INTRODUCTION

The trematodes that infect liver, lung, and intestine are all food-borne. Freshwater fish, crustaceans, and aquatic vegetation are the sources of human infection. Fluke diseases also are all zoonoses with reservoirs in a wide range of domestic and wild animals. It is estimated that more than 40 million people are infected with flukes, approximately 21 million with lung flukes, 20 million with liver flukes, and unknown millions with intestinal flukes. The geographic distribution is worldwide, but the highest prevalences are in East and Southeast Asia. Distribution is determined as much by local eating habits as by the presence of the obligatory freshwater snail, crustacean, fish, or edible aquatic plant intermediate hosts. Any of these flukes can produce serious clinical disease, especially when infections are heavy. The site of preference of adult flukes for liver, lung, and intestine; the migration of the fluke larvae to these sites; the intensity of infection; and the longevity of the parasite are the major determinants of clinical disease. A most remarkable clinical feature of food-borne trematodes is the causal association between liver fluke infection and cholangiocarcinoma of the liver.

These flukes are hermaphroditic, bilaterally symmetrical, and flattened dorsoventrally with an anterior oral and a ventral sucker. Different species measure from 1 mm to 12 cm in length and have been described as spatulate, piniform, lanceolate, or leaflike in shape (Fig. 117-1). Life cycles of the different fluke species have common features. Adult flukes in the mammalian host produce eggs that, when passed in feces or sputum, are ingested by, or hatch as, ciliated miracidia and penetrate appropriate first-intermediate-host snails, within which asexual multiplication through sporocysts, redia, and cercaria stages occurs. Free-swimming cercaria leave the snail and penetrate fish or shellfish or attach to aquatic vegetation to encyst as metacercaria. When eaten by the mammalian final host, the metacercaria excyst, migrate to liver or lungs, or stay in the small intestine and develop into adults.

LIVER FLUKES

Human liver flukes are members of two families, the Opisthorchiidae and the Fasciolidae, distinguished by differences in life cycle and pathogenesis. In human Opisthorchiidae there are three major species (Clonorchis sinensis in East Asia, Opisthorchis viverrini in Southeast Asia, and Opisthorchis felineus in countries of the former Soviet Union) and two minor species (Opisthorchis guayaquilensis in North and South America and Metorchis conjunctus in North America). In the Fasciolidae the species are Fasciola hepatica, which has a worldwide distribution, and Fasciola gigantica in South Asia, Southeast Asia, and Africa.

OPISTHORCHIASIS AND CLONORCHIASIS

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The three major Opisthorchiidae species—C. sinensis, O. viverrini, and O. felineus—have similar life cycles and pathogenic processes. Differentiation among species is usually based on adult fluke morphology or geographic distribution, as differences in egg morphologies are small. Adults, which live in the intrahepatic bile ducts of their host, are flat, spatulate to lanceolate, aspinous, and reddish to brown in color. C. sinensis is the largest (10 to 25 mm × 3 to 5 mm), in contrast to the smaller O. viverrini (5 to 10 mm × 1 to 2 mm) and O. felineus (7 to 12 mm × 2 to 3 mm, Fig. 117-2A). The adults produce ovoid eggs that are yellowish-brown, have opercula, and are of such overlapping and variable size (O. viverrini, 30 µm × 12 µm; O. felineus, 30 µm × 12 µm; C. sinensis 28 to 35 µm × 12 to 19 µm) that speciation is very difficult (Fig. 117-2B).

The eggs, if deposited in fresh water and ingested by the appropriate snail, hatch as miracidia and metamorphose into sporocysts and then redia. These then transform into free-swimming cercaria on leaving the snail and penetrate and then encyst as metacercaria in susceptible freshwater fish species. These metacercaria, in uncooked fish, are ingested by the final human host, excyst in the duodenum, mature rapidly into adults, and migrate through the sphincter of Oddi and up the common bile duct to become wedged in the intrahepatic biliary radicles. The prepatent period is 3 to 4 weeks, and the life span in the human host can be as long as 30 years.

EPIDEMIOLOGY

C. sinensis is endemic in China, Japan, Korea, Taiwan, Vietnam, and Asian Russia. In China, infection is endemic in 24 provinces, with prevalence rates between 1% and 57%; the greatest number of cases is in the southeastern province of Guangdong and the southern region of Guangxi Zhuangzu. Hong Kong is not an endemic area for the parasite; infections are acquired by eating fish imported from the mainland of China. In Korea rates of 8% to 22% were reported in the past, while prevalence rates in the 1990s dropped to 2%. People living along river basins are more commonly infected. This parasitosis is reported from all areas of Taiwan, with the highest infection rates of 52% to 57% from three widely separated
areas in northern, central, and southern counties of the island. Although clonorchiasis was found in up to 3% of the Japanese population prior to 1960, by 1991 the disease had almost disappeared. Endemic areas in Russia are in the Amur River area.

O. viverrini is highly endemic in the northeastern region of Thailand and Laos, where prevalence rates of more than 24% and 40% to 80%, respectively, are reported. There are reports of occurrence from Vietnam with rates of 0.3% to 37%. O. felineus has been reported from an estimated 16 million people in the former USSR, with endemic foci in western Siberia, the Russian Federation, Kazakhstan, and Ukraine; prevalences range from 40% to 95%.

Other opisthorchids reported from humans are Opisthorchis guayaquilensis (Amphimerus pseudofelineus) and Metorchis conjunctus. These have been reported from animals and humans in Latin America and North America. An epidemic of metorchiasis occurred in 19 persons in Canada who had eaten freshly caught white suckers (Catostomus commersoni) near Montreal.

A variety of hydrobid snails serve as first intermediate hosts for C. sinensis, O. viverrini, and O. felineus. Bithynia fuchsiana, Parafossarulus mansouri, and Simulicospicula libertina are important vectors of C. sinensis in most endemic areas, while Bithynia siamensis is a vector of O. viverrini in Thailand; Melanoides tuberculatus is an important vector in Vietnam; and Codiella inflata, Codiella troscheli, and Codiella leachi are vectors of O. felineus in the former USSR. These snails are found in freshwater bodies and are abundant in fish-raising ponds in China, Taiwan, and Thailand.

Over 100 species of fish, many of them synonyms, are reported as second-intermediate hosts of C. sinensis. Most are carps of the family Cyprinidae, Ctenopharyngodon idellus in China, Cyprinus carpio in Japan, and Pseudorasora parva in Korea are often eaten raw. Many of the fish are cultivated in ponds inhabited by snail hosts, and the ponds are contaminated or intentionally fertilized with human and animal feces. Fifteen species of cyprinodont fish such as Cyclocheilichthys spp. and Puntius spp. are sources of infections in Thailand, and Carassius carassius and seven other species are sources in Vietnam.
Cultured fish, as well as fish from natural sources, are infected, and as the streams dry up, fish clustering in shallow waters are easily caught and eaten raw. Twenty-two species of cyprinids are intermediate hosts for *O. felineus* in the former USSR. The fish, such as *Barbus barbus* and *Tinca tinca*, may be eaten raw, dried, salted, and sometimes frozen.

In endemic areas of opisthorchid liver fluke infections, a myriad of mammalian hosts such as dogs, cats, pigs, rats, rabbits, and other wild fish-eating animals serve as reservoir hosts.

**DISEASES**

There is consensus that the biologic and pathologic characteristics of *Opisthorchis* and *Clonorchis* are the same. Variations in clinical presentations seen in different geographic areas are thought to reflect the duration and intensity of infection as well as the genetics and nutrition of the host rather than parasite-specific characteristics. Acute disease has been recognized most frequently in *O. felineus* infections in Russia. The risk of cholangiocarcinoma appears greatest in *O. viverrini* infections in northern Thailand. Intrahepatic pigment stones are reported more frequently in association with *C. sinensis*. Chronic infections are usually asymptomatic, although symptoms may occur in heavier infections. The complications of chronic infection include acute cholangitis, frequently bacterial, and cholangiocarcinoma.

**Acute Opisthorchiasis and Clonorchiasis**

Acute illness due to new infections with *C. sinensis* has rarely been reported except for a large outbreak of acute clonorchiasis in Shanghai in the 1940s. The illness lasted several weeks and was characterized by persistent fever, abdominal pains, fatigue, an enlarged and tender liver, high eosinophil counts, and opisthorchiid eggs in the stool after 3 to 4 weeks. In Russia acute opisthorchiasis has been seen frequently in migrant populations settling in regions endemic to *O. felineus*. The presentation is fever, abdominal pain, and urticaria. In Canada an outbreak of acute illness due to *M. conjunctus* reported upper abdominal pain, moderate fever, anorexia, high eosinophil counts, and opisthorchiid eggs in the stool late in the second week of illness.

**Chronic Opisthorchiasis and Clonorchiasis**

Light to moderate infections, lasting for years or decades, are almost always asymptomatic. Case-control and
community-based studies have revealed no differences in the signs, symptoms, or laboratory findings between light infections and uninfected controls, but cases with heavy infections (more than 10,000 eggs per gram) show significantly more abdominal pain, fatigue, dyspepsia, and hepatomegaly. There is a correlation between stool egg counts, adult fluke counts, and host disease in *Opisthorchis* infection. But even in heavily infected persons, abdominal symptoms occur in only 10%. Such studies are difficult to interpret because raw fish consumption in many communities is frequent and reinfection likely.

Many uncontrolled hospital-based studies in endemic regions demonstrate a variety of intermittent symptoms that increase in frequency in those with heavy infections. These symptoms include intermittent fatigue, abdominal pain and fullness, anorexia, weight loss, and diarrhea. In these studies, physical signs, such as liver enlargement and tenderness, are more frequent in the heavily infected, and eosinophil counts are higher. Uncontrolled treatment trials with praziquantel have demonstrated a decrease in symptoms of upper abdominal pain, diarrhea, distention, dizziness, fatigue, and insomnia from 72% to 45%.

Ultrasonographic studies have revealed a high frequency of gallbladder enlargement, sludge, dysfunction, and stones in asymptomatic moderately to heavily infected patients. Treatment appears to reverse these parasite-associated gallbladder abnormalities.

Pathologic changes observed on necropsy and biopsy relate to intensity and duration of infection. Early infections reveal bile duct proliferation and pseudostratification of the

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**Liver Flukes**

*Clonorchis sinensis*  
*Opisthorchis viverrini/felineus*  

![Liver Flukes Diagram](image)

- Mature to adults over 4 weeks
- Metacercariae excyst in small bowel, migrate up common bile duct
- Encysted metacercariae ingested with fish (carp)
- Cercariae from snail penetrate under scales of fresh fish
- Eggs ingested by hydrobiid snails; miracidia hatch, develop sporocysts, rediae, cercariae over 4-6 wks
- ~15-30μ eggs in stool
- 5-25mm adults reside in bile ducts for up to 30 yrs causing:
  - Occasional (early) RUQ pain, eosinophilia (1-3 wks after exposure)
  - Ascending cholangitis (later)
  - Cholangiocarcinoma (late)

**Pathogens**

* C. sinensis is seen in the Orient,  
* O. viverrini in SE Asia and  
* O. felineus in Europe-Sibera

**About 0.1% of Bithynia snails (or less) are infected, produce ~200-300 cercariae per infected snail**
biliary epithelium. Later, metaplastic squamous cells and glandular proliferation appear, suggesting adenomatous hyperplasia. A small percentage of patients with chronic infection will develop complications, which include recurrent ascending cholangitis, pancreatitis, and cholangiocarcinoma.

Recurrent Ascending Cholangitis and Pancreatitis

Recurrent ascending cholangitis is characterized by repeated episodes of fever, chills, jaundice, right upper quadrant pain, gram-negative sepsis, and leukocytosis. Soft, mushy pigment stones are found in the biliary radicles and common bile duct and are associated with dilated intrahepatic bile ducts, ectasia, strictures, and multiple pyogenic abscesses, most notably of the left lobe of the liver. Recurrent exacerbations and remissions can occur over years. Pancreatitis at times is found on endoscopic retrograde cholangiopancreatography (ERCP), or at the time of surgery or autopsy, but it is rarely symptomatic or found in isolation without liver involvement.

Cholangiocarcinoma

An increased frequency of cholangiocarcinoma of the liver is seen in northern Thailand, where case-control studies reveal a fivefold increased risk in those infected. The risk increases to 15-fold in persons with heavier infections. In one endemic province of Thailand, the rate of cholangiocarcinoma in males and females was ten- and sixfold higher, respectively, than in a nonendemic area. In animal studies, nitrosamines increase the incidence of cholangiocarcinoma in Opisthorchis-infected animals. High levels of such substances have been noted in the northern Thai diet.

PATHOGENESIS AND IMMUNITY

The pathologic changes seen in the liver and biliary system in clonorchiasis and opisthorchiasis are believed to be the result of mechanical injury by the suckers of the flukes and host interactions with their secreted metabolic products. Dilated hyperplastic bile ducts have been associated with excess proline production by adult flukes. The eggs probably serve as nidi for biliary stones in the bile ducts and gallbladder. Immunohistochemical studies indicate that the excretory-secretory proteins from the digestive and excretory organs (i.e., the intestines and bladder) are the most potent antigens and likely induce the dominant immunologic response. Periductal infiltration with eosinophils and round cells with fibrosis of portal areas—a common finding—suggests that immune-mediated tissue damage is involved in the pathogenesis of disease. The local reactions to eggs and migrating parasites are driven by T-lymphocyte effector mechanisms and are regulated by the CD4+ subset of T lymphocytes. The presence of apparently uninfected persons in endemic regions with significantly higher levels of parasite-specific IgM, IgG, and IgA than egg-excreting persons has been used as evidence of protective immunity.
DIAGNOSIS

Asymptomatic infections with Opisthorchiidae are diagnosed by the presence of characteristic findings on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) or by the detection of eggs in stool. On ultrasound of the liver, the combination of cystic or mulberry-like dilations of intrahepatic bile ducts is pathognomonic of opisthorchiasis. With M-mode ultrasound, numerous spotty echoes and thin linear and moving intraductal echoes may be seen. Examination of multiple stool specimens may be necessary in lighter infections, but in infections of less than 20 adult flukes, no eggs may be found. While egg counts in stools are relatively stable over time and such egg counts have prognostic significance, low egg counts may be seen in the heaviest infections because of blockage of biliary radicles or because pyogenic ascending cholangitis has killed the adults. The eggs of Clonorchis, Opisthorchis, and Metorchis are essentially indistinguishable from one another by routine microscopy and can be confused with other fluke eggs as well. A definitive diagnosis may be made by examining the adult flukes in the stool immediately after a praziquantel treatment and purge or at the time of surgery.

The diagnosis of acute infection is based on a history of raw freshwater fish consumption (salted, fermented, or smoked fish, fish sauces, fish condiments), followed within several weeks by upper abdominal pain, high-grade eosinophilia, liver enzyme elevation, and the appearance of compatible eggs in the stool.

Immunodiagnosis

Immunologic tests generally complement parasitologic testing and until recently have not had a primary role in the diagnosis of opisthorchiasis and clonorchiasis. These tests are not widely available in endemic regions and do not distinguish active infections from past exposure or cured infections. Intraderal tests using crude extracts of adult flukes have been used for detection of infection in epidemiologic surveys and have proved very sensitive (92%), showing no cross-reactions with other nematode infections. However, these tests remain positive for many years after exposure to the parasite. The preferred assay for immunodiagnosis is the determination of antibody levels by enzyme-linked immunosorbent assay (ELISA). When compared with egg-positive stools, sensitivity can be high (79% to 96%). However, ELISA using crude worm extracts is handicapped by significant lack of specificity; antibody positivity is seen in cases of paragonimiasis (33%), schistosomiasis japonica (5% to 25%), cysticercosis, hepatitis, liver cancer, and tuberculosis. Specificity can be enhanced somewhat by using immune affinity–purified antigens. More recently, the use of monoclonal antibodies in an ELISA inhibition test has proved to be sensitive (77%) and more specific (virtually no cross-reactivity with other trematode infections) than the ELISA using crude worm extracts. Approaches used to refine and improve specificity of ELISA assays have included the use of excretory-secretory (ES) antigens as plate antigens. A number of proteins have been identified as major components of ES preparations of C. sinensis, including cysteine proteases and glutathione-S-transferase. The modifications to ELISAs have been reported to achieve sensitivities and specificities of greater than 95% in smaller serologic surveys, but their utility in large-scale surveillance is yet to be proved. After treatment, antibody levels return to normal by 6 months in more than half of cases. Circulating antigen detection with a monoclonal antibody–based assay has been found to detect as little as 30 ng/mL of C. sinensis antigen in serum. Antigen positivity is seen in 95% of antibody-positive infected patients. This test was reported to be positive in 95% of seropositive infected patients, declining to undetectable levels after 3 months in 81% of those parasitologically cured. Stool antigen detection techniques show similar promise.

TREATMENT

Praziquantel has been the drug of choice for opisthorchiasis and clonorchiasis since the 1970s because of ease of administration, lack of side effects, and demonstrated effectiveness. The recommended dosage of 25 mg/kg daily for 2 days has produced cure rates up to 100%, but patients with heavy infections (more than 5000 eggs per gram of stool) and some geographic regions where praziquantel cure rates are low (North Vietnam) may require retreatment. Albendazole has produced cure rates of 93% to 100% at a dosage of 10 mg/kg daily for 7 days. Although some studies have suggested that it may not be as effective as praziquantel, it has fewer side effects.

Treatment success is defined by the disappearance of fluke-induced symptoms and fecal egg output, reduction in liver size, and a reversal of biliary tract abnormalities. Recurrent pyogenic cholangitis is primarily a surgical problem, requiring relief of intrahepatic abnormalities due to strictures, stones, and sludge, and drainage of the associated abscesses. Antibiotics may be necessary to treat the associated sepsis, and praziquantel is used to eradicate the remaining flukes.

FASCIOILIASIS

Among the Fasciolidae there are two human flukes: Fasciola hepatica, the most common and widely distributed, and Fasciola gigantica, a fluke of much more focal distribution. Both have similar life cycles and produce similar human disease, but F. gigantica can be recognized by its larger adult and egg sizes.

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The adult F. hepatica is a large fluke (30 mm long × 15 mm wide), flat and leaflike along the margins, with a cephalic cone (Fig. 117-3A). As for other flukes, size, shape, and integumental and internal morphology are species-defining features. The adult fluke lives in the common and hepatic bile ducts of the human or animal host, and eggs reach the exterior via the sphincter of Oddi and the intestine. The eggs are large (130 to 150 µm × 60 to 90 µm), ovoid, and inconspicuously oculcinate (Fig. 117-3B). In water, miracidia hatch from the eggs and penetrate suitable snail hosts where, after multiplying as sporocysts and redia, they leave the snail as free-living cercaria.
These attach to suitable plants, evolve into metacercarial cysts, and when ingested by the human final host, excyst in the duodenum. The larvae migrate through the small intestinal wall and through the peritoneal cavity where they penetrate the liver capsule and slowly migrate to the large hepatic ducts. This prepatent period lasts 3 to 4 months. Anecdotal reports suggest that the life span in the human host can be up to 10 years.

**EPIDEMIOLOGY**

*F. hepatica* has been reported from 61 countries worldwide, especially in sheep-raising areas. More than 2 million people are infected, mostly in Bolivia, Peru, Iran, Egypt, Portugal, and France. A variety of freshwater plants upon which metacercariae encyst, such as watercress, water lettuce, mint, and parsley, are important sources of human infection because they are often eaten raw in salads. Over 25 species of amphibious lymnaeid snails serve as the first intermediate host for *F. hepatica*. The most important is *Lymnaea truncatula*, which lives in wet mud along the shoreline, rarely in fast-moving or deep waters. The major natural reservoirs for *F. hepatica* are cattle, sheep, goats, buffalo, camels, llamas, deer, pigs, horses, rabbits, and other wild animals. It is not uncommon to find high levels of infection with *F. hepatica* or *F. gigantica* in domestic and wild ruminants of endemic areas; prevalence rates of 25% to 92% are seen in Bolivia, 20% to 40% in Ecuador, 10% to 100% in Peru, and 20% to 40% in Iran. In humans, stool- or antibody-positive prevalence rates in these countries can be similarly high (65% to 92% in Bolivia, 24% to 53% in Ecuador, 2% to 17% in Egypt, and 10% in Peru).

**DISEASE**

The clinical presentation of infection with *F. hepatica* reflects its peregrinations in the human host. Hepatic transit, variably called the hepatic, larval, invasive, or acute stage, lasts several months. This is followed by the biliary, adult, or chronic stage, which can persist for years. Where repeated ingestion of metacercaria occurs over an extended period, these two stages can overlap.

**Acute Hepatic (Invasive) Stage**

Within 6 to 12 weeks of ingestion of metacercariae, symptoms occur that reflect larval migration through the small intestinal wall, the peritoneal cavity, and liver capsule. This acute stage can last for 2 to 4 months. One large study revealed typical findings of fairly marked eosinophilia (95%), abdominal pain (65%), intermittent fever (60%), malaise and weight loss (35%), urticaria (20%), and cough, dyspnea, and chest pain (15%). A change in bowel habits, anorexia, and nausea may occur. The abdominal pain may be generalized but frequently becomes localized to the right hypochondrium. Hepatomegaly is a variable finding, and the liver may be tender on palpation. In some cases, mild elevations of hepatic enzymes are noted. The pulmonary symptoms may be associated with right-sided pleural effusions, which, on aspiration, reveal increased eosinophils. Anemia has been reported.

Ultrasound examination of the liver in the acute stage is usually normal although small amounts of ascites have been found. CT scans frequently reveal single or, more frequently, multiple small hypodense lesions 2 to 10 mm in diameter. In addition, tunnel-like, branching, hypodense lesions (best delineated with contrast), most frequently situated peripherally
within the liver, are relatively specific for fascioliasis, representing the pathologic changes created by the migration of the immature fluke through the liver. The hepatic lesions are remarkable in that, on sequential CT scans, the position, attenuation, and shape of the lesions change over time. On laparoscopy, multiple gray-white and yellow nodules 2 to 20 mm in diameter and short vermiform cords are noted on the liver surface and at times on the adjacent peritoneal surface. Liver biopsies reveal microabscesses and tunnel-like areas of parenchymal necrosis surrounded by inflammatory infiltrates containing abundant eosinophils. Necropsies reveal multiple subscapular cavities 5 to 10 mm in diameter filled with necrotic material from which necrotic tracts radiate. Increasing fibrosis is seen in older lesions.

Rarely, immature flukes may migrate to nonhepatobiliary locations such as the skin, lung, intestinal wall, brain, and genitourinary tract, where granulomatous nodules or small abscesses lead to local clinical findings. Migrating erythematous 1.5- to 6.0-cm cutaneous nodules are another form of cutaneous larva migrans.

### Chronic Biliary (Obstructive) Stage

_F. hepatica_ has a propensity to migrate to the lumen of the common bile duct, where it reaches maturity. Eggs appear in the stool after a prepatent period of 3 to 4 months. Clinical findings reflect this new luminal location in that the liver-destructive phase of the infection ends. Fever, anorexia, and abdominal pain resolve, and the patient may become asymptomatic. Eosinophilia is infrequent. An unknown percentage of these cases develop the complication of intermittent biliary obstruction with symptoms that can include intermittent pain...
in the epigastrium or right hypochondrium, mimicking biliary colic or acute cholecystitis. At times the presentation is that of ascending cholangitis with fever, jaundice, and upper abdominal pain.

Ultrasound examination (more effective than CT examination at this stage) often reveals a soft intraluminal mass obstructing the extrahepatic biliary tree. Lithiasis of the common bile duct and gallbladder is a common sequela.

**PATHOGENESIS AND IMMUNITY**

Morbidity from *F. hepatica* is dependent on the number of worms and stage of infection. The characteristic hepatic (and extrahepatic) changes of fascioliasis result largely from the anatomic location and large size of the parasite, a foreign body that induces eosinophilic and mononuclear infiltration around the eggs and adult worms. As in other tissue-invasive helminthic infections, fascioliasis is associated with prominent eosinophilia, particularly in the early stages of infection. As with most helminths, immune responses to *F. hepatica* appear to be regulated by a subpopulation of T-helper cells designated as subtype 2 (Th2) cells, characterized by secretion of interleukin (IL)-4, IL-5, and IL-10. This pattern of T-helper cell response also appears to regulate granuloma formation and liver disease in schistosomiasis. However, the roles of T-cell- and other non-antibody-mediated effector systems in killing of the parasite and in the development of pathologic changes are not well understood.

The role of eosinophils in parasite killing is also unclear, although it has been noted that the invasive phase in the liver is associated with peripheral eosinophilia and eosinophilic infiltrates around the sites of parasites and eggs in the liver. Recombinant parasite-derived molecules have been used to vaccinate the host before challenge with infective stages of the parasite.

Immune evasion mechanisms are likely to play an important role in the survival of this long-lived parasite, and several evasion strategies have been proposed. The surface glycocalyx may mediate immune evasion in several ways. First, the glycocalyx changes in composition during development of the parasite. Second, the glycocalyx is continuously sloughed off by the maturing juvenile worm, by one estimate every 3 hours, thus presenting a moving target. Third, glycocalyx released from the surface can mop up circulating antibodies, interfering with immune effector functions that involve them, such as antibody-dependent cellular toxicity (ADCC). Other relevant strategies include migration away from inflammatory cells, inhibition of oxygen radical generation by macrophages and inhibition of T-cell function. Natural resistance to fatal infection with *F. hepatica* has been observed in sheep and several strains of mice. Relative resistance to infection in mice correlates with type 1 (IFN-γ) responses, whereas type 2 responses are associated with susceptibility. Protection from challenge infection in mice and rats can be transferred by passive transfer of serum, but this protective effect is limited to sera collected 7 to 8 weeks post–donor infection; after 25 weeks, serum from infected rats gave no protection, presumably owing to a decline in titers that accompanies the entry of the parasite into bile ducts. Several potential vaccine antigens have been identified from animal models of *F. hepatica* infection. Defined antigens that are targets of antibody responses include fatty acid-binding proteins, glutathione-S-transferase (GST), cathepsin-L, and fluke hemoglobin. Two molecules have
been shown to confer partial resistance to infection in experimental infections. One is a GST, and the second is a 14.7-kD polypeptide (Fh15) that has significant homology to, and cross-reacts with, Schistosoma mansoni fatty acid–binding protein. The F. hepatica GST has been shown to protect sheep against experimental infection. Overall, vaccine studies, using cocktails of recombinant antigens in animal models of fascioliasis, have shown that significant reductions in worm burdens (31% to 72%) and egg production (69% to 98%) can be achieved.

**DIAGNOSIS**

F. hepatica eggs are not found in stool specimens during the acute phase. The diagnosis must be based on the clinical findings of persistent pain and tenderness in the right hypochondrium or epigastrium, altered intestinal function, mild to moderate fever, and blood eosinophil counts in the thousands per microliter. CT scans (ultrasound is less sensitive) contribute to the diagnosis, since the majority of symptomatic patients have visible hypodense lesions and tracts in the liver and over time these lesions change in position and contour. The differential diagnosis of this clinical and radiologic syndrome includes visceral larva migrans caused by Toxocara canis, which usually also shows pulmonary symptoms. Needle biopsies of the liver have not been used for diagnosis. Laparoscopy may reveal elongated nodules in the liver capsule.

In the acute invasive period, lasting 3 to 4 months, immunologic techniques are valuable diagnostic tools. Skin tests using adult worm antigens or purified fractions of F. hepatica were used in the 1960s and 1970s; these tests were sensitive but not very specific. Other tests have been employed with varying success, including complement fixation (CF), immunofluorescent (IF) assays, indirect hemagglutination (IHA), enzyme-linked immunoblot transfer assay, has been used to detect circulating secreted proteins, is a first-generation vaccine. There have been attempts to improve the specificity of immunodiagnosis have used IgG subtype antibody levels instead of total IgG. Subtype analysis of antibody responses to excretory-secretory antigens such as the cathepsin protease (cathepsin L1) demonstrated that the predominant subtypes induced in human infections are IgG1 and IgG4, consistent with a predominant type 2 T-cell response. The detection of subtype-specific antibodies in ELISAs may improve the specificity of the diagnostic immunoassays and make it possible to distinguish recent from remote infections.

In chronic biliary fascioliasis, the diagnosis is made on finding F. hepatica eggs in stool specimens or at the time of surgery for bile duct obstruction when eggs or adult flukes are removed from the biliary tree. Because egg production tends to be low, it is advisable to examine multiple stool specimens. The formalin–ethyl acetate concentration technique appears to be less sensitive than the AMS iii (Twee 80) method or the Weller-Dammin modification method. Eggs of F. hepatica can be confused with those of the intestinal flukes Fasciolopsis buski and echinostomes. Recovery of adults after anthelmintic treatment will allow species identification. False-positive “spurious” stool results can occur after consumption of liver of infected animals and can be ruled out by repeated stool examinations.

**TREATMENT AND VACCINATION**

Triclabendazole, a benzimidazole, is now the drug of choice as a single 10 mg/kg oral dose or two doses 12 hours apart. Bioavailability is increased when triclabendazole is taken with food. Efficacy has been as high as 92% in humans, but significant resistance has been seen both in animal and in vitro studies and repeat treatment may be necessary. The most frequent side effect was colicky abdominal pain between days 3 and 7 posttreatment, compatible with fluke expulsion through the bile ducts.

Unlike other trematodes, F. hepatica is frequently resistant to praziquantel, although some studies have shown effectiveness. Animal studies show a lack of effectiveness of praziquantel against both immature and adult flukes in cattle and sheep. In the past bithionol has been considered the drug of choice at a dosage of 30 to 50 mg/kg/day in three divided doses on alternate days for 10 to 15 days. More than one course may be necessary. Side effects are mild and include anorexia, nausea, vomiting, abdominal pain, and pruritus.

Acute ascending cholangitis must be treated with antibiotics and surgery. A patient with a severe acute hepatic stage may benefit from the short-term use of systemic steroids. Other drugs used in the past include emetine, dehydroemetine, chloroquine, albendazole, and mebendazole, but all have been dropped because of toxicity or lack of effectiveness.

Fasciola is one of few trematodes for which vaccines have been developed and used to protect against veterinary disease. The F. hepatica cathepsin-L protein, an important virulence determinant that was identified as a dominant antigen in excreted-secreted proteins, is a first-generation vaccine. There have been a number of trials using this molecule in cattle and sheep, with protection against challenge infection ranging from 38% to 70%. In natural and experimental infections, F. hepatica induces a polarized Th2 response as evidenced by the generation of IgG1, but little or no IgG2, antibody subtypes, whereas vaccination induces antibody responses to cathepsin-L, the immunogen, that include high titers of both IgG1 and IgG2, indicating a mixed Th1/Th2 response. These observations have been interpreted to indicate that protection is associated with a Th1 or a mixed Th1/Th2 response. However, some vaccine trials with the same antigen have demonstrated...
little or no protection, suggesting that other factors, such as adjuvant and antigen formulation, may be important in generating protective immune responses. No vaccines have yet been developed for human infections.

**LUNG FLUKES**

**INTRODUCTION**

Lung flukes are members of the genus *Paragonimus* and while more than 40 species have been described, only eight are presently considered of human importance. Most of the 40 species are parasites of animals, and some may be synonymous. Twenty-eight are considered distinct species, with 21 from Asia, 2 from Africa, and 5 from the Americas; most are in tropical areas.

*P. westermani* is the best-known species and is found in humans and animals throughout the East, from India to Japan and the Philippines. *P. heterotremus* is reported from China and Southeast Asia, *P. skrjabini* and *P..huieitungensis* from China, *P. miyazaki* from Japan, *P. uterobilateralis* and *P. africanus* from central and western Africa, *P. mexicanus* from Central and South America, and *P. kellicotti* from North America.

**AGENT**

*P. westermani* was first found in a Bengal tiger that died in an Amsterdam zoo and was named after the zoo director, G. F. Westerman. The first human infection was found in a Portuguese sailor who died in Taiwan in 1879. He had earlier been a patient of Patrick Manson’s in Amoy, China, and Manson later concluded that the hemoptysis seen in this man and his Chinese patients was due to this parasite.

Adult *P. westermani* is reddish-brown in color, coffee bean–shaped, 7 to 16 mm in length, 4 to 8 mm in width, and 5 mm thick. The integument is spiny, and the anterior and ventral suckers are of equal size (Fig. 117-4A).

The eggs are yellow-brown in color, thick-shelled with a large operculum, and measure 80 to 120 µm × 50 to 65 µm (Fig. 117-4B). The eggs embryonate in water, and the miracidia hatch in 3 weeks and search for specific snail hosts. Development in snails yields free-swimming cercariae, which penetrate a crab or crayfish second intermediate host and encyst as metacercariae. When these are eaten raw, partially cooked, pickled, or salted, the metacercariae excyst and penetrate the intestinal wall of the definitive hosts and enter the peritoneal cavity. The larval worms remain here for several days, then cross the diaphragm, and enter the pleural cavity and eventually the lung parenchyma to mature to adults in 2 months. A fibrotic cyst wall develops around paired (or tripled) adults, but eggs that are produced escape through cyst-bronchial fistulas and are coughed up in sputum or swallowed and passed in the feces.

Other species of *Paragonimus* have life cycles similar to *P. westermani* but develop in different snail and crustacean intermediate hosts. Species differentiation is based on adult fluke rather than egg morphology.

**EPIDEMIOLOGY**

*Paragonimus* transmission occurs most notably in China (*P. westermani, P. skrjabini, P. heterotremus, and P. huieitungensis*), Korea (*P. westermani*), Japan (*P. westermani, P. miyazaki*), Vietnam (*P. heterotremus*), Cameroon (*P. africanus and P. uterobilateralis*), Ecuador (*P. mexicanus*), and Peru (*P. mexicanus*). Yet the range of each of the species includes
As an example, *P. westermani* is endemic to China, Japan, Korea, Taiwan, and the Philippines, and the parasite has also been found in Nepal, Bangladesh, Myanmar, Laos, Kampuchea, Vietnam, Thailand, Papua New Guinea, and the former USSR. *P. uterobilateralis*, while most prevalent in Cameroon, is found from Zambia west to Guinea. *P. mexicanus* is found from Mexico south to Peru and Ecuador.

In China, human disease caused by *P. westermani*, *P. skrjabini*, and *P. heterotremus* has been reported from 21 provinces with prevalences of up to 10.4% in some areas. Stool examination surveys of 146,698 people from seven prefectures between 1954 and 1968 yielded an egg-positive rate of 10.4%. Control programs in China had reduced the parasitosis to an estimated 1000 persons infected in 1991. In Korea, a national skin test survey revealed an overall prevalence of 13% in 1959. Control measures, disruption of the ecosystem, and pollution have reduced crab and crayfish populations, and only 16 of 16 million stools were egg-positive in 1990. Taiwan had several endemic foci in the past, but today human infections are rare owing to changes in eating habits and the effect of water pollution and industrialization on the intermediate hosts. Fewer than 300 human cases of paragonimiasis have been reported from a few areas of the Philippines, although infected crustaceans are easily found in endemic areas. Little epidemiologic information is available from other countries reporting this parasitosis. Despite the reductions in Southeast and East Asia, it has been estimated that there are 20.5 million cases worldwide.

More than 15 species of snails in the families Hydrobiidae, Thiaridae, and Pleuroceridae serve as the first intermediate hosts of *P. westermani*. The important second intermediate hosts are crabs in the genera *Eriocheir*, *Potamon*, and *Sundathelphusa*, and crayfish of the genus *Cambaroides*. Individuals become infected by eating these crustaceans raw or insufficiently cooked. The range of culinary artistry is wonderful. In China there is wine-soaked freshwater crab, crayfish curd, raw crab juice, and crab jam; in Thailand, raw freshwater shrimp salad or crab sauce; in Korea, raw crab in soy sauce; in the Philippines, roasted or raw crabs and crab juice seasoning. Crabs and crab juice have been used for medicinal purposes.

*Paragonimus* species can infect many mammalian species, but some will not mature in these hosts beyond the larval stage. When humans consume these paratenic hosts, the larvae survive stomach acid and penetrate the small intestine wall, completing their life cycle in the human host. Paratenic wild boars have served as a source of infection when eaten raw.

**DISEASE**

The different *Paragonimus* species each appear to have a different disease spectrum. *P. westermani* represents one clinical pole, with, most commonly, pleuropulmonary disease and relatively infrequent extrapulmonary disease. *P. heterotremus*, *P. africanus*, and *P. uterobilateralis* appear to be similar in presentation to *P. westermani*. The other clinical pole, represented by *P. skrjabini*, is mainly extrapulmonary, with cutaneous lesions the most frequent clinical presentation. Pulmonary disease tends to be caused by adult flukes and cutaneous disease by immature flukes. It is thought that host-fluke species compatibility helps determine which clinical pole a particular species will produce.

**Acute Paragonimiasis**

After an incubation period of between 2 and 15 days, the initial symptoms are diarrhea and abdominal pain, followed several days later by fever, chest pain, fatigue, urticaria, eosinophilia, or cough, or any combination of these, lasting several weeks.
Pleuropulmonary Paragonimiasis

Although acute paragonimiasis may occur, most infections are either silent or insidious in onset. The initial clinical presentation occurs early in the 5- to 10-year life span of the adult fluke, but in some cases it may occur many years after acquisition of the infection.158,159

In *P. westermani* infections, the initial presentation is often an abnormal chest film in an asymptomatic patient. Early clinical symptoms include cough or chest pain. The cough, initially dry, often becomes productive of viscous and rusty-colored or blood-tinged sputum and appears to be worsened by exertion.160 The sputum may be peppered with rusty-brown flecks consisting of clumps of eggs.2 Charcot-Leyden crystals are frequent. Occasionally there is profuse hemoptysis following paroxysmal coughing. The chest pain is often pleuritic. Fevers are infrequent and in spite of a prolonged clinical history the patient’s health usually remains relatively unimpaired. Eosinophilia may be present initially but is usually absent in chronic infections.

Radiographic findings include pulmonary lesions such as focal, segmental, or lobar air space consolidation, small cysts (5 to 30 mm), calcified spots, linear opacities, or nodules. The earliest infiltrates and nodules may show some limited migration.158,161 About 10% to 40% of egg-positive patients will have normal chest films.160 As the fluke matures, cavitary lesions of 1- to 4-cm diameter are seen, as the fibrotic reaction increases with time they appear as nodules, but their cavitary nature and associated burrow tracts of 0.5- to 1.0-cm diameter can be
visualized by CT scan. Eventually these lesions are replaced by oval to round calcifications.\textsuperscript{158} Bronchoscopy, other than as a means of retrieving eggs, does not reveal any diagnostic findings.\textsuperscript{158}

Pleural lesions have been found in 5% to 71% of patients in different clinical series of \textit{P} \textit{westermani} infections and include effusions, hydropneumothorax, and pleural thickening, which can be bilateral.\textsuperscript{158,159,162} The frequency of pleural disease appears to be greatest in \textit{P} \textit{skrjabini} infections.\textsuperscript{155} Pleural fluid is sterile, contains a leukocyte count over 1000/µL, many eosinophils, and elevated protein and lactate dehydrogenase (LDH) and decreased glucose values. Eggs are rarely found in sputum or pleural fluid.

Excised pulmonary lesions reveal a wide variety of histopathologic changes characterized by the presence of adult worms within fibrous cysts up to 1.5 cm in size, juxtaposed and often communicating with bronchioles or bronchi. Egg-induced granulomas are easily confused with tuberculosis. Adjacent to the cysts are bronchiectases, various pneumonic processes, and vasculitis. Both acute and chronic cellular reactions can coexist within the same lesions.\textsuperscript{159,160,163}

### Extrapulmonary Paragonimiasis

A percentage of patients with paragonimiasis will develop lesions in locations other than the lung. The frequency is dependent on the species of \textit{Paragonimus}, the intensity of the infection, and possibly the duration. The diagnosis of these ectopic infections depends on the organ involved; cerebral infection produces the most frequent morbidity.

#### Cerebral Paragonimiasis

Cerebral paragonimiasis is the most frequent form of extrapulmonary disease diagnosed, possibly reflecting the sensitivity of the central nervous system (CNS) to such an insult rather than a predilection of the parasite for that site. Cerebral involvement occurs in less than 1% of cases in community-based studies and up to 24% in hospital-based studies.\textsuperscript{164} Cerebral paragonimiasis most often occurs in younger age groups, 90% of patients are less than 30 years of age.\textsuperscript{167} Clinical findings in cerebral paragonimiasis are extremely varied, since they are dependent on the location of the parasite. They reflect parasite-induced meningitis, arachnoiditis, and cerebral and spinal space-occupying lesions. Meningitis tends to be acute in onset and to be the initial presentation of cerebral paragonimiasis in up to a third of cases. Intracerebral lesions occur usually in occipital or temporal lobes, or both. The clinical presentation, which tends to be insidious in onset, includes a history of seizures (80%), visual disturbances (60%), headache (55%), motor weakness (48%), sensory disturbances (40%), and vomiting (33%). Seizures are often focal motor initially, progressing to grand mal as the disease evolves.\textsuperscript{165,166} Physical findings include ophthalmologic abnormalities (75%), a decline in mental function (70%), hemiparesis (60%), and hemihypoesthesia (45%). Pulmonary paragonimiasis is seen in the majority of cases of CNS disease and, in fact, precedes CNS involvement in two thirds of patients.

Plain films show calcifications and characteristically aggregated, round or cyst-like soap bubbles in more than 40% of patients. Common CT and MRI findings are conglomerated, multiple ring-shaped enhancing lesions with surrounding edema, described as grape clusters.\textsuperscript{142} These rings are usually smooth and round, but may, at times, be irregular in outline. They are usually 1 to 3 cm in diameter and have contents with a density equal to or slightly greater than that of cerebrospinal fluid (CSF). At times hemorrhages up to 4 cm in diameter are associated with the ringlike structures, or the lesions may be nodular. Calcifications can be punctate, round, cystic, or amorphous and will increase in frequency with the duration of disease.\textsuperscript{168,165,167}

#### Cutaneous Paragonimiasis

Although a cutaneous presentation is uncommon in \textit{P} \textit{westermani} infections, it has been reported to occur in 80% of infections due to other species of \textit{Paragonimus} (e.g., \textit{P} \textit{skrjabini}, \textit{P} \textit{miyazakii}). The cutaneous presentation, which has been called trematode larva migrans, consists of painless and migratory subcutaneous swellings or subcutaneous nodules on the trunk and proximal extremities.\textsuperscript{168,169} There is often a peripheral blood eosinophilia, which can be extreme.

#### Miscellaneous Sites

Flukes, usually immature, may come to rest in ectopic intra-abdominal sites such as the liver, spleen, peritoneum, intestinal wall, or mesenteric lymph nodes. The clinical picture reflects the site and can include abdominal pain, diarrhea, and even dysentery.

### PATHOGENESIS AND IMMUNITY

As with other tissue-dwelling trematodes, infection with \textit{P} \textit{westermani} is also associated with eosinophilia and leukocytosis in the early stages of infection, reflecting activation of the immune system. Eosinophil infiltration around the sites of egg deposition is a consistent pathologic feature, as is eosinophilia and an elevated IgE level, indicative of a Th2 cell-regulated response.\textsuperscript{170} IgG\textsubscript{4} antibodies predominate among anti-\textit{Paragonimus} antibodies. However, it remains to be determined whether Th2 lymphocytes play an important role in resistance to the parasite.\textsuperscript{170} In rodent models, excreted-secreted products of \textit{Paragonimus} appear to regulate the innate and adaptive immune response in the host, by mechanisms such as attenuating the survival and function of eosinophils, and secreting pro-inflammatory cytokines and chemokines.\textsuperscript{171–174} However, these immune mechanisms have been studied only in rodent and bovine models of paragonimiasis, and their roles in human infections have not been elucidated.

### DIAGNOSIS

Pulmonary paragonimiasis must be suspected in persons from known endemic areas when a chronic cough is present, the most important differential diagnoses are tuberculosis, bronchiectasis, and chronic bronchitis. The diagnosis is almost always made by finding the characteristic eggs in sputum, stool, gastric aspirates, or tissue. Examination of blood-streaked sputum is the most productive. Egg detection in sputum may
require repeated examinations, and a 24-hour sputum collection can increase the sensitivity.175 This collection is centrifuged, the sediment dissolved in 3% sodium hydroxide, and then examined for eggs.147 In children and the elderly, in whom sputum swallowing is more frequent, the examination of stool and gastric aspirate specimens can be more productive. Ziehl-Neelsen stains of specimens for mycobacteria may destroy the fluke eggs, making separate examinations necessary.161 In patients who have pleural or CNS involvement, it is very uncommon to find eggs in pleural fluid or CSF aspirates.

Immunodiagnosis

Most immunologic tests used in the diagnosis of paragonimiasis employ crude extracts of flukes.114 The CF test has been a standard test for years. This test is sensitive and becomes negative 6 to 12 months after cure, making it useful for follow-up therapy.176,177 Some cross-reactivity with other trematode parasites has been noted, particularly in the chronic phase of paragonimiasis.178 A skin test using extracts of adult Paragonimus is useful for screening in epidemiologic surveys because of its high sensitivity (80% to 90%), but it remains positive 10 to 20 years after cure.179 ELISAs for detection of antibodies to P. westermani are both sensitive (92%) and highly specific (greater than 90%), but require longer (4 to 24 months) to become positive after infection and longer to normalize after cure.180–183 Crude worm extracts do not provide an acceptably specific ELISA.184,185 Consequently, the most sensitive ELISA to date has been developed by Centers for Disease Control and Prevention (CDC; sensitivity, 96%; specificity, 100%), using an 8-kD component of P. westermani as the antigen.186 Recently, antigen detection assays have been developed that utilize mixtures of monoclonal antibodies to capture P. westermani antigens from serum, with a sensitivity approaching 100% and specificity greater than 95%.187,188 The utility of these assays in the field remains to be evaluated, but they would likely provide as sensitive a measure of active infections in field surveys as is found in individuals.

TREATMENT

Praziquantel is the drug of choice because of minimal side effects and the short course of administration. A treatment of 75 mg/kg/day in three divided doses for 2 days is 90% to 100% effective.158,160,189,190 Symptoms improve within 2 to 3 days, although radiologic findings may worsen for the first 10 days.161 Adverse effects are mild and include headache, intestinal symptoms, and transient urticaria. Large pleural effusions may require drainage. Surgical intervention may be required for long-standing effusions (years) or empyemas (months).190

Triclabendazole, a drug recently introduced as therapy for fascioliasis, successfully treats pulmonary paragonimiasis at a dosage of 5 mg/kg daily for 3 days or 10 mg/kg bid for 1 day.191 Binthionol, available in the recent past, could cure 92% of pulmonary cases at a dosage of 40 mg/kg/day on alternate days for 10 to 15 doses.192 Gastrointestinal side effects in 70%, dermatologic side effects in 21%, and the duration of treatment are recognized limitations.

Untreated pulmonary paragonimiasis can resolve in 5 to 10 years, leaving dysfunction commensurate with the degree of scar tissue produced in the pleura or lungs.158

INTESTINAL FLUKES

About 70 trematode species are reported to inhabit the human intestinal tract. Knowledge of their clinical presentation is limited even for those that affect relatively large populations.1,193 The best known are Fasciolopsis buski; the Heterophyidae, including Heterophyes heterophyes and Metagonimus yokogawai; and several Echinostoma species. The intestinal flukes are thought to produce no symptoms except when present in very large numbers, which is a rare occurrence. Few cause serious disease, but community-based and case-control studies have yet to be done. Most of these flukes occur in Asia, but foci of these infections occur in other populations throughout the world. They are usually localized in areas where there are freshwater snail vectors and animal reservoir hosts and occur in people with particular dietary habits.194

FASCIOLOPSIS BUSKI

AGENT

F. buski, the giant intestinal fluke, was first found, by Busk, in an Indian sailor in London in 1843. The parasite is found in China, Taiwan, Thailand, Laos, Bangladesh, India, Indonesia, Vietnam, Myanmar, and Kampuchea. The worm is elongated, oval, and fleshy, measuring 20 to 75 mm × 8 to 20 mm × 0.5 to 3.0 mm. Eggs are large, operculate, and unembryonated when passed, and measure 130 to 140 µm × 80 to 85 µm. The miracidia develop in several weeks, hatch from the eggs, and infect planorbid snail intermediate hosts. After development in the snail, cercariae emerge and encyst as metacercariae on aquatic plants. When the plant is eaten, the attached metacercariae excyst and attach to the small intestinal mucosa. The prepatent period is 3 months, and the worms are known to live for 6 or more months in the human. Pigs and dogs act as reservoirs (see following discussion).

EPIDEMIOLOGY

Several planorbid snails serve as the first intermediate host of F. buski; these usually live in muddy ponds and streams, including those found adjacent to slaughterhouses where feces from pigs contaminate the waters. Snails and edible water plants also flourish in these waters. The metacercaria can attach to most aquatic plants, including water caltrop (Trapa bicornis, Trapa natans), water chestnut (Eleocharis tuberosa), water bamboo (Zizania aquatica), water hyacinth (Eichhornia crassipes), water morning glory (Ipomoea aquatica), watercress (Nasturtium officinale), lotus (Nymphaea lotus), and others.195 These plants may be cultivated near homes in water contaminated accidentally or fertilized intentionally with human or pig feces. Pigs are a major reservoir host, but there are some areas where humans are infected while pigs are not. Both ingested plants and water contaminated with detached metacercariae are
sources of infection. Children eating plants during play, especially in rural areas, have the highest prevalence rates.

**DISEASE**

This large fluke attaches to the duodenal and jejunal mucosa and produces local inflammation, ulceration, and small abscesses at the sites of attachment. However, community-based studies reveal no clinical or biochemical differences between lightly to moderately infected cases and controls. Early symptoms, which begin 30 to 60 days after exposure, are epigastric pain, mimicking peptic ulcer disease, and diarrhea. Hunger or anorexia, nausea, and vomiting may occur. Rarely, in heavy infections, edema of the face, abdominal wall, and legs, ascites, and severe prostration have been described. The cause of these is not understood. Large numbers of flukes may cause focal ileus or intermittent obstruction. Eosinophilia is variable but may be marked.

**HETEROPHYIDS (HETEROPHYES SPP., METAGONINUS SPP., ETC.)**

There are a large number of small intestinal flukes less than 2.5 mm long in humans, other mammals, and birds in the families Heterophyidae, Plagiorchidae, Lecithodendridae, Microphallidae, and others. The flukes in the Heterophyidae are the most prevalent and best studied.

**AGENTS**

Of at least 10 human species of intestinal fluke in the family Heterophyidae the three most prevalent are Heterophyes heterophyes, H. nosophis, and Metagonimus yokogawai. Bilharz described the first, H. heterophyes, at the autopsy of a native of Cairo. These are the smallest of the human flukes. They measure 1 to 2 mm in length, are oval to pear-shaped, and have spiny integuments. The eggs are operculate, ovoid, and yellowish in color, measure 27 to 30 µm x 15 to 17 µm, and are very difficult to speciate. The eggs are embryonated when passed and are ingested by a snail intermediate host. Cercariae from the snail enter freshwater fish, encyst as metacercariae, and, when eaten raw, excyst and complete their development to adult flukes within 1 to 2 weeks in the small intestine of humans, other mammals, and fish-eating birds. The prepatent period is only 9 days and the parasite may live for a few months to a year in the final host.

**EPIDEMIOLOGY**

The highest infection rates for H. heterophyes have been reported in Egypt, Iran, and Sudan; for M. yokogawai, in Korea, China, Taiwan, Indonesia, Russia, and Japan; and for H. nosophis, in Korea and Japan. However, there have been reports of these and other heterophyid species in scattered locations around the world, the greatest number occurring in Asia and Southeast Asia. Distributions of the different Heterophyidae greatly overlap. In Korea, of 19 different intestinal flukes reported in humans, 12 are different heterophyid species. The heterophyids are parasites of fish-eating mammals and birds, which, like humans, acquire the infection by eating raw or incompletely cooked freshwater or brackish water fish.

The overall prevalence of M. yokogawai in Japan is low (0.2% to 0.3%), but in some areas the prevalence is high (51% to 75%). In Korea, M. yokogawai infection rates of 1% to 2% have been reported for the population as a whole, reaching 29% along some coastal streams. Infection rates of M. yokogawai in Taiwan and the Philippines are around 1%. H. heterophyes infects the gray mullet Mugil cephalus in the brackish lagoons of Egypt’s Nile delta. Infection rates can reach 65% in children in villages where these fish are traditionally eaten raw.

**DISEASE**

Nine days on average following ingestion of the metacercaria, dyspepsia, colicky abdominal pain, diarrhea, and eosinophilia may occur. A mild focal inflammatory reaction and superficial erosions are produced at the site of attachment. The flukes appear to live for less than a year. The fluke may penetrate the mucosa, and eggs may embolize from these intramucosal sites via lymphatics to the systemic vascular system. Eggs of three different heterophyid species have been recovered from capillaries of brain, heart, lungs, spleen, and liver, where space-occupying granulomatous lesions induce clinical pathology. Myocarditis can follow the occlusion of myocardial vessels by eggs and the resultant granulomatous and fibrotic host reaction. Thickenened mitral valves containing ova have been reported.

**ECHINOSTOMA SPECIES**

**AGENT**

These trematodes are primarily parasites of birds and mammals but are common among certain populations of Asia. Fifteen species have been reported in humans. The parasites are elongate, tapered at both ends, and 5 to 15 mm x 1 to 2 mm in size. The name derives from a collar of spines in two rows surrounding the oral sucker. The anterior integument is also provided with tiny spines. Eggs are operculate, thin-shelled, and vary in size (83 to 130 µm x 58 to 90 µm). The eggs embryonate in freshwater in 14 days, and the miracidia enter the snail host. Cercariae emerge from the snail and encyst in the same snail from which they emerged or in other snails, clams, fish, or tadpoles, which serve as second intermediate hosts. Any of these, if eaten uncooked, infect the human final host.

**EPIDEMIOLOGY**

The most common of the 15 reported Echinostoma species in humans are E. ilocanum in the Philippines and Thailand, and both E. malayanum and E. revolutum in Thailand. In northern Luzon in the Philippines, E. malayanum infection rates have averaged 10% of surveyed populations, with highs of over 40%. In northern Thailand, a variety of echinostomes infect humans with prevalence rates as high as 50%. These and the other species are found at lower prevalences in Southeast Asia, eastern and South Asia, and also in Egypt and Central and South America. The major source of infection...
with *E. ilocanum* is the snail *Pila conica*, which is eaten uncooked in parts of the Philippines. Other sources of infections are clams, tadpoles, frogs, and fish, all serving as second intermediate hosts for echinostomes. Rats, dogs, cats, birds, and other fish-eating animals are reservoirs of infection.

**DISEASE**

These flukes attach to small intestinal mucosa, producing inflammatory lesions and shallow ulcers at the sites of attachment. A self-infection by ingestion of 113 metacercaria of *Echinococcus japonicus* resulted, after 10 days, in abdominal pain and diarrhea. There are no clinical epidemiology studies, but it is generally accepted that symptoms are rare in any but the heaviest infections (approximately 500 flukes), which are uncommon. The presentation may include colicky abdominal pain and loose bowel movements and at times diarrhea and eosinophilia.

**MISCELLANEOUS INTESTINAL FLUKES**

There are many other intestinal flukes within the preceding families—Fasciolidae, Heterophyidae, and Echinostomatidae. They have more limited distributions and are less well studied. Two flukes in two other families, Troglotremaidae and Pammphistomatidae, are worth mentioning.

*Neotrypanostoma salmincola* is a small fluke found in eastern Siberia and the northwestern coast of North America. It belongs to the same family, Troglotremaidae, as does *Paragonimus*. Adults are 0.8 to 2.5 mm × 0.3 to 0.5 mm, and eggs are 64 to 97 µm × 34 to 55 µm in size. Fish, such as salmon, are the second intermediate hosts. Intestinal symptoms can occur with heavy infections in a manner similar to that of other intestinal flukes. More unusually, this fluke is a vector for the rickettsial organism *Neorickettsia helminthoea*, which produces a fatal illness in dogs ("salmon poisoning").

*Gastrodiscoides hominis* is a piriform intestinal fluke that is 8 to 14 mm × 5 to 8 mm in size and produces eggs that measure 150 µm × 60 to 70 µm. It is widely distributed from India to the Philippines and north to Kazakhstan. The human colon can be colonized, with resultant mucoid diarrhea. Pigs and rodents appear to be the reservoir.

**DIAGNOSIS**

Since clinical presentations are nonspecific, indications that infections are present are, at times, eosinophilia, a particular dietary history, and the time interval since possible infection; *H. heterophyes* and *M. yokogawai* do not survive in the intestine for more than a year. The diagnosis is made on stool examination or by tissue biopsy or necropsy. Egg identification can be very difficult because many of the intestinal fluke eggs have similar morphology and overlapping sizes. Overlapping "small" fluke eggs include *H. heterophyes* (28 to 30 µm × 15 to 17 µm), *M. yokogawai* (26 to 28 µm × 15 to 17 µm), *C. sinensis* (28 to 35 µm × 12 to 19 µm), and *O. viverrini* (30 µm × 12 µm). Overlapping "large" fluke eggs are *Fasciolopsis buski* (130 to 140 µm × 80 to 85 µm), *Echinostoma* spp. (83 to 130 µm × 58 to 90 µm), and *Fasciola hepatica* (130 to 150 µm × 60 to 90 µm). As well, there are many other less common intestinal flukes with focal distribution that produce similarly sized eggs.

Examination of stools for expelled adult flukes after treatment with praziquantel is necessary to make a definitive diagnosis. Although praziquantel may damage the integument of the adult fluke, it is still often possible to make a species identification.

**TREATMENT**

Evidence from limited trials suggests that praziquantel is highly effective against intestinal flukes at 15 to 25 mg/kg given in a single dose. The new benzimidazole, triclabendazole, at 5 mg/kg twice daily after a meal at a 6- to 8-hour interval for 1 day, shows promise in the treatment of intestinal flukes. Alternative drugs include for *E. buski*, niclosamide 40 mg/kg/day for 1 to 2 days (maximum daily dose of 4 g), for *H. heterophyes*, niclosamide 1000 mg in a single dose; and for *Echinostoma* spp., albendazole 400 mg twice daily for 3 days.

**PREVENTION AND CONTROL**

Prevention and control of food-borne trematode infections require changes in habits that have been in practice for generations. These habits are variably dependent on attitudes, education, poverty, environmental degradation, food security, and other factors, and control strategies will have to take all these into account. Education can change habits. Such education should include understanding of the impact of the use of human and animal feces as fertilizer for aquatic plants and fishponds. Methods of food preservation must be addressed, since many foods deteriorate quickly in the tropics, and smoking, pickling, and fermentation methods often do not destroy metacercariae. Irradiation may offer an alternative. Preservation by cooking can be difficult in many heavily populated regions where fuel is scarce. On the other hand, some populations prefer to eat raw food, aware of the nutritional value of raw foods.

National strategies are necessary to control these parasites. Health education and appropriate regulations, both for water bodies used for pisciculture and aquatic plant crops, can have an impact. Mass treatment programs using praziquantel or triclabendazole may be beneficial but require more experience. Molluscicide or elimination of the animal host reservoirs does not appear to be realistic over the long term.
Liver, Lung, and Intestinal Fluke Infections


Liver, Lung, and Intestinal Fluke Infections


