CHAPTER 49

The Eosinophilic Patient with Suspected Parasitic Infection

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Elevations of the peripheral blood absolute eosinophil count (>450 eosinophils/mm^3) can occur in a wide variety of clinical situations, including parasitic infections, allergic states, collagen vascular diseases, hypereosinophilic syndromes, and other miscellaneous disorders (**Table 49.1**). The immunobiology of eosinophils is thoroughly described in Weller (1997). The absolute eosinophil count is a more reliable indicator of the presence of eosinophilia than is the relative eosinophil count (percentage of eosinophils), the normal level of which is less than 6%. For example, a person with a total white blood cell count of 4000 and a relative eosinophil count of 9% has an absolute eosinophil count of 360, which is not elevated.

CLINICAL FEATURES

Eosinophilia in a traveler returning from long-term residence or visit to the developing world or in an immigrant or refugee from a tropical area should first suggest the possible presence of a helminthic infection. Although eosinophilia particularly suggests presence of a helminth, the absence of eosinophilia cannot exclude these parasites. With a few notable exceptions, protozoan and other infections are seldom associated with eosinophilia, and as noted above, non-infectious etiologies must always be considered.

Eosinophil counts are generally higher in the early acute invasive phase than in chronic helminthic infections, particularly during initial infection with the parasite in a non-immune individual, and there may be considerable variation in the person-to-person response to the same helminth. Eosinophilia in the presence of a helminthic infection may be considered to be an adaptive increase in the number of eosinophilic cells available to damage the parasite. In addition, eosinophilia under these circumstances may be associated with qualitative changes in the eosinophils themselves.

The greatest number of tissue and blood eosinophils are found in infections in which the association of the parasite with host tissue is closest, that is, those with migrating larvae or extended retention of parasite lifecycle stages in tissue. Especially high eosinophil levels may be found in *Ascaris* pneumonia, strongyloidiasis, filariasis, tropical pulmonary eosinophilia, and acute schistosomiasis. Another situation leading to high eosinophilia is when humans become accidentally infected with parasites whose definitive host (host in which sexual maturity and reproduction of the parasite takes place) is in another animal species. The "lost" larval stages wander in the tissues until they die or become encysted; examples of such infections are trichinosis and visceral larva migrans (toxocariasis caused by dog and cat roundworm species). Intestinal helminths that remain in the bowel lumen and do not invade the intestinal mucosa (e.g., adult *Ascaris* and tapeworms) cause minor or no eosinophilia. Increased eosinophilia can develop after drug treatment of helminths, and it may take several months for elevated eosinophil levels to return to normal after initial parasite destruction.

TABLE 49.1 Less Common Causes of Eosinophilia

Rare Parasites
Capillaria hepatica
Fasciolopsis buski
Spirometra (sparganosis)
Anisakiasis
Skin Diseases
Eczema
Dermatitis herpetiformis
Eosinophilic cellulitis (Wells syndrome)
Malignancy
Eosinophilic leukemia
Myelogenous leukemia
Hodgkins disease and other lymphomas
Carcinoma of the bowel, ovary, lung, pancreas, and other solid organs
Collagen Vascular Disease
Polyarteritis nodosa
Dermatomyositis
Rheumatoid arthritis
Hypereosinophilic Syndromes
Löffler eosinophilic endomyocarditis
Löffler pulmonary syndrome
Pulmonary infiltration with eosinophilia
Eosinophilic gastroenteritis
Eosinophilic granuloma
Other
Drug reactions
Allergic disorders
Hypersensitivity pneumonitis
Wegener granulomatosis
Inflammatory bowel disease
Pernicious anemia
Eosinophilia-myalgia syndrome
Sarcoidosis
Hypoadrenalism

Reprinted from: Jong, E.C. (Ed.), 1999. Medical Clinics of North America: Travel Medicine. W.B. Saunders, Philadelphia, 83, p. 4.

DIAGNOSIS

The diagnosis of common intestinal helminths is usually made by finding the characteristic egg or larva in stool specimens submitted for microscopic examination. Clinical recognition and diagnosis of extraintestinal or disseminated parasites may be more difficult. If the stool examinations do not suggest a likely diagnosis, the following approach is suggested in the work-up of the patient with suspected parasite infection.

1. The *geographic or travel history* of the patient with eosinophilia may indicate a past exposure to parasites. Because the patient with tissue-stage parasites can have either multiple systemic symptoms or few clinical symptoms to report, and often will have negative stool examinations for ova and parasites, the geographic history is of prime importance. For instance, the history of swimming in freshwater lakes or rivers in endemic areas of Africa, South America, or Asia should suggest the possibility of schistosomiasis.

2. In the immunocompromised patient with fever, pneumonia, or central nervous system (CNS) signs, *Strongyloides* should be considered even in the absence of eosinophilia.
3. The history of exposure to pets, livestock, and wild animals or mosquito bites in rural areas may provide valuable clues to potential parasite exposure (e.g., filariasis, toxocariasis, cutaneous larva migrans, echinococcosis).
4. The history of eating exotic or raw, smoked, pickled, or undercooked food may provide additional clues to past opportunities for parasite exposure (e.g., liver and intestinal flukes, paragonimiasis, trichinosis, cysticercosis, anisakiasis, angiostrongyliasis, gnathostomiasis).

The diagnosis of a parasitic etiology for hypereosinophilia in a given patient is important for the following reasons:

1. Specific antiparasitic treatment may be indicated.
2. Prolonged hypereosinophilia can have uncomfortable and potentially life-threatening sequelae (pruritic skin rashes, painful subcutaneous swellings, endomyocardial fibrosis, and so forth).
3. The prompt search for other etiologies of hypereosinophilia may be indicated (e.g., allergy, occult tumor, leukemia, connective tissue disease, sarcoidosis, hypereosinophilic syndrome).

LABORATORY STUDIES IN EOSINOPHILIA

It is important to consider the long prepatent period of many helminth infections before the appearance of eggs or larvae in the stool or other body fluids or tissue. For intestinal helminths and protozoa, a series of three stool examinations (one every other day) should be collected in a preservative and examined by direct, concentration, and stained slide methods. Examinations of small bowel fluid taken via nasogastric tube or endoscopy, the string test (Enterotest), or small bowel biopsy may be required to confirm infection with *Strongyloides stercoralis*, hookworms, liver flukes, *Trichostrongylus* species, or the protozoan *Isospora belli*. Rectal biopsy has been used to diagnose cryptic cases of schistosomiasis species, including *Schistosoma haematobium*.

Filariasis infections of the blood can be diagnosed by concentration or microfilter examinations of blood taken at midday for all species except *Wuchereria bancrofti*, whose nocturnal periodicity makes midnight blood specimens optimal. A provocative challenge with a daytime dose of 100 mg of diethylcarbamazine and drawing blood 1 hour later can increase the number of *W. bancrofti* microfilariae to approximate midnight blood levels. For skin filariae, skin snips or biopsy specimens often reveal microfilariae (Chapter 47).

Sputum examination is useful in the detection of *Paragonimus* eggs and occasionally *Strongyloides* or *Ascaris* larvae. Eosinophils and Charcot-Leyden crystals in the sputum can suggest a pulmonary helminth larval migration, asthma and other nonparasitic allergic disorders, or a hypereosoniphilic syndrome. Eosinophilic pleural effusion can signify a pulmonary parasitic infection and various other causes of systemic and pulmonary eosinophilia.

The presence of eosinophils in the cerebrospinal fluid (CSF) is such an uncommon finding that it is most often the result of certain helminthic infections of the CNS. Parasitic infections to be considered in a returnee from the tropics with this finding include gnathostomiasis, cerebral cysticercosis, schistosomiasis, paragonimiasis, echinococcosis, and angiostrongyliasis. On the other hand, the absence of eosinophils in the CSF cannot rule out a CNS helminthic infection. Nonparasitic causes of CSF eosinophilia include tuberculosis, syphilis, coccidioidomycosis, viral infection, malignancy, and drug hypersensitivity, among others.

Charcot-Leyden crystals in the stool can be seen with a range of parasitic and noninfectious causes of bowel diseases. These crystals are hallmarks of eosinophil involvement in some tissue reactions. They are seen in amebic dysentery, and although not necessarily diagnostic, they may constitute a useful indicator. Charcot-Leyden crystals are also seen in the stool of patients with *Trichuris trichiura* and *I. belli* infections as well as in those with ulcerative colitis and carcinoma of the colon. They may also be seen in granulomas associated with tissue-invading helminths.

TABLE 49.2 Parasite Serologic Tests Useful in Evaluation of Eosinophilia

Disease	Test	Test Laboratory[a]
Toxocariasis	ELISA	CDC
Strongyloidiasis	ELISA	CDC
Filariasis	ELISA	NIH
Trichinosis	BFT, CIE, ELISA	State public health department
Cysticercosis	ELISA, Immunoblot	CDC
Schistosomiasis	ELISA, Immunoblot	CDC
Paragonimiasis	ELISA	CDC
Fascioliasis	ELISA	University of Puerto School of Medicine, Department of Pathology and Laboratory Medicine, Dr. George Hillyer
Gnathostomiasis	Immunoblot	Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Dr. Wanpen Chaicunpa, e-mail: tmwcc@mahidol.ac.th)

[a]Serum specimens are sent to the Centers for Disease Control (CDC) via the state public health department. Before serum specimens will be accepted for testing by the CDC, the clinician must furnish sufficient clinical and epidemiologic data to justify the request for the test. Depending on the suspected diagnosis, attempts must be made to make the diagnosis by prior laboratory testing, including (1) complete blood counts, (2) stool and/or urine specimens for ova and parasite examinations (strongyloidiasis, cysticercosis, schistosomiasis, paragonimiasis), (3) skin or tissue biopsies as appropriate (filariasis, trichinosis, cysticercosis), and (4) isolation of the parasite from blood by filtration or concentration techniques (filariasis). Similar serologic tests may be offered by commercial laboratories.

BFT, Bentonite flocculation; *CDC,* Centers for Disease Control and Prevention; *CIE,* counter immunoelectrophoresis; *ELISA,* enzyme-linked immunosorbent assay; *NIH,* National Institutes of Health.

Radiologic examinations are useful diagnostic aids. Chest radiographs can give evidence for pulmonary invasive infections such as migrating *Ascaris* and *Strongyloides* larvae, paragonimiasis, acute schistosomiasis, hydatid cyst, and tropical pulmonary eosinophilia. Ultrasound studies or computed tomography scans of the liver can identify lesions that are suggestive of early prepatent liver fluke infections or hydatid cyst. Soft tissue radiographs can identify calcified cysticerci. Radiographic imaging studies (computed tomography, magnetic resonance imaging) of the brain can reveal the presence of lesions compatible with invasive cerebral parasites such as cysticercosis, hydatid cyst, paragonimiasis, and schistosomiasis.

Serologic tests, not all commercially available, can provide evidence for the presence of particular helminth infections. Serologic tests are available from the Centers for Disease Control and Prevention (CDC) for strongyloidiasis, trichinosis, cysticercosis, schistosomiasis, paragonimiasis, toxocariasis, and echinococcosis. Serum and tissue specimens are submitted to the CDC through the state public health department or through direct consultation with CDC parasitology consultants (http://www.cdc.gov). Filariasis serology may be obtained from the Laboratory of Parasitic Diseases of the National Institutes of Health. *Fasciola hepatica* serology is performed at the University of Puerto Rico. A reliable gnathostomiasis test is available at the Department of Tropical Medicine, Mahidol University, Bangkok, Thailand (**Table 49.2**).

SPECIFIC INFECTIONS

Helminths

Ascariasis

In the early stage of *Ascaris* infection, before eggs are present in the stool, larvae migrate through the lungs. Although often unrecognized clinically, the larvae can cause a Löffler-like pneumonia, characterized by hypereosinophilia and pulmonary infiltrates and presenting

with cough, dyspnea, and malaise. The pathogenesis is believed to be a hypersensitivity response to highly allergenic components of *Ascaris* larvae. The most reliable diagnostic criterion is the finding of typical third-stage larvae in the sputum or gastric aspirate of suspected patients.

Most patients with established intestinal ascariasis are asymptomatic. Young children with heavy infections may develop intestinal obstruction. *Ascaris* infections produce a higher blood eosinophil count in children than in adults, in whom infections are associated with a mild eosinophilia. Infection is usually self-limited within 3 years. Diagnosis is by finding typical eggs on stool examination. Treatment is with mebendazole or albendazole (Chapter 48).

Strongyloidiasis

Infection with *Strongyloides stercoralis* is primarily from penetration of the exposed skin by infective stage larvae. Developing larvae migrate through the lungs and eventually reach the small bowel where they mature. Female worms invade the intestinal mucosa and deposit eggs, which hatch and liberate rhabdoid larvae. These larvae may then be passed in the feces, or they may develop within the lumen of the bowel into infective larvae that can autoinfect the carrier. Infections may therefore be long lived, 40 years or more in some cases.

Some infections are asymptomatic, but others may cause abdominal pain, intermittent diarrhea, asthma, or patchy pneumonitis. Urticaria may occur primarily on the buttocks and thighs, and creeping eruption may be present. Debilitated or immunocompromised patients may develop a lethal hyperinfection syndrome. Eosinophilia is often strikingly high in the earlier years of infection, although in long-established infections eosinophilia may be normal. Patients with the hyperinfection syndrome usually have a normal level of eosinophils. Diagnosis is by finding larvae in the stool, and often repeated special larval concentration tests are required. When strongyloidiasis is suspected and larvae cannot be found in the stool, duodenal fluid should be examined. An enzyme-linked immunosorbent assay (ELISA) serologic test (available at the CDC) is useful in making a presumptive diagnosis. Treatment is with ivermectin (Chapter 48).

Hookworm

Hookworm infection was the most common cause of eosinophilia in returned Vietnam veterans. It was also the most common intestinal helminthic cause of eosinophilia in Caucasians returning from the tropics to the United Kingdom. In 128 Indochinese refugees in the United States with persistent eosinophilia greater than 500/mm^3 for whom initial comprehensive routine screening had failed to yield an explanation, hookworm and *S. stercoralis* were among the potentially pathogenic intestinal parasites most frequently implicated (55% and 38%, respectively).

In the early stage of hookworm infection, pulmonary symptoms and hypereosinophilia may be present. Most established imported hookworm infections seen in temperate areas are with relatively few worms, and anemia does not occur. But vague upper abdominal pain and nausea may be present. Heavy infections are required to cause hookworm anemia. Eosinophilia is usually less than 1500/mm^3 but may reach 2500-3000/mm^3. Infections are self-limited within 3 years. Diagnosis is by finding eggs in the stool. Treatment is with mebendazole or albendazole (Chapter 48).

*Whipworm (*Trichuris trichiura*)*

Whipworm is a relatively commonly diagnosed intestinal helminth in travelers, most of whom have light, asymptomatic infections. Heavily infected children who are natives of endemic areas may have diarrhea, anemia, or rectal prolapse. The majority of cases in travelers have normal eosinophil counts, but levels of up to 1500/mm^3 may occur. This worm does not have a pulmonary migration stage, and infections seldom last more than 2 or 3 years. Diagnosis is by finding typical eggs on stool examination. Treatment is with mebendazole or albendazole (Chapter 48).

Trichostrongyliasis

Trichostrongyliasis, caused by various *Trichostrongylus* species, is particularly common in the Far East and Near East. Infections are usually light, and symptoms are unusual. Rarely, hypereosinophilia may be present, but in most cases infection is light, and eosinophils may be normal. Some infections may last for up to 8 years. Diagnosis is by finding typical eggs, which resemble but are larger than hookworms, either in the stool or in duodenal contents. Treatment is with pyrantel pamoate, mebendazole, or albendazole.

Pinworms

Infections with *Enterobius vermicularis* is more commonly present in young children, and prevalence is higher in temperate than in tropical climates. It is not well appreciated that pinworms may cause a low-grade eosinophilia. Diagnosis is by the examination of cellophane tape applied to the anus on arising in the morning and before bathing; the tape is placed sticky-side down on a glass slide and a search is made for eggs. Only 10-15% of those with pinworms pass eggs in stool. Treatment is with mebendazole, albendazole, or pyrantel pamoate (Chapter 48).

Trichinosis

Trichinosis infection usually occurs from ingestion of raw or undercooked pork products or from undercooked bear or walrus meat. Trichinosis has a worldwide distribution but is more frequently acquired in temperate than in tropical climates, and it is a rarely reported imported infection in the United States. Two outbreaks were reported in immigrant Thais in New York City. Thais can safely eat raw pork in Thailand where pigs are relatively trichinosis-free, but they probably lacked knowledge of the danger of eating raw pork in the United States.

Initial symptoms of trichinosis infection during the immediate period after ingestion are primarily diarrhea and abdominal pain, which usually precede the appearance of eosinophilia. In the second or third week after infection, penetration of muscle by larvae occurs, and the classic clinical picture of high eosinophilia (which can reach $\geq 7000/mm^3$), myalgias, periorbital edema, and fever appears. Definitive diagnosis is by biopsy of an involved muscle, pressing the tissue specimen between two glass slides, and microscopic examination to identify the larvae. Indirect evidence of infection can be made by specific serologic tests, but these may not become positive until about 4 weeks after infection. Severe infection can be treated with steroids and mebendazole or albendazole.

Visceral Larva Migrans

Infection occurs from ingestion of eggs of the dog or cat roundworms, *Toxocara canis* and *Toxocara cati*, usually in children who eat dirt contaminated by the feces of these domestic animals. Most cases seen in the United States are acquired domestically, although the risk of infection is present worldwide. The disease syndrome, visceral larva migrans, can then develop with the prolonged migration of parasitic larval forms in the internal organs. A child with a history of pica presenting hepatomegaly and pneumonitis must be considered to possibly have this syndrome. Infections are often self-limited, but deaths have been reported. Rarely, larvae may localize in the eye, and consideration must be given to their presence in the differential diagnosis of malignant tumor of the eye in young children, to avoid needless enucleation. Specific diagnosis requires identification of larvae from sputum or hepatic granulomas; an ELISA serologic test is also available. Drugs of choice are mebendazole or albendazole.

Gnathostomiasis

Gnathostoma spinigerum and other *Gnathostoma* species cause illnesses similar to visceral larva migrans and creeping eruption. Gnathostomiasis in humans occurs in Thailand, Japan, China, Vietnam, and East Africa. The definitive hosts for *Gnathostoma* species include dogs, cats, tigers, lions, leopards, minks, and raccoons. Humans are accidentally infected with intermediate larval forms of this animal nematode by eating infected raw undercooked freshwater

fish, eels, frogs, and snakes. If chicken and pigs have eaten infected fish, humans can acquire the infection from eating undercooked chicken and pork.

If intermediate hosts of *Gnathostoma* are eaten, encysted larvae in the muscle or connective tissue undergo excystation in the stomach of the new animal. The larvae then migrate in the internal organs or subcutaneous tissues. Symptoms of disease depend on the route of the larval migrations. Acute larval migration is accompanied by nausea, vomiting, pruritus, urticaria, and abdominal discomfort. Peripheral blood eosinophilia may be as high as 90%. The larval migrations usually go to the subcutaneous tissues after the acute phase, causing transitory subcutaneous swelling accompanied by local erythema, pruritus, and discomfort. Larval migration into the CNS is a serious complication and is in the differential diagnosis of eosinophilic myeloencephalitis. Diagnosis is made by identification of the parasite in biopsy specimens. A serological test may be available through consultation with medical scientists at Mahidol University in Bangkok, Thailand. Albendazole, 400 mg twice a day for 21 days, has been used as an effective tissue larvicidal agent for cutaneous gnathostomiasis.

Cerebral Angiostrongyliasis

In April 2000, 10 tourists from Chicago and other US cities developed symptoms and signs of meningitis a median of 10 days after leaving Jamaica, West Indies. Serology indicated that *Angiostrongylus cantonensis* was the etiologic agent. Eight of the tourists required hospitalization.

In the last 50 years, *Angiostrongylus cantonensis*, the rat lungworm, which is the most common cause of eosinophilic meningitis, has spread from Southeast Asia to the South Pacific, Africa, India, the Caribbean, and recently to Australia and North America. The primary mode of spread has been via rats on cargo ships. Infection in humans is acquired by eating snails or food items (prawns, crabs, vegetables) contaminated by the mucus of infected slugs, land snails, aquatic snails, or planarians. The definitive host is the rat, where the adult rat lungworms live in the pulmonary arteries and the right heart.

When humans become accidentally infected through contaminated food, the larvae migrate to the CNS and cause eosinophilic meningitis. The eyes also may be involved. The severe illness, lasting 2-4 weeks, either ends in death or becomes dormant with residual CNS findings (focal neurologic defects, cognitive impairment, blindness). People with light infections may spontaneously recover without neurologic residua. Diagnosis is made by identifying the parasite in the CSF or brain tissue.

There is no specific drug treatment recommended for this infection. Cautious removal of CSF at 3- to 7-day intervals, which causes marked improvement of headache, is advised until there is clinical and laboratory improvement. In severe cases, corticosteroids are used to reduce cerebral pressure. Although *A. cantonensis* is susceptible to multiple antihelmintic agents, including thiabendazole and mebendazole, these agents should not be used, since they can cause clinical deterioration or death from inflammation due to dead or dying worms in the brain.

Filariasis

The most common diagnosed blood filaria infection in returnees to North America and the United Kingdom from Africa is caused by *Loa loa*. This parasite is present primarily in the rain forests of West and Central Africa. The incubation period is 12 months or longer, and adult worms can live for 15 years or more. Classic symptoms are recurrent swellings (Calabar swellings) on the dorsa of the hands and forearms and on the lower limbs, which last 2-3 days, and movement of the adult worm across the conjunctiva. Eosinophilia may reach 5000-8000/mm^3, but the level may vary from time to time.

Mansonella perstans is also present throughout tropical Africa and has been one of the most frequently diagnosed filarial infections in the United Kingdom. There is some controversy regarding the pathogenicity of this parasite; symptoms associated with infection include abdominal pain, allergic symptoms, fever, headache, and exhaustion. Significant eosinophilia is frequently present in *M. perstans* infections.

The most common filaria infection worldwide is bancroftian filariasis, caused by *Wuchereria bancrofti*. Expatriates are rarely infected; the few cases seen are usually in longer-term expatriate residents or in natives of endemic areas, who have the prolonged, heavy exposure necessary for infection. In the acute stage of infection, symptoms are related to allergic inflammatory reactions to adult worms in the lymphatics and include recurrent swelling and tenderness of the genital organs and extremities, fever, chills, malaise, and headaches. After many years of infection, chronic elephantiasis of the limb or scrotum can occur, but it is virtually unheard of for an expatriate to develop these gross deformities. Eosinophilia in the range of 1000-2500/mm^3 or higher is a prominent characteristic in the acute stage of infection, but eosinophils may well be normal in chronic infections.

Brugia malayi occurs only in Asia, and symptoms are similar to those of *W. bancrofti*. *B. malayi* is rarely diagnosed in expatriates. Eosinophilia is common in the acute stage. *Mansonella ozzardi* occurs in tropical areas of Central and South America and on some Caribbean islands. Only a few cases of this infection have been documented in expatriates. Infections are usually asymptomatic, but eosinophilia commonly occurs.

Diagnosis of all forms of blood filariasis is by finding typical microfilariae in blood concentration tests. Most cases also have a positive filariasis serologic test. Treatment of all species of blood filariae is with diethylcarbamazine except for *M. perstans*, for which albendazole or mebendazole is recommended (Chapter 47).

Two species that cause filariasis, *Onchocerca volvulus* and *Mansonella streptocerca*, are parasites of the skin. The former occurs throughout tropical Africa, in a small area of the Yemen, and in parts of Central and South America and is, along with *Loa loa*, the most commonly diagnosed form of filariasis in North America and the United Kingdom. Only a few cases of *M. streptocerca* have been described in expatriates. Symptoms of both parasites include maculopapular pruritic rash, occurring most commonly on the buttocks, thighs, and trunk, and, less commonly, unilateral limb swelling. *O. volvulus* may also cause subcutaneous nodules and, in long-standing heavy infections in natives, may cause blindness. Blindness from this infection is almost unheard of in expatriates. Significant eosinophilia, often exceeding 5000/mm^3, is common with these parasites; in expatriates eosinophilia may be present with only minimal cutaneous lesions. Diagnosis is by finding microfilaria in skin snips or biopsy specimens taken from affected areas. The filariasis serologic test is usually positive. In suspected cases in which microfilariae cannot be found, administration of 50-100 mg of diethylcarbamazine (the Mazzotti test) almost invariably leads to an exacerbation of cutaneous symptoms and a rise in eosinophilia, strongly suggesting infection. Treatment is with ivermectin, which does not destroy adult worms and must be administered approximately yearly for the lifespan of the worms (12-14 years) (Chapter 47).

Tropical pulmonary eosinophilia is a disease syndrome related to occult infection with animal or human filariae and is most prevalent in South and Southeast Asia. It is particularly common in Indians, even outside India. The syndrome results when adult worms produce microfilariae, which are destroyed primarily in the lungs by an intense tissue reaction; this hypersensitive immune reaction leads to pulmonary symptoms, radiologic changes, lymphadenopathy, a positive filariasis serology test, and hypereosinophilia with leukocytosis. Characteristic symptoms are a nocturnal paroxysmal cough, asthma, fatigue, and low-grade fever. Diagnostic differentiation from other forms of eosinophilia present in the tropics is made on the basis of several major criteria: typical pulmonary symptoms, peripheral eosinophilia of 3000/mm^3 or greater, positive filarial serology, and response of the symptoms to diethylcarbamazine.

Cestode (Tapeworm) Infections

Intestinal cestode infections give rise to eosinophilia less commonly than nematode or trematode infections. Perhaps the most commonly diagnosed cestode is *Taenia saginata*, the beef tapeworm, contracted from eating raw or undercooked beef. Infection is particularly common in Africa but occurs worldwide. Patients are usually asymptomatic but may occasionally describe vague abdominal discomfort. Infection is often initially manifested by the

spontaneous passage per anus of motile tapeworm segments. *Taenia solium*, the pork tapeworm, also has a worldwide distribution wherever raw or undercooked pork is eaten. The mature intestinal tapeworm usually causes no symptoms, and intact segments are usually not passed. When humans ingest viable *T. solium* eggs or, more rarely, regurgitate eggs into the stomach after vomiting, however, cysticercosis of the muscles and brain can occur. *Hymenolepis nana*, or dwarf tapeworm, is common in drier parts of the world; humans become infected by ingesting eggs. Most infections are asymptomatic, but abdominal pain and diarrhea may result. *Diphyllobothrium latum*, the fish tapeworm, occurs primarily in northern climates, and infection results from eating certain fish raw or undercooked. Infections are usually asymptomatic.

Diagnosis of all these tapeworm infections is by finding eggs in the stool or by identification of gravid proglottids in the stool or passed spontaneously. Characteristic calcified cysticerci can be seen on radiographic film in cysticercosis, but these do not occur before 5-10 years after infection. Eosinophilia of up to 1000/mm^3 occurs in about half of *T. saginata* infections. A mild eosinophilia is also common in *H. nana*, *D. latum*, and intestinal *T. solium* infections. Eosinophilia has been described in the invasive stage of cysticercosis, and in cerebral cysticercosis with meningeal inflammation, eosinophils are commonly found in the CSF. Treatment of intestinal tapeworm infections is with praziquantel. Cysticercosis can be treated with praziquantel or albendazole (Chapter 46).

Echinococcosis (Hydatid Cyst)

Echinococcosis infection is common in sheep-raising countries where humans are closely associated with heavily infected sheepdogs and can ingest the eggs. Autochthonous cases are rare in North America, and most cases seen are contracted abroad, in areas such as the Mediterranean littoral, the Middle East, or South America. Symptoms may not present for 10 or more years after infection, because the cysts are slow growing. The usual cyst location is in the liver or lung. Eosinophilia does not usually occur with an intact cyst, and when it is present, it is usually related to some leakage of fluid. Approximately one-quarter of cases seen in North America had an eosinophilia of >500/mm^3. Cysts are often initially recognized with radiographic imaging studies, and confirmation can be made serologically. Depending on cyst location and complexity, treatment may include drug therapy (albendazole, mebendazole, praziquantel), surgery, and/or percutaneous aspiration–injection–reaspiration (Chapter 46).

Schistosomiasis

The acute stage of schistosomiasis may not be recognized in many of those infected, but in some cases, 4-8 weeks after infection the so-called Katayama syndrome may occur. This syndrome coincides with the initial deposition of eggs by recently matured worms and can include fever, chills, headache, diarrhea, hepatosplenomegaly, urticaria, pulmonary infiltrates, cough, wheezing, and eosinophilia, which may reach levels of 6000/mm^3 or greater. This syndrome occurs most frequently with *Schistosoma japonicum* infections contracted in the Far East; less frequently with *Schistosoma mansoni* infections contracted in Latin America or the Caribbean, Africa, or Southwest Asia; and least commonly with *S. haematobium* contracted in Africa or the Middle East. Acute schistosomiasis symptoms are usually self-limited, but some severely affected individuals may require praziquantel therapy with steroids.

Most established schistosomiasis infections in travelers and natives of endemic areas are asymptomatic, although some people may have gastrointestinal or urinary complaints, fatigue, or weight loss. Hematuria is the most typical presentation of *S. haematobium* infections. In established infections, eosinophilia is variable. In 173 white expatriates returning to Britain with the sole diagnosis of schistosomiasis, eosinophilia was found in 48% of those with *S. mansoni* and in 24% of those with *S. haematobium*. A history of freshwater exposure in an endemic area is necessary to make the presence of schistosomiasis tenable.

Diagnosis of the intestinal forms—*S. japonicum* or the related *Schistosoma mekongi* from Southeast Asia and *S. mansoni*—is by finding typical eggs in the stool. *S. haematobium* is

found by examination of urine sediment. When eggs cannot be found after concentration examination of stool or urine, a rectal biopsy specimen may show the presence of eggs of all the species; a rectal snip pressed out between two glass slides can give a rapid diagnosis. Fluorescent antibody, FAST (Falcon assay screening test)–ELISA, and specific *S. mansoni* and *S. haematobium* immunoblot tests can be used to serologically screen people with suspected cases and other travelers with a history of exposure to infections. Attempts can then be made to find eggs in stool or urine. Because eggs may be difficult to find in early infection or in lightly infected persons, praziquantel treatment in a 1-day, usually well-tolerated and effective course, can be considered for positive serologic reactors with an exposure history (Chapter 48).

Liver and Lung Flukes

Clonorchis sinensis and *Opisthorchis viverrini* are the most common liver flukes diagnosed in returnees to temperate areas, and eosinophilia frequently occurs in these infections. The former is not uncommon in Chinese immigrants, and both can occasionally be seen in returned expatriates. *O. viverrini* is commonly seen in Southeast Asian refugees, particularly those from Laos and Thailand. *Fasciola hepatica* is rarely seen in North America but is found in Europe and Latin America. Many liver fluke infections are relatively light, and patients may be asymptomatic. In more heavily infected individuals, manifestations can include low-grade fever, diarrhea, and liver pain. In the acute stage, a high eosinophilia may be present, but eosinophilia is usually mild in established infections. Diagnosis is by finding typical eggs in the stool or in duodenal contents. *Paragonimus westermani*, the lung fluke, is usually seen in Asian immigrants, rarely in West African immigrants, and rarely in expatriates. Clinical manifestations can resemble tuberculosis, with fever, weight loss, blood-tinged sputum, cough, chest pain, and pulmonary nodules and cavities. Eosinophilia is often present. Diagnosis is by finding typical eggs in the sputum or occasionally in the feces when eggs are coughed up and swallowed. Praziquantel is the treatment of choice for all these flukes except *F. hepatica*, which is best treated with bithionol or triclabendazole. However, both of these latter drugs are investigational in the United States.

Protozoan Infections

The more common intestinal protozoa, *Giardia lamblia* and *Entamoeba histolytica*, are not a cause of eosinophilia. *Dientamoeba fragilis*, an increasingly recognized flagellate parasite of the large bowel, may cause diarrhea, cramps, and gas. Infections appear to be somewhat more common in children. In one report, significant peripheral eosinophilia was found in 53% of adults with *D. fragilis* and chronic eosinophilia. Reports on eosinophilia in patients with *D. fragilis* have not been uncommon when a differential white blood cell count has been performed. There is some evidence that eosinophilia in children with *D. fragilis* infections may be associated with pinworms, but this is certainly not always the case. *Isospora belli*, a rarely diagnosed small bowel coccidial parasite, may occasionally cause long-lasting infections leading to chronic diarrhea, malabsorption, and fever. Eosinophilia, occasionally profound, has been associated with *I. belli* infections. Diagnosis of these infections is by finding parasites in the stool, and with *I. belli* also in duodenal contents or biopsy specimen. Patients with malaria who have eosinophilia are usually found also to have other parasitic infections as the cause.

Bacterial and Fungal Infections

Eosinophilia is not usually associated with bacterial, viral, rickettsial, and fungal infections. It has been irregularly described in late scarlet fever and chronic indolent tuberculosis. In primary coccidioidomycosis (which occurs not only in the southwestern United States, but also in parts of Central and South America), eosinophilia occurs in as many as 88% of patients. Eosinophils may also appear in the CSF in *Coccidioides immitis* meningitis. *Aspergillus fumigatus*, causing allergic bronchopulmonary aspergillosis, is associated with eosinophilia. Imported infections with these fungi are distinctly uncommon in the United States. Eosinophilia has been reported with human immunodeficiency virus infection.

Drug Reactions

Many drugs can cause eosinophilia as a feature of a hypersensitivity reaction. Products containing sulfa drugs, such as trimethoprim/sulfamethoxazole and the antimalarial Fansidar (pyrimethamine and sulfadoxine) should be considered as the cause of eosinophilia in patients taking these products. The initiation of treatment for helminthic infections such as schistosomiasis and filariasis may lead to an acute exacerbation of eosinophilia related to rapid destruction of parasites.

Endomyocardial Fibrosis

Endomyocardial fibrosis has been described primarily in tropical Africa and South America, especially in natives. There have also been convincing reports of endomyocardial fibrosis in Europeans who have lived for long periods in West and Central Africa. In most of them, filariasis was present, and there was marked eosinophilia. There are many hypotheses concerning endomyocardial fibrosis besides an association with filariasis, however, and the exact cause has not yet been established.

Other Diseases with Eosinophils

Other less common entities that can be considered in the cause of eosinophilia, although not all necessarily related to tropical exposure in returned travelers or immigrants from tropical areas, are listed in **Table 49.1**.

FURTHER READING

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Spencer, M.J., Chapin, M.R., Garcia, L.S., 1982. *Dientamoeba fragilis*: a gastrointestinal protozoan infection in adults. Am. J. Gastroenterol. 77, 565–569.
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Weller, P.F., 1997. Human eosinophils. J. Allergy Clin. Immunol. 100, 283–287.
A thorough discussion of immunobiology of eosinophilia.