14). The chagoma lasts only a few days to a couple of weeks. However, the hematogenous dissemination and subsequent widespread tissue invasion may precipitate an acute systemic illness with fever to 104°F, vomiting, diarrhea, cough, hepatosplenomegaly, edema, myocarditis, seizures, and meningoencephalitis. Occasionally, a transient morbilliform, urticarial, or erythema multiforme-like eruption precedes the hepatosplenomegaly.[39,40] Ninety percent or more of patients survive the acute stage,[40,44] which subsides in 1 to 3 months.[40]

Patients then enter a latent phase of disease during which they are relatively asymptomatic, and parasitemia is difficult to detect on a peripheral blood smear. Estimates vary, but after years or decades, 10% to 20% of patients[46] or 10% to 30% of patients[41] develop chronic symptomatic disease. Myocardial heart disease, with fibrosis, conduction defects, cardiomegaly, failure, and an apical ventricular aneurysm, is characteristic (Figures 12-15 and 12-16).[38,43–45,47] Local denervation is believed to be important in the pathogenesis of cardiac disease.[41]

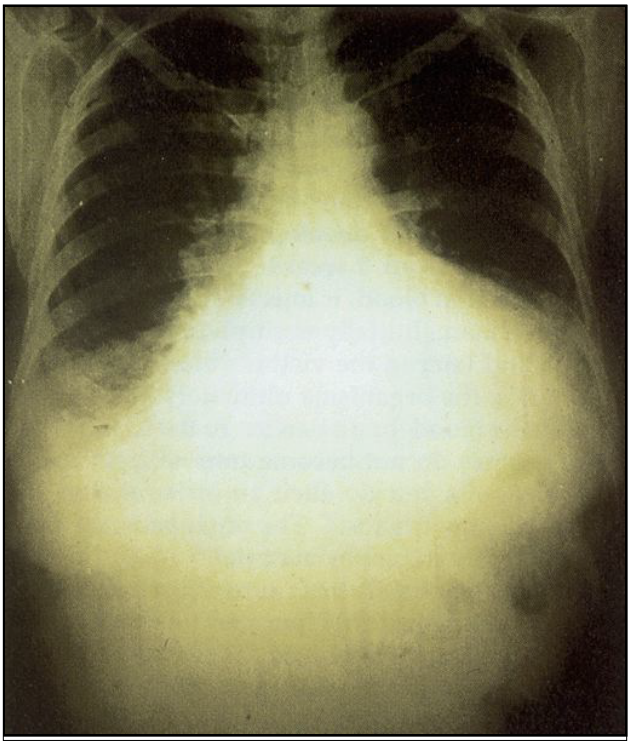


Fig. 12-15. Cardiomegaly of South American trypanosomiasis. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

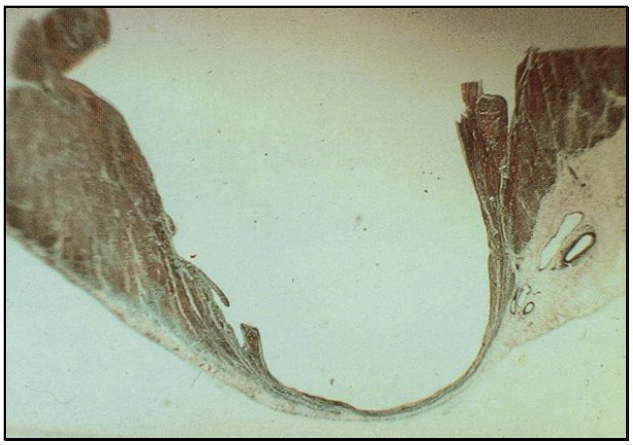


Fig. 12-16. This markedly thinned cardiac ventricular wall is due to chronic disease with *Trypanosoma cruzi*. Photograph: Courtesy of Colonel Alfred K. Cheng, Medical Corps, U.S. Air Force (ret), San Antonio, Tex.

Destruction of the parasympathetic ganglion leads to dilation of portions of the gastrointestinal tract, typically the esophagus and colon, which is known as mega syndrome.[38,40,44,48] Dysphagia, aperistalsis, regurgitation, and constipation may result.

Diagnosis and Treatment

In acute disease, diagnosis is established by finding trypomastigotes in the patient's blood. Complement fixation, indirect immunofluorescence, hemagglutination, and enzyme-linked immunosorbent assays (ELISAs) have been used for serologic diagnosis of chronic disease. However, because the tests lack specificity, it has been recommended that two different, positive assays be used to establish a diagnosis.[41] Organisms can be detected in about 50% of patients who have positive complement-fixation tests by allowing laboratory-raised reduviid bugs to feed on the individual and then identifying trypomastigotes in the bug—a technique known as xenodiagnosis.[44]

Nifurtimox (adult dose: 8–10 mg/kg/d, divided and administered orally 4 times daily for 120 days; the pediatric dosage is discussed elsewhere[32]) or benznidazole (5–7 mg/kg/d for 30–120 d, mode of administration not specified) are useful but toxic in the parasitemic phase of disease.[32,38,41] The amastigotes in tissue, however, are not eradicated by medication so the chronic disease persists despite treatment.[38,41,44,47] Therefore, control of the vector in the domestic setting is the key to preventing the disease.

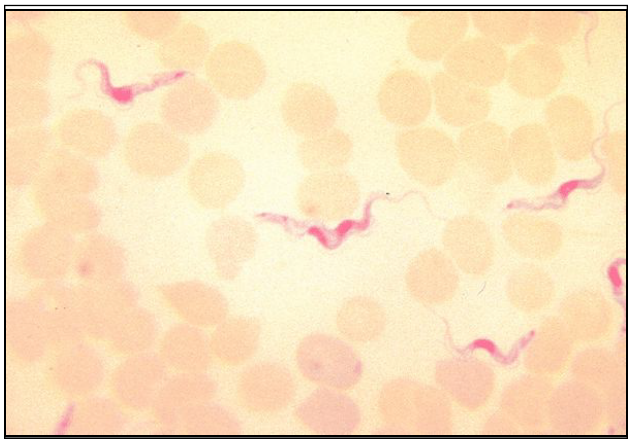


Fig. 12-17. This smear of peripheral blood shows the trypomastigotes of *Trypanosoma (T) b rhodesiense.* The flagellum, undulating membrane, large nucleus, and small terminal kinetoplast are apparent. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 74-19698.

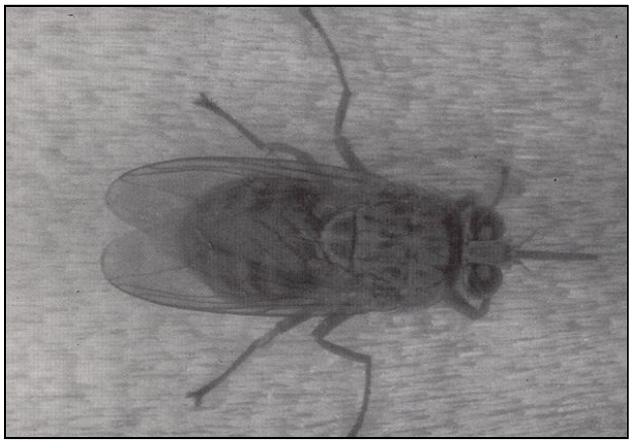


Fig. 12-18. A tseste fly—the vector of African trypanosomiasis. This specimen is *Glossina morsitans,* the vector of East African (*rhodesiense*) disease. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 75-14469.

African Trypanosomiasis

In sub-Saharan Africa, trypanosomes produce a disease known as African trypanosomiasis (sleeping sickness). Two morphologically similar organisms produce diseases with cutaneous, cardiac, and CNS manifestations that are ultimately fatal if not treated.[46] Geographical restrictions, rapidity of disease progression, and drug response are some features used to distinguish the two.[49]

Taxonomically, the organisms are placed in the genus *Trypanosoma* (subgenus *Trypanozoon*) and species *brucei*; *rhodesiense* is the subspecies in East Africa and *gambiense* in West Africa. The organisms are long and slender, measuring up to 30 x 3.5 µm, and each has a nucleus, kinetoplast, undulating membrane, and long flagellum (Figure 12-17). In East Africa, the reservoir is animal, while in West Africa, it is human.[49]

Hematophagous tsetse flies of the genus *Glossina* are the vectors of disease: *G morsitans* is the most important in East Africa (Figure 12-18) and *G palpalis* in West Africa.[49] *G morsitans* is found in savanna and woodland areas, while *G palpalis* is found in the thickets along rivers and lakes.[49,50] The flies have a painful bite, will follow moving objects, and will bite through thin clothing.[49] They are, however, susceptible to becoming desiccated; thus, brief exposures to light are potentially lethal.[50] Because the tsetse fly's distribution is widespread and the potential for resulting epidemics is great, one fourth of the African continent is effectively unavailable for human habitation.[51] In an endemic area, however, less than 1% of the flies are infected; the number increases to perhaps 5% in epidemic areas.[49] Once infected, the fly remains so for life.

In the production of human disease, the life cycle begins when the tsetse fly (*Glossina*) feeds on an infected reservoir animal.[49,50] The tsetse fly ingests trypomastigotes, which multiply by binary fission in the fly's midgut. Then moving to the fly's salivary gland, the trypomastigotes transform in stages to become infective metacyclic trypomastigotes. In those flies capable of transmitting disease, the time from ingestion to the development of infective trypanosomes is about 3 weeks. When the fly next feeds on human blood, it injects the trypanosomes into the human. Initially multiplying at the site of the bite and later in the victim's bloodstream and lymphatics, the organisms ultimately gain access, through the blood–brain barrier, to the CNS. These trypanosomes do not become internalized within the tissue cells, but do elicit an inflammatory response in many organs.[37] The organisms are difficult to identify in biopsy material.[50]

Trypanosomes shift their antigenic surface coat, with the result that effective immunological containment may not be achieved.[49] Because immunity is only type-specific, new antigenic strains of trypanosomes constantly appear in the infected host. There is an initial lymphatic and plasma cell response with a nonspecific elevation of immunoglobulin (Ig) M; later, though, a state of relative cellular and humoral immunosuppression develops.

Clinical Manifestations

The signs and symptoms of the disease vary somewhat according to the area in which the disease was contracted.[40,46,49,50,52] Within 1 to 2 weeks after the bite, a dusky red nodule, which can reach 5 cm in size, develops and lasts approximately 2 weeks. This lesion, the primary chancre, may be painful and often is located on the lower extremities. The lesion is reported more often in nonindigenous persons, who have no partial immunity, and in disease caused by *T (T) b rhodesiense*.[49,51,52]

The appearance of fever marks the beginning of the parasitemic phase of the disease; it may occur within a week in East African disease or, in West African disease, in the immunologically naive.[51,52] Then the patient may experience intermittent fevers, headache, dizziness, joint pain, hepatosplenomegaly, lymphadenopathy, malaise, anorexia, irritability, personality change, and insomnia. Posterior cervical lymphadenopathy (ie, Winterbottom's sign) is thought to be characteristic of the disease caused by *T (T) b gambiense* (Figure 12-19).[49,50] About 10 days after the initial fever, a cutaneous eruption occurs in almost 50% of the cases.[49] The asymptomatic, circinate or oval, erythematous macules with clear centers may suggest an erythema multiforme-like eruption on the trunk.[40,49,52] Kerandel's sign, variously described as a delayed sensation to pain or as a sensation of hyperesthesia, may be frequent.[37,46,49] Pancarditis and arrhythmias may develop, particularly in patients with East African (*rhodesiense*) disease. Presumably because of partial immunity, months or years may elapse before infected individuals who are long-term inhabitants of endemic West African areas experience clinical symptoms.[49,51]

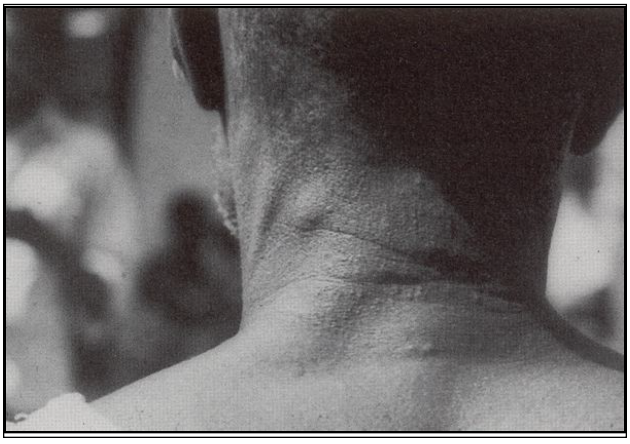


Fig. 12-19. Enlarged posterior cervical nodes—Winterbottom's sign of West African (*gambiense*) trypanosomiasis. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 74-8337.

The patient entering a late or chronic phase of disease develops signs of meningoencephalitis. Somnolence, lassitude, indifference, seizures, and personality changes may develop and, with further deterioration, coma ensues. These CNS changes may be more likely to develop in patients with West African (*gambiense*) disease because of its more gradual progression.[49] East African (*rhodesiense*) disease may be more acute and fulminant, with patients dying of cardiac disease sometimes within a few months of contracting the infection.

Diagnosis

Nonspecific abnormal laboratory findings include elevated erythrocyte sedimentation rate, markedly elevated IgM, moderately elevated IgG, cryoglobulinemia, anemia, thrombocytopenia, disseminated intravascular coagulation, and abnormal liver function tests.[46,49] Many of these are found more commonly in disease due to *T (T) b rhodesiense.*

Because of the greater degree of parasitemia, demonstration of *T (T) b rhodesiense* on thick and thin smears is easier than with *T (T) b gambiense*. Examination of aspirated fluid from a chancre or node, as well as bone marrow or cerebral spinal fluid, is useful in these situations. Increased leukocytes ($> 5/mm^3$) and protein (> 25 mg/dL), and/or increased IgM in the cerebral spinal fluid suggests a CNS invasion.[49] Serologic tests become positive 2 to 4 weeks after the onset of disease, which may be too late to be useful for diagnosing a patient with fulminant East African disease. Further, the antigenic variability of the trypanosomes makes standardizing immunofluorescence, hemagglutination, and ELISAs difficult.[46]

Therapy

Suramin, which does not cross the blood–brain barrier, is very effective in destroying trypanosomes and effecting a cure when there is no CNS disease.[34,50] The adult dose is 100 to 200 mg administered intravenously (as a test dose), then 1 g administered intravenously on days 1, 3, 7, 14, and 21.[32] The pediatric dose is 200 mg/kg administered on days 1, 3, 7, 14, and 21.

Melarsoprol is effective in all stages of sleeping sickness, including CNS involvement; but, because of its toxicity (the drug can produce a fatal reactive encephalopathy), it is used only when the CNS is involved or when other drugs fail. The adult dose is 2.0 to 3.6 mg/kg/d, administered intravenously for 3 days; after 1 week, the dose is 3.5 to 4.5 mg/kg/d, for 3 days; 7 days later, 5.0 mg/kg/d is given for 3 days. The pediatric dosage is discussed elsewhere.[32]

Amebiasis

Infection with the ameba *Entamoeba histolytica* is known as amebiasis. The spectrum of clinical presentation includes an acute dysenteric form and a less symptomatic, nondysenteric, intestinal form; some people with amebiasis are asymptomatic cyst passers. From these presentations, a variety of mechanisms have been proposed to explain the development of cutaneous lesions. In 1986, it was estimated that 480,000,000 people (slightly > 10% of the global population) were infected, with the majority (> 80%) asymptomatic.[53] Amebiasis causes 40,000 to 75,000 or more deaths per year and may be the third-leading parasitic cause of death.[53,54] Significant numbers of U.S. military personnel were exposed to amebiasis during World War I, World War II, and the Korean conflict. During World War II, at least 1.2 million man-days of duty may have been lost to this disease. Unfortunately, no reliable statistics are available to reflect the numbers or types of extraintestinal amebiasis cases. Cutaneous amebic disease was rarely seen in the Vietnam conflict.[55]

Although the organism has been identified in insects and other animals, humans are considered to be the reservoir of disease.[53,56] Infection is acquired when cysts from fecally contaminated sources (usually food or water) are ingested.[40,53,56–58] Cysts may survive for months in a warm, moist environment outside the host; further, they are resistant to chlorine concentrations that are usually used for water purification.[56] The spherical cysts (5–25 µm in diameter) have a thick wall that provides protection in the acidic gastric milieu. When they reach small intestine, excystation and division occur; each quadrinucleate cyst produces eight trophozoites that vary in size from 15 to 60 µm. Trophozoites are carried to the large intestine where various hosts or amebic factors (discussed below) determine whether tissue invasion or simple colonization of the bowel by trophozoites will occur. The cycle is established when trophozoites divide and form quadrinucleate cysts that are then passed in the stool. In patients who are experiencing diarrhea, trophozoites may be passed prior to becoming encysted.

Intestinal and Extraintestinal Manifestations

Symptomatic amebiasis is produced when the host's tissues are invaded. Bacterial flora in the gut, nutritional status, and cellular immune responses may be important host parameters; while amebic strains, adhesins, cytotoxins, and contact-dependent cytolysis are considered to be the parasitic determinants of tissue damage.[58,59]

Asymptomatic infections—detected only by the presence of cysts in screening examinations—account for most human infection. Acute disease may develop suddenly 1 to 3 weeks after the cysts are ingested. Abdominal cramps, fever, chills, headaches, tenesmus, and diarrheal stools with

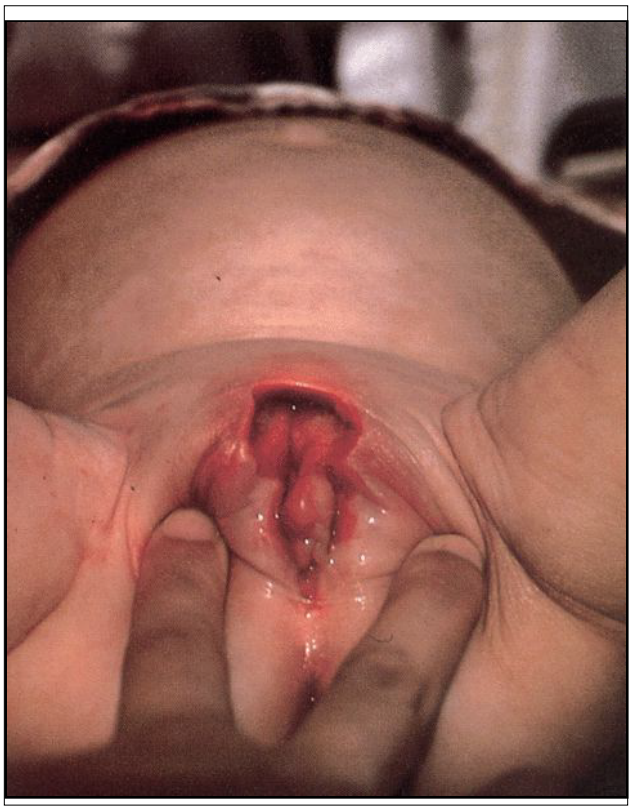


Fig. 12-20. Cutaneous amebiasis of the anterior portion of the external genitalia in a female child. Photograph: Courtesy of Jorge Molina, M.D., Honduras, Central America.

bloody mucus and fewer leukocytes than are characteristic of bacterial dysentery may develop. Nondysenteric intestinal disease may be characterized by intermittent constipation, watery or mushy stools, flatulence, abdominal cramps, fatigue, and weight loss. Extraintestinal disease, most often in the form of liver abscesses, can develop in patients who might not have manifested intestinal symptoms.[56]

Cutaneous Manifestation

Cutaneous lesions of amebiasis seem to be extremely rare and are reported in literature as isolated cases.[60–62] A review of 5,000 South African cases found only two patients with cutaneous disease.[63] Proposed mechanisms of cutaneous involvement include direct extension of intestinal disease onto the skin, extension of liver abscess to the skin, direct inoculation during anal intercourse, and, in young children, trophozoites retained in direct contact with the skin under diapers.[57,62] Hematogenous and lymphatic spread is controversial. Patients with lesions, which are most commonly located in the anogenital region, present with painful ulcerations that may enlarge rapidly (Figure 12-20). The border may be red or violaceous, and the edges may be verrucous or undermined. The base can have granulation tissue and may have a purulent exudate. The differential diagnosis includes syphilis, granuloma inguinale, leishmania, deep fungal infections, tuberculosis, condyloma, inflammatory bowel disease, pyoderma gangrenosum, pemphigus vegetans, and carcinoma.

Diagnosis

The diagnosis of cutaneous disease is established by finding trophozoites in scrapings or biopsy of the skin lesion. The presence of phagocytized erythrocytes or the use of special stains may be helpful in distinguishing trophozoites from histiocytes in tissue sections.[57] Thus, cutaneous amebiasis may be more amenable to direct diagnosis than intestinal or liver amebiasis, with their attendant difficulties of demonstrating the trophozoites or cysts. Indirect hemagglutination, immunofluorescence, and ELISAs are usually positive in patients with amebiasis, but these tests are variably sensitive in detecting asymptomatic carriers.[64]

Therapy

A variety of drugs are available to treat amebiasis of intestinal and extraintestinal sites.[32] Cutaneous disease seems to respond well to metronidazole; but emetine, dihydroemetine, and hydroxyquinolone have also been reported successful.[61,62] Because metronidazole is well absorbed, iodoquinol or paromomycin, which achieve higher luminal concentrations, should be used to eradicate noninvasive amebae in the intestine.[32,56] The doses are, for metronidazole, 750 mg administered three times daily for 10 days; for iodoquinol, 650 mg administered three times daily for 20 days (not to exceed 2 g/d and not to exceed 20 d); and for paromomycin, 25 to 30 mg/kg/d, divided and administered in three doses for 7 days. The pediatric dosage is discussed elsewhere.[32]

HELMINTHIC INFECTIONS

Helminth is derived from the Greek word *helmins*, meaning worm. For practical medical purposes, the helminths are categorized as annelids (ie, phylum Annelida, the segmented worms), nematodes (ie, phylum Nematoda, the roundworms), and platyhelminths (ie, phylum Platyhelminthes, the flatworms). The platyhelminths are further subdivided into trematodes (ie, flukes) and cestodes (ie, tapeworms) (Exhibit 12-1). While almost any worm infestation may elicit nonspecific cutaneous findings (eg, urticaria) or laboratory abnormalities (eg, eosinophilia), only the characteristic findings that would suggest skin penetration are emphasized. Thus, this discussion focuses on nematodes and trematodes; cestodes are not discussed.

Although sanitary and combat conditions amenable to the acquisition of helminthic infections existed in many of the theaters of operations in World War II, it was from the Pacific that infections were reported in significant numbers.[4,65–67] Prevalence surveys revealed that 10% to 40% of U.S. troops had human hookworm infection, perhaps in excess of 10,000 had filariasis, and more that 1,300 had schistosomiasis.[65–67] Strongyloidiasis was diagnosed in groups of U.S. military personnel who had been prisoners of war and who had worked on the Burma–Thailand Railroad during World War II.[68] Outbreaks of human hookworm disease were documented in the Vietnam conflict, and in one small study of 75 returning servicemen, the prevalence of human hook-

EXHIBIT 12-1

HELMINTHS THAT PRODUCE CUTANEOUS DISEASE

Nematodes (phylum Nematoda: Roundworms)
- Hookworms
  - Human
  - Animal
- *Strongyloides stercoralis*
- Filaria
- Dracuncula
- Trichinella

Platyhelminths (phylum Platyhelminthes: Flatworms)
- Trematodes (flukes)
  - Schistosomes
- Cestodes (tapeworms)

worm disease or strongyloidiasis or both ranged from 15% to 55%.[56] Although filariasis was endemic, few cases were ever documented among U.S. troops.[55] Finally, an outbreak of human hookworm disease involving over 200 soldiers who participated in military operations in Grenada has been reported.[69]

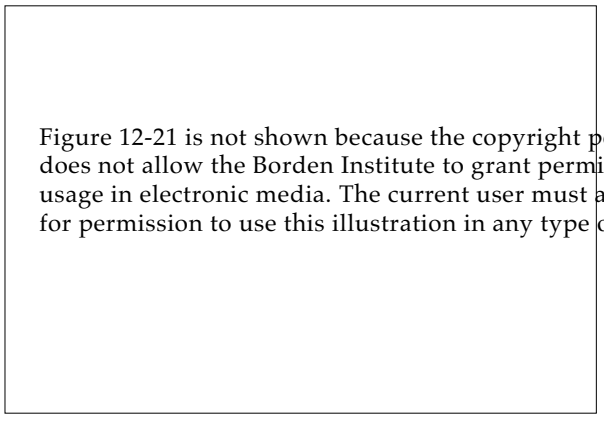
Human Hookworm Disease

Human hookworm disease is caused by the roundworms *Ancylostoma duodenale* and *Necator americanus*, both of which are found worldwide. The life cycle begins when female worms, residing in the host's small intestine, release eggs that are passed in the feces.[70,71] When the management of human waste is poor and the proper conditions of shade, sandy soil, warm temperature, and relatively high humidity prevail, the eggs hatch in the soil. Larvae emerge, develop through a series of stages, and become infective filariform larvae. On contact with human skin (eg, bare feet), the larvae penetrate the skin, pass into the venous circulation, and are carried to the lung where they rupture into the alveoli. Then moving up the victim's respiratory tree to the pharynx, the larvae are swallowed and come to rest in the host's gut, where the larvae mature without invading tissue. Adult females tend to be larger than males and may be 9 to 13 mm in length; adult worms may live 6 years or longer. Hookworm eggs begin to appear in human feces within approximately 2 months after the skin was penetrated.[71]

Cutaneous Manifestations

Manifestations of human hookworm infection may occur (*a*) coincident with larval migration to other tissues or (*b*) as a result of chronic parasitic infection of the bowel. Cutaneous disease develops when penetration of the skin occurs and is frequently described as "ground itch." Most often, disease develops among people who go into contaminated areas without wearing shoes; however, contaminated soil may come in contact with the skin by passing through the vents or eyelets in boots or through holes in torn uniforms, or by being flung about by troops actively engaged in digging.[55] Experimental studies showed that a first exposure to the larvae of *N americanus* produces erythematous patches 24 hours later at the site of penetration (Figure 12-21).[72] By 48 hours after penetration,

a



b

Fig. 12-21. (**a**) Erythematous patches apparent 24 hours after larvae of *Necator americanus* have penetrated the skin of a volunteer. (**b**) Punctate, petechial papules that developed 48 hours after larvae of *Necator americanus* penetrated the skin of a volunteer. Photographs reprinted by permision of Cline BL. *Am. J. Trop. Med. Hyg*. 1984;33:390.

discrete, punctate, erythematous papules are frequently present. Pruritus is common. If rechallenged with larvae several weeks after the initial exposure, the host develops pruritic, erythematous, edematous, linear, threadlike tracts marking larval migration in the skin (Figure 12-22). This burrow is referred to as cutaneous larva migrans (also called creeping eruption), a finding also noted in other parasitic helminthic infections (Table 12-2). The tract progresses for approximately 1 week. With long intervals between recurrent exposure, the intensity of the cutaneous reaction wanes.[73]

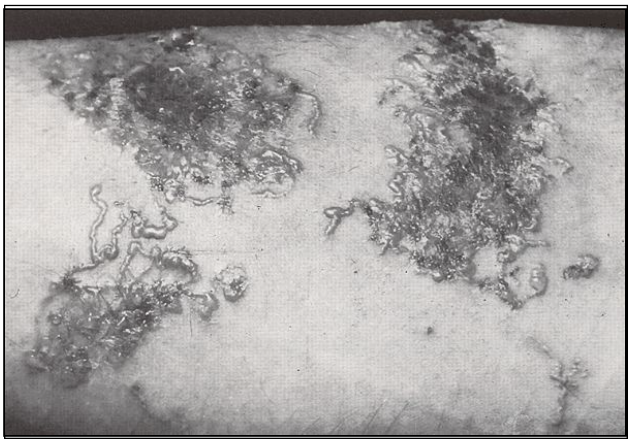


Fig. 12-22. These threadlike, meandering burrows are caused by *Necator americanus*. Known as cutaneous larva migrans, this lesion is typical in patients who are immunologically sensitized to the organism. Photograph: Courtesy of Paul C. Beaver, PhD, Tulane University, New Orleans, La.

Pulmonary and Gastrointestinal Manifestations

Pulmonary symptoms attributed to larval migration through the lung include cough and wheezing, and radiography may show associated pulmonary infiltrates. Gastrointestinal symptoms include abdominal pain, flatulence, nausea, vomiting, and diarrhea. Iron deficiency anemia is a characteristic finding, although it is dependent on the species, total worm burden, duration of infection, and nutri-

TABLE 12-2

PARASITES THAT PRODUCE A CUTANEOUS LARVA MIGRANS–LIKE ERUPTION

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tional status of the host. Eosinophilia may also be present.[69,71,74]

Diagnosis and Treatment

Diagnosis of human hookworm disease is made by finding hookworm ova in stool specimens. The current recommended treatment regimen for adults and pediatric patients is 100 mg of mebendazole administered orally twice daily for 3 days. A single, 400-mg dose of albendazole is an alternative.[32]

Animal Hookworm

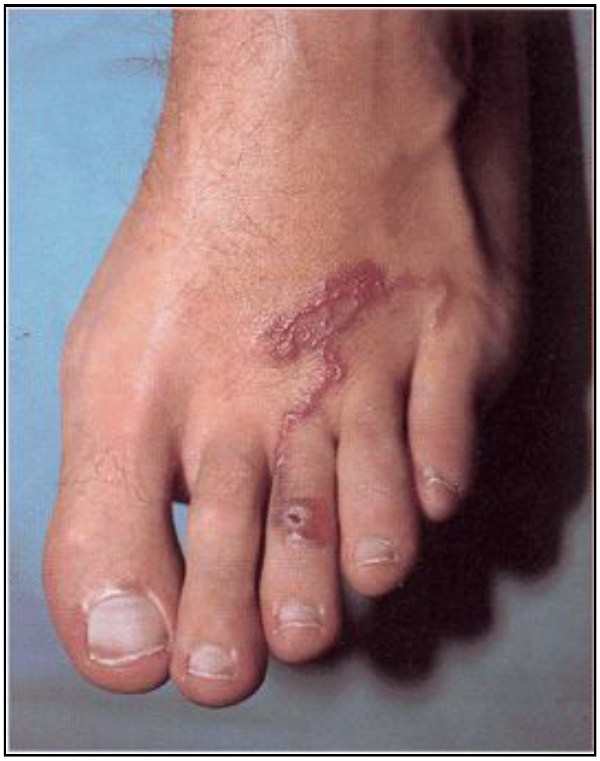
Worldwide, *Ancylostoma braziliense*, the dog or cat hookworm, is the most common cause of cutaneous larva migrans (see Table 12-2 and Figure 12-23).[75] Eggs passed in the feces of infected dogs or cats hatch in the soil and develop into infective filariform larvae. After they penetrate human skin, these larvae lack the ability to invade further and complete their life cycle. Thus, they meander erratically through the epidermis producing raised, threadlike, serpiginous, pruritic, erythematous tracks that extend a few centimeters a day. Attempts to demonstrate the worm by biopsy are usually futile because the cutaneous change develops after the larva's passage. Because the human is a "dead-end" host, the parasite usually dies. However, one study has shown that if untreated, 64% of patients continued to have lesions after 4 weeks, although the total number of lesions was markedly decreased.[76] Pulmonary and gastrointestinal symptoms do not develop because systemic invasion of and infection with these parasites do not occur.

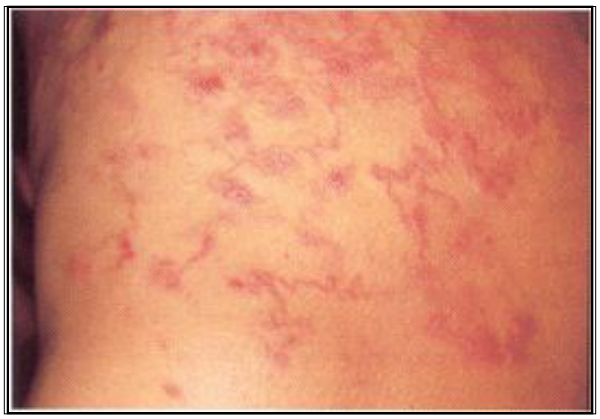
The cutaneous lesions of dog or cat hookworm may be treated topically with 10% thiabendazole suspension four times daily for 7 days, or until 1 or 2 days after the last tracks have resolved, is effective.[77,78] Thiabendazole (50 mg/kg/d, divided and administered in two doses, maximum 3 g/d, for 2–5 d) may be used if oral treatment is elected. Toxicity may require dose reduction.[32]

Strongyloidiasis

After penetrating the skin, *Strongyloides stercoralis* (commonly known as threadworm) takes a migratory pathway virtually identical to that of the human hookworm. Eggs generally hatch in the bowel mucosa, and thus the larval form rather than eggs are found most often in the feces. However, once the mature female worm (approximately 1 mm in

a





b

Fig. 12-23. (**a**) Thread-like serpiginous, meandering burrow of cutaneous larva migrans. (**b**) Multiple serpiginous burrows of cutaneous larva migrans of the back of a patient. Photograph b: Courtesy of Jorge Molina, M.D., Honduras, Central America.

size) starts producing eggs, propagation takes one of three forms[79]:

1. Passed in the feces, the larvae develop to an infectious stage, which finds another human host to penetrate.
2. Alternatively, under ideal climatic conditions, the larvae may develop into adults in the soil and thus propagate outside the host.
3. Finally, in the autoinfection cycle, the infectious larvae develop in the bowel of an infected host. Instead of passing in the feces, these infectious larvae penetrate the bowel mucosa or perianal skin and migrate back to the lung to resume the migratory cycle and perpetuate the infection in the same host.

Just as with human hookworm, the three phases of clinical manifestations of strongyloidiasis, which correspond to the migratory pathway, are the cutaneous, pulmonary, and gastrointestinal.[71,79]

Cutaneous Manifestations

Penetration of the skin and tissue migration are associated with parasitic secretion of a metalloprotease, which degrades the elastin and the dermal extracellular matrix.[80] Most often seen in the autoinfection cycle, the distinctive cutaneous eruption is that of a migratory linear or serpiginous, pruritic, erythematous, urticarial band (Figure 12-24), which may move as much as 10 cm or more per day. Because of its rapid movement, this eruption is often referred to as larva currens.

Pulmonary, Gastrointestinal, and Hematological Manifestations

Pulmonary symptoms or findings may include cough, hemoptysis, shortness of breath, wheezing, and transient pulmonary infiltrates. Gastrointestinal symptoms include abdominal pain, vomiting, bloating, and diarrhea. Weight loss and eosinophilia are common findings. Of particular significance is the fact that up to 40 years later the infection may persist.[68,81–85] Persistent infection, when combined with suppression of the immune system, may result in an overwhelming, potentially fatal, infection associated with multiorgan larval invasion and bacteremia.[86–88] In these patients, the multiple linear burrows of strongyloides may have a hemorrhagic or petechial component.[89]

Diagnosis and Treatment

The cutaneous eruption is diagnostic of strongyloidiasis, and in its absence the diagnosis can be quite difficult. Finding larvae or, rarely, eggs in feces is a tedious and time-consuming task. Serologic tests by means of ELISA or indirect immunofluorescence may be helpful.[90,91] Treatment for both children and adults is with thiabendazole 50 mg/kg/d, divided and administered in two doses (maximum 3 g/d) for 2 days. Patients with disseminated strongyloidiasis may require a 5-day course of therapy; treatment of patients who are immunocompromised may require further modification.[32]

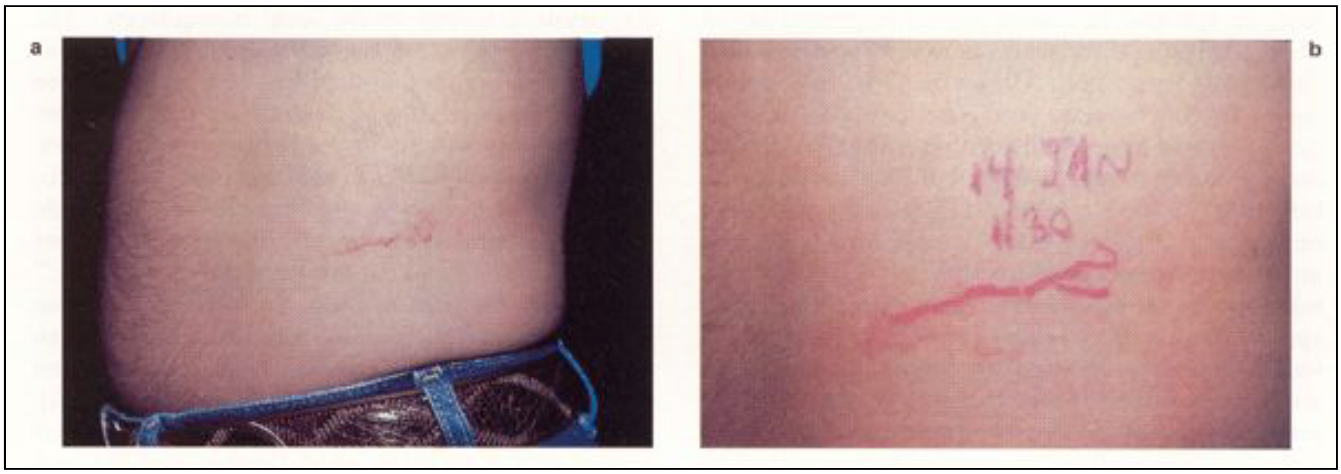


Fig. 12-24. (**a**) A serpiginous, urticarial track of *Strongyloides stercoralis*. (**b**) In the same patient, the eruption that was present on initial examination at 1130 hours was traced using a surgical marking pen. The unmarked portion shows how far the burrow had progressed in only 30 minutes (ie, by 1200 hours on the same day).

Filariasis

Eight species of roundworm belonging to the family Filarioidea (hence the name filariasis) develop to adulthood in humans; of them, six are generally accepted as being pathogenic (Table 12-3).[92] The life cycles of the filariae are similar.[92,93] Microfilarial larvae in the blood of the human host are ingested when the insect vectors feed on infected humans. Within the vector, the microfilariae migrate to specific sites and develop from first-stage larvae into infective third-stage larvae. Then, when feeding, the vector transmits the infective larvae into a human, where the organism molts twice more to become an adult worm. The adult worm may be found in the lymphatic vessels, lymph nodes, or subcutaneous tissue.

The following observations have been made regarding the host–parasite interaction[94]:

- In endemic areas, a large percentage of the populace may have microfilaremia but little detectable disease.
- Individuals immigrating to areas of endemicity may experience symptoms due to infection with adult worms and yet not have demonstrable microfilaremia.
- Symptoms may vary markedly among those who develop overt infection.

It is the interplay of humoral and cellular immune responses that determines the manifestation of disease.[95] Most individuals in endemic areas seem to develop a humoral antifilarial IgE response. Effector immunological responses (eg, lymphocyte proliferative response, gamma interferon generation, or IgE and IgG production) to microfilariae seem to be specifically and actively suppressed in those patients without clinical disease. In endemic areas, the effector responses are enhanced in a small percentage of individuals, who develop the clinical manifestations of the disease. Tolerance to parasitic infection (ie, there is no overt clinical disease) may be prenatally determined by exposure to filarial antigens. The mechanisms that cause a shift from tolerance (with suppression of specific immune responses) to responsiveness (with expression of effector immune responses) are unknown. Individuals from nonendemic areas develop characteristic inflammatory responses typical of the diseases by virtue of intact effector immune responses when they move into endemic areas. Thus, the vast majority of these individuals are without detectable microfilaremia.[66]

TABLE 12-3

FILARIAE OF MEDICAL SIGNIFICANCE

Organism	Vector
Wuchereria bancrofti	Mosquito
Brugia malayi	Mosquito
Brugia timori	Mosquito
Loa loa	Deerfly (*Chrysops*)
Onchocerca volvulus	Blackfly (*Simulium*)
Mansonella streptocerca	Midge (*Culicoides*)

Bancroftian Filariasis

Bancroftian filariasis is due to filarial infection with *Wuchereria bancrofti,* which is found focally in tropical and subtropical regions throughout the world: sub-Saharan Africa, Asia, the South Pacific and western areas of the Pacific, the Caribbean region, the eastern coastal plains of South America, and portions of Central America.[96–98] The adult worms are found in the patient's lymphatic vessels and nodes and may produce microfilariae over a 2- to 4-year period. Female worms measure approximately 100 mm x 0.3 mm; males are about one half that size. Microfilariae generally are absent from the bloodstream during the day and are found in greatest numbers during the 4-hour period before and after midnight (ie, nocturnal periodicity)—corresponding to the feeding habits of the mosquito. In contrast is the diurnal periodicity seen in the South Pacific—a phenomenon that is an adaptation to the day-feeding habits of the local mosquitoes. The vectors of disease are mosquito species of the genera *Anopheles*, *Culex*, and *Aedes*. Marked variation exists with regard to efficiency of transmission: in Rangoon, Burma (now known as Yangon, Myanmar), 16,000 bites of infected mosquitoes produced but one overt case of Bancroftian filariasis; whereas in rural Tanzania, 200 bites per person per year maintained infection within the population.[96]

Clinical Manifestations. In individuals from nonendemic areas, manifestations of Bancroftian filariasis begin within 5 to 18 months of being bitten and are localized to the genitalia (42%), arms (25%), and legs (11%).[96] Genital disease includes edema of scrotal skin, funiculitis, epididymitis, orchitis, and hydrocele. A distinctive lymphangitis of the arms or legs develops in many patients and is characterized by a unique retrograde spread or extension.

Starting in a single node, erythematous patches of subcutaneous edema, or diffuse erythema and edema, develop and progress distally. Although the nodes and lymphangitis are tender, pain is not significant. Constitutional signs and symptoms may vary from no symptoms at all to headache, backache, fatigue, and, in some cases, fever, chills, and malaise.[96,98,99] The onset of genital and adenolymphangitis is often acute, lasts a few days, and is recurrent. Increased heat, physical activity, and fatigue seem to precipitate relapses.

The inflammatory histological response to the adult and, more importantly, dead or dying filariae may result in the clinical manifestations of filariasis.[96] Yet, in a small study that spanned 16 years after World War II, while the percentages of infected servicemen who experienced recurring attacks of disease increased, none developed elephantiasis or chronic disabling disease.[100] This favorable outcome was attributed to rapid evacuation of servicemen with acute filariasis. For it is repeated, acute attacks from repeated infection that are thought to produce lymphatic scarring severe enough to obstruct the lymphatics, producing elephantiasis (Figure 12-25).

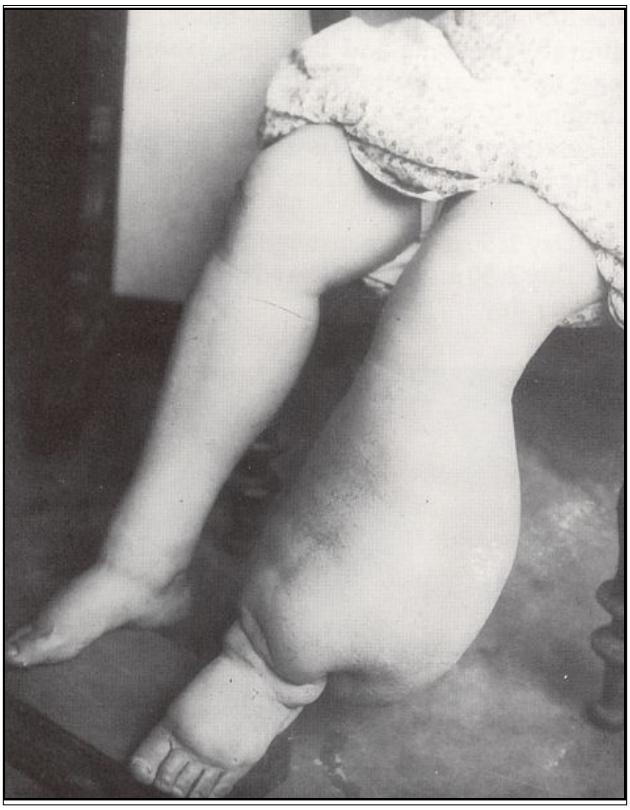


Fig. 12-25. This patient's unilateral elephantiasis is caused by filariasis. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 78873.

Diagnosis. Diagnosis of Bancroftian filariasis is made by associating signs and symptoms with a history of travel to endemic areas. Eosinophilia may be present in acute disease. Identification of microfilariae (among residents in endemic areas in whom this is typical) in peripheral blood smears is the best means to establish the diagnosis. Immunodiagnostic assays to detect infection are being actively pursued with deoxyribonucleic acid (DNA) probes showing great promise; ELISAs are available in some laboratories.[95,96]

Treatment. Diethylcarbamazine, which has been the standard of treatment for years, kills microfilariae and is toxic to adult worms when administered in the following adult doses[32,96]:

- Day 1: 50 mg, administered orally after a meal
- Day 2: 50 mg, administered orally three times per day
- Day 3: 100 mg, administered orally three times per day
- Days 4 through 21: 6 mg/kg/d, administered orally in three doses

However, in a study of asymptomatic patients with microfilaremia, ivermectin in single doses seems to be effective in long-term suppression of microfilaremia.[101,102] Ivermectin's effect on the adult parasite is unknown. Nevertheless, eradicating the microfilariae is the key to stopping vector-borne transmission.

Malayan Filariasis and Timorian Filariasis

Malayan filariasis and Timorian filariasis are due to *Brugia malayi* and *Brugia timori*, respectively, and are more limited in their geographical distribution than is Bancroftian filariasis.[96] Both diseases are found in or near Indonesia; *B malayi* is found in Malaysia and the Philippines as well. Humans still serve as the primary reservoir hosts; however, animals may also serve as reservoirs for *B malayi*. In both diseases, axillary or inguinal lymphadenitis, lymphangitis, and fever are common. Lymphatic abscesses and resultant scarring are common. In areas where Malayan filariasis is endemic, elephantiasis is uncommon; when it does occur, it tends to involve the distal portions of the extremity. Lymphedema of the leg frequently progresses to elephantiasis in Timorian disease.

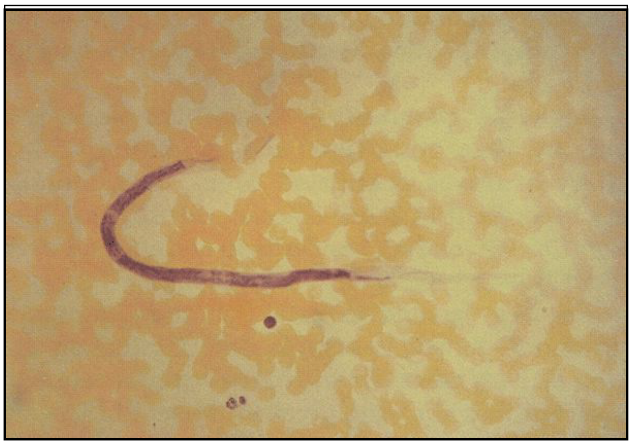


Fig. 12-26. Microfilaria of *Loa loa*. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 75-6618.

Loiasis

Loiasis is caused by infection with *Loa loa* and is found in the rain forests of central and West Africa.[103] The adult female worm measures 50 to 70 mm x 0.55 mm; the male is approximately one half the size. Both can be found in the subcutaneous tissue of the skin. In patients with microfilaremia, microfilariae are found in the bloodstream in highest numbers during the day, thus showing what is termed diurnal periodicity (Figure 12-26). Deerflies, large flies of the genus *Chrysops*, are the vectors of disease (Figure 12-27). The flies live under the rain forest canopy near streams and are attracted by the movement of people or vehicles below.

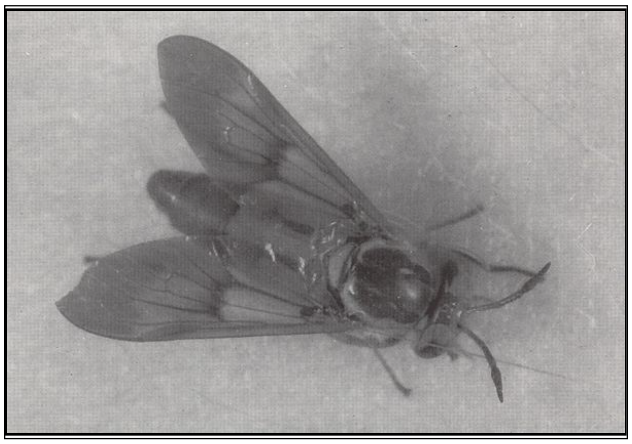


Fig. 12-27. A deerfly of the genus *Chrysops*—the usual vector of *Loa loa*. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 72-4516.

Clinical Manifestations. A study of 20 individuals from nonendemic areas who visited an endemic area found that generalized or localized pruritus (75%); transient, nontender areas of angioedema (70%); and urticaria (55%) were the major signs and symptoms.[104] Ocular involvement, manifested as a worm migrating subconjunctivally, was noted in only one patient (Figure 12-28). Five of the 20 patients were asymptomatic and their disease was detected only by virtue of eosinophilia. Laboratory abnormalities include marked eosinophilia, elevated IgE, and hematuria.

The transient sites of angioedema, known as Calabar swellings, are thought to represent allergic reactions to antigenic substances that are produced by the migrating adult worm.[103,104] These swellings persist for hours to days and 1 to 150 days can elapse between recurrences. Of the 14 patients with Calabar swellings, 8 had more than six episodes in the 11-month (on average) interval between the onset of symptoms and treatment.[104]

Diagnosis. Definitive diagnosis is made by recovering a worm, either one migrating under the conjunctiva or one from a subcutaneous nodule. In natives of endemic areas, diagnosis may be made by identifying microfilariae in the blood. Otherwise, clinical symptoms and findings, laboratory findings, and response to treatment are the means of diagnosis.[103,104]

Treatment. Treatment is with diethylcarbamazine in the following adult doses[32]:

- Day 1: 50 mg administered orally after a meal
- Day 2: 50 mg administered orally three times per day

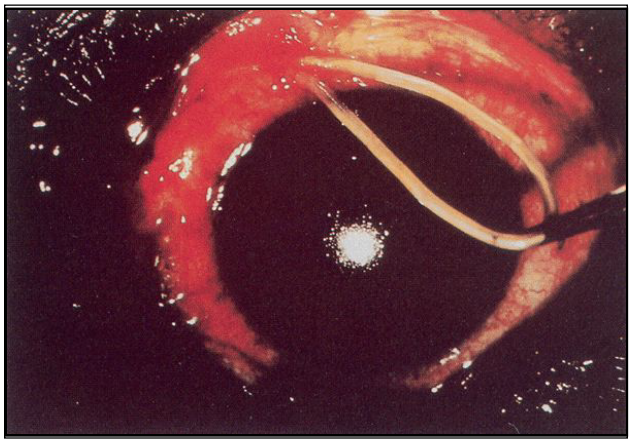


Fig. 12-28. An adult *Loa loa* being removed from a patient's eye. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 75-1789-4.

- Day 3: 100 mg administered orally three times per day
- Days 4 through 21: 9 mg/kg/d administered orally in three doses

However, in patients with marked microfilaremia, corticosteroid treatment (or even plasmapheresis) may be necessary to prevent iatrogenic meningoencephalitis, which may occur even when very low initial doses (ie, 10 mg) are used.[105] The appearance of subcutaneous nodules containing the worm and hematuria may be associated with treatment, as well.[105]

Onchocerciasis

Onchocerciasis develops in response to infection with *Onchocerca volvulus*. In 1985, it was estimated that 86 million people lived in endemic areas and of these, 17.8 million were infected.[106] More than 99% of infected individuals live in tropical Africa; the remainder are found in Yemen, Mexico, and countries in Central America and South America. Adult worms are often found encapsulated within fibrous nodules in the dermis and subcutaneous tissues near the bony prominences (Figure 12-29). Female worms, measuring 20 to 50 cm in length and 0.45 to 0.5 mm in width, may live up to 15 years, producing 1 million or more microfilariae per year. Microfilariae, which may live 6 months to 2 years, concentrate in the dermis, eyes, and regional lymph nodes (Figure 12-30).[106,107] In addition to the nodules formed in response to the adult worm, the disease manifestations are determined by the inflammatory response elicited by the migration or degeneration of microfilariae.[108] Furthermore, there are differences in the clinical presentations of the disease in different geographical locales.[107] Blackflies of the genus *Simulium* are the vectors of disease (Figure 12-31).[108] Because the flies favor habitats along rapidly moving streams or rivers, the disease tends to be focally distributed.

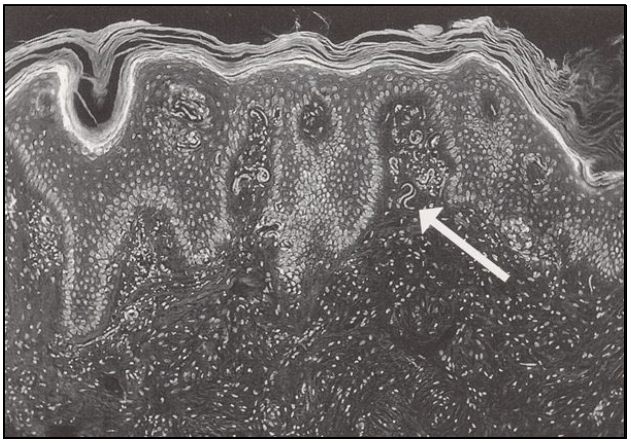


Fig. 12-30. A biopsy from a patient infected with *Onchocerca volvulus*. Numerous microfilariae (arrow) can be seen in the dermis. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 73-5681.

Clinical Manifestations. Dermatitis is one of the first signs of onchocerciasis.[106–109] In the typical African patient who is developing an immunological response to microfilariae, a symmetrical, pruritic, papular dermatitis of the lower trunk and extremities develops.[107,109] Chronic dermatitis secondary to the response to a heavy microfilarial load is associated with scaling, hypopigmentation (leop-

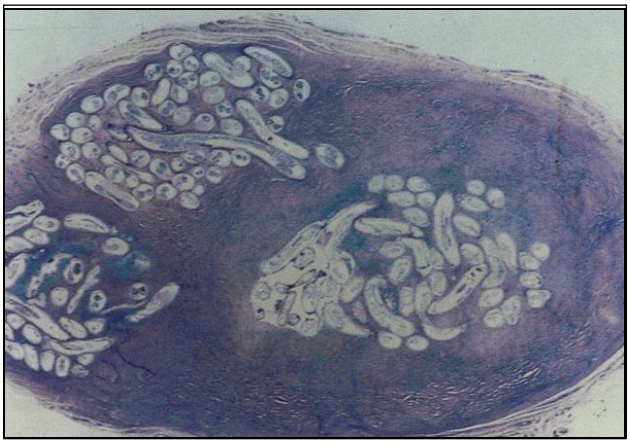


Fig. 12-29. Coiled worms can be seen in this fibrous nodule of onchocerciasis. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 69-3639.

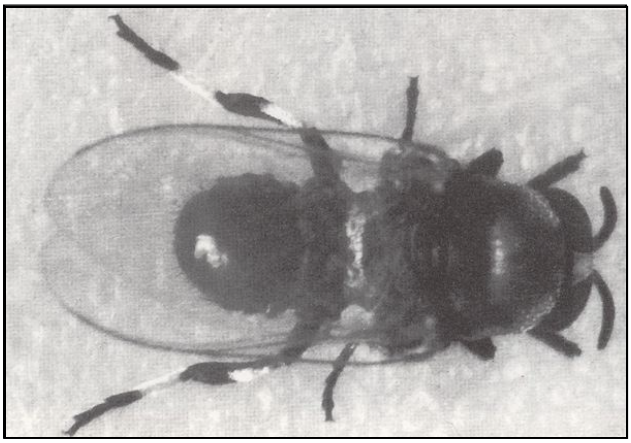


Fig. 12-31. A specimen of *Simulium damnosum*, the blackfly vector of onchocerciasis in Africa. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 72-4519-E.

ard skin), edema, and lichenification (elephant skin), ultimately followed by the appearance of atrophy (lizard skin) (Figure 12-32).[106,107,109] In Yemen, infected patients who mount a brisk immune response (with concomitant marked decrease or absence of microfilaremia) develop *sowda*: edema, hyperpigmentation, a pruritic papular eruption, and adenopathy; the condition is generally confined to one anatomical quarter or one limb.[109] In travelers who immigrate to endemic areas, sowda is the disease manifestation that commonly develops.[106] Early in the course of onchocerciasis, the differential diagnosis includes contact dermatitis, scabies, and miliaria; later manifestations of chronic disease might suggest vitiligo, pinta, yaws, streptocerciasis, or leprosy.

Dermal and subcutaneous fibrotic nodules enclose adult worms and tend to be located over bony prominences in the skin.[107] In Africa, these are found around the pelvis and lower extremities, whereas in Guatemala and Mexico, the head and upper part of the body are the more common sites (Figure 12-33). Microfilariae may accumulate in nodes that drain the areas of dermatitis. In some African patients, the inflammation and subsequent fibrosis and atrophy may cause lymph nodes or portions of bowel to hang in pockets of skin—the "hanging groin" of onchocerciasis (Figure 12-34).[106,107,110]

In heavily infected endemic areas, up to 15% of the community may be blind as the result of the inflammatory reaction to onchocercal microfilariae in the eye.[107] Patients who are acutely ill with onchocerciasis may have corneal opacites, while individuals who are chronically heavily infected may develop sclerosing keratitis, uveitis, and chorioretinitis.

Diagnosis. The diagnosis is usually established by obtaining bloodless skin snips taken over bony prominences or at sites of clinical manifestations.[107] Several hours after the specimens have been placed in saline or culture media, microscopical examina-

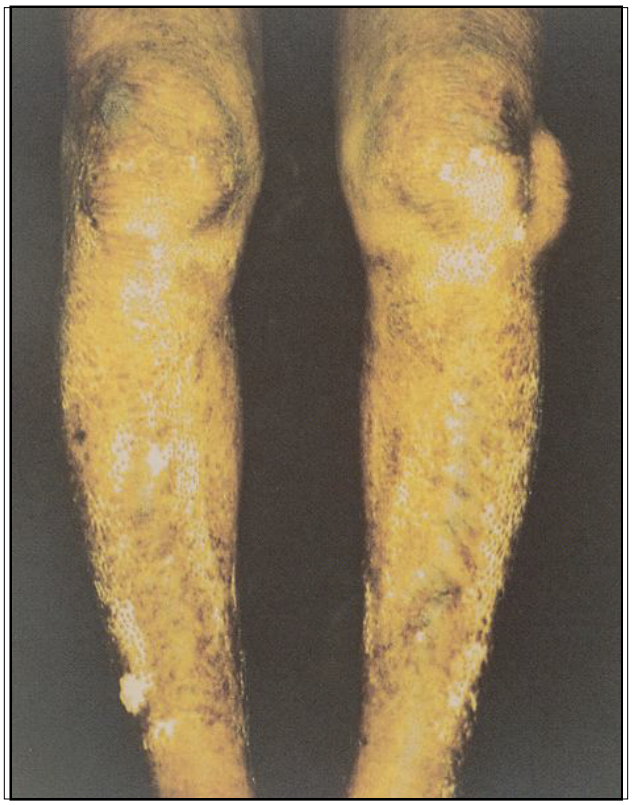


Fig. 12-32. The depigmentation found in chronic onchocerciasis. Note also the onchocercal nodule at the patient's left knee. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 72-17223.

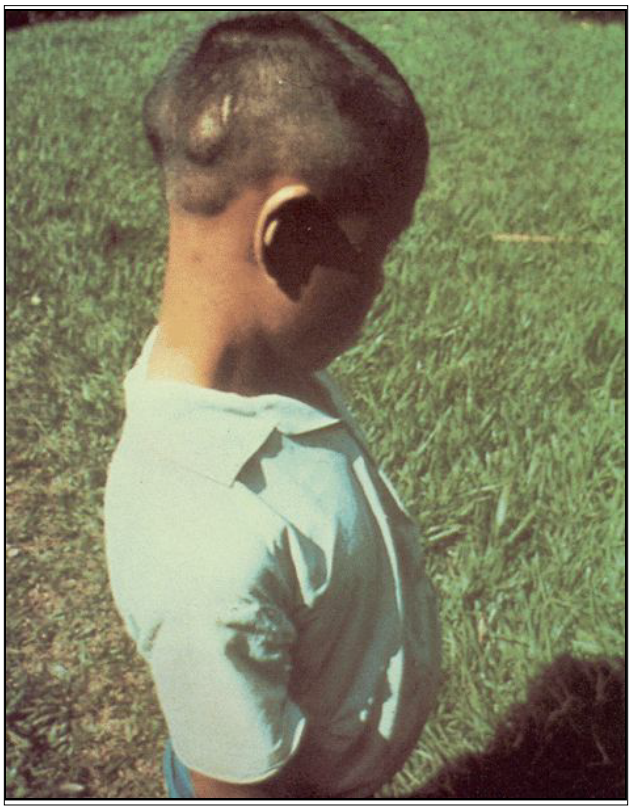


Fig. 12-33. Onchocercal nodules on the scalp of a child from Central America. Photograph: Courtesy of Captain Kenneth F. Wagner, Medical Corps, U.S. Navy (ret), Bethesda, Md.

Fig. 12-34. These bilateral inguinal and femoral adenolymphoceles are the "hanging groins" of onchocerciasis. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 73-6655.

tion of the fluid will reveal microfilariae. Biopsy of a nodule will reveal an adult worm. Slitlamp examination of the eye may reveal microfilariae. Eosinophilia is a characteristic, nonspecific finding. Serologic testing is hampered by false-positive cross-reactions with other helminths; however, more specific tests are being developed.

Treatment. Ivermectin 150 μg/kg administered orally once every 6 to 12 months is the treatment of choice for onchocerciasis.[32] Ivermectin is a well-tolerated drug that is toxic to microfilariae. Because it has no effect on the adult worms, it is given at regular intervals to destroy or stop the release of microfilariae.[32,106,107] Ivermectin is not used to treat disease in children under 5 years of age, pregnant or lactating women, or patients who are otherwise ill. In the past, diethylcarbamazine was employed in the treatment, but such treatment was fraught with problems.[107] When given to acutely ill patients, it caused a flare of the cutaneous symptoms; in heavily infected individuals, it caused severe constitutional symptoms, including marked worsening of the eye lesion. Administering doses small enough to elicit a mild exacerbation of symptoms was the basis of a potentially dangerous, indirect method of diagnosis known as the Mazzotti test, which has fallen into disfavor.

Streptocerciasis

The filarial disease streptocerciasis is caused by infection with *Mansonella streptocerca*. The disease is found in central and West Africa and is transmitted by the midge *Culicoides grahami*. Adult worms are found in the dermis of the patient's upper trunk. The microfilariae are found in the dermis and lymph nodes but have not been found in the eye. Pruritus, hypopigmented macules, axillary or inguinal adenopathy, and occasionally a few papules comprise the cutaneous manifestations. Diethylcarbamazine kills both the adult worm and microfilariae and prompts an exacerbation of cutaneous symptoms analogous to a Mazzotti reaction.[111]

Dracunculiasis

Dracunculiasis, also called Guinea worm or Medina worm, is caused by the nematode *Dracunculus medinensis* and is found focally in Africa, India, and Pakistan.[112,113] Of the 160 million people at risk, 10 to 15 million may be infected annually.[113] The cycle of human infection begins when the female worm discharges larvae into fresh-water sources. Copepods (microcrustaceans approximately 1–3 mm in length) of the genus *Cyclops* ingest the larvae, becoming the intermediate host. Copepods are found in bodies of standing (rather than flowing) water. Within this intermediate host, the larval parasite develops into an infective larva; humans become infected when they drink water containing the infected copepods. In the gastric milieu, the larva is freed from the copepod and proceeds to penetrate the human host's small intestine to reach the peritoneum, where it matures. The worm (measuring 70–120 cm x 0.17 cm) migrates to the skin where, when the human host is in contact with water, it ruptures through the skin to release the larvae into fresh water. The cycle from ingestion of filariae to release of filariae takes approximately 8 to 12 months.

Clinical Manifestations. Signs and symptoms of dracunculiasis are generally associated with the presence of the adult worm in the subcutaneous tissue.[112–114] In general, the site of eruption is on the lower extremity and is signified by the presence of a painful, erythematous nodule up to 7 cm in diameter, a pruritic blister, or both. At about the same time, constitutional symptoms such as urticaria, nausea, vomiting, diarrhea, syncope, and fever may occur. Eosinophilia is common and may be marked. Worms that migrate to aberrant locations (other than to the skin of a lower extremity) die and form abscesses that may resolve with calcification.

Diagnosis. Diagnosis may be readily obvious if the worm is carefully examined as it emerges from the nodule or blister (Figure 12-35**)**. Slowly extracting the worm by wrapping it around a small stick

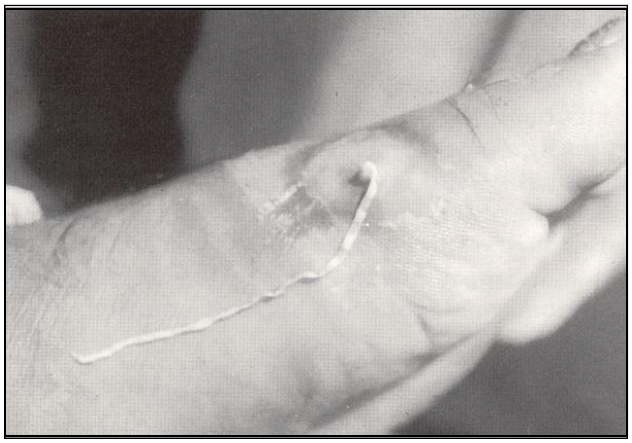


Fig. 12-35. *Dracunculus medinensis* that has been removed from its resting site at the surface of the patient's skin. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 67-1563-3.

has been tried, but excision of the nodule may be a better removal technique because it is less likely to incite inflammation.[112]

Treatment. Treatment is with metronidazole (for adults: 250 mg administered three times daily for 10 days; the dosage for children is discussed elsewhere) or thiabendazole (adult and pediatric doses: 50 mg/kg/d, divided and administered in two doses for 3 d).[32]

Neither metronidazole, which is the drug of choice, nor thiabendazole kills either the worm or the larvae, but both drugs may be useful in reducing inflammation caused by the emerging worm.[32,113] Development of safe water supplies may be the best method of eradicating the disease. Until water supplies are safe, water suspected of being contaminated should be avoided, and infected individuals should stay physically removed from the water supply source.

Trichinosis

Trichinosis develops when humans ingest inadequately cooked meat containing *Trichinella spiralis*.[115–117] Although traditionally pork is cited as the source of infection, any meat-eating animal may harbor infective larval cysts. *T spiralis* in pork is killed if the meat is fully cooked for 4 minutes at 135°F; however, 170°F is recommended to provide a margin for error. Refrigeration is another means for killing cysts.[115]

The acidity and enzymatic activity of the human digestive system disrupt the cyst and the larvae are released. Attaching to the luminal wall, the larvae mature into adults, with the female measuring 3 to 4 mm in length x 60 μm in width and the male one half that size. Before the adults are expelled from the gut about 2 weeks later, they produce larvae that penetrate the gut and disseminate through the venous and lymphatic circulation. The larvae preferentially invade skeletal muscle and encyst, where they remain viable for years. The animal sources of human infection acquire the disease by feeding on the raw flesh of infected prey or carrion or on uncooked household meat scraps.

Clinical Manifestations. Signs and symptoms of infection develop 2 to 12 days following infection; the severity is influenced by the number of cysts ingested as well as the immunological response, which is determined by previous infection.[116] Most infections are asymptomatic. While adult worms inhabit the intestine, patients may experience diarrhea, constipation, abdominal pain, and anorexia or vomiting as a result of mucosal irritation.[115–117] The phase of muscle invasion is associated with myalgias, fever, and periorbital edema. Splinter hemorrhages, conjunctival hemorrhages, and maculopapular eruptions may also be found.[116] Severely infected patients may develop encephalitis, meningitis, myocarditis, bronchopneumonia, and nephritis.[115,117] Eosinophilia is a characteristic finding, although it may not occur during the first week of disease.

Diagnosis. The larvae may be found by incision biopsy of an infected muscle. However, serologic tests such as the bentonite flocculation test, the fluorescent antibody test, or the ELISA can detect the disease 2 to 3 weeks after the infection occurs.

Treatment. The disease is usually self-limited and requires no treatment. Corticosteroids have been used to reduce severe inflammation. Additionally, patients experiencing prolonged or severe illness, may be given mebendazole in the following adult dose: 200 to 400 mg three times daily for 3 days, then 400 to 500 mg three times daily for 10 days.[32]

Schistosomiasis

The phylum Platyhelminthes contains the dorsoventrally flattened worms; of these parasites, blood flukes (schistosomes) belonging to the class Trematoda and genus *Schistosoma* are the most important producers of disease in humans. Schistosomiasis is the term generally reserved for disease produced in humans by the schistosomes *Schistosoma mansoni, S haematobium, S japonicum, S mekongi,* and *S intercalatum.*

Of the estimated 1 billion people worldwide at risk for schistosomiasis, 200 million living in 75 countries are thought to be infected.[118] *S mansoni* occurs throughout much of sub-Saharan Africa, portions of the Arabian peninsula, countries along the eastern coast of South America, and in the Caribbean. *S haematobium* is found in Africa and the Middle East, while *S japonicum* is restricted to China, Indonesia, and the Philippines.[119,120] Of these three, schistosomiasis produced by *S japonicum* is the most pathogenic, due to the greater number of eggs produced, and the most widespread. Two other species of limited geographical distribution also produce disease: *S mekongi* in Southeast Asia and *S intercalatum* in central Africa.[120]

During World War II, approximately 1,300 to 2,000 servicemen developed acute schistosomiasis in the Philippines.[67,121] Outbreaks of an acute systemic illness were reported from Vietnam; however, investigations suggested they were caused by schistosomes that typically do not parasitize humans.[122] Although no large-scale infections of schistosomiasis have been reported recently among U.S. military forces, outbreaks with high rates of infection among groups traveling in endemic areas emphasize the significant potential risk.[123]

The life cycle of the parasite begins with the production of eggs by an adult pair of flukes, which live in the venous plexus of the bladder or mesenteric plexus of the human host.[118] The species of schistosomes differ in their rate of egg production. The egg contains a *miracidium* (a larval form) that secretes enzymes that allow the egg to pass through the blood vessel and into the lumen of the bowel or bladder, from which it is then expelled. On reaching fresh standing or slowly moving water, and with correct conditions of light and temperature, the egg hatches, releasing the miracidium. First, the miracidium finds and penetrates one of the specific snails that serve as intermediate hosts; then each miracidium undergoes extensive asexual multiplication, with the result that a multitude of *cercariae* (final-stage larvae) are produced within the snail. With proper conditions of light, the cercariae, which have a head and a Y-shaped tail, are released into the water. Then, encountering humans, individual cercaria attach and release proteolytic enzymes that enable the cercaria to penetrate human skin. At the same time, the cercaria's tail is lost. Now known as a *schistosomulum*, it penetrates the dermis and passes to the lungs. From the lung, by mechanisms that are unclear, the schistosomulum passes to the host's liver, where it matures in the portal circulation to an adult schistosome. Adult worms then migrate to specific venous plexuses, where they produce eggs that are either (*a*) excreted to repeat the cycle or (*b*) pass in the venous system to other organs.

Humans are thought to be the main reservoir host for *S mansoni* and *S haematobium*.[121] On the other hand, *S japonicum* has been shown to infect a wide variety of domestic animals (eg, dogs, cats, goats, pigs, horses, water buffalo, cattle) and rodents, which then serve as additional reservoirs.[119,121]

The host–parasite interaction in the production of disease is complex.[119,124] By acquiring host antigens, the adult worm may effectively disguise itself and not incite a host immunological response. Thus, an adult fluke (measuring 12–26 mm x 0.3–0.6 mm) may reside in vessels of the venous plexus for 3 to 7 years, on average.[118] However, penetration of the schistosomulum elicits a brisk cell-mediated cytotoxic response, in which IgE and eosinophils are important components. A reaction similar to that elicited by an immune complex formation is precipitated by worm migration, the initial reaction to egg production by mature female worms, or both. The granulomatous response to the eggs, which results in obstruction of vessels, is thought to be the major determinant of pathological manifestations of chronic disease. Acute schistosomiasis is a disease usually limited to travelers entering endemic areas and being exposed for the first time. In endemic areas, most of those infected are asymptomatic and major disease manifestations develop only in a small percentage of heavily infected individuals.[119]

Clinical Manifestations. When the cercariae contact the skin and begin their penetration, a transient pruritus or burning and erythematous macules or urticarial papules may develop.[119,125,126] Over the next 3 days, a punctate hemorrhagic component followed by crusting develops at the site. After several weeks, the eruption resolves, leaving postinflammatory hyperpigmentation. In humans, this cercarial dermatitis is known as schistosomal dermatitis, is less severe than that produced by nonhuman schistosomes, and may be more severe in individuals who have been sensitized by previous exposure.[119]

An acute syndrome that begins suddenly occurs in infected individuals and seems to be related to either migration of the worm or the initial release of eggs by the mature worm.[119,121,125–127] The acute syndrome, known as Katayama fever, occurs 2 to 6 weeks after penetration by cercariae and may last 1 to 2 months. Manifestations include spiking afternoon fevers, chills, bronchitis, pneumonitis, headache, lymphadenopathy, hepatosplenomegaly, joint

pain, diarrhea, urticaria, eosinophilia, leukocytosis, and an elevated erythrocyte sedimentation rate. Katayama fever is thought to be due to immune complex formation, but, interestingly, proteinuria and glomerulonephritis are not features of this stage of disease.[124]

A late hypersensitivity reaction characterized by generalized urticaria, pruritus, lichenified papules, or dermatographism occasionally develops (Figure 12-36). This may be due to a nonspecific reaction to egg deposition.[126]

Chronic schistosomiasis is due to a granulomatous response to egg deposition in target tissues. Localized in the venous plexus of the host's bladder, *S haematobium* releases its eggs, resulting in a characteristic urogenital syndrome in which hematuria, obstructive uropathy, and bladder cancer figure prominently. The other schistosomes that cause disease in humans are found in the venous plexus of the bowel: *S japonicum* in the superior mesenteric plexus and *S mansoni* in the inferior mesenteric plexus.[119] Egg granulomas in portal presinusoidal vessels result in hepatomegaly, splenomegaly, varices, ascites, and fibrosis (Symmers' clay pipestem); those in the mesenteric distribution produce protein-losing enteropathies, malabsorption anemias, hemorrhagic intestinal polyps, and fibrosis.

Aberrant or embolic lodgment of eggs may produce lesions in a variety of other tissues, including the kidney, lung, CNS, and, rarely, the skin.[119] When skin lesions occur, they are most commonly due to *S haematobium*; genital and perigenital sites are more frequent and periumbilical less frequent sites of involvement.[119,125–132] The lesions may be papules, macules, or, especially in the female genitalia, warty tumors. Cutaneous lesions may be asymptomatic, pruritic, or painful. Complications of disease may include ulcerations, fissures, multiple sinuses, fistulae, and fibrosis.

Diagnosis. It is systemic illness rather than cutaneous disease that leads the patient to seek treatment.[125] The diagnosis of Katayama fever is considered when patients who recently have been in an endemic area present with fever, headache, fatigue, diarrhea, or eosinophilia.[123] Chronic illness due to complications of egg granulomas is suspected more readily because patients are in endemic areas. Difficulties may arise, though, when such patients present in nonendemic areas to physicians who may be less familiar with the disease.

Finding ova in the feces or urine is the standard method of diagnosis: *S haematobium* is an oval egg with a terminal spine, while the spine of *S mansoni* is lateral, and that of *S japonicum* is small and rudimentary. In acute schistosomiasis, egg production may not be detectable. Biopsy of specific (ie, egg-induced) cutaneous lesions may well reveal granulomas. Reliable serologic diagnosis is currently limited to a few research laboratories; a sensitive ELISA seems to be the most promising.[119]

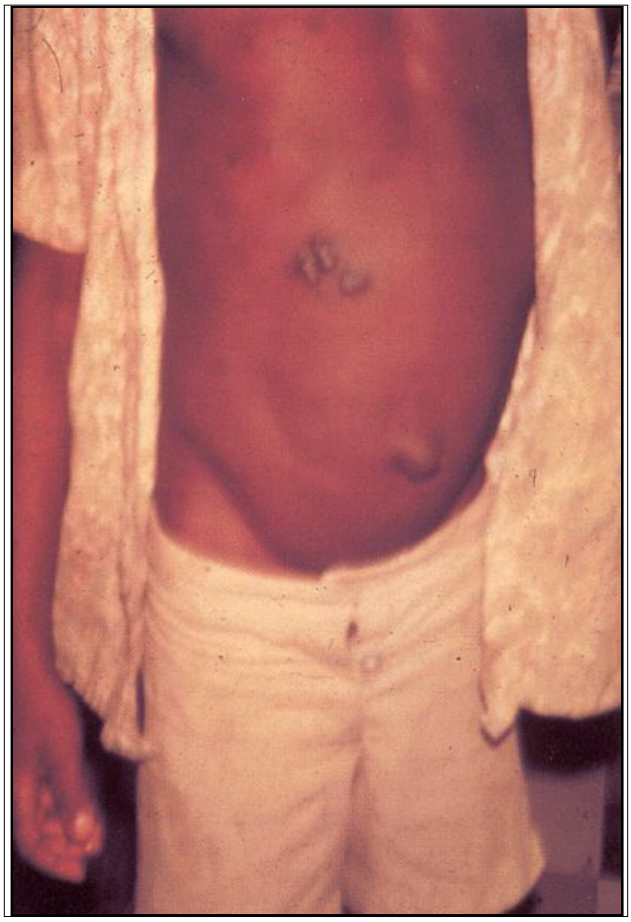


Fig. 12-36. This African patient developed these hyperpigmented nodules of cutaneous schistosomiasis on his abdomen as a manifestation of his infection with *Schistosoma mansoni*. Photograph: Courtesy of Armed Forces Institute of Pathology. Negative 78-3500-1.

Treatment. Treatment of all human schistosomiasis is with praziquantel. One schedule calls for 40 mg/kg/d administered orally in two doses for 1 day, except for *S japonicum* and *S mekongi*, which are treated by administering 60 mg/kg/d in three doses for 1 day.[32]

Because of water-control measures, bodies of water in which snails, the fluke's intermediate host,

thrive are increasing. With population migration, then, schistosomiasis is actually spreading. In endemic areas, all fresh water should be considered contaminated. When using such water for bathing purposes, pretreatment by heating to 122°F for 5 minutes or by using chlorine or iodine in concentrations similar to those used for treatment of drinking water should be used. Also, vigorous toweling or application of rubbing alcohol after potential exposure may prevent cercarial penetration.[123] Studies are ongoing to develop barrier substances that would limit skin penetration and subsequent infection.

SUMMARY

Medical support of U.S. armed forces is critical to soldiers' health and effectiveness. The failure to provide timely diagnoses and effective treatment of cutaneous diseases may cause a serious degradation in the individual's physical condition and, therefore, effectiveness. Further, the psychological impediment that can develop in soldiers so afflicted should not be denigrated. Thus, the medical officer should never forget the maxim that common diseases are common. While this generally is construed to mean that bacterial and, perhaps, fungal diseases will cause the bulk of cutaneous disease, in the tropics we should not underestimate the morbidity that indigenous diseases can cause.

Tropical regions are host to a number of diseases with which physicians trained in the United States have little practical experience. With proper clothing, appropriate use of insect repellents, proper food handling, and good training in sanitation and hygiene, soldiers may be able to avoid some of these diseases. Nevertheless, the wary medical officer must remain alert to the possibility that these conditions may develop among the troops; the physician will certainly encounter them in the population native to the area. Medical personnel who live in these areas are excellent and important sources of information about local health risks. The Armed Forces Medical Intelligence Center at Fort Detrick, Frederick, Maryland, can provide information about regional risks. Coupled with that information, knowledge of the cutaneous manifestations that are often keys to the diagnosis should provide the medical officer the opportunity to diagnose accurately and to initiate effective treatment in a timely fashion.

Finally, medical officers should make every effort to consult regularly published periodicals for the latest treatment update, as treatments for these diseases are evolving. The doses listed in this chapter generally apply to adults. It is important to note that treatment of debilitated, frail patients; the elderly; children; and pregnant women may vary from the drugs and schedules listed in this chapter. The *Medical Letter on Drugs and Therapeutics* publishes a regular update of the drugs used for treatment of parasitic infection.

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