32 *Schistosoma* spp.

A 25-year-old male was admitted to hospital vomiting blood. On examination of the abdomen, both the liver and spleen were enlarged. A full blood count revealed a reduced hemoglobin level of 90 g l^{-1} and the white cell differential showed a raised eosinophil count of $1.1\times10^{9}L^{-1}$ (normal range $<0.45\times10^{9}$ L^{-1}). Endoscopic examination revealed dilated **esophageal varices** (Figure 32.1). **Cirrhosis** of the liver was suspected, but the patient denied any excessive drinking of alcohol and tests showed that he was negative for hepatitis B and C. A liver biopsy was performed and confirmed an abnormal liver, with extensive granulomatous change and **fibrosis**. On further questioning, it transpired that he had spent much of his childhood living in a small village in Kenya. His parents had been working there on a farm. He would regularly paddle and swim in a nearby lake. He recalled no particular illness while living in Africa. Urine examination was negative but stool microscopy demonstrated the presence of *Schistosoma mansoni* eggs. A rectal biopsy obtained at **sigmoidoscopy** showed **granulomas**, containing *Schistosoma* eggs. Schistosomal **serology** was also positive. He was treated with praziquantel and his stool was monitored for the disappearance of *Schistosoma* eggs. He was referred to a hepatologist for further management of his esophageal varices. Serial ultrasounds were performed to monitor the liver fibrosis.

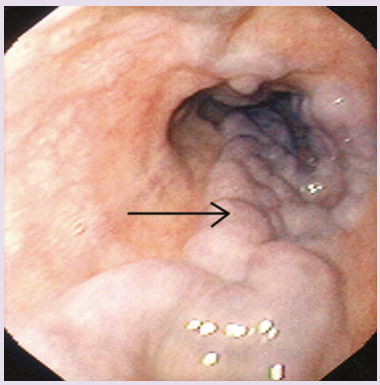

Figure 32.1 Endoscopic view of large esophageal varices (arrowed). *Courtesy of Dr Alan Mills and the Virginia Commonwealth University Department of Pathology.*

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

CAUSATIVE AGENT

Human schistosomiasis, also known as bilharzia, is mainly caused by three species of *Schistosoma*. *S. mansoni* occurs in Africa, parts of the Arabian peninsula, the Caribbean, and South America. *S. haematobium* occurs in Africa and parts of the Arabian peninsula. *S. japonicum* is now found in China, the Philippines, and Indonesia. *S. intercalatum* occurs in pockets in west and central Africa and *S. mekongi* is restricted to small pockets in Cambodia and Laos.

Schistosomes are blood flukes, which are also known as trematodes. Adult worms are less than 2cm long (Figure 32.2). Males have a longitudinal groove in which the female worm resides. They live in the veins around the bladder in the case of *S. haematobium* or in the mesenteric veins of the intestine in the case of *S. mansoni* and *S. japonicum*.

Figure 32.2 Adult schistosome worms. The female (on the left) is slender and fits into a groove on the ventral surface of the male. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #5252.*

ENTRY AND SPREAD WITHIN THE BODY

The lifecycle of schistosomiasis is shown in Figure 32.3. Humans are infected when they enter water containing

Schistosoma cercariae (**Figure 32.4**). These larvae penetrate the skin. The cercariae transform into a larval stage called the schistosomulum. These enter blood vessels and pass round the venous circulation, through the lungs and then enter the arterial circulation. They reach the liver. The schistosomula mature over about one month to adult worms in the portal vein. Males and females pair and then migrate distally to the veins around the bladder and the intestine. They usually live for 5–7 years. However, there are reports of individuals who have left endemic areas for several years and show signs of active infection many years later. From such reports, it is thought that occasionally adult pairs may survive for up to 30 years. The case history illustrates this prolonged survival.

PERSON-TO-PERSON SPREAD

Schistosomiasis does not spread directly from person to person but the life cycle involves a snail intermediate host. Once adults have matured, eggs are laid after 1–3 months. *S. mansoni* and *S. haematobium* females lay between 20 and 300 eggs per day. The figure can be considerably higher for *S. japonicum*, with an estimated 500–3500 eggs per day. About

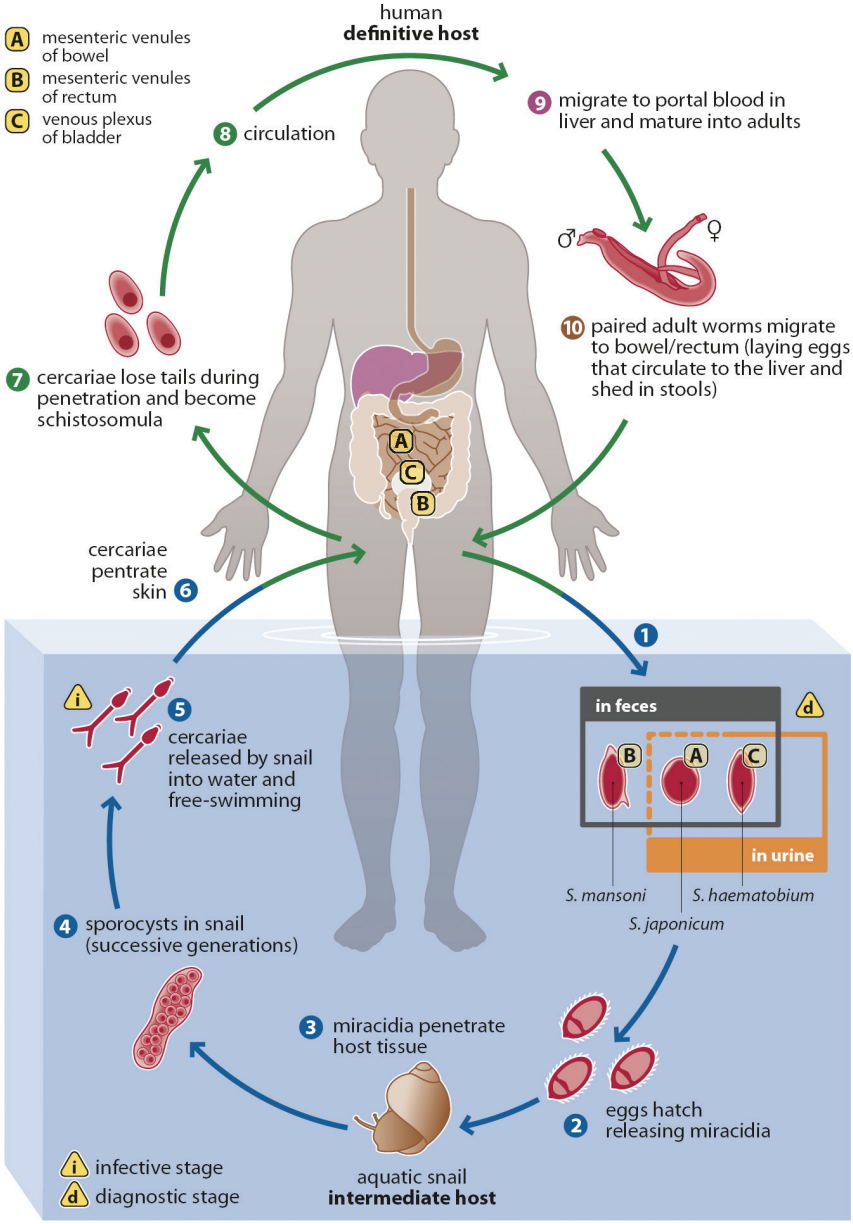

Figure 32.3 Lifecycle of *Schistosoma* spp. Eggs shed in urine or feces (1) from human hosts release miracidia on contact with fresh water (2) and then enter intermediate snail hosts (3). After multiplication in the snail hosts (4) cercariae arise (5), which penetrate human skin on water contact (6). They develop into schistosomula (7), which mature into adult worms and live within blood vessels (10) around the bladder or intestine (A, B, C). Adult male and female pairs shed eggs, about half of which exit from the body and the other half are deposited in tissues, causing pathology. *Adapted from the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #3417. Additional photographic credit is given to Alexander J da Silva, PhD, and Melanie Moser who created the image in 2002.*

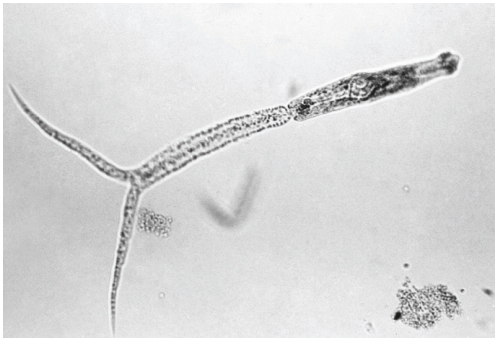

Figure 32.4 A Schistosome cercaria, which emerges from snails and penetrates human skin. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #8556. Additional photographic credit is given to Minnesota Department of Health, RN Barr Library; Librarians Melissa Rethlefsen and Marie Jones, Prof William A Riley and the photo was created in 1942.*

half of these eggs succeed in passing through the wall of the bladder or intestine to emerge in urine or feces. Otherwise, eggs get stuck in the bladder or intestinal wall or embolize in the venous circulation to the liver. In advanced, heavy infections collateral circulation around the liver develops and eggs disseminate into the lungs, brain, and other organs.

Eggs have a spinous process. The shape of the egg and the position of the spine is characteristic for each species of *Schistosoma* (**Figure 32.5**). *S. haematobium* has a terminal spine. *S. mansoni* and *S. japonicum* have lateral spines, with *S. japonicum* having smaller-sized eggs.

The eggs contain a ciliated larval form called the miracidium, which is released when the eggs come into contact with fresh water in lakes, rivers, and streams. Miracidia go on to infect specific aquatic snails. Within the snails, they multiply into sporocysts from which arise the cercariae that close the life cycle. The species of snails differs between the species of *Schistosoma*. *S. mansoni* is transmitted by *Biomphalaria* snails, *S. haematobium* by *Bulinus*. These are aquatic snails, while *S. japonicum* is transmitted by an amphibious snail called **Oncomelania**.

EPIDEMIOLOGY

Schistosomiasis is endemic in many tropical and subtropical countries and affects more than 240 million people worldwide. Some estimate mortality reaching 200 000 per annum.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

A host immune inflammatory response may be directed against the antigens of the schistosomula larvae, the adult worms or the eggs. There is evidence that the host response provides some level of protective immunity to re-infection. Rates of re-infection have been studied in endemic areas when adults or children are treated to clear infection. The rate of re-infection can only partly be explained by behavior and intensity of water contact. Correcting for the extent of water contact, adults who have had a greater lifetime exposure to schistosomiasis are less likely to be re-infected than children.

In vitro studies have shown that schistosomula are more susceptible to immune attack than adult worms. Immunity correlates with levels of **IgE** directed against schistosomulum or adult worm antigens. Key antigens include schistosomal glutathione-*S*-transferase and glyceraldehyde-3-phosphate. The levels of antibodies rise with age. *In vitro*, IgE mediates killing of schistosomula by **opsonization** to eosinophils. The eosinophils degranulate to release toxic molecules such as eosinophil cationic protein. However, immunity is inversely correlated with levels of **IgG_2** and IgG_4 antibody directed against egg polysaccharide antigens. It is thought that these IgG isotypes also bind to schistosomula and block the binding of effector IgE antibodies.

Larval, adult, and egg antigens are sometimes released in such quantities, that together with significant levels of circulating IgG, an **immune complex** disease develops (**type III hypersensitivity**). This occurs early in infection and is referred to as **Katayama syndrome**. Some observations also implicate **tumor necrosis factor-α** (**TNF-α**) in severe symptomatology.

Once adults mature, there seems to be a ceiling to the number of adults present in the vasculature. This may be because of the physical space available. Adults become coated with host proteins, including self-HLA molecules, and this "host mimicry" may confuse the immune response, leading the host to believe the worm is "self". Very little, if any, inflammation is seen around adult worms.

A considerable immune and inflammatory response occurs against the eggs that lodge in tissues. Blood **eosinophilia** is

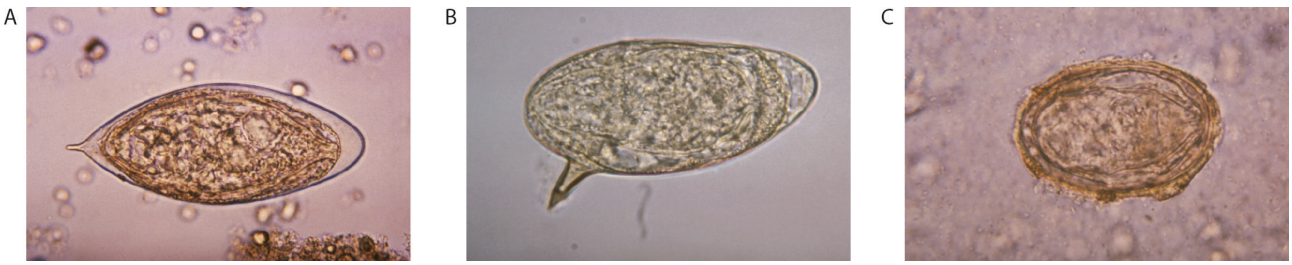

Figure 32.5 Eggs of (A) *S. haematobium* with a terminal spine, (B) *S. mansoni* with a lateral spine, and (C) *S. japonicum*, which are smaller and rounder. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Images are found in the Public Health Image Library (A) #4843; (B) #4841; (C) #4842.*

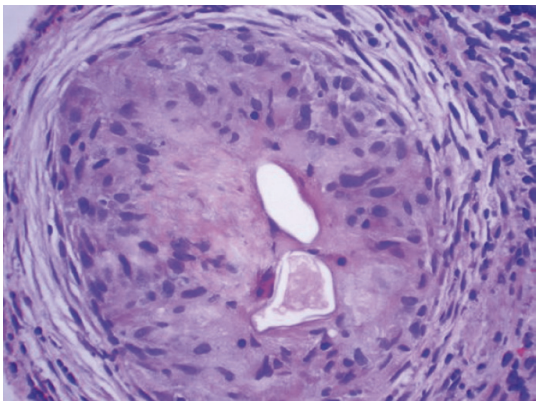

Figure 32.6 Granuloma formed around a schistosome egg. *Courtesy of Dr Yale Rosen and his website Atlas of Granuloma Diseases: http://granuloma.home-stead.com/.*

often observed in association with considerable egg deposition. These eggs release soluble antigens that present a strong stimulus to **CD4**+ T-helper lymphocytes, which orchestrate an inflammatory response. The human immune response is skewed to a Th-2 response. Granulomas form around the eggs with an influx of lymphocytes and macrophages. Fibroblasts deposit collagen and extracellular matrix proteins. The extent of resulting fibrosis depends on the balance of activities between matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). In turn, these enzymes are affected by the balance of a variety of cytokines. **Transforming growth factor-β** (**TGF-β**), **interleukin** (IL)-1, IL-4, IL-13, and TNF-α promote fibrosis, while **interferon** (**IFN**)-γ is associated with reduced fibrosis. The actions of these **cytokines** in turn are affected by other regulatory cytokines such as IL-10 and IL-12. About 5–10% of patients develop extensive fibrosis (**Figure 32.6**). Numerous granulomas with surrounding fibrosis constitute a major part of tissue pathology. In time, there can be remodeling of granulomas with some resorption of fibrotic tissue.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

Many individuals do not develop symptoms but, when present, clinical features may occur at different stages of infection. Even without symptoms, eosinophilia may be an indicator of infection. When cercariae first penetrate the skin, there can be local irritation, which may appear immediately or within a few days. Raised, red spots may last a few days. Similarly, a swimmers' itch can be caused by trematodes of animal origin, particularly in temperate climatic zones.

A type III hypersensitivity reaction to high-antigen release is referred to as Katayama syndrome, named after a region in Japan. This may occur between 2 and 12 weeks after infection, particularly when egg production increases the antigenic burden. It is more likely in non-immune travelers unable to curtail the maturation of schistosomula. There is an abrupt onset of fever, malaise, aches, and tiredness. The lung becomes involved, with patchy shadowing on a chest X-ray. This is accompanied by a dry cough. There is also abdominal pain with diarrhea and both liver and spleen can be enlarged. On blood tests, there is a high eosinophil count.

No symptomatology is attributed to the adult worms. Even once eggs are being deposited in tissues, symptoms may be absent or mild. Nonspecific features include malaise and tiredness. When considerable numbers of eggs settle in the intestine, bladder, liver, lung or other tissues, problems arise as described below. These take some time to develop.

With *S. haematobium* granulomatous inflammation of the bladder wall can also result in ulceration (**Figure 32.7**). Bleeding into urine may be microscopic or macroscopic. Chronic lesions can progress to fibrosis and bladder calcification. This can block the ureters, with back pressure dilating the ureters and compromising kidney function. In the long term, there is a risk that the damaged mucosal epithelium undergoes malignant change, resulting mainly in squamous cell carcinomas rather than transitional cell carcinomas. This is more common in smokers.

With *S. mansoni* and *S. japonicum*, granulomatous inflammation of the intestine is principally found in the rectum and distal bowel. The mucosa may ulcerate. Abdominal pain is accompanied by diarrhea that may contain blood. From the peri-intestinal blood vessels eggs laid by adults embolize through the portal vein to the liver. In heavily infected or genetically predisposed individuals, the granulomatous reaction in the liver results in considerable fibrosis; this periportal fibrosis – described as "clay pipe stem" fibrosis – develops along the portal veins (**Figure 32.8**). The liver can enlarge and can feel hard and uncomfortable in the right upper abdomen. As blood flow through the liver is impaired by fibrosis, **portal hypertension** develops. This enlarges the spleen, which causes discomfort in the left upper abdomen. Gastro-esophageal varices develop and can bleed, as illustrated in the case history. Eventually, damage to the liver may be so extensive that liver failure results in death.

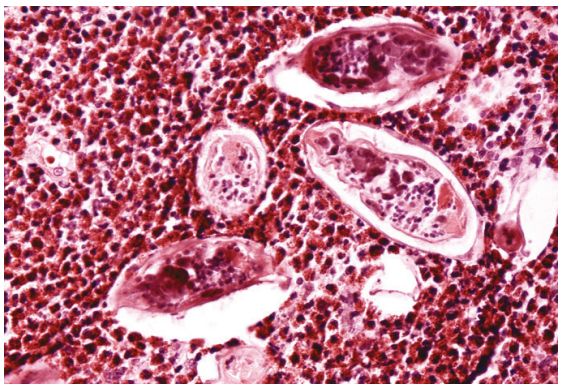

Figure 32.7 Granuloma formed around a schistosome egg. *Courtesy of Dr Yale Rosen and his website Atlas of Granuloma Diseases: http://granuloma.home-stead.com/.*

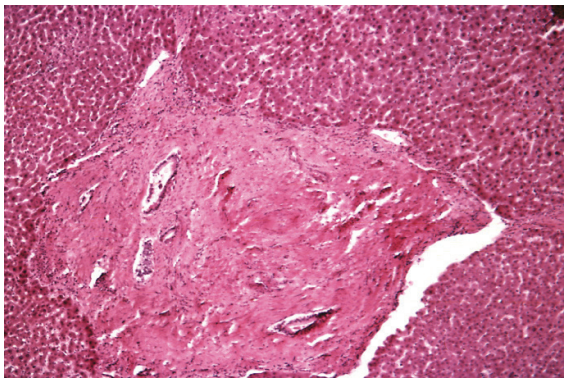

Figure 32.8 Intense eosinophilic inflammation around *S. haematobium* eggs in the bladder wall. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #35. Additional photographic credit is given Dr Edwin P Ewing, Jr who took the photo in 1973.*

In 5–10% of infected individuals, portal hypertension becomes well established and collateral blood vessels open up around the liver. Eggs from the peri-intestinal blood vessels pass toward the liver but then bypass through these dilated blood vessels into the lung. This results in granulomatous inflammation in lung tissue. Eggs may reach any part of the body. *S. japonicum* worms lay more eggs than the other species and, in the Far East, granulomas may develop in the central nervous system (CNS) and be a cause of epilepsy and other neurologic features.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

The diagnosis of schistosomiasis can be made by microscopic analysis through finding eggs in urine or stool. Urine collected at the end of micturition provided at mid-day is the best specimen in which to look for *S. haematobium* eggs. This terminal specimen is likely to have a higher concentration of eggs. Egg shedding is also maximal about mid-day. Multiple stool specimens may be required to find eggs, as egg shedding is variable. Stool specimens can be suspended and concentrated. If eggs are not seen in urine or stool, endoscopic examination of bowel or bladder may show inflammatory changes and biopsies may yield granulomas containing eggs. Where available, another direct assay for infection is the detection of schistosomal antigen in urine, stool or blood.

In endemic areas, the presence of **IgM**, IgG and IgE antibodies in serum does not distinguish current from past infection. In returned travelers who have not previously been to a schistosomiasis-endemic area, positive serology may be diagnostic of exposure. Serology does not become positive till about 12 weeks after infection, and occasionally longer.

Eosinophilia is suggestive of ongoing infection in the absence of another explanation. Ultrasonography can be used to detect complications of infection such as changes in the bladder, ureters, kidneys, and liver.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses to be considered depend on the presentation (**Table 32.1**). In people who have traveled from endemic areas, one may have to consider differential diagnoses for hematuria, diarrhea with or without blood, eosinophilia, and granulomas on biopsy. Diarrhea with blood is also known as **dysentery**. The case history illustrates late-stage presentation when one also has to think of cirrhosis of the liver due, for instance, to alcohol or chronic viral hepatitis B or C. In endemic areas, it is possible to get both schistosomiasis and chronic viral hepatitis.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

MANAGEMENT

Standard treatment is monotherapy with oral praziquantel in a single dose or two doses 4–6 hours apart. In mass chemotherapy programs, single doses are more practical. Praziquantel acts against the adult worms, causing damage to their surface, increased calcium influx, and paralysis. It does not act on schistosomula and cannot be used very soon after infection, before adults have matured. Treatment should be deferred to 6–12 weeks after the last known fresh-water exposure. Artemisinin derivatives have activity against schistosomula. Praziquantel cures up to 90% of patients. Treatment success is gauged by the disappearance of egg excretion after treatment. Any eosinophilia usually settles by 12 weeks post-treatment, but persistent eosinophilia and detectable egg excretion at that point will merit a repeat course of praziquantel. Concern about reduced efficacy of praziquantel is a concern in some regions but may be overcome by more prolonged courses with higher doses. The cessation of egg production stops new granuloma formation. The host may be able to reverse early fibrotic reactions with some clinical improvement.

As Katayama syndrome is due to a type III hypersensitivity reaction, the mainstay of treatment is steroids as an anti-inflammatory. Steroids also have a role in reducing inflammatory changes in neurologic involvement.

PREVENTION

Vaccines against schistosomiasis are under investigation. While we wait in hope for an effective vaccine, prevention

Table 32.1 Differential diagnoses to be considered with different presentations of schistosomiasis

Hematuria (blood in urine)
Urinary tract infection
Bladder or ureteric stones
Tumor of bladder or prostate in adults
Glomerulonephritis
Polycystic kidneys
Coagulopathy
Dysentery (bloody diarrhea)
Infections due to
Campylobacter
Shigella
Enterohemorrhagic *Escherichia coli*
Entamoeba histolytica
Colonic tumor
Inflammatory bowel disease, particularly Crohn's disease, which also causes granulomas
Eosinophilia
Infections due to:
Strongyloides
Filaria (e.g. *Wuchereria*, *Onchocerca*)
Migrating larval stages of intestinal nematodes (e.g. *Ascaris*, hookworms)
Atopic/allergic reactions
Asthma
Eczema
Drug reactions
Vasculitis
Malignancy
Granulomas
Infections due to:
Mycobacteria
Brucella
Chlamydia granulomatosis
Francisella tularensis
Listeria monocytogenes
Nocardia spp.
Histoplasma
Coccidiodes
Fasciola hepatica
Paragonimus
Sarcoidosis
Crohn's disease
Vasculitis
Lymphoma
Primary biliary cirrhosis
Chronic granulomatous disease
Berylliosis

depends on health education, control of intermediate host snail populations, reducing contaminated water contact, and mass drug administration to treat infected individuals and reduce egg shedding. Environmental management to reduce intermediate host snail populations is difficult, as is separating humans from water contact. The building of dams for irrigation and hydroelectric purposes has had mainly negative effects on the incidence of infection. The provision of safe water supply and sanitation infrastructure are very important in reducing episodes of contaminated water contact. Several countries have undertaken population-wide mass drug administration with repeated cycles of treatment. This has reaped success in countries such as Brazil, China, and Egypt. The World Health Organization (WHO) has extended this approach to many more countries, especially in the most stricken countries of sub-Saharan Africa.

SUMMARY

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

- Schistosomiasis in humans is caused by three main species of blood flukes (trematodes) – *S. mansoni*, *S. haematobium*, and *S. japonicum* (two further species are of regional importance only).
- Adult male and female worms lodge together in blood vessels around the bladder (*S. haematobium*) or the intestine (*S. mansoni* and *S. japonicum*). Females lay eggs, about half of which pass into urine (*S. haematobium*) or feces (*S. mansoni* and *S. japonicum*) and others disseminate into various organs.
- Upon fresh-water contact in lakes, rivers, and streams eggs release a larva called a miracidium that infects specific aquatic snails (*Biomphalaria* in the case of *S. mansoni*, *Bulinus* for *S. haematobium*) or the amphibious snail *Oncomelania* (in the case of *S. japonicum*).
- Cercariae arise from snails and transcutaneously infect humans when they are in contact with water. The first larval stage in humans is the schistosomulum.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

- Schistosomula are susceptible to immune attack by IgE and eosinophils. The binding of IgE may be blocked by IgG_2 and IgG_4 antibody against egg antigens.
- There is virtually no inflammation around adult worms living in blood vessels.
- Granulomas form around eggs that deposit in tissues. These granulomas are subsequently surrounded by fibrosis. Disease is largely due to granulomatous inflammation and extensive post-granulomatous fibrosis.
- Very occasionally, excessive antigen release results in an immune complex disease.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

- An itch and rash may occur when cercariae first penetrate the skin, particularly after primary infection.
- The occasional immune complex disease is called Katayama syndrome and comprises high fever, aches, cough, and later diarrhea.
- Disease of the bladder can cause bleeding into urine (hematuria) and, later, fibrosis can block the flow of urine with ureteral dilatation and renal failure. There is a risk of developing bladder cancer.
- Disease of the intestine can cause diarrhea with (dysentery) or without blood.
- Severe granulomatous change and fibrosis in the liver lead to portal hypertension with the risk of life-threatening bleeding from esophageal varices. The liver and spleen become enlarged.
- When collateral circulation develops, granulomas can appear elsewhere such as in the lung or the central nervous system.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

- Diagnosis is based on visualizing characteristic eggs in urine, feces or biopsies.
- Serologic tests are also available and are most useful in returned travelers.
- On routine blood testing, eosinophilia may be found.
- The differential diagnosis includes other causes of hematuria, dysentery, eosinophilia, and granulomas.
- Ultrasonography is useful for identifying structural changes in the renal tract or liver.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

- Praziquantel is the mainstay of treatment.
- Prevention requires health education, environmental management to control intermediate host snail populations, and decreasing opportunities for water contact (through improved access to clean water and adequate sanitation).
- The provision of a safe water supply and sanitation infrastructure are important for schistosomiasis and many other diseases.
- Some countries undertake population-wide mass drug administration.

FURTHER READING

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WEBSITES

Centers for Disease Control, Atlanta, GA, USA: https://www.cdc.gov/parasites/schistosomiasis/index.htmlSchistosomiasis

SCI Foundation, Control Initiative: https://schistosomiasiscontrolinitiative.org/

World Health Organization, Schistosomiasis (Bilharzia): https://www.who.int/health-topics/schistosomiasis

Students can test their knowledge of this case study by visiting the Instructor and Student Resources: [www.routledge.com/cw/lydyard] where several multiple choice questions can be found.