Parasites

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Introduction

Infections caused by parasites are among the most prevalent diseases affecting humans, yet they are diagnosed relatively infrequently in the developed world. Both the rising popularity of international travel and the continued arrival of immigrants and refugees in developed nations have resulted in an increase in the frequency with which parasitic and other tropical diseases are encountered in these countries. Such infections, if untreated, may have severe consequences, including significant long-term morbidity or death. However, clinical manifestations of these infections are often absent, or may be protean and nonspecific and therefore unrecognized in developed countries. Although pulmonary symptoms are distinctly uncommon, parasitic etiologies of pulmonary disease should be considered in patients with appropriate exposure histories, as early treatment may reduce morbidity and mortality.

This chapter discusses the epidemiologic features of tropical pulmonary disease, and will outline an approach to the patient presenting with this problem. Selected parasitic causes of pulmonary disease are discussed, with emphasis on the epidemiology, clinical manifestations, diagnosis, and treatment of these disorders. One notable exclusion from this

chapter is *Pneumocystis carinii*, which is discussed in detail elsewhere in this text.

Tropical Lung Disease

Epidemiology and Etiology

Acute pulmonary disease is common in the tropics. In Thailand, for example, an estimated 25% of both outpatient visits and hospital admissions are due to respiratory disease (Charoenratanakul, 1997), and statistics for African nations are similar (Stein-hoff, 1991). Radiographic abnormalities are also common in hospitalized patients in the tropics, occurring in 16% of adults and 36% of children in one study, regardless of the reason for admission (Reeder & Palmer, 1980). In returned travelers evaluated for fever in specialized centers, respiratory infection is an uncommon final diagnosis and accounts for only 2.6% to 11% of febrile illnesses (MacLean et al., 1994; Doherty et al., 1995); however, those with typical upper respiratory tract infections are more likely to be assessed by a primary care physician. Respiratory symptoms may be manifestations of other systemic tropical infections in travelers, such as malaria, typhoid, and Q fever.

Bacteria, particularly *Streptococcus pneumoniae* (and *Haemophilus influenzae* in children), and viruses are responsible for most cases of pneumonia in the developing world. Shann (1986) summarized 13 studies in Africa, Asia, Oceania, and South America that attempted to determine the bacterial etiology of pneumonia in children using lung aspirates. Overall, 62% of bacterial cultures yielded pathogens, of which *S. pneumoniae* and *H. influenzae* were predominant. A small study in Gambia,

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which included some adults, showed similar findings (Wall et al., 1986). In a review of nine studies in which viral pathogens were sought, 23% of children with pneumonia had culture or serologic evidence of a viral infection; 60% of these were due to respiratory syncytial, influenza, or parainfluenza viruses (Shann, 1986). With the exception of pneumonia, viruses are responsible for the majority of respiratory infections in the developed world; although studies are lacking, this is presumably also true in developing and tropical nations.

Other less familiar causes of pulmonary disease are endemic in particular geographic regions; these include bacteria such as *Pseudomonas pseudomallei* and *Pseudomonas mallei*, which cause melioidosis and glanders, respectively; fungi such as *Penicillium marneffe* and *Paracoccidioides brasiliensis*; and some viral causes of pulmonary disease such as viral hemorrhagic fevers (Table 1). Although some diseases such as pneumonic plague (*Yersinia pestis*), anthrax, and tuberculosis are widespread, they are more common in developing countries.

While some parasitic infections are restricted to specific geographic areas as a result of favorable climatic, socioeconomic, and ecologic factors, many are surprisingly widespread and may be found in industrialized countries. Parasitic causes of pulmonary disease are often overlooked. A compatible exposure history, and/or the presence of eosinophilia, should raise the possibility of a parasitic infection as the cause of respiratory symptoms or an abnormal chest radiograph, particularly in the absence of a response to conventional antimicrobial therapy.

Eosinophilia and Parasitic Infections

Eosinophilia is defined as an absolute eosinophil count of $\geq 450/\text{mm}^3$ in peripheral blood. In the returned traveler or immigrant, eosinophilia is often associated with an underlying parasitic infection, which may or may not be symptomatic but which nonetheless may require treatment. Review of pre-travel bloodwork, if available, can be helpful in determining whether eosinophilia is travel-related.

TABLE 1. Geographically Restricted Causes of Pulmonary Infections

	North America	Central/South America	Caribbean	Europe	Middle East	Africa	Asia	Oceania
Bacterial infections								
Glanders		Occ			Occ	Occ		
Melioidosis		Very rare				✓	✓	✓
Plague	Very rare	Occ		Very rare		✓	✓	
Viral infections								
Hemorrhagic fevers				✓		✓	✓	
Fungal infections								
Blastomycosis	✓	Occ			Occ	✓	Occ	
Coccidioidomycosis	✓	✓						
Paracoccidioidomycosis	Mexico	✓						
Penicilliosis							✓	
Helminthic infections								
Echinococcosis	Southwestern U.S.	✓	✓	✓	✓	✓	✓	
Filariasis		✓	Haiti, DR			✓	✓	✓
Paragonimiasis	Mexico	✓		✓		✓	✓	✓
Schistosomiasis		✓	✓		✓	✓	✓	
Strongyloidiasis	Southeastern U.S., PR	✓	✓	South, east		✓	✓	✓
Protozoal infections								
Malaria		✓	Haiti, DR			✓	✓	✓

Occ, occasionally; PR, Puerto Rico; DR, Dominican Republic.

TABLE 2. Noninfectious Causes of Eosinophilia

Allergic diseases	Immunodeficiency syndromes
Allergic broncho-pulmonary aspergillosis	Wiskott–Aldrich syndrome
Allergic rhinitis	IgA deficiency
Asthma	Job's syndrome
Drug allergy, including eosinophilia-myalgia syndrome	Skin diseases
Gastrointestinal diseases	Pemphigus
Inflammatory bowel disease	Bullous pemphigoid
Neoplastic diseases	Atopic dermatitis
Lymphoma	Hypereosinophilic syndromes
Leukemia	Eosinophilic pneumonia and gastroenteritis
Adenocarcinomas (solid organ)	Hereditary eosinophilia
Rheumatologic diseases	Loeffler's syndrome
Churg-Strauss vasculitis	Pulmonary infiltrates with eosinophilia
Polyarteritis nodosa	Other causes
Rheumatoid arthritis	Hypoadrenalism
Wegener's granulomatosis	Serum sickness
	Sarcoidosis
	Irradiation
	Kimura's disease
	Idiopathic

While eosinophilia in these settings should prompt investigations for parasitic infection(s), other causes of elevated eosinophil counts should also be kept in mind (Table 2).

With few exceptions, parasitic infections in which eosinophilia occurs are caused by helminths; of the more common helminths are listed in Table 3.

TABLE 3. Helminthic Infections Causing Eosinophilia and Pulmonary Symptoms

Infection	Degree of eosinophilia ^a
Ascariasis	Mild; marked in larval phase
Echinococcosis	None to mild
Filariasis	Variable, usually moderate to marked
Tropical pulmonary eosinophilia	Marked
Gnathostomiasis	Moderate to marked
Hookworm	Mild to moderate
Paragonimiasis	Mild to marked
Schistosomiasis	Marked in early stage
Strongyloidiasis	Mild to marked (usually mild to moderate)
Trichinosis	Moderate to marked
Toxocariasis	Marked

^aMild: 450 to 1000 eosinophils/mm³; moderate: 1000 to 3000 eosinophils/mm³; marked: >3000 eosinophils/mm³.

Protozoan infections, on the other hand, are not generally associated with eosinophilia. Since helminths produce eosinophilia during tissue migration and invasion, a specific parasitologic diagnosis is often not possible during this pre-patent period; weeks to months may be required before characteristic ova or microfilariae (larvae) can be detected in clinical specimens. Also, in some infections, eosinophilia may persist for several months after successful antihelminthic therapy (Klion et al., 1994).

The degree of eosinophilia is correlated with the extent of tissue invasion. While the majority of helminths cause mild (450 to 1000/mm³) or moderate (1000 to 3000/mm³) eosinophilia, absolute eosinophil counts greater than 3000/mm³ are typically present in infections caused by *Trichinella spiralis*, *Toxocara canis*, and some filariae (*Wuchereria bancrofti*, *Brugia malayi*, *Loa loa*, *Onchocerca volvulus*). During the larval stage, *Strongyloides stercoralis*, *Ascaris lumbricoides*, and hookworm produce maximal eosinophilia that often resolves when migration is complete. However, the absence of eosinophilia does not rule out a helminthic infection. One classical example is disseminated strongyloidiasis in the immunocompromised host, where the eosinophil count is usually low or normal.

Approach to the Patient with Tropical Lung Disease

History and Physical Examination

A complete history and physical examination are essential in assessing the patient with a tropical lung disease. In addition to eliciting any associated symptoms, a detailed geographic history, the duration and dates of travel or residence abroad, the interval to development of symptoms, a thorough exposure history, and assessment of the immune status of the patient are all important factors to consider. Recent and current medications and underlying medical conditions should also be determined.

A careful geographic history can narrow the diagnostic possibilities (Table 1). Regions of travel or residence within each country should be determined since the risk of acquiring a given disease may vary within a country. Wilson's *A World Guide to Infections* (1991) can be very useful in determin-

ing the geographic extent of disease on a country-by-country basis. The dates of travel may define exposures to seasonal pathogens or epidemics, although seasonality may be altered or absent in tropical regions. The duration spent in specific areas affects the likelihood of contracting infection. Bacterial and viral infections and malaria often require only brief exposures, whereas filariasis and most cestode and trematode infections (with the exception of schistosomiasis) usually require prolonged exposure (>3 months). Tuberculosis, melioidosis, fungal infections, echinococcosis, and paragonimiasis may produce chronic symptoms, or may present many years after initial infection. Interestingly, the incidence of tuberculosis reactivation and invasive amoebiasis in immigrants from the developing world is greatest in the first few years after immigration to industrialized countries (Lyche et al., 1990; Centers for Disease Control and Prevention, 1998).

The exposure history is often the most important clue to the diagnosis of a tropical lung infection. Exposures to certain foods and impure water, insect vectors, animals, or other infected persons, in addition to specific environmental exposures, are associated with pathogens that may cause pulmonary disease (Table 4).

Immunocompromised hosts, including individuals who are infected with HIV or who have AIDS, transplant recipients, and those receiving chemotherapy or corticosteroids, are predisposed to pneumonia caused by *Pneumocystis carinii*, opportunistic fungi, *Toxoplasma gondii*, *Cryptosporidium*, and *Microsporidium*. *S. stercoralis* can produce over-

whelming infection (hyperinfection syndrome) in these individuals, and in those with human T-cell lymphotropic virus (HTLV)-I infection, with a high mortality rate. Splenectomized and hypogammaglobulinemic individuals are at increased risk for infections due to encapsulated organisms, and in the case of the splenectomized patient, to babesiosis and malaria as well.

Finally, as in all patients, noninfectious causes of pulmonary symptoms such as congestive heart failure, primary lung diseases, and pulmonary manifestations of other systemic diseases must also be considered in patients who have been to the tropics.

Laboratory Investigations

A complete blood count and differential count should be performed, looking particularly for eosinophilia. Other investigations should be guided by the clinical, geographic, and exposure history, and physical findings. Thick and thin blood films should be performed whenever the diagnosis of malaria is considered. Cultures of blood, urine, and stool should be obtained if indicated (e. g., typhoid fever). Sputum samples should be obtained for bacterial, mycobacterial, and fungal cultures, and studies for *P. carinii* if appropriate. Examination of sputum for parasites is indicated in specific circumstances; paragonimiasis and occasionally other helminthic infections such as strongyloidiasis and echinococcosis can be diagnosed by recovery of characteristic larvae in sputum. Stool and/or urine samples are usually free of parasites at the time of pulmonary helminthic disease. However, identification of ova or larvae in stool specimens obtained weeks to months after a respiratory illness may allow a retrospective diagnosis to be made. Additional investigations, including serology (for amoebiasis, filariasis, paragonimiasis, schistosomiasis, strongyloidiasis, trichinosis, and toxocarasis), examination of blood and skin snips for microfilariae, and biopsy of other tissues may also be necessary.

Radiologic Investigations

Chest radiographs in patients with tropical lung diseases may reveal nonspecific pulmonary infiltrates or consolidation. Certain findings are suggestive of an underlying diagnosis, however.

TABLE 4. Exposures to Parasites Affecting the Lung

Exposure	Parasitic infection
Untreated drinking water	Amoebiasis, cryptosporidiosis, microsporidiosis
Contaminated soil or food	Ascariasis, toxocarasis
Raw or undercooked fish	Capillariasis, gnathostomiasis, paragonimiasis
Raw or undercooked meat	Trichinosis, toxoplasmosis
Animal contact	Echinococcosis, toxoplasmosis
Vectors—mosquitoes	Dirofilariasis, filariasis, malaria
Freshwater exposure	Schistosomiasis
Barefoot walking	Hookworm, strongyloidosis

Migratory pulmonary infiltrates of varying sizes that are associated with eosinophilia are characteristic of the larval phase of ascariasis, hookworm, and strongyloidiasis, tropical pulmonary eosinophilia caused by *W. bancrofti* or *B. malayi*, or paragonimiasis. Reticulonodular infiltrates may be seen in tropical pulmonary eosinophilia due to Bancroftian filariasis and schistosomiasis. Cavitory lung lesions are associated with tuberculosis and fungal infections (with the exception of blastomycosis and paracoccidioidomycosis) and may also be present in melioidosis, plague, paragonimiasis, and echinococcosis. Mycobacterial and fungal infections can also produce prominent hilar lymphadenopathy, as can some zoonoses such as tularemia or anthrax. Solitary or multiple pulmonary cysts are suggestive of echinococcosis. Coin lesions are characteristic of dirofilariasis. A pleural effusion may be seen in tuberculosis, paragonimiasis, and, when right-sided, pulmonary amoebiasis. Elevation of the right hemidiaphragm may suggest an underlying amoebic abscess of the liver.

Selected Parasitic Pulmonary Diseases

Helminthic Infections

Overview

Helminths, or parasitic worms, are classified into two major groups: nematodes (roundworms) and platyhelminths (flatworms). The latter comprises cestodes (tapeworms), which are segmented, and trematodes (flukes), which are not.

Helminths may produce pulmonary symptoms by three mechanisms: transgression of alveoli during larval migration in association with eosinophilia and pulmonary infiltration (Loeffler's syndrome) (Table 3); migration through the pulmonary vasculature (e.g., filariasis); or residence in the lung parenchyma as mature adult worms (e.g., paragonimiasis) or larval cysts (e.g., echinococcosis).

Nematode Infections

Ascariasis Ascariasis, caused by the nematode *Ascaris lumbricoides*, is among the most prevalent helminthic infections in the world, affecting

more than 1.4 billion people worldwide (Crompton, 1988). Human infection has rarely been caused by the pig roundworm *Ascaris suum* (Phills et al., 1972). Tropical climates, overcrowding, and poor sanitation enhance the transmission of *Ascaris* by the fecal–oral route. Cases occurring in North America and Europe are largely in immigrants from endemic areas.

Eggs produced by mature female worms in the small intestine are excreted in stool. Fertilized eggs embryonate following weeks to months of development in soil, depending on environmental conditions. One to 2 days after ingestion of embryonated eggs, larvae hatch in the small bowel and penetrate the intestinal wall, entering the portal circulation. Within 2 weeks, larvae reach the pulmonary circulation and enter the alveoli, occasionally resulting in clinically apparent pulmonary disease. Larvae then ascend the tracheobronchial tree, are swallowed, and reach the small intestine, where they develop into mature adults and live for 10 to 12 months. Sexual maturation and egg production begin 3 to 4 months after initial infection.

Infection with *A. lumbricoides* is usually asymptomatic. Pulmonary symptoms, due to migration of larvae through the alveoli, are rare even in endemic areas (Spillman, 1975), although the exact incidence is difficult to determine. Clinical disease is more common in children, and with re-infection (Khuroo, 1996). A seasonal variation in pulmonary ascariasis has also been noted in some areas (Gelpi & Mustafa, 1967).

Pulmonary ascariasis is among the most common causes of Loeffler's syndrome (Spillman, 1975; Allen & Davis, 1994). Low-grade fever, chills, dyspnea, wheezing, and dry cough develop 5 to 26 days after ingestion of viable larvae. A productive cough and hemoptysis may occur with a higher parasite burden (Khuroo, 1996). Skin lesions, often urticarial, are present in approximately 15% of patients (Gelpi & Mustafa, 1968). Pulmonary symptoms are a result of hypersensitivity to *Ascaris* larvae, local inflammation, and bronchospasm (Sarinas & Chitkara, 1997). Chest radiographs show bilateral, migratory patchy infiltrates, often perihilar, of varying sizes (Gelpi & Mustafa, 1968). Marked peripheral eosinophilia is the rule. Eosinophils, Charcot–Leyden crystals, and *Ascaris* larvae may be seen in sputum, and larvae can also

be recovered in gastric aspirates. Since lung involvement precedes egg production by 8 to 10 weeks, stool examination for *Ascaris* ova is usually negative.

Ascaris pneumonia is self-limited. Symptoms and radiographic abnormalities improve in 1 to 2 weeks, but eosinophilia may persist for many weeks (Gelpi & Mustafa, 1968). Bronchodilators, antitussives, and rarely steroids may be required to control symptoms. Anthelmintic therapy is not beneficial in the pulmonary stage of disease, but is indicated to eradicate adult worms in the intestine. Mebendazole 100 mg twice daily for 3 days, albendazole 400 mg once, or pyrantel pamoate 11 mg/kg (maximum 1 g) are all effective oral agents.

Filariasis (Tropical Pulmonary Eosinophilia) Tropical pulmonary eosinophilia (TPE), also known as eosinophilic lung, tropical eosinophilia, and Weingarten's syndrome, refers to the pulmonary manifestations of infection with *W. bancrofti* or *B. malayi*.

The World Health Organization (1992) has estimated that almost 80 million people worldwide have filariasis, the majority caused by *W. bancrofti*. Filariasis is endemic in most tropical countries, where it is transmitted by mosquitoes; infection usually requires prolonged exposure in an endemic area. Although infection is common in early childhood, the prevalence of microfilaremia increases with age. Lymphatic filariasis, the most common manifestation, begins in the second decade of life and results in progressive lymphatic obstruction. TPE is a rare consequence of filarial infection, occurring in less than 1% of infected individuals (Marshall et al., 1998; Ong & Doyle, 1998). It is particularly common in India, Sri Lanka, Southeast Asia, Guyana, and South America, although cases have been reported in Africa, China, and the West Indies. TPE appears to be due to hypersensitivity to microfilariae; other factors that may predispose to TPE are unclear. Eighty percent of patients are male, most in their third and fourth decades (Udwadia, 1975).

The life cycles of *W. bancrofti* and *B. malayi* are similar. Infective larvae enter the human circulation at the time of a mosquito bite. Larvae (microfilariae) migrate to the lymphatics, mature to adult worms, and mate. Six to 12 months after infection,

and for a duration of up to 10 years, microfilariae are released into the circulation, where they are ingested by night-biting mosquitoes to complete the cycle. In sensitized individuals with antifilarial antibodies, microfilariae are opsonized and carried to the pulmonary vasculature, where an IgE-mediated immune response results in TPE.

The absence of pulmonary symptoms is extremely rare in TPE. Udwadia (1975) found that 90% of patients have cough, typically worse at night, which may be associated with dyspnea or sputum production. Wheezing occurs in one quarter of patients. Constitutional symptoms are common, including fatigue (75%), weight loss (52%), and fever (35%). The illness may be present for weeks to months, remit, and recur (Neva & Ottesen, 1978). Physical findings may be absent in 25% of patients, but wheezing, adventitious breath sounds, or both are generally present on auscultation (Udwadia, 1975). Fluffy reticulonodular infiltrates in the mid- to lower-lung zones, a miliary pattern, or bibasilar vascular prominence are usually seen; in some series, hilar prominence and pleural thickening without effusion have been common (Ball, 1950; Khoo & Danaraj, 1960; Islam & Huque, 1965; Udwadia, 1975). Chest radiographs are normal in as many as 20% to 25% of patients with TPE (Islam & Huque, 1965; Udwadia, 1975). Marked eosinophilia is the rule, sometimes above 50,000/mm³ (Udwadia, 1975). Total and filaria-specific levels of IgG and IgE are increased, with total IgE levels usually above 1000 U/mL (Neva et al., 1975). Pulmonary function tests initially show airway obstruction, but a restrictive pattern is more common with chronic infection. Eosinophils and Charcot-Leyden crystals may be noted in bronchoalveolar washings (Enzenauer et al., 1990).

The diagnosis of TPE is based on the symptoms, radiologic findings, markedly elevated eosinophil count, and filarial antibody titers in the setting of compatible exposure. In contrast to lymphatic filariasis, microfilariae are notably absent from day and night blood samples, but may be seen in lung biopsy specimens.

Although spontaneous remission can occur, TPE usually worsens without treatment and may progress to chronic pulmonary insufficiency or pulmonary hypertension (Udwadia, 1975; Enzenauer et al., 1990). Diethylcarbamazine (DEC) is the

treatment of choice; 6 mg/kg daily for 21 days kills both microfilariae and adult worms, and is well tolerated. A response to DEC can distinguish TPE from other eosinophilic pneumonias and is sometimes included in the case definition. Clinical improvement and a decrease in eosinophilia are seen after 7 to 10 days of treatment. Twenty percent of patients relapse and will require retreatment with 6 to 12 mg/kg of DEC daily, for 21 to 30 days (World Health Organization, 1992). Higher doses of DEC may produce nausea, vomiting, weakness, and dizziness. An immunologic reaction to microfilarial death may develop, with fever, malaise, anorexia, vomiting, wheezing, and arthralgias. In spite of effective treatment, chronic lung disease may develop in up to 25% of patients (Udwadia, 1975).

Hookworm Infections caused by the human hookworms *Ancylostoma duodenale*, *Necator americanus*, and rarely *A. ceylonicum* and *A. braziliense*, affect approximately 1 billion people worldwide (Hotez & Pritchard, 1995). Immigrants from endemic areas are frequently infected. Both species are found in varying degrees throughout Asia and Africa. *A. duodenale* is also endemic in South America, North Africa, southern Europe, and the Middle East, while *N. americanus* is found in the southeastern United States. Moist tropical climates, poor sanitation, and lack of footwear perpetuate transmission.

Adult hookworms in the small intestine produce eggs, which are shed in feces. In favorable soil conditions, larvae hatch rapidly and in 5 to 10 days develop into infective filariform larvae that penetrate intact skin, enter the bloodstream, and travel to the lungs, where they ascend the tracheobronchial tree and are swallowed. Once in the small intestines, larvae mature into adult worms. Egg production begins 6 to 8 weeks after infection; adult worms live for several years.

Pulmonary symptoms rarely occur as larvae migrate through the lungs, usually within 2 weeks of infection. Symptoms are not severe and may be preceded by dermatitis at the sites of larval entry. The diagnosis is suggested by a compatible exposure history, dermatitis, and eosinophilia. Chest radiographs are similar to those seen in ascariasis. Identification of larvae in sputum or gastric aspirates is diagnostic. Stool examinations for ova are

invariably negative during the pulmonary phase of infection.

Hookworm pneumonitis is mild and self-limited. Treatment is symptomatic. Orally administered mebendazole, albendazole, or pyrantel pamoate are all effective treatments of the adult worm infection (see ascariasis).

Strongyloidiasis Infections with *S. stercoralis* (threadworm), although less prevalent than those caused by *Ascaris* or hookworm, are a more significant cause of morbidity and mortality, particularly in immunocompromised hosts. A unique feature of *Strongyloides* is its ability to replicate within the human host and cause overwhelming infection in susceptible individuals.

S. stercoralis is endemic in Asia, Africa, Central America, southern Europe, and the southeastern United States and Puerto Rico, where warm tropical soil conditions prevail. Immigrants and war veterans who have lived in endemic areas frequently have asymptomatic infection.

The life cycle of *S. stercoralis* is complicated (Fig. 1). It is the only nematode that can complete its life cycle entirely within humans, by internal and external autoinfection, or entirely in the soil (the free-living cycle). Penetration of skin by infective filariform larvae in soil is followed by larval entry into the circulation and migration to the lungs. Over the course of several days, larvae enter the alveoli, ascend the trachea, and are swallowed. Maturation into adult worms in the proximal small intestine leads to mating and egg production within the intestinal submucosa. Rhabditiform larvae that hatch in the small intestine are usually expelled in feces and develop into infective filariform larvae or adult worms in soil. However, rhabditiform larvae may rapidly transform into filariform larvae while still in the intestinal lumen. If this occurs, infective larvae may re-enter the circulation from within the bowel lumen (internal autoinfection) or through the perianal skin (external autoinfection) and reach the lungs. Either route of entry results in ongoing infection in the absence of additional exposure.

Pulmonary symptoms may occur in acute infection as larvae migrate through the lungs. The resulting clinical picture of Loeffler's syndrome is similar to that seen with *Ascaris* and hookworm, but seems to be quite uncommon. Prolonged infection

FIGURE 1. The life cycle of *Strongyloides stercoralis*. Reproduced from Melvin et al., 1964.

with *S. stercoralis* can cause wheezing and obstructive symptoms, which may be misdiagnosed as primary asthma (Bruno et al., 1982; Dunlap et al., 1984). Strongyloidiasis has also presented as a primary lung abscess, an eosinophilic pleural effusion, and restrictive lung disease (Ford et al., 1981; Lin et al., 1995; Goyal, 1998).

Clinically apparent pulmonary involvement by *Strongyloides* usually occurs in patients with hyperinfection syndrome, in which an overwhelming parasite burden is present in the lungs. Patients generally have compromised cell-mediated immunity as a result of advanced age, malignancy, or immunosuppression. Systemic corticosteroids, often in the setting of chronic lung disease, are well-documented risk factors. Histamine (H_2) blockers, antacid use, and prior gastric surgery have also been associated with pulmonary strongyloidiasis (Igra-Siegmán et al., 1981; Davidson et al., 1984; Berk et al., 1987; Davidson, 1992; Woodring et al., 1996). In addition, hyperinfection has also been described in patients infected with HIV and HTLV-1 (Ferreira et al., 1999; Newton et al., 1992).

The hyperinfection syndrome is a manifestation of remotely acquired, asymptomatic infection. Pulmonary symptoms include productive cough, dyspnea, and wheezing; hemoptysis and chest pain are uncommon (Woodring et al., 1996). Concomitant gastrointestinal symptoms, including epigastric or abdominal pain, gastrointestinal bleeding, nausea, vomiting, or diarrhea, are present in 75% of patients; fever is seen in 25%, and rash or larva currens is rare (Woodring et al., 1996). Adult respiratory distress syndrome (ARDS) and respiratory failure may develop rapidly, necessitating mechanical ventilation. Secondary bacterial infections and sepsis, due to enteric pathogens that exit from the bowel along with migrating larvae, occur in up to 50% of patients and may contribute to respiratory compromise; secondary fungal infections are also common (Igra-Siegmán et al., 1981; Woodring et al., 1996). Dissemination of larvae to the central nervous system, heart, thyroid, and other organs has been noted at autopsy (Igra-Siegmán et al., 1981).

Pulmonary strongyloidiasis is rarely suspected but should be considered as a cause of respiratory

symptoms in an immunocompromised patient from an endemic area. Chest x-rays are usually abnormal; focal and diffuse pulmonary infiltrates are most common and may progress to ARDS. Pleural effusions are frequently present (in 40% of patients) but cavitary lesions are rare (Woodring et al., 1996). The diagnosis can be confirmed by identifying *Strongyloides* larvae, which are almost always present in stool. Sputum, bronchoalveolar washings, and lung biopsy specimens may also contain characteristic larvae. Eosinophilia is rarely a feature of hyperinfection (Ingra-Siegmán et al., 1981; Davidson, 1992) and its absence should not be relied on to exclude the diagnosis.

The outcome of pulmonary strongyloidiasis is variable. With treatment, immunocompetent hosts and those with mild disease do well, but infection is fatal in 30% to 86% of immunocompromised patients (Ingra-Siegmán et al., 1981; Woodring et al., 1996). Early diagnosis and treatment optimize the chance of survival. Bacterial superinfections also contribute to mortality and must be treated appropriately.

Strongyloidiasis should always be treated, regardless of symptoms. Oral thiabendazole 25 mg/kg twice daily for 2 days, oral albendazole 400 mg twice daily for 7 days, or ivermectin 150 µg/kg once is adequate for uncomplicated infection, but 14 to 28 days of therapy may be required for hyperinfection. Thiabendazole may increase theophylline levels. Relapse rates may be as high as 15%; multiple follow-up stool examinations should be performed and retreatment may be necessary. Patients from endemic areas who are or will be immunosuppressed should be screened for strongyloidiasis and treated if screening is positive, or treated presumptively if screening is not possible. Serology using an enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence has a sensitivity and specificity of 85% to 95% (Liu & Weller, 1993). Serology is much more sensitive and specific than stool examination for screening, but results are often not available soon enough in urgent situations.

Toxocariasis Toxocariasis, infection by the dog roundworm *Toxocara canis* and to a much lesser extent the cat roundworm *Toxocara cati*, is common worldwide. Eighty percent of puppies and 20% of adult dogs in North America harbor *T.*

canis, and the prevalence of eggs in soil is high (Shantz & Glickman, 1978). Human infection is most common in children less than 4 years, who place objects contaminated with soil in their mouths. Although rare, infections in adults have been well described (Glickman et al., 1987; Bartelink et al., 1993; Bourée et al., 1997).

Eggs excreted in animal feces embryonate in soil in 2 to 3 weeks. After ingestion of embryonated eggs by humans, larvae hatch in the small intestine, penetrate the mucosa, and travel to the liver. While some larvae remain in the liver, others migrate to the eye (ocular larva migrans) or to other organs including the lungs (visceral larva migrans [VLM]). When larvae are too large to pass through blood vessels, they exit and migrate into local tissues, where they may cause clinical symptoms. Development of adult worms and production of eggs do not occur in humans.

Larval migration through the lungs produces wheezing, dyspnea, or cough in 20% to 86% of symptomatic patients (Snyder, 1961; Huntley et al., 1965; Glickman et al., 1987). Respiratory failure requiring intubation may occur (Beshear & Hendley, 1973; Bartelink et al., 1993). Fever is rare in adults but is present in 55% to 80% of children; rash may also be present (Snyder, 1961; Huntley et al., 1965; Glickman et al., 1987). On examination, 40% have wheezes or crackles (Huntley et al., 1965). Radiologic abnormalities, evident in 40% of cases, include mild pulmonary and peribronchial infiltrates (Snyder, 1961; Huntley et al., 1965). Granulomas may form once acute infection has resolved. Marked eosinophilia is usually present.

Definitive diagnosis of VLM requires demonstration of larvae in tissue biopsies. A presumptive diagnosis is usually based on an appropriate exposure history and the clinical, radiologic, and laboratory findings. Serology (ELISA) is 72% sensitive and 92% specific and is often helpful in confirming the diagnosis (DeSavigny et al., 1979).

Although VLM is self-limited and generally benign, steroids may be required in severe infections (Beshear & Hendley, 1973; Bartelink et al., 1993). The benefit of antihelminthic drugs is unclear; oral diethylcarbamazine (2 mg/kg three times a day for 7 to 10 days) or albendazole (400 mg twice daily) or mebendazole (100 mg twice daily) for 5 days has been recommended.

Trichinosis Trichinosis (trichinellosis) is acquired by ingestion of raw or undercooked meat, usually pork, that contains *Trichinella spiralis* cysts. In the United States, the prevalence of trichinosis has been steadily decreasing and it is now uncommon (Bailey & Schantz, 1990). A simultaneous decline in porcine infection has also occurred. Trichinosis is still common in southern and eastern Europe, Asia, and Latin America, and in other countries where raw or undercooked pork is consumed and where raw garbage is used as pig feed. In developed nations, outbreaks of trichinosis have been associated with pork as well as wild boar, bear, walrus, and horse meat (Clark et al., 1972; Bouree et al., 1979; Margolis et al., 1979; Rodriguez-Osorio et al., 1990). Asymptomatic infection is common.

After consumption of infected meat, the larval cyst wall is digested in the stomach and the released larvae penetrate the small intestinal mucosa, where, within 1 week, they mature into adults, mate, and produce more larvae. Adult worms are expelled in feces within several weeks. The newly formed larvae enter the arterial circulation via the lymphatic system and are distributed to striated muscle, the only tissue in which they can survive. Approximately 3 weeks after infection, larvae encyst in muscle, where they may remain viable for many years.

With a high infectious load, gastrointestinal symptoms develop within 1 week of exposure. Invasion of striated muscle, including respiratory muscles and particularly the diaphragm, begins 7 to 9 days after exposure and lasts for up to 4 weeks. Facial and periorbital edema, myositis, and constitutional symptoms are common; a maculopapular rash, urticaria, or pruritus may be present. Dyspnea and painful respirations result from larval infiltration of respiratory muscles. Severe involvement may occasionally culminate in respiratory failure (Brashear et al., 1971; Compton et al., 1993; Clausen et al., 1996). Myocarditis and heart failure, which develop 4 to 8 weeks into the illness, and neurologic involvement may also contribute to respiratory failure and other pulmonary complications. Direct involvement of the lung parenchyma is rare. In a review of 856 cases of trichinosis in Poland, Januszkiewicz (1967) noted pulmonary involvement in 6.4%; pneumonia, pleural effusion, and

spastic bronchitis were most common. Radiographic findings may include increased vascular markings, basilar consolidation or infiltrates, effusions, and rarely a miliary pattern.

Clinical features, a history of recent consumption of poorly cooked meat, and eosinophilia should raise suspicion of trichinosis. Confirmation of the diagnosis requires the demonstration of larvae in muscle biopsy, or may be provided by serologic tests. Serology may be negative early in infection and may need to be repeated.

Although death from trichinosis is rare, morbidity may be significant (Bailey & Schantz, 1986). High-dose steroids, in addition to symptomatic therapy, are recommended for cardiac, pulmonary, or neurologic involvement (Most, 1978). It is unclear whether antihelminthic therapy influences the course of illness and which treatment is most effective, although mebendazole or albendazole are usually recommended.

Trematode Infections

Paragonimiasis Paragonimiasis is a widespread disease caused by several species of the genus *Paragonimus*. The most well known, *P. westermani*, is also the most widely distributed and is endemic in Asia as well as some areas of Africa. In Mexico and Central and South America, *P. mexicanus* is the most common species. Ingestion of raw meat or juices from crabs or crayfish that contain encysted *Paragonimus* larvae is the usual route of infection.

Adult worms reside in the lungs, where they produce eggs that are either expectorated in sputum, or swallowed and excreted in stool. Maturation of eggs to infective larvae in fresh water requires two intermediate hosts—the freshwater snail and subsequently crayfish or crabs. Approximately 3 weeks after ingestion of infected crustaceans by mammalian hosts, immature flukes emerge in the duodenum and penetrate the bowel wall. They migrate through the peritoneum and diaphragm to the pleural space and lungs, causing acute inflammation. Once in the lungs, encapsulation in cystic cavities occurs. Mature adults develop within these cavities and produce eggs after 6 to 10 weeks. When cysts rupture, eggs are discharged in bronchioles, causing cough and hemoptysis. Encapsulated adult

worms may survive and reproduce in the lungs for many years, leading to chronic symptoms.

The spectrum of disease ranges from asymptomatic infection to chronic lung disease, which is often mistaken for bronchiectasis or tuberculosis. Early infection, as flukes enter the thorax, is rarely symptomatic but may cause pleuritic chest pain, cough, pulmonary infiltrates, and eosinophilia. Typically, however, patients present with a chronic cough productive of blood-tinged sputum, often beginning 6 months after initial infection (Shim et al., 1991; Yee et al., 1992). Massive hemoptysis is rare. Frequently associated symptoms include dyspnea (42%), chest pain that is usually pleuritic and intermittent (41%), and rarely fever (11%) (Shim et al., 1991). Most patients appear well despite chronic symptoms, and examination is usually unrevealing. Chest x-rays may be normal in up to 20% (Nana &

Bovornkitti, 1991; Shim et al., 1991). Pleural disease, including effusions, hydropneumothorax, and pleural thickening, are found on 70% of x-rays (Kagawa, 1997). Bilateral pleural effusions, rare in tuberculosis, should raise suspicion of paragonimiasis in the appropriate setting. Multiple, low-density patchy infiltrates are present in 60% (Kagawa, 1997). Other parenchymal abnormalities include cystic lesions, cavities, linear densities, or pulmonary nodules that may be calcified (Fig. 2). Peripheral eosinophilia is often but not always present.

Detection of eggs in sputum is diagnostic. Sensitivity is low (30% to 40%) but may be increased with multiple sputum examinations or pooled sputum samples (Coleman & Root, 1981; Kagawa, 1997). Stool examination for ova is even less sensitive (10% to 25%). Pleural fluid is exudative and may be eosinophilic but rarely contains

FIGURE 2. Severe paragonimiasis in a Korean male with numerous bilateral cavitary lesions (1–3 cm in size), chiefly in the middle and lower lung fields. Reproduced, with permission, from Reeder and Palmer, 1981.

eggs (Nana & Bovornkitti, 1991). Serologic tests by complement fixation or ELISA are significantly more sensitive than parasitologic examination of specimens and are recommended when paragonimiasis is suspected.

Paragonimiasis is benign and easily treated with oral praziquantel, 25 mg/kg three times daily for 2 days. Clinical improvement is rapid, with a cure rate of >90% (Kagawa, 1997). Response to therapy can be confirmed by declining serologic titers and stool or sputum examination. Radiologic improvement is gradual, requiring up to 12 months for resolution; calcified granulomas may persist indefinitely. Rarely, surgical treatment may be required.

Schistosomiasis Two hundred million people worldwide are infected with schistosome species, and 200,000 deaths annually are attributable to schistosomiasis (Hopkins, 1992). Most infections are caused by three species of *Schistosoma* that are endemic in many countries. *Schistosoma mansoni* is found in Africa, the Middle East, South America, and the Caribbean; *S. japonicum* in southeast Asia, Japan, and China; and *S. hematobium* in Africa and the Middle East. Transmission of infection is not uniform within each area and is highest in regions with poor sanitation and limited water supply. Infection results from brief exposure to fresh water containing infective cercariae. In endemic areas, infection begins in infancy and peaks in pre-adolescent children. Adults in endemic regions are less commonly infected, in part because of acquired immunity.

After penetration of intact skin, cercariae become schistosomulae and enter the circulation. Within 1 week they reach the heart, lungs, and finally the liver, where they mature into adults within portal vessels. *S. mansoni* and *S. japonicum* migrate to the veins of the intestines, and *S. hematobium* to the vesical plexus, where they reside and mate. Four to 6 weeks after initial infection, eggs are produced, and excreted in stool or urine. Eggs that reach fresh water hatch to release miracidia, which penetrate the freshwater snail and emerge 3 to 5 weeks later as infective cercariae.

A history of cercarial-induced dermatitis may precede the earliest pulmonary symptoms, which occur as schistosomulae enter the lungs. In this rare condition, acute inflammation may produce transient fever dry cough, and dyspnea; wheezes and crackles may be audible on auscultation. Eosino-

philia is common, and chest x-rays may reveal pulmonary infiltrates or mottling.

Katayama fever refers to the acute symptoms of schistosomiasis that develop 2 to 8 weeks after infection by *S. mansoni* or *S. japonicum*. *S. hematobium* rarely causes this syndrome (Lucey & Maguire, 1993). Symptoms are coincident with the onset of egg production and typically occur with heavy infections in nonimmune individuals (such as children and travelers), in whom they are felt to represent a hypersensitivity reaction to egg antigens (Hiatt et al., 1980). Fever malaise, weight loss, arthralgias, myalgias, and abdominal pain are prominent. Respiratory symptoms were present in 19 of 30 patients followed by Rocha et al. (1995). Dry cough, wheezing, dyspnea, and chest pain may be accompanied by pulmonary infiltrates or a miliary pattern on x-ray (Ritchken & Gelfand, 1954; Gelfand, 1966; Rocha et al., 1995). A cavitary lung lesion has also been reported in acute infection (Schaberg et al., 1991). Marked eosinophilia is generally present.

Since acute schistosomiasis occurs prior to excretion of eggs, initial stool (or urine) examinations are unhelpful. Eggs may be detected in subsequent specimens obtained several weeks later. Highly sensitive serologic tests (ELISA, immunoblot) are available but may be negative in early infection. Furthermore, a positive result may not distinguish between recent and remote infection. Therefore, the diagnosis is based on clinical presentation in a patient with recent freshwater exposure in an endemic area. Although not usually necessary, bronchoscopy or lung biopsy specimens may reveal ova (Bethlem et al., 1997).

Acute schistosomiasis is generally benign and self-limited. Treatment should be given, however, to prevent long-term complications. Praziquantel is the treatment of choice; 1 day of treatment (20 mg/kg for two doses for *S. mansoni* and *S. hematobium* and 20 mg/kg for three doses for *S. japonicum*) cures 75% to 100% of infections (Morris & Knauer, 1997). Nausea, vomiting, and abdominal pain may occur transiently after treatment. Steroids should be considered if infection is severe or refractory to antihelminthic therapy (Lucey & Maguire, 1993).

Chronic pulmonary schistosomiasis is a consequence of *S. mansoni* and to a lesser extent *S. japonicum* infection, occurring in 5% of infected individuals from endemic areas, and is rarely caused

by *S. hematobium* (Morris & Knauer, 1997). Eggs lodged in the hepatic venules lead to granulomatous inflammation, presinusoidal obstruction, and periportal fibrosis ("pipestem" or Symmer's fibrosis) in up to 20% of infected patients (Morris & Knauer, 1997). Portosystemic shunting allows eggs to be carried to the pulmonary vasculature, where they cause granulomatous arteritis and may ultimately lead to pulmonary hypertension and cor pulmonale. Eggs may also reach the lungs in the absence of hepatic involvement, however. Interstitial lung disease and arteriovenous shunting may also occur with chronic infection (Bethlem et al., 1997). Previously untreated patients should receive praziquantel, although the benefit in chronic pulmonary infection is unknown (Morris & Knauer, 1997).

Cestode Infections

Echinococcosis Human echinococcosis is caused by four species of the dog tapeworm *Echinococcus*. Most cases are due to *E. granulosus* or, less commonly, to *E. multilocularis*. Infection with *E. vogeli* and *E. oligarthus*, a rare occurrence in Central and South America, is beyond the scope of this review.

E. granulosus is widely distributed throughout the world, particularly in sheep-herding regions (temperate regions of South America, Australia, New Zealand, southern Europe, and the former Yugoslavia). Dogs and other canids are definitive hosts, harboring the adult worm, whereas sheep, pigs, cattle, horses, and other mammals act as intermediate hosts containing the cystic larval stage; humans are accidental intermediate hosts. Regional differences in cultural and religious beliefs and farming practices result in a highly variable prevalence of disease: from 3.4 to >200 cases per 100,000 in Algeria and northern Kenya, respectively (Bhatia, 1997). A wild (sylvatic) cycle exists in northern climates (e.g., *E. granulosus* var. *canadensis*), involving hunting dogs and wolves as definitive hosts and moose, caribou, and reindeer as intermediate hosts.

Adult worms, consisting of two to five proglottids, reside in the small intestine of the dog. The terminal proglottid is shed in feces and releases eggs. Dogs may release over 1 million eggs daily (Kammerer & Schantz, 1993). Eggs ingested by an intermediate host or human hatch in the small intestine

and release an oncosphere, which penetrates the intestinal wall and enters the portal circulation to reach the liver; hematogenous spread may occur directly to other organs. Relatively few oncospheres continue past the liver and travel to the lungs, or rarely to other organs. Once deposited in an organ, oncospheres evolve to form larval cysts containing infective protoscolices that grow approximately 0.5 to 1 cm per year and may bud internally to produce daughter cysts. The cycle is completed when viscera containing cysts are consumed by dogs, and protoscolices develop into adult tapeworms.

Most infections with *E. granulosus* are asymptomatic and are discovered incidentally by radiography or ultrasound. Symptomatic disease usually presents many years after infection and results from the mass effect of the cysts.

The lungs are involved in 30% of cases. In a review of 11 case series of pulmonary disease, Bhatia (1997) noted that most cases occurred in the second and third decades, one third of cases involved multiple or bilateral cysts, and 60% of cysts were right-sided. Disease was asymptomatic in 68% of cases, and particularly in the sylvatic form. Cough, hemoptysis, dyspnea, and fever were present in up to 69% of cases. Cysts may rupture into bronchi, sometimes with expectoration of cyst contents and membranes, or into the pleural space with a resultant pleural effusion. Anaphylaxis with intrapulmonary rupture is rare (0.3% to 7.5% of cases) (Bhatia, 1997).

E. granulosus infections, or cystic hydatid disease, should be suspected on the basis of historical, clinical, and radiologic features. Eosinophilia is present in up to 40% of patients. Chest x-rays show a pulmonary mass lesion in 50% to 60% of cases (Bhatia, 1997) (Fig. 3). Other radiographic findings may include evidence of fistula formation, a "crescent" or "meniscus" sign, and fluid-filled cavities; calcification is rare (Ramos et al., 1975; Beggs, 1985; von Sinner, 1991). Computed tomography and MRI imaging may be used to define cyst anatomy and the extent of disease, to detect unsuspected lesions, and to monitor for recurrence after treatment (Gouliamos et al., 1991; von Sinner, 1991; von Sinner et al., 1991). The serologic response to infection is influenced by host factors as well as the number, integrity, viability, and location of cysts (Kammerer & Shantz, 1993; Bhatia, 1997). Anti-

FIGURE 3. Multiple *E. granulosus* cysts found on the routine chest x-ray of a 25-year-old asymptomatic Lebanese woman.

body response is poor in children, with lesions outside of the liver (including the lungs), and with cysts that are solitary, intact, or dead. The suboptimal sensitivity and specificity of these tests warrant caution when interpreting the results. Finally, although therapeutic percutaneous aspiration of liver cysts has become commonplace (von Sonnenberg et al., 1994), pulmonary cyst aspiration is not generally recommended for diagnosis because of the possible risk of anaphylaxis (Kammerer & Shantz, 1993) and spillage of viable protoscolices. However, one small case series found the procedure to be effective, but associated with complications in almost one third of cases (Akhan et al., 1994).

Treatment goals include the elimination of parasites, prevention of cyst rupture, and preservation of involved organs. Surgery, the treatment of

choice, leads to few complications and has the best prognosis, with cure rates of up to 90% (Kammerer & Shantz, 1993; Bhatia, 1997; Salih et al., 1998). The recurrence rate is 2% to 10%. Medical therapy is reserved for patients who refuse or are poor candidates for surgery. Albendazole (10 mg/kg per day) or mebendazole (40 to 50 mg/kg daily) for 3 to 6 months has an overall cure rate of 30% and provides symptomatic improvement in 40% to 70% of patients; because of its superior absorption, albendazole is more effective (Davis et al., 1989; Todo-rov et al., 1992; Nahmias et al., 1994). The optimal duration of antihelminthic therapy is unknown. Regardless of treatment, all patients should be followed clinically, radiologically, and serologically for recurrence, for at least 10 years (Kammerer & Schantz, 1993).

In view of the low risk of complications and the benign nature of the infection, surgical and drug therapy of sylvatic cystic hydatid disease is unnecessary in asymptomatic individuals (Finlay & Speert, 1992).

E. multilocularis infection or alveolar hydatid disease, has been documented in northern Europe, the former Soviet Union, China, Alaska, southwestern Canada, and the northern United States—areas inhabited by the Arctic and red fox. Other definitive hosts include coyotes and wolves. Mice, voles, and other rodents are intermediate hosts.

Disease is most commonly diagnosed in adults >50 years of age who have lived in an endemic area. Symptoms occur years to decades after infection. The liver is always involved; pulmonary disease, usually a result of hematogenous spread, occurs in less than 2% of cases (Bhatia, 1997). Abdominal symptoms are predominant, and respiratory complaints are rare; dyspnea, the most common, is present in less than 10% of patients (Wilson & Rausch, 1980). Chest x-rays may show multiple peripheral, nodular lung lesions consistent with hematogenous dissemination, or involvement of the right lower lobe by contiguous spread (Treugut et al., 1980). Solid lesions with necrosis and calcification are the most frequent CT findings (Didier et al., 1985). Serology is positive in 90% of patients and is specific; titers are usually high.

Without therapy, *E. multilocularis* infection is uniformly fatal. Surgery with wide excision of infective tissue can be curative and is the preferred treatment, but is often not possible because of extensive disease at the time of diagnosis. In such cases, albendazole or mebendazole, used indefinitely, can improve symptoms and prolong survival (Wilson et al., 1992). As in cystic disease, close follow-up for disease progression and recurrence is imperative.

Protozoal Infections

Amoebiasis

Epidemiology *Entamoeba histolytica/dispar* complex infects an estimated 10% of the world's population and is the third most common cause of death due to parasitic infection, preceded only by malaria and schistosomiasis (Guerrant, 1986; Reed,

1992). *E. histolytica*, distributed worldwide, is especially prevalent in tropical areas where poor personal hygiene and sanitation facilitate fecal-oral spread. Humans are the primary reservoir. Males and females are infected at equal rates, although extraintestinal disease has a striking male preponderance and commonly develops in recent immigrants from endemic areas (Ibarra-Perez, 1981; Adeyemo & Aderounmu, 1984; Lyche et al., 1990; Chuah et al., 1992; Reed, 1992). The risk of invasive disease, including colitis, is increased in children, pregnant women, and those receiving steroids (Reed, 1992). In developed countries, the prevalence of asymptomatic infection is high, and it is more common in the institutionalized and in homosexual men. This finding can be ascribed to infection with *E. dispar*, a nonpathogenic species that is morphologically identical to *E. histolytica* and can only be distinguished by serology or DNA and antigen detection methods (Jackson & Ravdin, 1996). It is estimated that, globally, 85% of *E. histolytica* are actually *E. dispar*.

Life Cycle Ingestion of the relatively hardy cysts of *E. histolytica* is followed by excystation in the distal small intestine and leads to development of trophozoites that colonize the large bowel, particularly the cecum. Trophozoites invade the intestinal wall and disseminate to extraintestinal sites, most commonly the liver and rarely to other organs; those that are carried to the rectum evolve into cysts that are subsequently shed in feces.

Clinical Syndromes Ninety percent of amoebic infections are asymptomatic (Reed, 1992). Gastrointestinal manifestations include colitis, bowel perforation, or formation of an intestinal mass (amoeboma) or stricture. Amoebic liver abscesses usually develop in the right lobe of the liver, leading to acute or subacute onset of constitutional symptoms, weight loss, and right upper quadrant pain. Stool specimens are positive for *E. histolytica* in less than one fifth of cases of liver abscess.

Pleuropulmonary Disease Virtually all cases of pleuropulmonary amoebiasis occur in patients with a hepatic abscess, and up to 75% of patients with an abscess will have pleuropulmonary involvement (Adams & MacLeod, 1977; Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche

et al., 1990). Insidious extension or acute rupture of a hepatic abscess into the pleural space or lung often leads to the development of a dry or productive cough, hemoptysis, dyspnea, and pleuritic or right shoulder pain. Acute, tearing pleuritic chest pain or respiratory distress occurs with rupture. "Anchovy-paste" or "chocolate sauce" sputum is pathognomonic of a hepatopulmonary fistula (Adeyemo & Aderounmu, 1984). Evidence of consolidation or pleural effusion, almost always right-sided, is present in over 75% of patients (Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche et al., 1990). Fever, hepatomegaly, and hepatic tenderness are also common. Chest radiographs are abnormal in over 50% of patients (Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche et al., 1990). Right pleural effusion is the most frequent finding, but right hemidiaphragmatic elevation, or right lower-lobe atelectasis or consolidation may be seen. Left-sided abnormalities and cavitory lesions are rare. Leukocytosis without eosinophilia is the rule.

The diagnosis is made largely on clinical suspicion. Stool, sputum, and pleural fluid rarely contain trophozoites or cysts. Serologic tests are useful for diagnosis and are positive in >90% of patients with amoebic abscess (Reed, 1992).

Metronidazole is highly effective treatment, with cure rates of >95% in hepatic and pulmonary disease (Adeyemo & Aderounmu, 1984; Kubitschek et al., 1985; Lyche et al., 1990; Reed, 1992). A 5-day course (750 mg orally or intravenously every 8 hours) should be followed by iodoquinol 650 mg three times daily for 20 days or paromomycin 500 mg three times daily for 10 days, to eliminate cysts in the intestinal lumen. Recent studies have shown identical cure rates with one to three doses of metronidazole (2 to 2.5 grams daily in a single dose) followed by a lumen-active agent (Irusen et al., 1992). Rarely thoracentesis, chest tube drainage, or other surgical intervention may be indicated for severe or refractory symptoms.

Cryptosporidiosis

Cryptosporidium species are widely distributed intracellular parasites that have a broad host range. They have been increasingly recognized as a cause of acute diarrheal illness in children and travelers. In patients with AIDS and other immune

deficiency states, *Cryptosporidium* can cause intractable diarrhea and disseminated disease that may be life-threatening. The prevalence of cryptosporidial infection varies; up to 10% of diarrheal illness in the tropics may be caused by *Cryptosporidium* (Griffiths, 1998), and an estimated 3% to 4% of AIDS patients in North America are infected (Sorvillo et al., 1994). Infection results from ingestion of oocysts, and transmission occurs via person-to-person or water-borne spread.

Respiratory symptoms may be common in the presence of cryptosporidial diarrhea (Griffiths, 1998). In AIDS patients, *Cryptosporidium* has been detected in sputum in the absence of respiratory symptoms (Lopez-Velez et al., 1995) and rarely has been identified as a cause of pneumonia (Lopez-Velez et al., 1995; Mohri et al., 1995; Clavel et al., 1996; Dupont et al., 1996). The pathogenesis of pneumonia is unclear, but it may be a result of aspiration of parasites from the gastrointestinal tract rather than hematogenous dissemination or contiguous spread (Mohri et al., 1996). Pneumonia in immunocompromised hosts usually occurs in association with gastrointestinal disease but may be isolated (Lopez-Velez et al., 1995; Clavel et al., 1996). Diarrhea and cough are present in >75% of patients, and dyspnea, sputum production, and fever are common. Chest x-rays are nonspecific, showing infiltrates or interstitial disease (Lopez-Velez et al., 1995; Dupont et al., 1996).

Cryptosporidial pneumonia may be diagnosed by demonstrating oocysts in sputum or bronchoalveolar lavage specimens in the presence of compatible symptoms. Other pathogens are often identified simultaneously, leading to uncertainty regarding the role of *Cryptosporidium* in these cases. Successful treatment of pneumonia has been reported with inhaled paromomycin and systemic azithromycin (Mohri et al., 1995; Dupont et al., 1996).

Malaria

Epidemiology Malaria is the most important parasitic infection in the world. Each year, 300 to 500 million people are infected, most in Africa, and 1 to 2 million die. Endemic areas include Africa, Asia, Oceania, and Central and South America. Cases in nonmalarious areas are usually imported by travelers and immigrants. Malaria is transmitted by night-biting species of *Anopheles* mosquitoes

and is caused by four species of *Plasmodium*. *P. falciparum* is the most severe form, responsible for 40% to 60% of infections but >95% of malaria deaths (Hoffman, 1992). *Plasmodium vivax* causes the majority of non-falciparum malaria, with few cases due to *Plasmodium ovale* and *Plasmodium malariae* infection.

Pulmonary Manifestations Symptoms of falciparum malaria usually develop within 6 weeks of departure from an endemic area. Fever, chills, malaise, headache, and myalgia are prominent. Pulmonary symptoms, most often but not exclusively seen in *P. falciparum* infection, are thought to be caused by alterations in pulmonary vascular flow. Fewer than 20% of patients have cough, and less than 5% complain of dyspnea, wheezing, or chest pain on presentation (Froude et al., 1992; Gozal, 1992; Winters & Murray, 1992; Svenson et al., 1995). Chest radiographs may be normal or demonstrate increased vascular markings or variable infiltrates (Cayea et al., 1981; Gozal, 1992). Bilateral pleural effusions have also been described (Cayea et al., 1992). In severe and potentially fatal infections (greater than 5% parasitemia), noncardiogenic pulmonary edema is common and results from increased pulmonary capillary leakage. ARDS associated with severe infections is likely immune-mediated and tends to occur 2 or 3 days after treatment is initiated, when blood parasitemia is decreasing (Feldman & Singer, 1987).

The diagnosis of malaria is confirmed by detection of intraerythrocytic parasites on thick and/or thin smears. Treatment should be administered promptly, specific therapy depending on the species identified. *P. falciparum* malaria should be treated with 5 to 7 days of quinine in combination with 7 days of doxycycline; both can be administered orally or intravenously. Noncardiogenic pulmonary edema is managed no differently from that which occurs with other conditions. Mortality from falciparum malaria is less than 4%, although severe malaria is fatal in 20% or more of cases (Greenberg & Lovel, 1990; Warrell et al., 1990).

Microsporidiosis

Microsporidia are ubiquitous, obligate intracellular parasites that infect a wide variety of hosts through the ingestion of spores. Most infections in

humans are caused by *Enterocytozoon bieneusi* and *Encephalitozoon* species. On the basis of seroprevalence surveys, immunocompetent hosts are frequently infected (van Gool et al., 1997); 7% to 50% of AIDS patients are infected (Didier, 1998) and present most commonly with chronic diarrhea.

Pneumonia attributed to microsporidia has been reported mainly in AIDS patients, most of whom also have microsporidial diarrhea (Gunnarsson et al., 1995; Remadi et al., 1995; Georges et al., 1998). Pneumonia without evidence of infection in other sites has also been reported (Scaglia et al., 1997), and disseminated microsporidiosis with lung involvement has occurred following bone marrow transplantation (Kelkar et al., 1997). Symptoms include cough, dyspnea, and fever, sometimes accompanied by interstitial infiltrates on chest x-ray. Diagnosis has been based on identification of spores in sputum or bronchoalveolar lavage specimens, especially in the absence of other pathogens. Treatment with albendazole has not been consistently effective.

Toxoplasmosis

Epidemiology *Toxoplasma gondii* is ubiquitous and causes infection in a variety of mammals, including humans. It is estimated that globally, 50% of people have been infected, although the seroprevalence varies worldwide (Campagna, 1997). In developing nations, infection most often occurs early in childhood due to contact with contaminated soil, while in developed countries seroprevalence rates are lower and infection occurs later in life, as a result of consumption of infected, poorly cooked meat (Frenkel, 1991), or contact with cats.

The Organism *T. gondii* exists in three forms: oocyst, tachyzoite, and bradyzoite. The oocyst, containing sporozoites, is the product of sexual reproduction, which occurs only in the small intestine of the definitive host, the cat. Oocysts are shed in cat feces in large quantity and must mature in soil before they become infective. Intermediate hosts (usually birds and rodents) and humans may acquire infection by ingesting oocysts. Tachyzoites are seen in acute infection and can invade most cell types. Once in tissue, *T. gondii* survives for the lifetime of the host in an encysted form containing bradyzoites. Cysts are found mostly in skeletal

muscle, heart, eye, and brain. Humans are usually infected by ingesting these tissue cysts in raw or poorly cooked meat, but transmission can occur transplacentally, by organ transplantation, or by white blood cell transfusion.

Pulmonary Toxoplasmosis The exact incidence of pulmonary toxoplasmosis is unknown but has increased with the advent of AIDS (Catterall, 1986). Most cases of pulmonary disease develop in immunocompromised hosts, but immunocompetent hosts may also be affected (Pomeroy & Filice, 1992). Patients with AIDS or hematologic malignancy and organ transplant recipients are at highest risk (Israelski & Remington, 1993). Pneumonia is usually due to reactivation of latent infection (Derouin et al., 1992; Campagna, 1997), but it may occur with primary infection in AIDS, or with transplantation of an organ from a seropositive donor to a seronegative recipient (Luft et al., 1983; Renold et al., 1995). Evidence of disseminated infection is frequently present in immunocompromised patients (Derouin et al., 1992).

Transplant patients develop toxoplasmic pneumonia in the first 6 months after transplant (Derouin et al., 1992). The clinical presentation and radiologic findings are nonspecific. The most common symptoms are dyspnea (26% to 83%) and cough (22% to 100%), and fever is almost always present (Oksenhendler et al., 1990; Pomeroy & Filice, 1992; Schnapp et al., 1992). Crackles, wheezes, and other pulmonary findings are uncommon, but patients may be severely hypoxic. Diffuse interstitial infiltrates are the most frequently observed radiographic finding, although lobar consolidation, pleural effusion, nodular densities, and cavitation have all been reported.

The diagnosis is difficult to establish on the basis of clinical and radiologic findings and is often only made at autopsy. A 4-fold rise in *Toxoplasma* IgG titer or detection of new IgM antibodies supports the diagnosis of acute infection, but many immunocompromised patients cannot generate an antibody response, or the titer may be maximal at presentation. Demonstration of *T. gondii* in bronchoalveolar washings, or histology showing both tachyzoites and evidence of acute inflammation, are diagnostic.

Of those with *Toxoplasma* pneumonia, 25% to

50% die (Oksenhendler et al., 1990; Pomeroy & Filice, 1992; Schnapp et al., 1992). Pyrimethamine combined with sulfadiazine is the treatment of choice, with folinic acid supplementation to reduce bone marrow suppression. Clindamycin may be substituted for sulfadiazine in sulfa-intolerant patients. Relapse is inevitable in immunocompromised patients if treatment is stopped, necessitating lifelong suppressive therapy.

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