Schistosomes and Other Trematodes

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General Concepts

Clinical Manifestations

Signs and symptoms are related largely to the location of the adult worms. Infections with *Schistosoma mansoni* and *S. japonicum* (mesenteric venules) result in eosinophilia, hepatomegaly, splenomegaly, and hematemesis. *Schistosoma haematobium* (vesical venules) causes dysuria, hema turia, and uremia. *Fasciola hepatica*, *Clonorchis sinensis*, and *Opisthorchis viverrini* (bile ducts) cause fever, hepatomegaly, abdominal pain, and jaundice. Infections with *Paragonimus westermani* (lungs, brain) result in cough, hemoptysis, chest pain, and epilepsy. *Fasciolopsis buski* (intestines) causes abdominal pain, diarrhea, and edema.

Structure

Trematodes are multicellular eukaryotic helminths.

Multiplication and Life Cycle

Free-swimming larvae (cercariae) are given off by infected snails. These either penetrate the skin of the human definitive host (schistosomes) or are ingested after encysting as metacercariae in or on various edible plants or animals (all other trematodes). After entering a human the larvae develop into adult males and females (schistosomes) or hermaphrodites (other flukes), which produce eggs that pass out of the host in excreta. These eggs hatch in fresh water into miracidia which infect snails.

Pathogenesis

In schistosomiasis, eggs trapped in the tissues produce granulomatous inflammatory reactions, fibrosis, and obstruction. The hermaphroditic flukes of the liver, lungs, and intestines induce inflammatory and toxic reactions.

Host Defenses
Host defenses against schistosomiasis include antibody or complement-dependent cellular cytotoxicity and modulation of granulomatous hypersensitivity. The defenses against hermaphroditic flukes are unknown.

**Epidemiology**

Most infected individuals show no overt disease. In a relatively small proportion of individuals, heavy infections due to repeated exposure to parasitic larvae will lead to the development of clinical manifestations. The distribution of flukes is limited by the distribution of their snail intermediate host. Larvae from snails infect a human by penetrating the skin (schistosomes) or by being eaten (encysted larvae of other trematodes).

**Diagnosis**

Diagnosis is suggested by clinical manifestations, geographic history, and exposure to infective larvae. The diagnosis is confirmed by the presence of parasite eggs in excreta.

**Control**

As a control measure, exposure to parasite larvae in water and food should be prevented. Treatment with praziquantel is effective.

**INTRODUCTION**

Trematodes, or flukes, are parasitic flatworms with unique life cycles involving sexual reproduction in mammalian and other vertebrate definitive hosts and asexual reproduction in snail intermediate hosts. These organisms are divided into four groups on the basis of their final habitats in humans: (1) the hermaphroditic liver flukes which reside in the bile ducts and infect humans on ingestion of watercress (*Fasciola*) or raw fish (*Clonorchis* and *Opisthorchis*); (2) the hermaphroditic intestinal fluke (*Fasciolopsis*), which infects humans on ingestion of water chestnuts; (3) the hermaphroditic lung fluke (*Paragonimus*), which infects humans on ingestion of raw crabs or crayfish; and (4) the bisexual blood flukes (*Schistosoma*), which live in the intestinal or vesical (urinary bladder) venules and infect humans by direct penetration through the skin.

Fascioliasis is a cosmopolitan zoonosis; sporadic cases in humans have appeared in most parts of the world. The remaining hermaphroditic fluke infections of humans are confined largely to Asia. Schistosomiasis occurs in South America, the Caribbean, Africa, the Middle East, and Asia, and is spreading in many areas due to the introduction of dams and irrigation systems.
Flukes do not multiply in humans, so the intensity of infection is related to the degree of exposure to the infective larvae. In most endemic areas, the majority of infected individuals have light or moderate worm burdens. Overt disease occurs largely in the relatively small proportion of the population with a heavy worm burden, although genetic predisposition may also play a role. Pathology may be caused by the worms themselves (as with liver flukes, which damage the bile ducts) or by their eggs (for example, schistosome eggs, which induce granulomatous inflammation in the venules or tissues). Treatment of all fluke infections has been greatly improved by the introduction of the anthelminthic drug praziquantel.

Clinical Manifestations

Schistosomiasis

Three major disease syndromes occur in schistosomiasis: schistosome dermatitis, acute schistosomiasis, and chronic schistosomiasis. The first is a pruritic rash that appears after repeated exposure to cercariae, usually those of birds and small mammals. Acute schistosomiasis (Katayama fever) begins 4 to 8 weeks after primary exposure and may last for a few weeks. It appears most commonly in *Schistosoma japonicum* infection, is much less common in *S. mansoni* infections, and is seen rarely in patients infected with *S. haematobium*. Acute schistosomiasis is the self-limited febrile illness that occurs on primary exposure to the parasite. It is characterized by cough, hepatosplenomegaly, lymphadenopathy, and eosinophilia. It may be fatal.

A wide variety of symptoms have been associated with chronic schistosomiasis mansoni and japonica, including fatigue, abdominal pain, and intermittent diarrhea or dysentery. Over the past 15 years, however, field studies have demonstrated that few infected individuals seven those with heavy infections show such symptoms. Similar findings were reported in hospitalized patients in the United Kingdom. In schistosomiasis haematobia, dysuria and hematuria are frequently seen in the early stages of infection. Chronic disease may appear many years later, developing usually in individuals with a heavy worm burden. In schistosomiasis japonica and mansoni, chronic disease is characterized by hepatomegaly, splenomegaly, portal hypertension, and bleeding esophageal varices. In schistosomiasis haematobia, inflammation and fibrosis of the bladder and ureters occur; obstruction of the ureters leads to hydronephrosis and eventually to uremia.

Hermaphroditic Flukes

The signs and symptoms of infection with the hermaphroditic flukes are related largely to the location of the adult worms—the bile ducts (*Fasciola hepatica, Clonorchis sinensis, Opisthorchis viverrini*), the intestines (*Fasciolopsis buski*), or the lungs (*Paragonimus westermani*). *Fasciola hepatica* infection is the one exception, in that the disease has two distinct phases. The first occurs in the initial 6 to 9 weeks of infection when the larvae migrate through the liver; the second begins when they enter the bile ducts. The acute clinical syndrome is characterized by prolonged fever, pain in the right hypochondrium, and sometimes hepatomegaly, asthenia, and urticaria; also marked eosinophilia usually occurs during this period. Asymptomatic acute infection has been reported in England and seems to be common in Peru. After the flukes enter the bile ducts, the symptoms decline and then disappear completely. Although animals with particularly heavy worm burdens may develop chronic biliary tract disease, this
condition is rare in humans, and when reported is usually an incidental finding at surgery or autopsy.

In contrast, an acute syndrome does not occur in clonorchiasis and opisthorchiasis because the larval flukes enter directly into the bile ducts. Most individuals with Clonorchis and Opisthorchis infections show no significant signs or symptoms of disease. Pathologic studies have revealed no gross changes in the liver in mild, early infections. Despite these generally negative findings, patients with severe chronic disease, manifested by cholangitis, cholangiohepatitis and cholangiocarcinoma, occasionally appear at hospitals.

Fasciolopsiasis caused by the intestinal fluke also appears to be associated with few or no disease manifestations in individuals examined in field environments. In a controlled study involving clinical examination, evaluation of growth and development, hematologic studies, and screening tests for intestinal malabsorption, no significant differences between infected and uninfected subjects were found. However, cases of severe clinical illness characterized by diarrhea, abdominal pain, edema (often facial), and passage of undigested food in the feces have been reported in patients with heavy infections.

Paragonimiasis due to the lung fluke usually comes to the attention of the physician when the patient complains of cough or intermittent hemoptysis. Profuse expectoration and chest pain of a pleuritic type are also found. Nevertheless, clinical studies indicate that in most endemic areas most infections are light or moderate and are associated with few signs or symptoms. Cerebral paragonimiasis is encountered in highly endemic regions and is manifested as Jacksonian epilepsy, tumors, or embolism of the brain.

**Structure and Life Cycle**

The trematodes or flukes are multicellular flatworms. Different species range in length from less than 1 mm to several centimeters. The flukes of medical importance are all digenetic, reproducing sexually in a definitive vertebrate host and asexually in a snail intermediate host. Flukes have a variety of different life cycle stages (Figs. 88-1 and 88-2; also see Ch. 86, Figs. 86-1 and 86-2). Adult male and female or hermaphroditic flukes inhabit the definitive vertebrate host and lay eggs. Free-swimming ciliated miracidia hatch from the eggs and infect snails, in which they give rise to sporocysts and rediae. The snails emit cercariae, which infect the vertebrate host either directly or via an encysted form known as a metacercaria.
FIGURE 88-1 Life Cycle of Schistosome

I. Definitive host: humans passing eggs into the environment

1. Mature eggs reach the freshwater environment in excreta.

2. Miracidium hatches from the egg under optimal conditions of temperature, light and fresh water

and seeks an appropriate intermediate host. Asexual reproduction takes place within the intermediate host.

II. Intermediate Host: aquatic snails

1. Miracidium penetrates the snail's soft tissue and undergoes differentiation into mother sporocysts which produce a second order daughter sporocyst.

2. Daughter sporocyst migrates to the digestive gland where it produces cercariae by asexual reproduction.

3. Motile cercaria emerges from the snail and seeks contact with a vertebrate host.

III. Migrating larvae and other life cycle stages resident in human host tissue
1. Cercaria penetrates through the skin of the vertebrate host where it undergoes transformation into schistosomulum.

2. The schistosomulum undergo growth and differentiation while migrating into the vasculature through the heart, lungs and hepatic portal system.

3. Juvenile worm resides in the hepatic portal system continuing maturation to male and female adults.

4. Adult worms mate in the hepatic portal vessels and migrate to the mesenteric venules where they continuously lay eggs.

5. Some eggs are swept into the precapillary sinusoids of the liver where they become the nidus of a granulomatous reaction.

6. Chronic hyper-responsiveness to soluble egg antigens leads to the immunopathological consequence of "clay pipe-stem" fibrosis.

**FIGURE 88-2 Life Cycle of other Trematodes of Human Health Significance**

I. Definitive Host: humans, ruminants, dogs, cats and other companion animals

1. Operculated - type mature trematode egg with miracidium

2. Free swimming miracidium, life cycle stage infective to snail intermediate host
II. First Intermediate Hosts: operculated amphibious or semi-amphibious snail of the genera *Bulimus* sp; *Pseudofossarulus* sp; *Lymnaea* sp; *Bithynia* sp. and others

3. Sporocyst

4. Mother/daughter redia

5. Free swimming cercariae

III. Second Intermediate Host: (if applicable, i.e., *Opisthorchis* spp.) encysted in the tissue of cyprinid-type freshwater fish

6. Cercariae encysted in the fish's soft tissue

IV. Infective Stage to the Definitive Host

7. Encysted metacercariae on aquatic/semi-aquatic vegetation, i.e., watercress, fodder

**Schistosomes**

Three major species of schistosomes infect humans: *Schistosoma mansoni*, *S japonica*, and *S haematobium*. The adult male and female schistosomes reside in human mesenteric or vesical venules. Fertilized female worms produce large numbers of egg, which pass out of the blood vessels, through the tissues, and into the lumen of the gut (*S mansoni* and *S japonicum*) or urinary bladder (*S haematobium*), from which they are shed into the environment, where they may infect a snail intermediate host. After a period of asexual multiplication in the snail, the cercariae pass out into water from which they directly penetrate into human skin. The young schistosomes migrate from the skin to the lungs and then to the hepatoporal system, where they mature, mate and pass down into the mesenteric or vesical venules (Fig. 88-1).

**Liver Flukes**

*Fasciola hepatica* is a hermaphroditic liver fluke that infects mainly ruminants but may incidentally, infect humans. It resides in the bile ducts of the liver, where it produces large numbers of eggs daily for many years. The eggs pass into the lumen of the small intestine and leave the body in the feces. If deposited in fresh water, the eggs hatch into ciliated miracidia, which, upon penetration of the correct species of snail, undergo several developmental stages and produce large numbers of cercariae. These tailed, free-swimming organisms leave the snail and encyst as metacercariae on the leaves of freshwater plants, particularly watercress. When ingested by the definitive host, the larvae excyst, penetrate through the gut wall into the peritoneal cavity, enter the liver capsule, and begin to wander through the hepatic tissues. This migratory phase continues for about 7 weeks. The half-grown flukes then enter the bile ducts, mature, and begin to produce eggs.

*Clonorchis sinensis* and *Opisthorchis viverrini* are also liver flukes; in the case of these flukes, however, the eggs hatch only after ingestion by certain species of snails, and the cercariae penetrate under the scales or into the flesh of certain freshwater fishes, where they encyst as metacercariae. After they are ingested in raw or inadequately cooked fish,
the organisms excyst within the duodenum and, in contrast to *F. hepatica*, pass directly into the bile ducts through the ampulla of Vater (Fig. 88-2).

**Intestinal and Lung Flukes**

The cercariae of *Fasciolopsis buski*, the intestinal fluke, encyst on certain species of water plants. When ingested, the metacercariae excyst within the duodenum, attach to the nearby intestinal wall, develop into adult worms, and begin egg production. The eggs pass out in the feces into fresh water, where the hatched miracidia penetrate into snails and develop into cercariae. The eggs of *Paragonimus westermani*, the lung fluke, pass into the bronchioles, are coughed up, and are voided in the sputum or swallowed and passed in the feces. After undergoing a period of embryonation, the eggs hatch and the miracidia penetrate into certain species of fresh water snails. Cercariae develop within the snails and then pass out into the water and penetrate crustaceans, in which they encyst. When inadequately cooked freshwater crayfish and crabs are eaten, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and enter the peritoneal cavity, from which they migrate through the diaphragm and pleural cavity into the lungs and, occasionally, into the brain.

**Pathogenesis**

The diseases caused by flukes result from the inflammation, and in most cases fibrosis, elicited by the parasites and their products. The severity of disease is clearly related to intensity of infection, as shown in both experimental models and at autopsy. In schistosomiasis, the adult worms reside in the intestinal venules and produce large numbers of eggs. The embryo is enclosed in a semipermeable membrane, which in turn is protected by a tanned protein eggshell pierced by ultramicroscopic pores. The mature embryo (miracidium) secretes a variety of antigenic molecules, including enzymes.

While approximately fifty percent of the eggs pass through the mucosa into the lumen of the intestine, the rest remain within the mammalian host, many breaking free into the mesenteric veins, from which they pass into the liver via the portal venous system and become trapped in the presinusoidal venules. They survive in this milieu for approximately 3 weeks. During that period the host tissues react to the egg secretions by forming a focal granulomatous lesion of the kind seen in tuberculosis (see Ch. 87, Fig. 87-3). This lesion has been shown to be essentially a cell-mediated immunologic reaction of the delayed hypersensitivity type i.e., based on an anamnestic reaction specific to egg antigens that is transferrable by cells but not by serum. Furthermore, granuloma formation can be suppressed by inhibitors of cell-mediated immune reactivity and do not occur in nude athymic mice. Investigations of granuloma formation around fluke eggs both in vivo and in vitro have demonstrated a high rate of collagen synthesis. That is later balanced by collagen degradation, fibrosis being the net result of both the intensity of infection and an imbalance toward collagen synthesis (see Fig. 87-3). After treatment with drugs that kill the flukes, collagen tends to be resorbed; that occurs at a higher rate in early than in late infections.

Studies of the hepatic microcirculation in experimentally infected animals have revealed that portal venous obstruction is caused not by the eggs alone but by the granulomas around them. Portal vein obstruction leads to portal hypertension, splenomegaly, and the development of esophageal varices. In spite of severe portal venous obstruction, the
total liver blood flow remains within normal limits, as there is marked neovascular formation of arterial vessels in the areas of inflammation and fibrosis.

The typical lesions of advanced hepatosplenic schistosomiasis, called "pipestem fibrosis," consist of enlarged, whitish, fibrous triads surrounding portal vein lumina and resembling clay pipestems in cross section. The liver parenchymal cells appear normal. The spleen may become markedly enlarged and is firm in consistency, fibrotic, and congested. Hypersplenism may occur, with attendant anemia and pancytopenia.

The acute clinical syndrome of *Fasciola hepatica* infection occurs during migration of the fluke larvae in the liver parenchyma, with resultant inflammation and localized destruction of liver cells. Once in the bile ducts, liver flukes of all species produce inflammation due to mechanical irritation and toxic secretions. Highly immunogenic predominant antigens have been found in the eggs of *Opisthorchis*. Studies in humans have revealed hyperplasia of the epithelial cells lining the biliary tract, periductal fibrosis, thickening of the duct wall, and dilation and obstruction of the duct lumen. Secondary infection occurs due to biliary stasis, resulting in chronic recurrent, suppurative infections; cholangiocarcinoma also may occur.

The intestinal fluke *Fasciolopsis buski* attaches to the duodenal and jejunal mucosa. Inflammation at the site of attachment may be followed by ulceration and even bleeding. The flukes affect the secretion of intestinal fluids and mucus. The adults of the lung fluke *Paragonimus* are usually found just beneath the pleural surface, where they induce local necrosis, hemorrhage, inflammation and fibrous encapsulation. These flukes may also be found in other tissues including the brain. In heavy infections a syndrome similar to that of chronic bronchitis occurs, with cough and sputum production, sometimes accompanied by intermittent hemoptysis. Cerebral lesions are characterized by necrosis and an eosinophilic granulomatous reaction.

**Host Defenses**

**Schistosomes**

Host immune responses to infection with schistosomes are complex due to the developmental nature of multicellular-life cycle stages within the definitive host. The antigenic mosaic, presented to the host immune system by the infective cercariae, migrating schistosomula, adult worms and eggs, provides the basis for understanding the complexity of the host immune response as well as a paradigm for generating protective immunity through non-living vaccines. Our understanding of host immunity to schistosomiasis has been generated from data collected from experimental models of infection and vaccination. Based on these data, immune responses to schistosomiasis can be summarized as either anti-egg or anti-worm. Immune responses against antigens that are secreted by the egg stage include granulomatous hypersensitivity, antibody production, anti-fecundity, and transmission blocking immunity. Anti-worm immunity involves both cellular and humoral responses against adult worms and migrating larvae. Some of these responses are characterized as protective and mediate resistance to reinfection.

Granuloma formation around the parasite egg has been intensely studied by numerous investigators, because it plays a central role in the pathology of schistosomiasis.
Experimental models of granuloma formation involve parasite egg embolization into the lungs of rodents, followed by sequential analysis of granuloma size, and immune components. Natural infections of mice with experimentally-induced or genetic immune deficiencies, have been used to delineate the role of certain immune components in granuloma formation. Finally, cytokine responses of egg-specific T cell clones, isolated and characterized from mice and humans, have provided additional information on the role of T helper subset responses to egg antigens.

Recently, the cell mediated components of granuloma formation have been redefined based on cytokine profiles of CD4 helper T cell subsets. Cytokines are signaling molecules that are secreted by lymphocytes and inflammatory cells that act on lymphoid cells to initiate differentiation, proliferation and/or activation. Three major T helper subsets have been defined as Th0, Th1, and Th2 cells. The cytokines IL-2 and IFN-γ define the Th1 subset that predominates in delayed hypersensitivity responses and macrophage activation. The Th2 subset produces IL-4, IL-5, and IL-10 and provides help for B cell differentiation, control of IgE production and eosinophilia. Th0 subset secretes both sets of cytokines and appears as an intermediate undifferentiated subset.

The cytokines that are associated with granuloma formation in response to egg antigens are IL-2, IL-4, and IL-5. The T helper subsets defined by these cytokines are Th0 and Th2. These data do not abrogate a role for Th1 helper cells in immunity to schistosome eggs, since adoptive transfer of murine Th1 T cell clones into naive recipient mice has demonstrated transfer of granulomatous hypersensitivity to eggs. The cellular components in the Th1 T cell clone-induced granuloma were accompanied by Th2-like eosinophilia from probable Th2 subset recruitment into the granulomatous response by the egg-specific Th1 clone. These data illustrate the complexity of interacting cellular immune components in granuloma formation.

As a consequence of long term infection with schistosomiasis, granulomatous hypersensitivity, initiated by continual parasite egg deposition in tissues, undergoes immune modulation. Several mechanisms appear to be responsible for granuloma modulation. The predominance of the Th2 helper subset and IL-10 production renders Th1 helper subsets anergic or unresponsive to antigen. This unresponsiveness is due to IL-10 downregulation of the expression of a macrophage costimulatory molecule, B7. Absence of the B7 ligand prevents delivery of a costimulatory signal from the macrophage to the Th1 cell through the CD28 receptor which would normally activate Th1 cells. This evidence supports the premise that egg-specific undifferentiated Th cells become activated without essential costimulatory signals and therefore do not undergo clonal expansion and differentiation in models of chronic schistosomiasis. Evidence for CD8 T cell involvement in granuloma modulation is based on adoptive cell transfer experiments in the mouse and characterization of some human soluble egg antigen-specific regulatory CD8 T cell lines and clones. The exact mechanism for CD8 T cell involvement remains unclear.

Another manifestation of anti-egg immunity involves egg production, egg viability and egg excretion. Reduction in egg numbers, viability and egg excretion rates associated with specific anti-egg immune responses have been observed in both natural and vaccine models of schistosomiasis. The immune etiology of these phenomena have been confirmed by several investigators, although the exact mechanisms require further elucidation.
Experimental animals demonstrate some degree of resistance or susceptibility to a primary or single infection with schistosomes. The rat is an exceptionally resistant animal model demonstrating low numbers of developing worms even after a massive experimental exposure to thousands of cercariae. The mouse and hamster are at the other end of the spectrum, and develop a larger percentage of worms in response to smaller numbers of infective cercariae.

Acquired resistance is the term used to describe protective immunity, which develops as a result of a primary immunizing infection against adult worms. Although the immune response against adult worms of a primary infection is only partially protective, when that immunity targets larval schistosomes of a secondary challenge infection for immune elimination, it is more evident. Antibody-dependent cellular cytotoxicity involving eosinophils and/or macrophages has been the predominant protective mechanism described in experimental models of acquired resistance. Protective immunity in experimental models of resistance or vaccine models is not complete, as some challenge parasites always survive. Vaccine models of schistosomiasis have evolved from crude antigen-adjuvant mixtures or radiation-attenuated inocula to recombinant vaccines. Studies on resistance to re-infection in mice with known immune defects have shown that protective immunity involved IFN-g and cell mediated immunity. Advances in gene cloning and recombinant DNA technology have produced many defined antigen vaccines. Three of the most promising candidate vaccine molecules are glutathione S-transferase (Sm28-GST), rIrV-5 (myosin-like protein) and triose phosphate isomerase (TPI). All vaccine-candidate antigens induce protective immunity that is incomplete, i.e., some percentage of challenge cercariae will escape protective immune responses and develop to egg-laying adults. Partial protection, however, does reduce the number of surviving worms, therefore reducing the risk of severe disease.

Cross-sectional and longitudinal studies of the clinical, parasitologic, epidemiologic and immunologic aspects of human schistosomiasis, utilizing endemic and hospitalized-based patients, have shown that peak prevalence and intensity of infection occur between the ages of 10 and 30 years. The majority of infected patients in endemic populations are asymptomatic with only 5-10% of the infected population presenting with clinical disease. The chronic responses are in chronic schistosomiasis patients that are clinically classified as asymptomatic or symptomatic exhibiting hepatosplenic disease. Immunologic differences have been documented in egg-specific cellular responses, granulomatous hypersensitivity, cytokine profiles and presence or absence of regulatory receptors or idiotypes on immune T and B cell receptors. Other longitudinal studies of endemic populations have analyzed the distribution of infection intensity before and after drug treatment and natural re-exposure to infective cercariae. These studies have documented that younger people excrete more eggs than older individuals. Additionally, younger people regain heavy infections after treatment and re-exposure while older people do not become reinfected or are reinfected at low levels. The subset of individuals living in endemic areas with documented re-exposure with no evidence of reinfection, or low levels of infection, have been studied for evidence of protective immunity. These studies have shown that anti-parasite IgE levels correlate with low egg output. The importance of the longitudinal endemic population studies cannot be overstated as these data will be used in the design and selection of endemic populations for future vaccine trials.
Hermaphroditic Flukes

With respect to the hermaphroditic flukes, studies of *Fasciola hepatica* in experimental animals have revealed resistance to reinfection. Adoptive and passive transfer of resistance has been achieved with cells and serum. Immunity has also been induced by nonliving vaccines. It is of interest that immunization with *Fasciola* antigens will induce resistance to *Schistosoma* infection and vice versa. The defined antigen responsible for protective immunity in this model is a *F hepatica* 12 kDa fatty acid binding protein and *S mansoni* 14 kDa fatty acid binding protein. Relatively little work in this area has been performed with the other trematodes.

Epidemiology

Trematodes do not multiply directly in humans, but instead mate and produce large numbers of eggs that pass out of the body in the feces, urine, or sputum. Thus, the intensity of human infection is related largely to the rate of exposure to infective larvae, i.e., to the frequency and extent of contact with water and of consumption of contaminated foods. Mathematical models suggest that the intensity of infections in mammalian populations follows a negative binomial distribution, with most individuals having light to moderate infections. In recent years, controlled studies have revealed that most infected individuals show no overt signs or symptoms of disease. Significant disease occurs mainly in the few individuals with a heavy burden of flukes.

Three different species of human schistosome parasites are responsible for two hundred million infections. *Schistosoma mansoni* occurs in South America, the Caribbean, and Africa; *S japonicum* in the Far East; and *S haematobium* in Africa and the Middle East. *S japonicum* is the only species that has significant animal reservoirs. The distribution of all the flukes is limited by the distribution of their snail intermediate host.

*Fasciola hepatica* occurs worldwide in ruminants and causes significant morbidity and mortality in sheep and cattle. For the most part, human infection is sporadic; only a few hundred cases have been reported in the world literature, usually associated with ingestion of wild watercress. Fascioliasis in humans has almost always been identified during the acute migratory stage of infection; occasionally, worms are found in the bile ducts at surgery or autopsy. Foci of chronic human fascioliasis have been found in rural areas of Peru.

*Clonorchis sinensis* and *O viverrini* are common liver flukes of cats and dogs; they also infect many other mammalian hosts. Although humans are incidental hosts, millions of individuals are infected with these organisms. Clonorchiasis is prevalent in China, Hong Kong, Vietnam, Korea, and Taiwan. *Opisthorchis viverrini* infection is widespread in Thailand. Infection with another species, *O fe lineus*, has been reported in many parts of Southeast Asia and Asia as well as Eastern Europe and the Soviet Union. Infection occurs after ingestion of raw or inadequately cooked freshwater fish (saltwater fish do not carry these parasites). *Fasciolopsis buski* is a common parasite of humans and pigs in the Far East and Southeast Asia. Infection results from consumption of the raw pods, roots, stems, or bulbs of certain water plants, often water chestnuts, and is related to the habit of peeling the metacercaria-infested hull of these vegetables with the teeth before consumption.
*Paragonimus westermani* has a cosmopolitan distribution among mammals; human infection is found largely in the Far East. Closely related species have been reported in Africa and in South and Central America. Paragonimiasis is transmitted by eating uncooked freshwater crayfish or crabs.

**Diagnosis**

The anatomic locations of the symptoms and signs suggest a diagnosis of schistosomiasis or of disease caused by the liver, intestinal, urinary tract, or lung flukes. Except in the case of fascioliasis, the geographic history should be of particular value, because all other fluke infections of humans have relatively specific distributions. A careful dietary history is important in the case of the hermaphroditic flukes and provides relatively clear-cut evidence. In diagnosing schistosomiasis, a history of significant contact with fresh water is of diagnostic value.

Demonstrating the eggs of the parasite in the excreta provides the definitive diagnosis in all cases of fluke infection. A quantitative method is of great importance because of the relationship between the intensity of infection and the development of disease. The best method for doing this, which is equivalent in many ways to a concentration technique, is the Kato thick smear method, in which a 50 mg feces sample is placed on a slide covered with a plastic coverslip soaked in glycerol and is allowed to clear for 24 hr. For *S haematobium* infections, Nucleopore filtration of 10 ml of urine is the simplest and most rapid method. Most immunodiagnostic methods are not specific or sensitive enough to assess these infections.

**Control**

A key control measure for all fluke infections is preventing egg-containing excreta from contaminating water sources. Another approach is to control snail populations, largely by the use of molluscicides. For schistosomiasis, contact with infected water should be minimized. For the hermaphroditic flukes, infection can be avoided by careful preparation and cooking of fresh water fish, crustacea, and vegetables. Treatment of all fluke infections other than fascioliasis is accomplished by a one-day course of the oral drug praziquantel. For *Fasciola hepatica*, the current drug of choice is bithional, given orally for 15 days.

**REFERENCES**


