14. Helminthic Infections

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General Considerations

Parasites are generally subdivided into three categories: protozoans, helminths, and arthropods such as ticks and insects. This chapter focuses on helminthic pathogens; protozoans are discussed elsewhere, as are general characteristics of parasite-host relationships.

Helminthic parasites are divided into three major groups: nematodes (roundworms), cestodes (tapeworms), and trematodes (flukes) [see Figure 1]. Helminthic parasites differ from protozoan parasites in several respects. First, protozoan parasites are unicellular organisms, whereas helminthic parasites are metazoan (multicellular) worms that possess differentiated organ systems. Second, most helminthic parasites do not replicate within the human host; rather, they develop to a certain stage within the human body and mature further outside the human body. During their extrahuman life cycle, helminths exist either as free-living organisms or as parasites within another host species and mature into new developmental stages capable of reinfecting humans. Thus, with only a few exceptions (i.e., those parasites capable of internal reinfection, notably, Strongyloides stercoralis and Capillaria philippinensis), augmentation of the number of adult helminthic parasites that reside within the human host requires exogenous reinfection.

A third attribute of helminthic parasites but not of protozoan parasites is their tendency to elicit eosinophilia within the tissues and blood of infected humans. The magnitude of eosinophilia tends to correlate with the extent of tissue invasion by larvae or adult helminths. For example, in several helminthic infections, such as paragonimiasis, acute schistosomiasis, and Ascaris and hookworm infections, the elicited eosinophilia is greatest during the early phases of infection, when migrations of infecting larvae and the progression of subsequent developmental stages through the tissues are greatest. In established infections, local tissue eosinophil infiltration is often present around helminths within tissues, but blood eosinophilia may be intermittent, mild, or absent. There may be no eosinophilia in established infections that are well contained within tissues (e.g., intact echinococcal cysts) or confined within the lumen of the intestinal tract (e.g., Ascaris and tapeworms). For some established infections, increases in blood eosinophilia may be episodic. Intermittent leakage of fluids from echinococcal cysts can elicit transient increases in blood eosinophil levels, as well as symptoms attributable to allergic or anaphylactic reactions (e.g., urticaria and bronchospasm). With tissue-dwelling helminths, increased eosinophilia may be associated with the migration of adult parasites, as in loiasis and gnathostomiasis.

Figure 1. Phylogenetic tree of the major helminths that afflict humans.

Certain established infections—including trichinellosis, anisakiasis, gnathostomiasis, visceral larva migrans, echinococcosis, and the several forms of filariasis—are capable of inducing eosinophilia but cannot be diagnosed on the basis of stool examination. In addition, some intestinal helminths may not be readily detectable on routine stool examination. The intestinal nematode that is most likely to cause persistent eosinophilia and that may not be detected on initial stool examination is S.
Intestinal Nematode Infections

Introduction

The major intestinal nematodes are roundworms, hookworms, whipworms, pinworms, and S. stercoralis [see Table 1]. Infection with these parasites occurs in many hundreds of millions of persons worldwide, especially in tropical areas. Children are particularly affected.

Roundworm, Hookworm, and Whipworm

Roundworms, hookworms, and whipworms are geohelminths, requiring a soil phase for the fecally expelled eggs to develop into their infective stages. Thus, infections from these parasites usually occur in rural areas with poor sanitation. In these areas, highly prevalent infections with these intestinal nematodes are major contributors to malnutrition in children.3

Epidemiology, Pathogenesis, and Clinical Features

Hookworm The World Health Organization (WHO) estimates that 700 million persons are infected with Ancylostoma duodenale or Necator americanus. Hookworm infection is more likely where the following conditions coexist: sanitary practices that permit human fecal contamination of the soil, soil that is damp enough for larval survival, and human contact with contaminated soil. Persons at risk include children, gardeners, plumbers or electricians in contact with soil, and infantry personnel.

Hookworm eggs excreted in feces hatch in the soil, releasing larvae that develop into infective larvae [see Figure 2]. Percutaneous larval penetration is the principal mode of human infection, but infections with A. duodenale may also be acquired by oral ingestion. Larval penetration of the skin often produces a pruritic, maculopapular eruption at each site of entry. In persons previously infected, serpiginous tracts of intracutaneous larval migration, as in cutaneous larva migrans, can occur. From the skin, hookworm larvae travel via the bloodstream to the lungs. The hookworm larvae enter the alveoli, ascend the tracheobronchial tree to the pharynx, and are swallowed. The development of A. duodenale larvae can be arrested for many months before the larvae proceed to the lungs for subsequent maturation. Although transpulmonary larval passage may elicit a transient eosinophilic pneumonitis, this phenomenon is much less common with hookworm infections than with roundworm infections.4 Larvae and young adult worms in the intestinal tract may cause gastrointestinal symptoms, including nausea, diarrhea, vomiting, abdominal pain (often with postprandial accentuation), and flatulence.

A major health impact of hookworm infection is iron loss resulting from the 0.1 to 0.4 ml of blood ingested daily by each adult worm [see Figure 3]. In malnourished hosts, such blood loss can lead to severe iron deficiency anemia. The number of parasites necessary to cause anemia varies with host iron and protein stores, but hookworm burdens of 40 to 160 worms are associated with hemoglobin levels below 11 g/dl. Severe anemia from the interaction of malnutrition, malaria, and hookworm infection is a major contributor to childhood mortality in areas of the world where these conditions coexist.

Roundworm Ascaris lumbricoides is the most prevalent intestinal helminthic parasite, infecting well over one billion people worldwide. Each adult female can produce up to 200,000 eggs a day. Passed in feces, these eggs are remarkably resistant to environmental stresses and are capable of remaining viable for up to 6 years. With exposure to warm, humid soil, fertilized eggs become embryonated and infectious. Most transmission occurs by ingestion of fertilized eggs on dirty hands, in fecally contaminated agricultural products or other foodstuffs, or through geophagia (the life cycle of Ascaris is illustrated in the Centers for Disease Control and Prevention Public Health Image Library [CDC PHIL], at http://phil.cdc.gov/Phil; photograph 5231). Infection is more common in areas with poor sanitation. In regions with large concentrations of Ascaris eggs in the soil, eggs may be
disseminated in the air, where they are inhaled and swallowed later with respiratory secretions.

From swallowed *Ascaris* eggs, larvae hatch in the intestine within 1 to 2 days and molt into second-stage larvae, which are carried hematogenously to the liver and lungs. Roughly 1 to 2 weeks after infection, larvae penetrate alveoli from the capillary bed and molt into third-stage larvae, which ascend the tracheobronchial tree, are swallowed, and return to the intestine. These larvae mature into adult male and female worms, measuring 10 to 30 cm in length [see Figure 4]. The fertilized adult females begin producing eggs 2 to 3 months after the initial infection.

The clinical manifestations of ascariasis occur during early larval migration or with established intestinal infections. During the phase of transpulmonary migration, eosinophilic, often migratory, pulmonary infiltrates (Loffler syndrome) can develop, especially in previously sensitized hosts. The large adult worms in the intestine usually elicit no symptoms, although they may contribute to malnutrition.

Infrequently, adult *Ascaris* worms cause serious complications. In heavy infections, especially in children, the mass of entangled adult worms may cause partial or complete intestinal obstruction. A second type of complication can develop even when only a single adult worm migrates from its normal location within the intestinal lumen. Migration into the appendix can precipitate acute appendicitis. Acute or recurrent migrations of one or more adult worms into the biliary tract can cause obstruction leading to acalculous cholecystitis, pyogenic cholangitis, pancreatitis, or liver abscesses. If the bowel wall is thinned or ulcerated by typhoid enteritis or other diseases, adult *Ascaris* worms may penetrate and perforate the intestine.

Heavy worm burden is more frequently seen in children younger than 10 years. Worm burden tends to decrease with increasing age, in correlation with increased secretion of cytokines by type 2 helper T cells (Th2) in response to

![Table 1. Intestinal Nematodes](image)

*Ascaris* antigens. Thus, Th2 cytokine responses may protect against heavy infections.

**Whipworm** Infection with *Trichuris trichiura* is widespread in tropical regions throughout the world and also occurs in rural areas of the southern United States. Whipworm infection results from ingestion of eggs that have embryonated in the soil for 15 to 30 days (the life cycle of *Trichuris* is illustrated in the CDC PHIL [http://phil.cdc.gov/Phil](http://phil.cdc.gov/Phil), photograph 5231; a whipworm is shown in photograph 414).

Moderate whipworm infection provokes gastrointestinal complaints; heavy infections (> 200 worms) in children cause the *Trichuris* dysentery syndrome, characterized by chronic diarrhea, anemia, growth retardation, and, occasionally, rectal prolapse.

![Figure 2. Hookworm infection](image)

Figure 2. Hookworm infection typically begins when filariform larvae in soil penetrate the skin and enter the circulation. The larvae travel via the bloodstream to the lungs, where they cross into the alveolar air space and ascend the tracheobronchial tree. They are then swallowed and attach to the small intestine. There they develop into adults, which feed on blood. Adult females lay eggs that are excreted in feces and hatch in the soil, releasing rhabditiform larvae that develop into infective filariform larvae. The hookworm *Ancylostoma duodenale* may also be acquired by oral ingestion of larvae.
Figure 3. The mouthparts (arrows) of an *Ancylostoma duodenale* hookworm are visible on an unstained micrograph.

**Laboratory Findings and Imaging Studies**

Intestinal infections with roundworm, hookworm, or whipworm are usually easily diagnosed by finding the eggs of the responsible parasite on stool examination. During the pulmonary phase of *Ascaris* or hookworm infections, the diagnosis is made by finding larvae in respiratory secretions. Results of stool examinations are usually negative during the pulmonary phase because this phase occurs early in infection, weeks or months before adult worms have matured sufficiently to liberate eggs into the feces. Positive stool samples during the respiratory phase indicate earlier long-standing infection. Thus, in eosinophilic pneumonitis, negative stool examination results do not exclude a parasitic etiology.

Adult *Ascaris* worms can be readily detected in upper gastrointestinal series; the large worms are outlined by contrast material, and in late follow-up films, the parasite's alimentary tract may be defined by a thin line of ingested contrast medium. Ultrasonography can detect adult worms in the small intestine, facilitating diagnosis of *Ascaris* as the cause of abdominal symptoms. Adult worms in the biliary tract can be detected by ultrasonography or endoscopic cholangiopancreatography. At times, patients may note the passage of the large, smooth adult *Ascaris* worms in the stool or may cough up an adult worm.

Figure 4. Adult *Ascaris lumbricoides* roundworms are 10 to 30 cm in length.

Adult whipworms, which are 3 to 5 cm in length, may be visualized by anoscopy or colonoscopy. Adult hookworms, which are 0.6 to 1.2 cm in length, may be visualized by endoscopy of the proximal small intestine.

**Treatment**

Therapy for roundworm, hookworm, and whipworm infections uses the well-tolerated broad-spectrum anthelmintic agents mebendazole, albendazole, and, in some cases, pyrantel pamoate, ivermectin, and nitazoxanide [see Table 1]. Several caveats apply, however. Pyrantel is not used for whipworm or roundworm; ivermectin and nitazoxanide are not used for hookworm. Because mebendazole and albendazole may be teratogenic, they are contraindicated during pregnancy. Albendazole, ivermectin, and nitazoxanide are not yet approved by the Food and Drug Administration (FDA) for these indications.

Therapy for *Ascaris* is mandatory to prevent unusual complications resulting from aberrant migration of the large adult worms. Adult *Ascaris* worms causing biliary and pancreatic obstruction may be removed at endoscopy.

Anemia caused by hookworm responds to iron supplementation. Early trials have shown that vaccination with recombinant hookworm antigens shows great promise in reducing the worm burden in humans and alleviating anemia.
Pinworms

Pinworms (*Enterobius vermicularis*) often affect groups of children, such as in schools or families, because the eggs are infectious when passed and can be transmitted from person to person and by fomites in the environment (the life cycle of *Enterobius* is illustrated in the CDC PHIL [http://phil.cdc.gov/Phil ]; photograph 5228). The cardinal symptom of pinworm infection is perianal pruritus, but some infected patients remain asymptomatic. The pruritus often worsens at night, when the worms tend to migrate. Occasionally, migration of adult worms into or through the female genital tract results in vaginitis or peritoneal inflammation associated with granuloma formation. Pinworm larvae may also cause eosinophilic enterocolitis or appendicitis. 17

**Diagnosis**

Because pinworm eggs are deposited by female worms on the perianal skin, stool examinations usually are not revealing. Pinworm infections are diagnosed by applying cellulose acetate tape to the perianal skin in the morning and microscopically examining the tape on a slide to detect the eggs (a photograph of pinworm eggs is available in the CDC PHIL [http://phil.cdc.gov/Phil ]; photograph 4818). Adult pinworms, which are about 1 cm in length, may be visualized by anoscopy or colonoscopy.

**Treatment**

Pinworm infection is treated with mebendazole, pyrantel pamoate, or albendazole (not yet FDA approved for this indication) [see Table 1]. Because mebendazole and albendazole may be teratogenic, they are contraindicated during pregnancy. A second treatment should be given 2 weeks after the initial course. Even with repeat treatment, however, reinfection is common. Before treatment, hygienic measures such as frequent baths, the clipping of fingernails, and cleaning of the egg-contaminated household environment should be instituted to reduce the opportunity for reinfection. Because household members are often infected and can provide a source for reinfection, simultaneous treatment of all household members is indicated.

**Strongyloidiasis**

Although *S. stercoralis* is the least prevalent of the intestinal nematodes in the United States, it is widely distributed within the tropics and subtropics. In the United States, *Strongyloides* infection is more prevalent in persons residing in the southern states; in persons living in institutions with poor sanitation; and in immigrants, military veterans, and other persons who have traveled or resided in locales where *Strongyloides* is endemic. *Strongyloides* is one of the few helminths capable of internal reinfection; it can multiply in the human host without reinfection by soil-dwelling larvae. As a result of ongoing internal reinfection, strongyloidiasis may persist for decades, as has been documented in some World War II and Vietnam War veterans. If host immunity is suppressed, the internal reinfection cycle may become unbridled, leading to hyperinfection that can result in an overwhelming and frequently fatal illness.

**Pathogenesis and Clinical Features**

Eggs of *S. stercoralis* hatch in the intestine into rhabditiform larvae, which develop further by one of three routes [see Figure 5]. Two of the routes occur after stool passage: the larvae may develop in the soil into infective filariform larvae either immediately or after an intervening stage as free-living adults. The filariform larvae penetrate the skin and travel via the bloodstream to the lungs, where they enter the alveoli, ascend the trachea, and are swallowed; adult worms subsequently develop in the small intestine.

Figure 5. Filariform larvae of the intestinal nematode *Strongyloides stercoralis* penetrate the skin or mucous membranes and enter the circulation. Larvae travel
to the lungs, where they cross into the alveolar air space and ascend the tracheobronchial tree. They are then swallowed and develop into adults, which may mate or undergo parthenogenetic fertilization, penetrate the mucosa of the proximal small bowel, and lay eggs. The eggs hatch within the small intestine and develop into rhabditiform larvae, which then follow one of two paths: a soil phase or an autoinfection cycle. In the soil phase, larvae are passed in the feces and contaminate the soil, where they either transform directly into infectious filariform larvae or develop into free-living adults that generate new infectious larvae. In the autoinfection cycle, rhabditiform larvae penetrate the colonic wall or perianal skin and enter the circulation.

The third route is the autoinfection cycle, in which the rhabditiform larvae mature directly within the intestine into filariform larvae, which penetrate the colon or the perianal skin to enter the circulation and complete the cycle of maturation into adult worms. This last route can increase the parasitic burden and permit the infection to become chronic.

Invasion of the small intestine wall by adult *S. stercoralis* worms may produce abdominal pain that is often localized to the midepigastrium; the pain is similar to that of peptic ulcer but is aggravated by food consumption. Diarrhea, nausea, and vomiting often occur; less commonly, urticaria, asthma, and weight loss may occur. Patients with heavy infection may experience malabsorption, gastrointestinal bleeding, and a protein-losing enteropathy. In cases of chronic infection, symptoms may be absent or may be mild and intermittent; symptoms include diarrhea, abdominal pain, and recurring episodes of urticaria, especially on the buttocks and the wrists. Less commonly, larva currens, which is a pathognomonic, serpiginous, pruritic, elevated eruption, evolves along the tract of larval migration in the skin of the perianal, gluteal, or other body areas.

Disseminated strongyloidiasis may occur, especially in patients who have a malignant disorder or who are immunocompromised as a result of malnutrition or the administration of corticosteroids or other immunosuppressive medications. Disseminated strongyloidiasis occurs but is uncommon in patients with AIDS, although strongyloidiasis is encountered in patients who are infected with human T cell lymphotropic virus type I. In immunocompromised patients, the autoinfection cycle produces large numbers of filariform larvae that may disseminate from the colon and invade any organ system. Colonic leakage or carriage of intestinal bacteria by larvae into the bloodstream often produces concomitant bacterial infection and pneumonia. This progression of events frequently results in a fatal hyperinfection syndrome in the immunocompromised host.

**Laboratory Findings**

Eosinophilia is elicited in strongyloidiasis but may be minimal or only episodic in chronic infection and absent in the hyperinfection syndrome, especially if the patient has taken corticosteroids. Midepigastric discomfort or unexplained eosinophilia in a patient about to receive immunosuppressive therapy should prompt a diagnostic search for the larvae of *Strongyloides*. Serial stool samples should be examined with the use of concentration techniques. Stool examinations are repeatedly negative in about 25% of patients with strongyloidiasis. An enzyme-linked immunosorbent assay (ELISA) is an especially useful diagnostic test. When hyperinfection is present, *Strongyloides* larvae may be found in other fluids, such as surgical drainage fluid and sputum, and the stool may contain filariform and rhabditiform larvae.

**Treatment**

Strongyloidiasis must be treated because of the potential for subsequent fatal hyperinfection. The anthelmintic agents used are ivermectin and albendazole [see Table 1]. Ivermectin, approved in the United States for uncomplicated infection, is safe and effective.

Albendazole is an effective agent but is less effective than ivermectin in clearing larvae from
Serial stool examinations should be obtained in the weeks and months after therapy to confirm eradication of the parasite. Immunocompromised hosts may require prolonged anthelmintic therapy.

**Trichostrongyliasis**

Although *Trichostrongylus* are usually intestinal pathogens of herbivores, several species may infect humans. Infection is most common in Asia and is acquired by consuming food that harbors infectious larvae. Adult worms attach to the proximal small bowel and in most cases do not produce symptoms, but mild gastrointestinal distress and eosinophilia have been reported. The eggs of *Trichostrongylus* are somewhat larger and have less rounded ends than hookworm eggs. Trichostrongyliasis is treated with pyrantel pamoate (a single oral 11 mg/kg dose, to a maximum of 1 g), mebendazole (100 mg p.o., b.i.d., for 3 days), or albendazole (400 mg p.o., once).

**Capillariosis**

Most human infection with *Capillaria* is caused by *C. philippinensis*, which is found primarily in the northern Philippines, Thailand, and Egypt. Humans acquire the infection by eating raw freshwater fish, but birds that eat fish are the major host. The small (3 to 4 mm long) adult worms dwell in the small intestine. Females produce unembryonated eggs that mature in the environment. However, a small percentage of these eggs embryonate and hatch in the intestine, leading to an internal autoinfection similar to that seen in strongyloidiasis. Symptomatic intestinal capillariosis is marked by diarrhea and abdominal pain. When infection is severe, edema, muscle wasting, fat and sugar malabsorption, and a protein-losing enteropathy may ensue. Because of the autoinfection cycle, untreated severe infection may result in death after several months.

Hepatic and pulmonary capillariosis are rare diseases that are found worldwide. Hepatic capillariosis, from *Capillaria hepatica*, manifests as acute or subacute hepatitis; pulmonary capillariosis, from *Capillaria aerophila*, manifests as fever, cough, asthma, and pneumonia. Capillariosis is treated with mebendazole (200 mg orally twice daily for 20 days) or albendazole (400 mg orally daily for 10 days).

**Canine Hookworms**

Two canine hookworms, *Ancylostoma ceylanicum* and *Ancylostoma caninum*, can cause human intestinal infections; a third canine hookworm, *Ancylostoma braziliense*, can cause cutaneous larva migrans [see Larva Migrans, below]. *A. ceylanicum* is a widely distributed canine and feline parasite of the tropics and subtropics. Like human hookworm parasites, the sexually mature, egg-laying adult worms of this species can cause blood loss and consequent iron deficiency.

Most cases of *A. caninum* infection in humans have been recognized in Australia and Egypt. Reported clinical features have been variable, ranging from acute intestinal obstruction to subclinical infections. Eosinophilic enteritis is common, and some patients have experienced acute or recurrent abdominal pain, rectal bleeding, or diarrhea. Worms—often a single worm—have been recovered at surgery or colonoscopy in many patients. The immature worms do not produce eggs and hence are not detectable by stool examinations. An ELISA serologic test has helped with diagnosis. As in human hookworm infections [see Table 1], mebendazole or albendazole has been effective.

**Tissue Nematode Infections**

**Trichinellosis**

*Trichinella* are nematodes whose larvae typically become encysted in striated muscle. Transmission of *Trichinella* occurs via ingestion of infected meat, usually pork or the meat of certain carnivores. Mild to moderate trichinellosis is usually asymptomatic or mildly symptomatic; heavy infection can
cause myalgias, periorbital edema, eosinophilia, and, in rare cases, death.

**Etiology and Epidemiology**

Five species of *Trichinella* are now recognized to infect humans. *Trichinella spiralis*, found in many carnivorous and omnivorous animals, and *Trichinella pseudospiralis*, found in mammals and birds, are distributed throughout the world. *Trichinella nativa* is present in arctic regions and infects bears and arctic mammals; *Trichinella nelsoni* is present in equatorial Africa, where it is common in felid predators and scavenger animals (e.g., hyenas and bush pigs); and *Trichinella bitovi* is present in temperate areas of Europe and western Asia, where it is found in carnivores but not domestic swine.\(^{24,25}\)

*Trichinella* is transmitted by the consumption of meat containing encysted larvae [see Figure 6]. In its sylvatic life cycle, the parasite is ingested by wild animals that eat trichinous carcasses; in its domestic life cycle, the parasite is ingested by pigs that eat contaminated meat in garbage. Worldwide, most human trichinellosis is caused by ingestion of infected pork products; in the United States, however, ingestion of wild carnivores has surpassed pork in transmitting the infection.\(^{26}\) Although cattle are not natural hosts of the parasite, beef may be implicated in outbreaks because of adulteration with pork, either intentional or incidental, through the common use of a meat grinder. Human trichinellosis can also be acquired from horse meat or the meat of wild animals such as bears, walrus, boars, and cougars.\(^{27}\)

Although meat in the United States is not inspected for *Trichinella* larvae, laws proscribing the feeding of uncooked garbage to pigs have reduced the transmission of the disease.\(^{26}\) Most cases in the United States are attributable to noncommercial pork, bear, and cougar meat. About 12 cases of trichinellosis, occasionally leading to death, are reported annually in the United States, but more cases, especially mild ones, probably remain undiagnosed.\(^{26}\)

Larvae in pork may be rendered noninfective by heating to a temperature of 77°C. Freezing at -15°C for 3 weeks, as in a home freezer, will generally kill larvae in meat; however, arctic species of the parasite, which may be present in walrus or bear meat, are more resistant to freezing and thus may remain viable.

**Pathogenesis and Clinical Features**

The severity of clinical illness in trichinellosis usually correlates with the number of ingested larvae. In most infections, there are only one to 10 larvae per gram of muscle, and prominent symptoms are absent; however, in some infections, there are more than 50 larvae per gram of muscle. The symptoms of these heavier infections may reflect the two phases of the parasite's development (i.e., the intestinal phase and the muscle phase).

![Figure 6. *Trichinella* infection is acquired by the consumption of meat containing encysted larvae. Digestion liberates the larvae, which penetrate into the small intestine, mature into adult worms, and mate. Adult females produce larvae, which enter the circulation and spread to striated muscle, where they become encysted.](image)

**Intestinal phase** Encysted larvae are liberated from infected meat by the action of gastric acid and peptic enzymes. The larvae burrow into the villi of the small intestine and mature into adult worms. Within 4 to 5 days, the adult worms produce larvae, which enter the circulation. During this enteric phase, which usually lasts from 1 to 7 days, patients may be asymptomatic or may experience nausea, vomiting, constipation, or abdominal aches. Prolonged diarrhea that lasts for weeks, as noted in patients with arctic trichinellosis, may be the result of secondary infections in previously infected and sensitized patients.\(^{28}\)
**Muscle phase**  After the intestinal phase, larvae are carried by the bloodstream to various organs. In the early muscle phase, periorbital and facial edema, subconjunctival and retinal hemorrhages, and subungual splinter hemorrhages commonly develop.

After about 3 weeks of infection, larval encystment in muscles begins. Patients experience myalgias, muscle edema and weakness, fever, and eosinophilia. Headache, cough, dyspnea, dysphagia, and macular or urticarial skin lesions develop less commonly. Although larvae only become encysted in striated muscle, inflammatory lesions may develop in the heart, lungs, and central nervous system (CNS). Deaths usually result from myocarditis. Symptoms generally abate slowly after the third week of infection. Infections with *T. pseudospiralis* may be associated with years of myositis.29

**Laboratory Findings**

Eosinophilia develops in more than 85% of patients with symptomatic trichinellosis.26 Elevations of muscle enzymes (i.e., serum aspartate aminotransferase and creatine kinase) often accompany symptomatic muscle involvement. Serologic tests are positive in most patients with acute infection, but diagnostic antibody titers may not be detectable until the third week of infection.

Definitive diagnosis requires demonstration of larvae in muscle [see Figure 7]. The likelihood of obtaining a positive muscle biopsy specimen increases if the specimen is taken from a clinically involved muscle; if it is taken near a tendinous insertion, where the density of larvae is greatest; and if it is obtained after the third week of infection, when larvae are more numerous, larger, and more resistant to digestion. A portion of the muscle biopsy specimen should be submitted for histopathologic examination. In addition, another portion should be compressed between glass slides and examined microscopically for larvae. Because a larger volume of muscle can be examined by this technique, it is more sensitive than histopathologic examination for detecting larvae. Differentiation of *Trichinella* species can be based on the absence of larval encystment with *T. pseudospiralis* and on DNA-based molecular biologic techniques.25

**Differential Diagnosis**

The triad of periorbital edema, myalgias, and eosinophilia strongly suggests the diagnosis of trichinellosis. Most patients with trichinellosis have a history of consuming pork products or the meat of wild mammals. The development of symptomatic infection or eosinophilia in other persons who have eaten the meat incriminated in a case of trichinellosis provides epidemiologic confirmation of the diagnosis. Persons with light infections may have minimal symptoms, or the symptoms may suggest diagnoses other than trichinellosis, such as diarrheal or influenzal syndromes or polymyositis. In rare instances, CNS involvement may suggest aseptic meningitis or encephalitis.30

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**Figure 7. A micrograph shows developing *Trichinella* cysts in human muscle tissue (hematoxylin-eosin stain).**

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**Treatment**

Specific therapy for trichinellosis is unsatisfactory. Most infections, however, are not life threatening and are self-limited; bed rest, analgesics, and antipyretics suffice to alleviate myalgias and fever. If serious cardiac, neurologic, or pulmonary involvement occurs, corticosteroid therapy with prednisone (40 to 60 mg daily) is indicated.31 Prednisone is often given with oral mebendazole (200 to 400 mg t.i.d. for 3 days, then 400 to 500 mg t.i.d. for 10 days) or oral albendazole (400 mg b.i.d. for 8 to 14 days).13 Limited experience suggests that *T. nativa* and *T. pseudospiralis* infection may respond to albendazole.29,32
Anisakiasis

Anisakiasis is a zoonotic infection that develops in persons who consume fish infected with anisakine or related parasites. Anisakis species are present in the muscle of mackerel, herring, and salmon. Anisakis simplex has now also been discovered very early in the marine migration of Atlantic salmon. Infection caused by Pseudoterranova (previously termed Phocanema) species is referred to as codworm anisakiasis. Pseudoterranova parasites are found most frequently in cod, but they have also been detected in the muscle of pollack, halibut, flatfish, greenling, Pacific rockfish (Pacific red snapper), and squid. Infective third-stage larvae in fish are killed by heating to 60°C, by commercial blast freezing, or by freezing at -20°C for 3 days. Salting, cold smoking, and marinating do not normally kill either Anisakis or Pseudoterranova larvae.

The number of cases of anisakiasis recognized in the United States, Japan, Europe, and other countries has increased in recent years, probably as a result of three developments. First, raw fish dishes, including sushi, sashimi, and lomi lomi salmon, have become increasingly popular. Second, the population of marine mammals, including sea lions and seals, has increased as a result of legal protection; these marine mammals are the definitive hosts for anisakine nematodes that in a later stage of their life cycle infect fish. Third, there has been an increase in awareness of anisakiasis and, especially in Japan, greater use of endoscopy as a diagnostic modality.

In addition to anisakine nematodes, other parasites, including Diphyllobothrium latum [see Cestode Infections, Fish Tapeworm, below], the intestinal fluke Nanophyetus salmincola, and larval Eustrongylides nematodes, can be acquired by eating raw fish.

Pathogenesis and Clinical Features

The clinical manifestations of infection after the ingestion of fish containing live anisakine larvae depend in part on the genus of the infecting parasite and on the anatomic localization of the larvae. Typically, in the United States, infection with Pseudoterranova species becomes apparent when a patient coughs up a live worm, often within 48 hours after eating raw or undercooked fish. Some patients have experienced mild epigastric pain and a tingling throat and have sensed the worm in the oropharynx or proximal esophagus. In the United States, the infection has only infrequently been associated with serious illness. In Japan, by contrast, codworm anisakiasis has been associated with gastric, but usually not intestinal, invasion. Within several hours after infected fish have been consumed, the larvae can invade the stomach mucosa and produce severe epigastric pain that recurs every 5 to 10 minutes. Patients may experience nausea, vomiting, urticaria, and a tingling throat. Endoscopy at this time will reveal the invading larvae at a site that is swollen and hemorrhagic; often the site is the posterior wall of the stomach.

Infections with Anisakis species can cause either gastric or intestinal involvement. Invasion of the gastric mucosa produces the same clinical syndrome that occurs in gastric codworm anisakiasis but without the tingling throat; the pathologic findings on endoscopy are also the same. Larval invasion of the intestinal mucosa can produce abdominal pain, fever, nausea, vomiting, and diarrhea. Larvae can elicit an eosinophil-rich granulomatous reaction in the submucosa and infrequently penetrate the peritoneum. The clinical presentation of intestinal anisakiasis often mimics that of acute appendicitis, but it can also be confused with gastrointestinal ulcers or neoplasms, acute Crohn disease, or ischemic ileitis. In addition to causing invasive disease, Anisakis parasites may elicit allergic reactions. Patients may develop IgE-mediated reactions to Anisakis proteins and experience urticaria, angioedema, and anaphylactic reactions after ingesting even adequately cooked infected fish.

Laboratory Findings and Imaging Studies

In gastric anisakiasis, eosinophilia is often present, and occult blood is frequently detectable in gastric fluid or stool. In intestinal anisakiasis, eosinophilia may be absent, and a leukocytosis may
develop. In either form of anisakiasis, a history of recent raw fish ingestion before the onset of symptoms can strongly suggest the diagnosis. The definitive diagnosis of anisakiasis involving the stomach or proximal intestine can be made with endoscopy, which will reveal the invading larva. The codworm larva resembles a thick piece of yellowish string, whereas the Anisakis larva is fine and whitish. Eustrongylides larvae, which have infrequently been reported to cause intestinal perforation in humans, have a distinctive bright-red coloration.

Radiographic studies can help identify gastric anisakiasis. In intestinal anisakiasis, such studies may show thickening of the involved bowel area and may detect the larva.

**Treatment**

Endoscopic or surgical removal of the larva is the only proven treatment. Although surgery for presumed appendicitis is often performed in patients with intestinal anisakiasis, surgical resection may not be needed if the correct diagnosis is considered in time. With conservative care, the illness may be self-limited, and patients may recover without surgical treatment. The efficacy of anthelmintic medications against human anisakiasis has not been properly evaluated. Animal studies suggest that ivermectin and albendazole have activity against *A. simplex*, and there are anecdotal reports of successful treatment of human anisakiasis with albendazole; because anisakiasis is often self-limited, however, the true utility of albendazole therapy is unknown.

**Larva Migrans**

Humans may occasionally act as the nondefinitive host for nematode parasites that normally infect animals. In such cases, the parasites usually do not mature completely, but the introduced larvae may persist and induce an inflammatory reaction in the skin, viscera, or eyes.

**Cutaneous Larva Migrans**

The syndrome of cutaneous larva migrans (creeping eruption) develops when the larvae of various parasites, including the dog or cat hookworm *A. braziliense*, penetrate human skin. Pruritic, serpiginous cutaneous lesions form along the migratory tracts of the larvae [see Figure 8]. These lesions can be treated with oral albendazole (400 mg daily for 3 days) or oral ivermectin (200 μg/kg daily for 1 to 2 days).

Figure 8. Cutaneous larva migrans in a person who had recently been on a beach vacation in Haiti is evident as a serpiginous tract that moves over time.

**Visceral and Ocular Larva Migrans**

The syndrome of visceral larva migrans develops when nematode larvae of animal parasites migrate in human tissues. Visceral larva migrans with fatal eosinophilic meningoencephalitis has been caused by the raccoon ascarid *Baylisascaris procyonis*, but visceral larva migrans is most commonly caused by dog or cat ascarids. *Toxocara canis*, the canine roundworm, is common in North American dogs. Although fewer than 20% of adult dogs are infected, transplacental migration of larvae from infected females results in an incidence of infection that may exceed 80% in their puppies at 2 to 6 months of age. Both the puppies and the lactating mother shed large numbers of *T. canis* eggs in their stools within a month after parturition. The prevalence of *Toxocara cati* in cats is generally lower than that of *T. canis* in dogs; kittens do not become infected before birth.
After *Toxocara* eggs are shed in the feces, about 3 weeks must elapse before the eggs develop sufficiently to become infectious; thereafter, they may remain viable for several months. Humans acquire infection principally by ingesting eggs in soil; public playgrounds have been implicated [see Figure 9]. Direct contact with infected animals is not a major source of infection because of the time required for eggs to become infectious. A history of eating soil is strongly associated with the risk of acquiring infection. Thus, visceral larva migrans is most likely to develop in children with geophagia.

**Pathogenesis and clinical features** After infectious *Toxocara* eggs are ingested, the larvae hatch and penetrate the gastrointestinal mucosa. They are carried to the liver in the portal circulation; from there, they move into the systemic circulation. When the larvae enter vessels too small to allow their passage, they exit and migrate into the surrounding tissues. The manifestations of visceral larva migrans are a consequence of both the damage done by the migrating *Toxocara* larvae and the induced eosinophilic granulomatous inflammatory reaction.

Many infections are mild and subclinical. Clinically apparent infections may present in one of two distinct patterns: visceral and ocular. In the visceral form of infection, patients are usually 1 to 5 years of age and generally have a history of geophagia. Malaise, irritability, weight loss, wheezing, cough, fever, hepatomegaly, and pruritic cutaneous eruptions are common. Neurologic involvement may produce seizures and behavioral disorders. In rare instances, death results from severe neurologic or myocardial involvement.

In the ocular form of larva migrans, patients are older: the mean age is 7.5 years, and the range includes young adults. A history of geophagia is unusual; a history of an antecedent symptomatic visceral form of the disease is rare. Common symptoms of ocular larva migrans are strabismus and failing vision. The characteristic ocular lesion is a whitish elevated granuloma measuring one to two disk diameters that is located in the posterior pole of the retina; however, the disease may also present as endophthalmitis or uveitis. The ocular lesions may be mistaken for a retinoblastoma, which can lead to unnecessary surgical enucleation of the eye.

**Laboratory findings and imaging studies** Usual findings in the visceral form of larva migrans are leukocytosis, prominent blood eosinophilia (generally in excess of 1,000/μL), and hypergammaglobulinemia (increased levels of IgG, IgM, and IgE). On chest x-ray, transient pulmonary infiltrates are found in about half of the patients with pulmonary symptoms. All these findings are uncommon, however, in the ocular form of larva migrans.

An ELISA serologic test has proved to be a sensitive, specific diagnostic test for both the visceral and the ocular forms; it can detect subclinical cases that may present only as an unexplained eosinophilia.

**Treatment** The visceral form of larva migrans is often self-limited. However, anthelmintic and antinflammatory therapy have been shown to be beneficial. Albendazole (400 mg p.o., b.i.d., for 5 days), although not licensed by the FDA for this indication, is the drug of choice for toxocariasis and has been shown to be superior to thiabendazole. Corticosteroids are used to treat patients with severe respiratory, myocardial, or CNS involvement or, in the ocular form, to suppress active inflammation.

**Angiostrongyliasis**

Infection of humans with the parasite *Angiostrongylus cantonensis* may produce eosinophilic meningitis. The rat is the definitive host of *A. cantonensis*, but the larval stages develop in mollusks, which serve as intermediate hosts. Humans acquire the infection either by ingesting infected mollusks (i.e., land snails or slugs) or by consuming inadequately cooked carrier hosts (i.e., freshwater shrimp, aquatic and amphibious crabs, and certain marine fish) that have previously ingested infected mollusks. In the United States, *A. cantonensis* is endemic to the Hawaiian Islands, and the parasite has been found in rats in New Orleans. *A. cantonensis* is found throughout the
Pacific Basin and in Southeast Asia, Australia, and the Caribbean. Eosinophilic meningitis from this parasite occurs in all these areas. An outbreak associated with drinking raw vegetable juice has been described.  

Pathogenesis and Clinical Features

After *A. cantonensis* larvae are ingested, they migrate to the CNS. There the parasites die, but their passage into the CNS induces an eosinophilic inflammatory reaction. The most common symptom of *A. cantonensis* infection is a severe frontal or bitemporal headache, which is usually the reason patients seek medical attention. More than half of patients experience stiff neck, vomiting, or paresthesias. Extraocular muscle palsies, seizures, and significant fever are uncommon. Although some deaths have been recorded, symptoms generally resolve in 1 to 2 weeks; however, paresthesias may persist for months.  

Laboratory Findings

Peripheral blood eosinophilia usually accompanies eosinophilic meningitis caused by *A. cantonensis*; however, the eosinophilia may be mild, and eosinophil levels may not be elevated initially. In the cerebrospinal fluid (CSF), the white blood cell counts ordinarily range from 150 to 1,500/μL, with eosinophils accounting for more than 20% of the leukocytes. CSF protein levels are usually elevated, and glucose levels are at the low end of the normal range. On rare occasions, larvae of *A. cantonensis* are found in the CSF. No serologic tests are available for identifying the organism, so diagnosis is based on a compatible epidemiologic history and clinical course together with eosinophilic pleocytosis in the CSF. Eosinophils in the CSF, which are also found in other diseases, may be misidentified if they are not specifically stained.

![Figure 9. Life cycle of *Toxocara canis*, one of the principal agents of visceral larva migrans. Humans are nondefinitive hosts for *Toxocara*; after infectious eggs are ingested, the larvae hatch and penetrate the gastrointestinal mucosa. They are carried to the liver in the portal circulation; from there, they move into the systemic circulation. When the larvae enter vessels too small to allow their passage, they exit and migrate into the surrounding tissues, where they may cause an inflammatory reaction.](image)

Treatment

Although there is no specific treatment for eosinophilic meningitis caused by *A. cantonensis*, prednisolone (with or without albendazole) or albendazole and corticosteroids have been shown to provide symptomatic relief of headaches caused by eosinophilic meningitis.

Mammomonogamosis (Syngamosis)

Nematodes of the genus *Mammomonogamus* (*Syngamus*) inhabit the trachea of cattle and other herbivores. Although the life cycle of the parasite is unknown, human infection is believed to result from the ingestion of foodstuffs that contain some intermediate host of the parasite. Of the several dozen cases recognized in humans, most have been acquired in the Caribbean area. A chronic, nonproductive cough is characteristic in such patients. No blood eosinophilia is elicited, and no parenchymal lesions are seen on chest x-ray. The diagnosis is made when an adult worm is expectorated or found at bronchoscopy or when eggs are found in sputum or feces. Therapy consists of the removal of the worms during bronchoscopy, but mebendazole and thiabendazole have been used in case reports.

Gnathostomiasis
Nematodes of the genus *Gnathostoma* are widely distributed and usually infect the intestinal tract of carnivorous animals. Most human infections have been reported from Asia and have been caused by *Gnathostoma spinigerum*, although human gnathostomiasis has also been described in Central and South America.\(^{48,49}\) Infectious larvae are found in the tissues of freshwater fish, eels, frogs, and snakes and in animals fed on infected fish (e.g., poultry and pigs). Humans may be infected if they ingest any infected tissues or possibly by accidental ingestion of the copepod (a tiny freshwater crustacean) that serves as an intermediate host. The larvae fail to develop to maturity within humans, but acute symptoms of nausea, vomiting, and urticaria may develop 1 to 2 days after infection. Larval penetration of the liver produces inflammation and right upper quadrant pain. Subsequently, larvae may migrate within the abdominal or thoracic cavities. Eosinophilia is initially marked but diminishes after about a month, when the larvae reach subcutaneous tissues. Ensuing larval migrations produce foci of serpiginous cutaneous or migratory subcutaneous inflammation and swelling. On occasion, larvae enter the CNS and cause eosinophilic meningitis.\(^{41}\) Treatment options are oral albendazole (400 mg b.i.d. for 21 days), ivermectin (200 μg/kg/day for 2 days), surgical removal, or both.\(^{13,50}\)

**Dracunculiasis**

*Dracunculus medinensis*, the guinea worm, infects persons in 12 countries of Central and West Africa. A global eradication effort has reduced the annual incidence from 3.5 million cases in 1986 to 9,585 reported cases in 2007.\(^{51}\) Infection results from drinking water containing microcrustacean *Cyclops* species that harbor larvae of the parasite. Gastric acid digests the *Cyclops*, releasing the larvae. The larvae then penetrate the duodenum, where they develop into adult worms within the subcutaneous tissues over the course of 60 to 90 days. Male and female worms then mate; after mating, adult male worms die. Adult females, however, move into the lower extremities, grow to 70 cm in length or more, and then emerge through the skin after about a year. This emergence, which may be preceded by a few days of urticaria, fever, and dyspnea, occurs with the formation of a blister that becomes pruritic and painful before rupturing. Larvae are released from the ruptured blister site if the lesion is immersed in water, as occurs during wading to fetch drinking water. The life cycle is completed when larvae are ingested by *Cyclops* and mature within them.

Clinical manifestations of dracunculiasis are usually related to the emergence of the worm and include premonitory symptoms and blister formation. Secondary bacterial infection often develops at the site of the blister and may extend retrograde along the length of the worm.

The conventional method of winding several centimeters of slowly emerging worm around a stick each day until the worm has fully emerged is an effective treatment. Removal is eased by administration of metronidazole (250 mg p.o. t.i.d. for 10 days), but surgical extraction is more rapid and effective.\(^{52}\) In endemic areas, preventive efforts focus on breaking the *Dracunculus* life cycle by improving the safety of drinking water.

**Filariasis**

Several insect-transmitted filarial nematodes cause chronic infections in humans [see Table 2]. The major filarial nematodes are responsible for lymphatic filariasis, onchocerciasis, and loiasis. Other filarial nematodes include *Mansonella ozzardi*, *Mansonella perstans* (formerly called *Tetrapetalonema perstans*), and *Mansonella streptocerca* (formerly called *Tetrapetalonema streptocerca*); these nematode species cause fewer cases of human infection than the major filarial nematodes and are of less certain pathogenicity, but they are thought to cause bronchospastic tropical pulmonary eosinophilic syndrome.

**Lymphatic Filariasis**

The most common filarial infections are caused by lymphatic tissue-dwelling filarial parasites, three species of which infect humans. It is estimated that 120 million persons in 76 countries are infected with lymphatic filarial parasites and that 44 million have overt clinical disease. However, the Global
Alliance to Eliminate Lymphatic Filariasis (http://www.filariasis.org) has brought the eradication of lymphatic filariasis within reach over the next decade by bringing together a strong group of collaborators whose efforts include the provision of powerful antiparasitic drugs.

*Wuchereria bancrofti*, the most common lymphatic filarial parasite, is broadly distributed in tropical regions. *Brugia malayi* is found in areas of Southeast Asia, and *Brugia timori* is found in parts of Indonesia. Mosquitoes serve as an intermediate host for all three species of filarial nematodes and introduce infectious larvae into humans by means of their bite (the life cycle of *B. malayi* is illustrated in the CDC PHIL [http://phil.cdc.gov/Ph...]; photograph 3379). Different mosquito species are responsible for transmission in different areas; the major vectors include *Culex, Anopheles, Aedes*, and *Mansonella* species. The larvae develop into adult worms, which reside within lymphatic vessels and tissues. Offspring of the adult worms, called microfilariae, are covered by sheaths and may circulate in the bloodstream. In most endemic regions, microfilariae of *W. bancrofti* circulate in the bloodstream in greatest numbers during the night; in the South Pacific, however, no pronounced diurnal variation occurs. The time of day when the greatest numbers of microfilariae circulate correlates with the time of day when the principal mosquito vectors feed. Thousands of mosquito bites are probably required to produce an infection that results in patent microfilaraemia. The incubation period until patent microfilaraemia for *W. bancrofti* develops ranges from 3 months to the more usual 8 to 12 months.

### Table 2. Filarial Parasites of Humans

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Geographical Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Southeast Asia, Indonesia</td>
</tr>
<tr>
<td><em>Brugia malayi</em></td>
<td>Southeast Asia</td>
</tr>
<tr>
<td><em>Brugia timori</em></td>
<td>Indonesia</td>
</tr>
</tbody>
</table>

**Pathogenesis and clinical features** Most clinical manifestations of lymphatic filariasis are attributable to inflammatory reactions caused by the adult worm; the immunopathogenesis, however, is poorly understood.53 Many patients with microfilaraemia experience no symptoms, although lymphadenopathy of the axillary, epitrochlear, and inguinal-femoral areas is common.

The more prominent clinical manifestations of lymphatic filariasis may be divided into two categories: inflammatory and obstructive. Inflammatory manifestations, which often become recurrent, include lymphadenitis, lymphangitis, funiculitis, orchitis, and epididymitis.53 A typical presentation is the triad of lymphadenitis, lymphangitis, and fever. In contrast to bacterial ascending lymphangitis, the lymphangitis of filariasis characteristically progresses centripetally down involved extremities. Staphylococcal and streptococcal superinfections are commonly the cause. Fever is variable and may be associated with frank rigors; the patient's temperature may reach 40°C (104°F). Systemic symptoms, such as nausea and vomiting, develop in many of these recurrent episodes. Urticaria and areas of cutaneous erythema commonly develop. The episodes may continue for as long as 7 to 10 days before spontaneously resolving. In filariasis caused by *Brugia* species, suppurative abscesses may form in areas of involved lymphatic channels.

The obstructive phase of filariasis usually develops after decades of exposure to the parasite and reflects lymphatic compromise, the mechanism of which is poorly understood. Inflammatory features may coexist with the obstructive phase. Features of the obstructive phase include hydrocele formation, chyluria, elephantiasis of the extremities (shown in the CDC PHIL [http://phil.cdc.gov/Ph...]; photograph 373), and, less commonly, elephantiasis of the breast.53

Tropical pulmonary eosinophilia develops in some individuals infected with lymphatic tissue-dwelling filarial parasites.54 This illness is characterized by paroxysmal asthmalike attacks that are often nocturnal; by blood and pulmonary eosinophilia; and by elevated titers of antifilarial IgG, IgM, and especially IgE. Tropical pulmonary eosinophilia should be distinguished from the transient eosinophilic pneumonitis termed Loffler syndrome, which results from a transpulmonary migration of larval forms of *Ascaris* and, less commonly, hookworm and *Strongyloides* [see Intestinal Nematode]
Infections, above].

**Laboratory findings**  Definitive diagnosis of lymphatic filariasis requires the demonstration of microfilariae or microfilarial antigens in the blood.\textsuperscript{55} Stained blood smears may reveal microfilariae, but often larger volumes of blood need to be examined either by centrifugal concentration after erythrocyte lysis or by filtration through 3 μm polycarbonate (Nuclepore) filters. In endemic areas where *W. bancrofti* microfilariae display nocturnal periodicity, detection of microfilariae requires examination of blood obtained after midnight or 60 to 90 minutes after daytime administration of a 2 mg/kg provocative dose of diethylcarbamazine (care should be taken if the patient is from a region where onchocerciasis is endemic because diethylcarbamazine may precipitate a severe reaction as a result of lysis of *Onchocerca microfilariae*). Because microfilarial antigen of *W. bancrofti* can be found in the blood throughout the day, antigen measurement is more convenient than direct microfilaria determination. Microfilariae are rarely found in patients with elephantiasis or with tropical pulmonary eosinophilia and often cannot be found in patients with inflammatory or obstructive filarial manifestations. In males, ultrasonography can detect adult filariae within scrotal lymphatics.\textsuperscript{53} Serologic tests may be helpful in making a diagnosis. Mild eosinophilia and elevations of serum IgE are common in lymphatic filariasis.

**Treatment**

Lymphatic filariasis can be treated with diethylcarbamazine (2 mg/kg orally three times daily for 2 to 3 weeks). Treatment with ivermectin or a single dose of diethylcarbamazine (6 mg/kg)\textsuperscript{50} is also effective at clearing microfilariaemia, and the combination of these two anthelmintics has led to rapid and long-term clearance of microfilariae. There is insufficient reliable research to ascertain whether albendazole, alone or in combination with diethylcarbamazine, is an effective treatment for lymphatic filariasis,\textsuperscript{13,56} but there is growing evidence that such treatment helps suppress microfilariaemia in patients from endemic areas. These short-term and combination therapies have been used more often in treatment of populations in filariasis control projects; for individual treatment, most experts favor the use of diethylcarbamazine for 2 to 3 weeks.\textsuperscript{57} Diethylcarbamazine must be used cautiously in patients exposed to *Loa loa* or *Onchocerca volvulus* because patients infected with these filariae tend to have severe reactions to this drug.

**Onchocerciasis**

*O. volvulus*, the causative agent of onchocerciasis (river blindness), is found in equatorial Africa and in elevated regions of Mexico and Guatemala, with smaller foci in Yemen, Brazil, Ecuador, and Venezuela. It is estimated that 17 million people are infected. *Simulium* species (blackflies) transmit the infection. Onchocerciasis control programs, which are based on community therapy with ivermectin, have led to a substantial reduction in the incidence of disease. Repeated therapy is necessary, however, and control programs will have to continue for decades to eliminate onchocerciasis altogether.

Onchocerciasis typically occurs within several kilometers of rapidly flowing rivers and streams where blackflies breed. The life cycle of *O. volvulus* is similar to that of species causing lymphatic filariasis [see Figure 10]. Adult worms, however, reside in subcutaneous tissues, often enclosed in fibrous nodules. Microfilariae, which in this species lack an enveloping sheath, are released from female adults and localize in skin and subcutaneous tissues. Symbiotic endobacteria (of the genus *Wolbachia*) in filaria may cause some of the inflammatory damage of onchocerciasis.

**Clinical features**  The skin is frequently involved in onchocerciasis, and pruritus is the most common clinical manifestation. With time, such complications as wrinkling, loss of elastic tissue, hypopigmentation or hyperpigmentation, papulovesicular lesions, and localized areas of eczematoid dermatitis may develop. Firm, non-tender nodules containing adult worms surrounded by fibrous tissue are often palpable in subcutaneous tissues. In Central America, nodules commonly occur on the head; in Africa, nodules are more common over bony prominences of the body. Regional lymphadenopathy also develops.
Ocular involvement is characteristic of onchocerciasis and may result in blindness. Conjunctivitis with photophobia is common. Punctate keratitis, which is caused by the accumulation of inflammatory cells around dying microfilariae, may develop within the cornea and usually resolves without consequence. However, sclerosing keratitis and chorioretinal lesions may ensue and are the major causes of onchocercal blindness. Anterior uveitis, iridocyclitis, and, less frequently, optic nerve lesions may develop as well.

**Laboratory findings** The principal method of diagnosis involves finding microfilariae in the skin. A small piece of superficial skin obtained by excision or punch biopsy is weighed and then incubated for several hours in saline or tissue culture media. Microfilariae that exit the skin sample are then counted in the fluid. Care should be taken not to contaminate the skin with blood that might harbor microfilariae of other species. Skin snip sites can include scapular and gluteal areas and, in Africa, leg areas. A count of more than 100 microfilariae/mg of skin indicates a heavy infection.

Another diagnostic method involves administering a 50 mg provocative dose of diethylcarbamazine; the subsequent onset of symptoms, which may include pruritus, rash, fever, and conjunctivitis, constitutes the Mazzotti reaction, which strongly suggests a diagnosis of onchocerciasis. Caution must be exercised in the use of this test because heavily infected patients may experience serious adverse reactions.

Eosinophilia is often prominent during onchocerciasis. Serology can be helpful when parasite demonstration is difficult.

**Treatment** Therapy for onchocerciasis improved dramatically with the introduction of ivermectin. Single-dose ivermectin therapy is free of most of the immediate cutaneous, ocular, and systemic reactions that complicated therapy with diethylcarbamazine, the agent previously used to treat onchocerciasis. Ivermectin, given orally in a single dose of 150 μg/kg, leads to symptomatic improvement in and clearance of microfilariae from the skin.13 This dose is repeated every 3 to 12 months for 3 to 4 years. Ivermectin may be showing signs of resistance. In a study carried out in Ghana, statistically faster rates of skin repopulation were observed in three villages (treated 12 to 17 times), despite the wide variability in repopulation rates observed in ivermectin-naïve populations.58 Doxycycline is effective, and the depletion of *Wolbachia endobacteria* using doxycycline leads to long-term sterilizing effects and macrofilaricidal activity against female filariae of more than 60%. The worms die or degenerate 18 to 27 months after doxycycline. However, during this time, patients may be exposed to new infections.59

**Loiasis**

Loiasis, which is caused by the filarial nematode *Loa loa*, occurs in the rainforest areas of central and western Africa and is transmitted by *Chrysops* species of horseflies and deerflies. Adult worms reside in subcutaneous tissues (the life cycle of *Loa loa* is illustrated in the CDC PHIL [http://phil.cdc.gov/Ph il ]; photograph 3399). The microfilariae, which are sheathed, circulate in the bloodstream with a diurnal periodicity in which peak levels are reached at about noon.

Many residents of endemic areas who have loiasis have asymptomatic microfilaraemia. The prominent clinical presentations are related to migrations of adult worms. In the subcutaneous tissues, migrations may produce recurrent lesions termed Calabar swellings, which are erythematous areas of swelling and edema up to 10 cm in diameter that resolve after 1 to 3 days. Infection may also present dramatically when the worm migrates subconjunctivally across the eye.

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Figure 10. Life cycle of *Onchocerca volvulus*, which causes river blindness and severe skin disease.
In contrast, patients who acquire loiasis after brief stays in central and West Africa exhibit different clinical and immunologic responses. They are usually free of detectable microfilaremia but may experience more severe and pruritic episodes of angioedema and have brisk immunologic responses, including elevated antifilarial antibody titers, an elevated serum IgE level, and prominent eosinophilia—often greater than 3,000 eosinophils/μL.

Parasitologic diagnosis of loiasis is made by demonstrating adult worms in subconjunctival or subcutaneous tissues or demonstrating microfilariae in the blood by means of a Nuclepore filter concentration technique. In contrast to Wuchereria microfilaria, Loa loa microfilaria is found throughout the day. Microfilaremia may not be detectable, however. Eosinophilia may be marked, with elevations of 50% or greater. Filarial antibody titers are usually elevated. In the absence of detectable microfilaria, the diagnosis is suggested by clinical features, a history of exposure, and eosinophilia.

Therapy consists of diethylcarbamazine (6 mg/kg/day) orally for 3 weeks and may require adjunctive antihistamines or corticosteroids. Patients with microfilaria should be treated initially with escalating doses of diethylcarbamazine for 3 days (one 50 mg dose on the first day, three 50 mg doses on the second day, and three 100 mg doses on the third day), followed by the full 3-week course. Albendazole therapy is useful to reduce microfilaria in patients who cannot tolerate diethylcarbamazine. Some patients require repeated courses of therapy.

Acceptability and compliance with ivermectin treatment continues in many areas, despite side effects, which are usually mild and include itching, edema, rashes, and body weakness; however, encephalopathy has been reported. Diethylcarbamazine, given in a dosage of 300 mg orally once a week, is an effective chemoprophylactic agent against loiasis for persons who are planning long-term visits to areas of Africa where this infection is endemic.

**Zoonotic Filarial Infections**

Although no human filarial parasites are indigenous to the continental United States, a variety of filarial parasites infect animals. In rare cases, these organisms may be transmitted via insect vectors to humans. Within the human host, they may develop into adult worms, which localize in the same organs in humans as in the definitive animal hosts. In this way, dog heartworm (*Dirofilaria immitis*), endemic in dogs along the Atlantic and Gulf coasts, in the Mississippi Valley, and in California, localizes to the human pulmonary arteries. A granulomatous response develops around the worm, producing a pulmonary nodule. Some patients experience chest discomfort, malaise, low-grade fever, cough, and, occasionally, hemoptyis. Typically, however, the pulmonary lesions are detected as a coin lesion on a chest x-ray. Prominent blood eosinophilia is absent, and serologic tests for filariasis are negative. In the absence of reliable diagnostic tests for human pulmonary dirofilariasis, excisional biopsy serves both diagnostic and therapeutic purposes.

Other zoonotic filarial parasites include *Dirofilaria repens*, which causes subcutaneous abscesses, and *Brugia beaveri*, which produces focal lymphadenopathy. No chemotherapy is required for these infections or for infections caused by *D. immitis*.

**Trematode Infections**
Schistosomiasis

Schistosomiasis, a chronic trematode (fluke) infection of humans, is second only to malaria in public health significance, with an estimated 200 million people infected worldwide. Three major species—*Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*—infect humans. *S. mansoni* is found in Africa, the Arabian Peninsula, South America, and parts of the Caribbean; *S. japonicum* is found in Japan, China, and the Philippines; and *S. haematobium* is found in Africa and the Middle East. Two minor species, *Schistosoma mekongi* and *Schistosoma intercalatum*, are found in mainland Indochina and central West Africa, respectively. Transmission of schistosomiasis cannot occur in the United States because of the absence of the specific freshwater snail that is a requisite intermediary host [see Figure 11]. However, the disease may be encountered in immigrants or travelers from endemic areas.

**Diagnosis**

The diagnosis of schistosomiasis is suggested by a history of possible exposure, even exposure that occurred many years ago, along with compatible gastrointestinal or urinary tract symptoms, hepatosplenomegaly, eosinophilia, or a combination of these findings.

**Clinical features** Three stages of disease may occur in schistosomiasis. The first stage, schistosomal dermatitis, may develop acutely within a day of cercarial penetration of the skin. Because this entity develops early after exposure, it usually will have subsided in patients before they are seen by physicians in the continental United States. Swimmer's itch, a similar reaction caused by exposure to animal schistosomes in freshwater and saltwater, is seen in the United States [see Figure 12]. The schistosomes penetrate human skin and then die, causing no further infection.

The second stage of disease, acute schistosomiasis, or Katayama fever, develops 4 to 8 weeks after heavy (presumably, primary) infection. This stage is thought to be caused by a severe allergic response at the onset of egg-laying by the schistosomes. Patients have fever, cough (up to 10% also have pulmonary nodules), hepatosplenomegaly, malaise, myalgias, urticaria, and eosinophilia. Deaths have ensued. Katayama fever is more severe in infection with *S. japonicum* than with other species because of the high quantities of eggs produced by *S. japonicum*.

Chronic schistosomiasis, the third stage, is caused by the heavy deposition of eggs in the intestine or bladder and in the liver. In *S. haematobium* infection, the principal symptoms are hematuria, dysuria, and frequent urination. Hydronephrosis and pyelonephritis may develop as a result of fibrosis and infection. In *S. mansoni*, *S. mekongi*, or *S. japonicum* infection, manifestations may include fever, malaise, abdominal pain, diarrhea, blood in stools, and hepatosplenomegaly. Presinusoidal hepatic trapping of *S. mansoni*, *S. mekongi*, or *S. japonicum* eggs and the consequent granulomatous reaction induce portal hypertension and collateral esophageal varices. Eggs may then be shunted from the liver to the lung, with the possible sequela of pulmonary hypertension. Death may occur as a result of variceal bleeding. Hepatic encephalopathy rarely develops because the hepatic parenchyma is spared. Coinfection with *S. mansoni* and hepatitis B or C virus is associated with accelerated clinical deterioration. Less common sequelae of chronic schistosomiasis include intestinal polyps, bladder carcinoma, and persistent *Salmonella* infections. An uncommon sequela of both acute and chronic schistosomiasis is focal neurologic dysfunction from aberrant localization of eggs in CNS tissue. Embolic deposition of *S. japonicum* eggs may produce cerebral granulomas, whereas *S. haematobium* and *S. mansoni* eggs may cause transverse myelitis involving the midthoracic or lumbar spinal cord.

**Laboratory findings and imaging studies** Computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography may detect hepatic periportal fibrosis and calcification, colonic wall calcifications, and changes in the bladder and ureter resulting from schistosomiasis. Serologic tests can help confirm the diagnosis; an indirect immunofluorescent test for gut-associated schistosome antigens is especially sensitive for the detection of acute schistosomiasis. Stool examination should include a search for eggs of all *Schistosoma* species [see Figure 13]. Urine
specimens for detection of *S. haematobium* should be obtained between 10 am and 2 pm. If stool and urine specimens are negative, microscopic examination of biopsy specimens of rectal or bladder mucosa may demonstrate eggs of all species. Detection of circulating antigens from adult worms and eggs are promising techniques that may supersede traditional egg demonstration.

**Treatment**

Praziquantel is used to treat infection caused by any of the five *Schistosoma* species; it reliably cures 60 to 90% of infected persons and reduces egg burden substantially in most others. For *S. haematobium* and *S. mansoni*, two oral doses of 20 mg/kg are given in 1 day. For *S. japonicum* and *S. mekongi*, the dosage is 20 mg/kg given orally three times in 1 day. The efficacy, the paucity of side effects, and the convenience of single-day therapy make praziquantel the drug of choice for all forms of schistosomiasis. Resistance to praziquantel has been reported in *S. haematobium* and *S. mansoni* infections in Egypt and Kenya but has not yet become a widespread problem. In addition to praziquantel, corticosteroids are beneficial for patients with spinal cord schistosomiasis and acute schistosomiasis.

![Figure 11. Freshwater snails and the human body provide the living environment of the schistosomes *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma mekongi, and Schistosoma intercalatum.* Eggs of each species hatch into schistosomal miracidia, which enter snails. Free-swimming cercariae released by the snails rapidly penetrate human skin and become tailless schistosomula, which enter the blood vessels. The schistosomula mature in the intrahepatic portal blood, form male-female pairs, and begin to mate. The pairs, still copulating, migrate to various sites: *S. mansoni, S. intercalatum,* and *S. mekongi* ultimately lodge in the blood vessels of the lower intestine; *S. japonicum* lodges in blood vessels throughout the intestine; and *S. haematobium* settles in blood vessels around the bladder. Adult worms subsequently begin laying eggs in the wall of the urinary bladder or intestine. From the intestinal sites, the eggs may be transported in the portal circulation to the liver, or they may be excreted in the feces. *S. haematobium,* by contrast, is excreted in the urine and does not tend to lead to liver disease but rather causes local bladder damage.](image)

**Paragonimiasis**

Humans acquire paragonimiasis after consumption of raw, salted, or wine-soaked crustacea (freshwater crabs or crayfish) infested with the metacercarial stage of lung flukes belonging to the genus *Paragonimus* (the life cycle of *Paragonimus* is illustrated in the CDC PHIL [http://phil.cdc.gov/P hil ]; photograph 3415). It is estimated that 21 million people are infected with *Paragonimus* species. *Paragonimus westermani* is endemic in parts of China, Korea, Japan, the Philippines, and Taiwan. Other *Paragonimus* species infect humans in western Africa and Central and South America. Although paragonimiasis is rare in the United States, it has developed. Ingested metacercariae undergo excystation in the duodenum and migrate through the wall of the gut into the peritoneal cavity. Most pass through the diaphragm and penetrate the parenchyma of the lung. Neutrophilic and eosinophilic reactions, followed by a mononuclear leukocytic inflammatory reaction, develop around the fluke. As the lung parenchyma necrotizes, a fibrous capsule begins to surround the fluke. By about 5 to 6 weeks after ingestion, the flukes have matured and start laying eggs, which causes the capsule to enlarge and rupture, often into a bronchiole. The most common presentation of paragonimiasis is the production of brown-tinged sputum or hemoptysis, which derives from the admixture of eggs, inflammatory cells, and blood in the sputum. Sputum is often gelatinous and purulent as well as bloody. Patients usually appear well but may have a chronic cough, pleuritic pain, or night sweats.
Figure 12. Swimmer's itch is a cutaneous reaction caused by exposure to animal schistosomes in freshwater and saltwater. The schistosomes penetrate the skin and then die, causing no further infection.

Young flukes may migrate to nonpulmonary sites. Localization in the CNS produces signs and symptoms from a cerebral or spinal inflammatory mass lesion, which may calcify. Less commonly, the parasites lodge in cutaneous or peritoneal sites.

During the early stages of infection, when the larvae migrate, blood eosinophilia is prominent. The chest x-ray may show transient, often basilar, infiltrations, as in Loffler syndrome. Later in the course of the disease, blood eosinophilia commonly disappears, and the chest x-ray may show areas of cavitation; ill-defined, so-called cotton-wool and streaky densities; and bubblelike cavities. Pleural reaction, with or without pleural effusion or pneumothorax, can occur.

The diagnosis of paragonimiasis should be considered for patients from endemic areas with compatible clinical presentations. Examination of the sputum for ova may confirm the diagnosis by revealing the operculated eggs of Paragonimus. Swallowed eggs appear in the stool; therefore, examining the stool for eggs may be helpful, especially in children. Fine-needle aspiration of pulmonary lesions also yields diagnostic eggs. Paragonimiasis may resemble pulmonary tuberculosis both clinically and radiographically, yet Paragonimus eggs are usually not seen in acid-fast stains.

Praziquantel is an effective treatment of paragonimiasis, although it is not easy to eradicate. The dosage is 25 mg/kg orally three times a day for 2 days. Bithionol is somewhat effective, but its use is limited because of side effects such as diarrhea. Triclabendazole is a useful therapeutic alternative to praziquantel.

**Clonorchiasis**

*Clonorchis sinensis*, the Chinese liver fluke, infects approximately seven million persons in the Far East, including South China, Hong Kong, Taiwan, Japan, Korea, and Vietnam. Humans become infected with *C. sinensis*, a parasite of freshwater fish, by eating raw or undercooked fish containing encysted metacercariae (the life cycle of *C. sinensis* is illustrated in the CDC PHIL [http://phil.cdc.gov/Phil ]; photograph 3385). Larvae, liberated by trypsin in the duodenum, migrate to the common bile duct and then to the distal biliary tree. There they mature into adult worms, which may persist for more than 20 years. Less commonly, adult worms are found in the gallbladder and pancreatic ducts.

In the acute phase of the infection, the epithelium of the biliary tree undergoes early desquamation, which is followed by hyperplasia and increased mucin production by the epithelial cells. The hyperplasia may progress to adenomatous changes. With chronic infection, fibrosis develops around dilated bile ducts. Clinically, the syndrome of acute clonorchiasis, manifested by fever, chills, and tender hepatomegaly, may develop 1 week after ingestion of infected fish. Later in the course of the infection, however, most patients with light infection and many with heavy infection are asymptomatic. Occasionally, adult worms block pancreatic ducts, causing pancreatitis. By occluding the biliary tract, worms may contribute to acute suppurative cholangitis. Clonorchiasis predisposes to intrahepatic bile duct stone formation and to recurrent pyogenic cholangitis; infection with *C. sinensis* has been associated with cholangiocarcinoma.

Leukocytosis, prominent eosinophilia, and elevation of alkaline phosphatase levels occur in symptomatic acute clonorchiasis. Sonography often detects diffuse dilatation of small intrahepatic bile ducts without dilatation of large intrahepatic or extrahepatic ducts. Adult flukes may be
visualized in the gallbladder by ultrasonography and in the bile ducts by cholangiography. In asymptomatic chronic clonorchiasis, eosinophilia is not present, and liver function tests and liver scans are normal. Egg laying begins within 2 to 3 weeks after infection; eggs may be found either in the stool or in duodenal aspirate. Diagnostic serologic tests are neither sensitive nor specific. The diagnosis should be considered in patients who have a history of travel or residence in the Far East, have eaten undercooked fish, and have a compatible clinical syndrome.

Treatment and control of clonorchiasis generally rely only on praziquantel and constitute effective and well-tolerated therapy for this disease. Praziquantel is administered at a dosage of 25 mg/kg orally three times a day for 1 day. An alternative investigative therapy is albendazole, 10 mg/kg/day for 7 days. Initially, complications of

![Eggs of Schistosoma japonicum (a), Schistosoma haematobium (b), or Schistosoma mansoni (c) detected by microscopic examination of the stool, urine, or rectal mucosa biopsy specimens confirm the diagnosis of schistosomiasis. The magnification is about 400 times. (d) This Schistosoma mekongi egg was found in the stool of a Laotian refugee in the United States. The magnification is about 1,000 times.](image)

*C. sinensis* infection, including calculi, cholangitis, and pancreatitis, are managed medically, although surgical drainage may be required.

### Opisthorchiasis

Opisthorchiasis represents infection by either *Opisthorchis felineus* or *Opisthorchis viverrini*. *O. felineus* infects 1.5 million persons in Kazakhstan, the Ukraine, central Europe, western Siberia, and parts of Asia; *O. viverrini* infects nine million persons in Thailand, Laos, and Cambodia.

Cats and wild carnivores are the definitive hosts of these species. Humans acquire infection by eating raw or undercooked fish that contains metacercariae of the parasite. Metacercariae undergo excystation in the duodenum and migrate into the bile ducts, where they mature.

Clinical features of opisthorchiasis are similar to those of clonorchiasis; complications include the development of cholangiocarcinomas. The diagnosis is made by finding eggs in feces or in duodenal aspirate.

Therapy, which is considered investigational by the FDA, consists of praziquantel (25 mg/kg orally three times in 1 day). The antimalarial mefloquine is being studied. Complications involving biliary tract sepsis require the administration of antibacterial agents.

### Fascioliasis

*Fasciola hepatica*, the liver fluke of sheep and cattle, is a major veterinary problem and can give rise to human fascioliasis. Human infection with *F. hepatica* shows a wide geographic distribution that includes Europe, China, Africa, and Latin America; the disease is considered a public health problem in the Andean countries of South America, Iran, and western Europe. Despite the prevalence of the parasite in sheep and cattle of the southern and western United States, autochthonous human cases are rare. Humans generally become infected by ingesting parasitic cysts attached to aquatic plants, most notably wild watercress.

Ingested metacercariae burrow through the intestinal wall into the peritoneal cavity and then penetrate the hepatic capsule and parenchyma; they then enter the bile ducts, where they mature into adults after 3 to 4 months. Acute fascioliasis runs its course during the months of penetration and maturation. Symptoms may be minimal or include fever, upper abdominal pain, hepatomegaly,
and malaise. Pruritus, urticaria, jaundice, nonproductive coughing, and anemia occur less often.\textsuperscript{93}

After the flukes mature in the biliary passages, hyperplasia and dilatation of the biliary ducts, as well as periductal fibrosis, develop. Clinical manifestations in the chronic stage of infection are variable and may include the same signs and symptoms experienced in the acute phase. Obstruction of the biliary tract, cholecystitis, and biliary cirrhosis are uncommon. In rare instances, flukes migrate to other tissues, including the lungs, muscles, and CNS.

Ingestion of raw sheep or goat liver containing young flukes produces halzoun, a disease recognized in the Near East. Lodging of the flukes in the pharynx produces a pharyngeal inflammatory mass lesion with attendant dysphagia and dyspnea.

Acute fascioliasis usually produces leukocytosis, marked eosinophilia, and cholestatic-type abnormalities on liver function testing. Eggs are not found until approximately 3 months after infection, when they may be detected in the stool or, with a higher yield, in biliary or duodenal fluid samples. Thus, the triad of fever, marked eosinophilia, and hepatomegaly suggests acute fascioliasis. A history of ingestion of potentially infected watercress supports the diagnosis. Serologic tests are available but may reflect cross-reactions with other helminthic parasites. Nodular hepatic lesions with diminished density may be visualized by CT or MRI.\textsuperscript{94,95} In chronic fascioliasis, the extent of the abnormalities in liver function tests and cholangiograms correlates with the magnitude of biliary tract obstruction and hepatocellular damage.

Triclabendazole, given in a single oral dose of 10 mg/kg, is the drug of choice for fascioliasis. Bithionol (30 to 50 mg/kg on alternate days for 10 to 15 doses) and nitazoxanide (500 mg p.o., b.i.d. for 3 days) are alternatives.\textsuperscript{13,96} Praziquantel is not effective for fascioliasis.

**Intestinal Flukes**

**Fasciolopsiasis**

Fasciolopsiasis results from infection with the intestinal fluke \textit{Fasciolopsis buski}, which is found in many parts of Asia.\textsuperscript{97} This fluke principally parasitizes the intestine of the pig. Human infection is acquired by ingestion of water plants such as water chestnuts, which bear metacercaiae of the parasite. The larvae undergo excystation in the duodenum and develop into large adult flukes, up to 7 cm long, that attach to the mucosa of the proximal small intestine. Inflammation and ulceration may occur at these intestinal sites. Light infection is asymptomatic; heavy infection is associated with abdominal pain, ulceration, hemorrhage, intestinal obstruction, malabsorption, and facial and generalized edema.\textsuperscript{98} Blood eosinophilia is common. Diagnosis is made by finding adult flukes or, more commonly, by finding in feces the eggs of \textit{F. buski}, which are difficult to distinguish from the eggs of \textit{Fasciola hepatica}. Fasciolopsiasis is treated, on an investigational basis, with praziquantel, 25 mg/kg orally three times in 1 day,\textsuperscript{10} although some sources advise that a single 15 mg/kg dose is effective.\textsuperscript{97}

**Other Intestinal Flukes**

Infection with two small intestinal flukes, \textit{Metagonimus yokogawai} (found in the Far East and Indonesia) and \textit{Heterophyes heterophyes} (found in Tunisia, Egypt, and the Far East), occurs when humans ingest raw or undercooked fish that contains metacercaiae of the parasites. The adult flukes are 2 to 3 cm long and attach to the mucosa of the small intestine. Heavy infection may cause abdominal pain and diarrhea.\textsuperscript{99} Diagnosis is made by finding eggs, which resemble the eggs of \textit{Clonorchis} species, in feces. Therapy consists of the investigational drug praziquantel (25 mg/kg orally three times in 1 day).\textsuperscript{13}

Human infection with the intestinal fluke \textit{Metorchis conjunctus}, acquired near Montreal, Canada, by consumption of the white sucker fish, has been described. Illness consisted of upper abdominal pain,
low-grade fever, eosinophilia, and elevated liver enzyme levels. Diagnosis was made by finding eggs in the stool and by serology. Praziquantel (25 mg/kg three times in 1 day) is beneficial.\textsuperscript{13,100}

The intestinal fluke \textit{Nanophyetus salmincola} has been recognized in humans who ate raw or kippered salmon. In most patients, symptoms and infection resolved without therapy, although treatment can be provided with praziquantel (20 mg/kg given three times in 1 day).\textsuperscript{13,101}

\textbf{Cestode Infections}

\textbf{Introduction}

Humans can harbor the adult form of fish, pork, and beef tapeworms (cestodes). These often do not cause disease but are noticed when segments of the worm are passed. Most often these segments can be distinguished from other worms by their flat, tapelike appearance and their segmented proglottids. Examination of these proglottids or the head of the tapeworm can differentiate these three species. In general, larval forms of tapeworms, such as \textit{Cysticercus} (pork) and \textit{Echinococcus} (dog), cause more severe disease by mass effect and inflammation.

\textbf{Fish Tapeworm}

Humans acquire fish tapeworm infection by ingestion of inadequately cooked fish containing the infective plerocercoid stage of parasitic \textit{Diphyllobothrium} species, including \textit{D. latum} (the life cycle of \textit{D. latum} is illustrated in the CDC PHIL [\url{http://phil.cdc.gov/Phil}]; photograph 5257).\textsuperscript{102-104} The growing popularity of raw fish dishes, such as sushi, sashimi, seviche, and Dutch green herring, has increased the risk of acquiring diphyllobothriasis. Freshwater fish, including pike and yellow perch caught in the United States, may harbor \textit{Diphyllobothrium} species, as may anadromous salmon. \textit{Diphyllobothrium} species other than \textit{D. latum} are found in Pacific salmon and Alaskan blackfish.\textsuperscript{105} Adult tapeworms may grow up to 15 meters in length and live for 20 years or longer in the small intestine. Human infections are often asymptomatic, although some patients experience anorexia, nausea, or weight loss. Because \textit{D. latum} competes with the host for vitamin B\textsubscript{12}, megaloblastic anemia and neuropathy from vitamin B\textsubscript{12} deficiency may develop. Diagnosis is made by finding the operculated eggs in the stool or by recovering proglottids in the stool after a saline purge. Therapy is with praziquantel (5 to 10 mg/kg, given once) or niclosamide (2 g, given once).\textsuperscript{13}

\textbf{Pork Tapeworm}

\textit{Taenia solium}, or pork tapeworm, causes two distinct types of disease, depending on the stage of the parasite that is ingested [see \textbf{Figure 14}].\textsuperscript{106} If cysticerci in inadequately cooked pork are ingested, the adult tapeworm develops in the intestine, causing symptoms such as abdominal pain, weight loss, and weakness. Patients may describe passing proglottid segments of the worm. Eggs of \textit{T. solium} are also passed in the feces. Eggs can be detected with greater frequency by applying clear cellulose acetate tape to the perianal skin and examining the tape, as described for pinworm [see \textbf{Intestinal Nematode Infections}, above]. \textit{T. solium} eggs are indistinguishable from eggs of \textit{Taenia saginata} (beef tapeworm); diagnostic differentiation between the two species requires recovery of mature proglottids or the head (scolex) from the stool [see \textbf{Figure 15}]. Therapy for adults infected with intestinal pork tapeworm consists of praziquantel (5 to 10 mg/kg, given once) or niclosamide (2 g, given once).\textsuperscript{13}

Cysticercosis, the second disease entity, is caused by the ingestion of \textit{T. solium} eggs. In an uninfected person, such ingestion may occur by consumption of food contaminated by egg-containing feces from an infected person. In persons with an intestinal worm, ingestion may occur by autoinfection involving hand-to-mouth fecal carriage or by regurgitation of egg-laden proglottids into the duodenum or stomach. Most infections are encountered in developing countries, where intestinal \textit{T. solium} infections occur frequently. Experience in the United States has demonstrated, however, that cysticercosis may develop in those who have never traveled abroad, through transmission of
infectious eggs from family members, domestic workers, or others infected with *T. solium*. 107-109

Figure 14. Life cycle of *Taenia solium*, the pork tapeworm, which causes cysticercosis, and of *Taenia saginata*, the beef tapeworm.

Figure 15. Hooklets on the scolex (head) of *Taenia solium* give it an "armed" appearance.

The ingested eggs hatch in the stomach and upper intestine, and the resultant oncospheres circulate in the blood to various tissues. Cysticerci develop most often in subcutaneous tissue, skeletal muscle, and the brain, as well as in other organs, including the eyes, heart, liver, and lungs. Developing cysticerci elicit little host reaction, but as the cysticerci begin to degenerate, usually after several years, inflammation develops. Ultimately, the cysts, which range from 0.5 to about 2.0 cm in diameter, undergo necrosis and may become calcified.

**Diagnosis**

Clinical signs and symptoms depend on the organ compromised by the cysticerci, the specific localization of a cysticercus within the organ, the state of inflammation surrounding the cysticerci, and the viability of the cestode. The most serious forms of cysticercosis are those with ocular, cardiac, and neurologic involvement. It is the most common helminthic infestation of the CNS and a leading cause of acquired epilepsy worldwide; the manifestations of neurocysticercosis vary from an asymptomatic infection to sudden death. 110 Neuroimaging is the mainstay of diagnosis. 110 CNS imaging studies may reveal cysticerci in the brain parenchyma, within the ventricles, at the surface or the base of the brain, or within the subarachnoid space.

CT may miss early lesions, which have the same x-ray density as the brain, but hypodensity and contrast-enhancing ring lesions are seen with the development of inflammation around the cyst. As sclerosis occurs, a cystic lesion develops, and the cyst wall may calcify. Ultimately, degenerated cysts are replaced by small (1 to 4 mm in diameter) calcified lesions within the brain [see Figure 16].

The diagnosis of cysticercosis can be made with certainty only by biopsy of a cyst. Calcified cysts in subcutaneous tissue and muscle, which have a puffed-rice appearance on radiographs, should be sought. Although the signs and symptoms of neurocysticercosis are not specific, this diagnosis is supported by the finding of characteristic multiple cystic or calcified lesions on CT scans in a patient from an endemic area.

Although the sensitivity of serologic testing for *T. solium* approaches 100% in patients with multiple intraparenchymal cysts, the sensitivity of testing for patients with solitary cysts is less than 50%, which makes serologic testing a less useful diagnostic tool for patients with solitary CNS lesions. 111 Stool examination for *Taenia* eggs may detect concurrent infection with the tapeworm but is not directly pertinent to the diagnosis of cysticercosis.

**Treatment**

Therapy for cysticercosis may be medical or surgical. Patients with only calcified soft tissue or CNS lesions do not require medical therapy. Surgical excision was once the only approach for viable
cysts, but praziquantel and albendazole have proved to be effective against neurocysticercosis.\textsuperscript{112-114} Despite the improvements noted after medical therapy, the absence of controlled trials specifically comparing medically treated patients with untreated patients has left room for uncertainty concerning the efficacy of medical therapy for neurocysticercosis.\textsuperscript{113,115} However, a randomized trial has demonstrated a trend toward fewer seizures in patients treated with albendazole and steroids compared with those treated with placebo.\textsuperscript{116}

Typically, albendazole is given in a dosage of 400 mg orally twice daily for 10 to 28 days; praziquantel is given in a dosage of 50 to 100 mg/kg/day in three divided doses for 30 days.\textsuperscript{13} Because treatment may cause inflammatory reactions to develop around cysticerci, ocular cysticercosis and spinal cysticercosis are not usually treated medically; an ophthalmologic examination is indicated before drug therapy to rule out intraocular cysticercosis, which could lead to devastating inflammation. For patients with neurocysticercosis, corticosteroids (e.g., dexamethasone, 4 to 16 mg/day, or prednisone, 60 to 100 mg/day) are usually given 1 to 2 days before and during treatment with albendazole or praziquantel to minimize inflammatory reactions. Patients who are taking anticonvulsant medications for neurocysticercosis should continue to use them during this treatment, but many such patients can stop taking antiseizure medications after cysticercosis therapy.\textsuperscript{116,117} CT scanning should be repeated 3 to 6 months after therapy to determine whether any of the cysts are still viable; therapy should be repeated if viable cysts remain.

**Beef Tapeworm**

*T. saginata,* or beef tapeworm, causes an intestinal infection in persons who have eaten undercooked beef containing cysticerci.\textsuperscript{104} The infection is usually asymptomatic, although abdominal pain, weight loss, increased appetite, or passage of lengths of proglottids may be noticed because proglottids of *T. saginata* tend to be more motile than those of the other tapeworms [see Figure 17]. As noted, the detection of eggs in the feces or on the perianal skin is diagnostic of tapeworm infection, but differentiation between *Taenia* species requires identification of the proglottids. Therapy consists of praziquantel or niclosamide, as given for

![Figure 16. Shown are computed tomographic (CT) scans of two patients (a, c) with seizures resulting from neurocysticercosis. The CT scans on the left are without contrast; those on the right are with contrast. Multiple cystic and calcified lesions are evident in both patients (the contrast agent enhances the cystic lesions). The scans from the first patient (a) show multiple cystic lesions, with a denser central spot that represents the scolex, a pathognomonic finding for neurocysticercosis.](image)

*T. solium* intestinal infection.\textsuperscript{13} Infection with *T. saginata* does not lead to cysticercosis in humans.

**Dwarf Tapeworm**

*Hymenolepis nana,* a tapeworm measuring 3 to 4 cm long and 1 mm wide, has a broad geographic distribution.\textsuperscript{102} In the United States, it is most commonly encountered in persons living in the southern states, in institutionalized patients, and in children. Unlike the other tapeworms, the larval and adult stages of *H. nana* develop in the same host. Infection is spread by the fecal-oral route and occurs when eggs, which are immediately infectious, are ingested. Thus, *H. nana* is one of the few helminths (along with *Enterobius, Capillaria,* and *Strongyloides*) that can propagate by autoinfection; children, in particular, can develop huge worm burdens and become symptomatic.

After an egg of *H. nana* has been ingested, an oncosphere hatches from the egg and penetrates the intestinal villi, where it develops into a cerocyst; the cerocyst reenters the lumen of the small intestine and develops into an adult worm. Eggs are liberated from the distal segments of the adult worm, which lives for about 1 year. The eggs may cause internal reinfestation. Light infection is
usually asymptomatic; diarrhea and abdominal pain may accompany heavy infection. Diagnosis is made by finding eggs in feces. Therapy consists of praziquantel (25 mg/kg given once);

Figure 17. Persons infected with the beef tapeworm, *Taenia saginata*, may pass lengths of proglottid in the stool. An entire adult beef tapeworm is shown.

this use of praziquantel is currently considered investigational.13 An alternative investigational therapy is nitazoxanide (500 mg p.o. daily for 3 days).13

**Other Tapeworms**

Human infection with *Hymenolepis diminuta*, a tapeworm of mice and rats, occasionally occurs when humans ingest insects that harbor developing cerocysts of the tapeworm; one such insect is the flea. Infection is more common in children and is associated with few or no symptoms. Diagnosis and treatment are the same as described for the dwarf tapeworm *H. nana* (see above).

Children are also more commonly infected with the dog tapeworm *Dipylidium caninum*. Infection is acquired by consuming infected fleas or lice. Adult worms develop in the small intestine and measure 15 to 70 cm in length. Mild intestinal symptoms may or may not be present. Diagnosis is made by finding proglottids or eggs in feces. Therapy for adults consists of praziquantel (5 to 10 mg/kg given once).13

Human infection with dog tapeworms of the genus *Multiceps* results in a syndrome termed coenurosis, which is similar to cysticercosis.118 At present, surgical excision forms the basis of diagnosis and treatment.

Sparganosis represents infection by larval tapeworms of the genus *Spirometra*, which are closely related to tapeworms of the genus *Diphyllobothrium*. Most such infections occur in the Far East. Human infection results from drinking water containing microcrustacean *Cyclops* species that harbor procercoid larvae (spargana) of the parasite. Human infection may also be acquired by ingesting raw flesh of amphibians or snakes that contains larvae of the parasite or from applying such flesh to the skin as a poultice. After ingestion, the procercoid larvae migrate into subcutaneous tissues, where they usually present as a painless subcutaneous nodule that enlarges during the course of many months. Larvae may also migrate to the CNS.119,120 Blood eosinophilia is commonly elicited. Surgical excision of larvae-containing nodules remains the basis of diagnosis and treatment.

**Hydatid Disease**

Echinococcosis in humans may result from infection with *Echinococcus granulosus*, which causes cystic hydatid disease; *Echinococcus multilocularis*, which causes alveolar hydatid disease; or *Echinococcus vogeli* or *Echinococcus oligarthrus*, which causes polycystic hydatid disease and is found in areas of Central and South America.104,121,122 Adult *E. granulosus* cestodes live in the intestine of dogs and wolves. Infectious eggs are passed in the feces of these animals and may be ingested by intermediate hosts such as sheep, cattle, or humans [see Figure 18]. The cycle is maintained when dogs or wolves ingest the carcasses of intermediate hosts. *E. granulosus* infection is most prevalent in sheep- and cattle-raising countries. It is also found in a number of western states, Alaska, and Canada, where autochthonous cases of human infection have been recorded.123

After the eggs are ingested, oncospheres are carried in the bloodstream to the liver, lungs, and other organs. Unilocular cysts, which may contain daughter cysts, develop most commonly in the liver; the second most common site is the lungs. In children, pulmonary involvement may be more common
than hepatic involvement. Unilocular hydatid cysts enlarge concentrically, increasing in diameter by about 1 to 5 cm a year, depending on the density of the organs in which they are located. A cyst may attain a large size before the initial symptoms develop; these symptoms are usually attributable to a space-occupying mass lesion. The onset of symptoms has been reported to occur from before 1 year of age to 75 years of age, but in large series, most persons become symptomatic between 4 and 15 years of age. Pathologic fractures or neurologic symptoms can occur with osseous or CNS localization, respectively. When cysts leak, patients may experience bronchospasm, urticaria, or anaphylaxis; blood eosinophilia, which is otherwise usually not prominent, may increase. Communicating rupture of pulmonary or hepatic cysts can lead to the release of cyst contents into the bronchial or biliary systems. Because cysts contain multiple infective protoscolices, rupture of cysts can lead to dissemination of infection and the generation of new cysts from each released protoscolex.

*E. multilocularis* lives in the intestine of foxes and dogs. Its intermediate hosts are mice and other small mammals. *E. multilocularis* is found only in the Northern Hemisphere, including central western Europe, Russia, the central Asian republics, China, northern Japan, Canada, Alaska, and the north central United States. Because the cysts of *E. multilocularis* lack a containing capsule, they progressively invade involved tissues and produce honeycombed alveolar hydatid cysts. The liver is most commonly affected. Severe damage caused by extensive alveolar hydatid cysts can result in jaundice and portal hypertension. The mortality in untreated alveolar disease is 90%.

The diagnosis of hydatid disease can be strongly suggested by the results of radiographic studies. Plain films detect pulmonary cysts but often do not visualize cysts in other organs unless they are calcified—a process that occurs mostly in hepatic cysts. On CT and MRI, echinococcal cysts appear as well-defined, thick- or thin-walled cysts that may have calcified rims. In older lesions, where scolices and daughter cysts form hydatid sand that settles in the dependent portion of the cyst, a layer of fluid can be visualized. Dependent movement of calcified hydatid sand, on repositioning and ultrasound monitoring, is strongly suggestive, if not pathognomonic, of a hydatid cyst. A pathognomonic CT finding in intact cysts is the presence of daughter cysts that are either free within the cyst or adherent to the inner germinal layer. Separation and collapse of cyst wall layers and the introduction of air into the space between the layers can be detected on plain films (as the meniscus, double arch, or water lily signs) and by CT scan.

![Figure 18. Life cycle of Echinococcus granulosus. Adult E. granulosus cestodes live in the intestine of dogs and wolves. Infectious eggs are passed in the feces of these animals and may be ingested by intermediate hosts such as sheep, cattle, or humans. After the eggs are ingested, oncospheres are carried in the bloodstream to the liver, lungs, and other organs, where they form hydatid cysts. The cycle is maintained when dogs or wolves ingest the carcasses of intermediate hosts.](image)

Serologic tests can be helpful in making the diagnosis of echinococciosis but are not uniformly sensitive or specific. A sensitive assay, such as ELISA or indirect hemagglutination, is performed first. Because of the possibility of false positive results produced by cross-reacting helminthic infections, specificity is confirmed with a less sensitive but more specific assay, such as an antigen-specific immunoblot or a gel diffusion assay for the *Echinococcus*-specific arc 5 immunoprecipitin band. Even with these assays, 5 to 25% of patients with neurocysticercosis have false positive results. Conversely, negative tests do not exclude the diagnosis, because approximately 50% of patients with isolated pulmonary cysts and 10 to 15% of those with hepatic cysts lack detectable antibodies against *Echinococcus*. Although leakage of cyst fluid poses risks of anaphylaxis or dissemination of infection, percutaneous aspiration of a cyst in a seronegative patient, with guidance provided by CT or ultrasonography, can yield diagnostic protoscolices or hydatid membranes.

Therapeutic approaches to cystic and alveolar hydatid disease are quite complex, and consultation
for expert advice is highly recommended.122,124 For cystic hydatid disease, treatment should be reserved for symptomatic lesions or those affecting vital anatomic structures because 75% of asymptomatic persons with cysts remain symptom-free for more than a decade.125 When therapy is needed, the options are surgery, PAIR (puncture, aspiration, injection, and reaspiration; see below), or chemotherapy. Surgery offers the potential for total parasite removal and complete cure; nevertheless, cysts recur in 2 to 25% of patients treated with surgery.122 Preoperative and postoperative albendazole therapy is highly advisable. The past practice of injecting protoscolicidal solutions (7 to 90% ethanol, 0.5% percent cetrime, or 15 to 20% hypertonic saline) before resection is no longer recommended, because these agents are of uncertain efficacy and potentially dangerous to the patient because of chemical cholangitis and other complications.

The PAIR procedure, which consists of percutaneous aspiration, injection of protoscolicidal agents (e.g., 95% ethanol or 0.5% cetrime), and reaspiration, has demonstrated efficacy as an alternative to surgery. A randomized, controlled trial showed PAIR to be as effective as surgery for hepatic cystic echinococcosis; moreover, patients treated with PAIR had lower postprocedure morbidity and a shorter hospital stay.130-132 Like surgery, PAIR should be performed with albendazole therapy before and after the procedure to minimize dissemination of any leaked fluids containing infectious protoscolices.133 PAIR is best used for liver cysts of 5 cm or greater that are anechoic, multiseptate, or multiple.122 The PAIR procedure should not be performed if hepatic cysts communicate with the biliary tract. Complications are more common when PAIR is used to treat pulmonary lesions. PAIR may provoke acute allergic reactions.122

If neither surgery nor PAIR therapy is an option, medical therapy with albendazole is administered (mebendazole is an alternative that is considered less effective). Albendazole is given as a 400 mg dose twice a day for 28 days, often with additional 28-day courses given in subsequent months, with each course separated by 14-day treatment-free periods.134 Most commonly, albendazole therapy is continued for 6 months. Patients need to be monitored for complications during long-term albendazole therapy because hepatotoxicity, nausea, and neutropenia are common. Neither mebendazole nor albendazole is completely effective: 20 to 40% of patients experience no improvement. Albendazole therapy results in a cure in about one third of patients and leads to regression in cyst size and improvement in symptoms in another third. Both agents are contraindicated during pregnancy. Serial titers of echinococcal antibodies can be useful in monitoring therapeutic success.

Because alveolar hydatid disease is an aggressive and often fatal illness, the preferred therapy is radical resection of cysts, followed by albendazole therapy (up to 20 mg/kg/day) for at least 2 years.122 Long-term chemotherapy can benefit patients who are not candidates for operation, as well as those patients who have undergone nonradical resections or liver transplantation.122,135,136

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Figures 3, 7, 12, and 15 Centers for Disease Control and Prevention Public Health Image Library

Figure 4 University of Washington Microbiology Laboratory

Figures 2, 5, 6, 9, 10, 11, 14, and 18 Seward Hung

Figure 8 Courtesy of Drs. Herbert Cushing and Ken Fife, Indiana University

Figures a13 through c13 Courtesy of Dr. Steve Pan, Department of Tropical Public Health, Harvard School of Public Health

Figure 13 d Courtesy of Dr. Allen W. Cheever, National Institutes of Health

Figure 16 Courtesy of Dr. Theodore E. Nash, National Institutes of Health
14. Helminthic Infections

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