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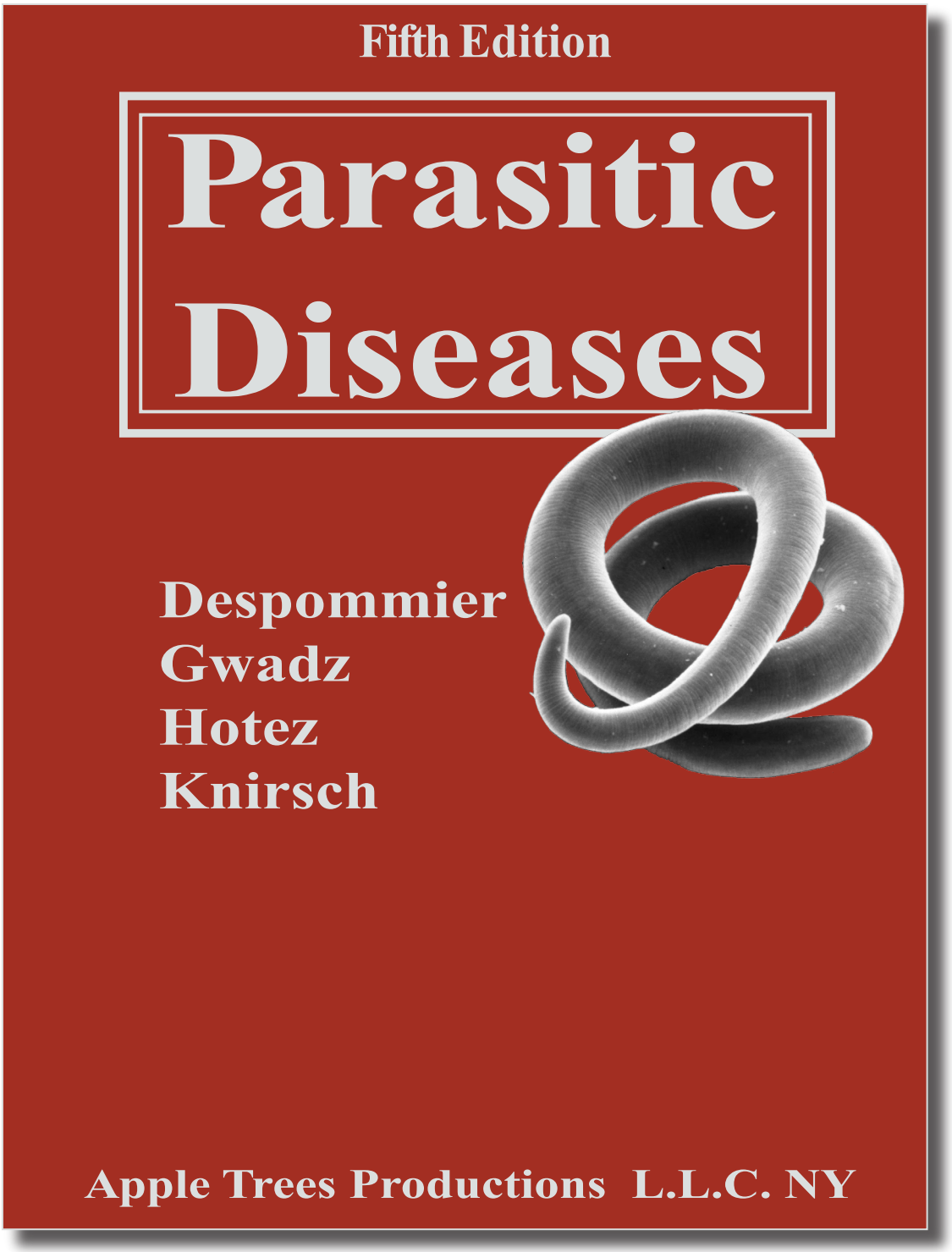


33. The Schistosomes:

Schistosoma mansoni
(Sambon 1907)

Schistosoma japonicum
(Katsurada 1904)

Schistosoma haematobium
(Bilharz 1852)

Schistosoma mekongi
(Bilharz 1852)

Introduction

Four trematode species in the genus Schistosoma; *Schistosoma mansoni, S. haematobium, S. japonicum,* and *S. mekongi,* cause a series of related diseases in humans referred to as schistosomiasis. *S. intercalatum*, a parasite of cattle in West Africa, also occasionally causes the disease in humans. Except for *S. haematobium* that produces urinary tract disease, the human schistosomes primarily affect the intestine and liver. Chronic schistosomiasis also causes physical growth and cognitive delays in children. The World Health Organization estimates that 85% of the 200 million people infected with one or more of these agents live in Africa, while another 600 million people are at risk worldwide. Their largely tropical distribution reflects the geographical distribution of their intermediate host snail species. Forced migration of people due to armed conflict throughout many parts of Africa, and encroachment into natural systems (e.g., constructing irrigation canals and dams), have resulted in regional increases in schistosomiasis.

Schistosoma mansoni is found throughout most of sub-Saharan Africa, Egypt and Sudan, parts of the Middle East, some parts of South America (including Brazil and the Guyanas), and some islands in the Caribbean. Its intermediate hosts are aquatic snails in the genus Biomphalaria. Reservoir hosts for *S. mansoni* include baboons and monkeys in Africa. However, they play no significant role in the epidemiology of human disease.

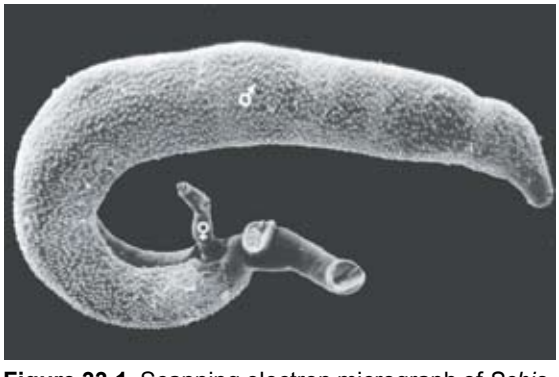


Figure 33.1. Scanning electron micrograph of *Schistosoma mansoni* adults. (From Kessel and Shih: Scanning Electron Microscopy in Biology. Springer-Verlag, 1976. Reproduced with permission).

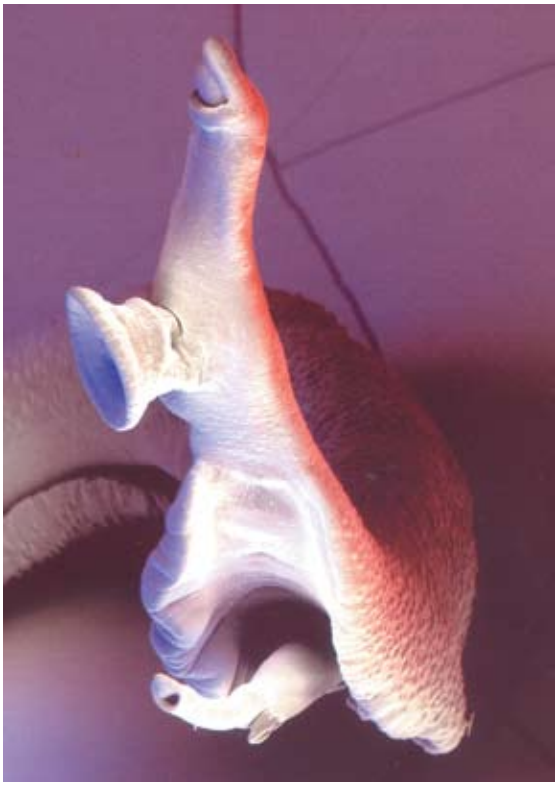


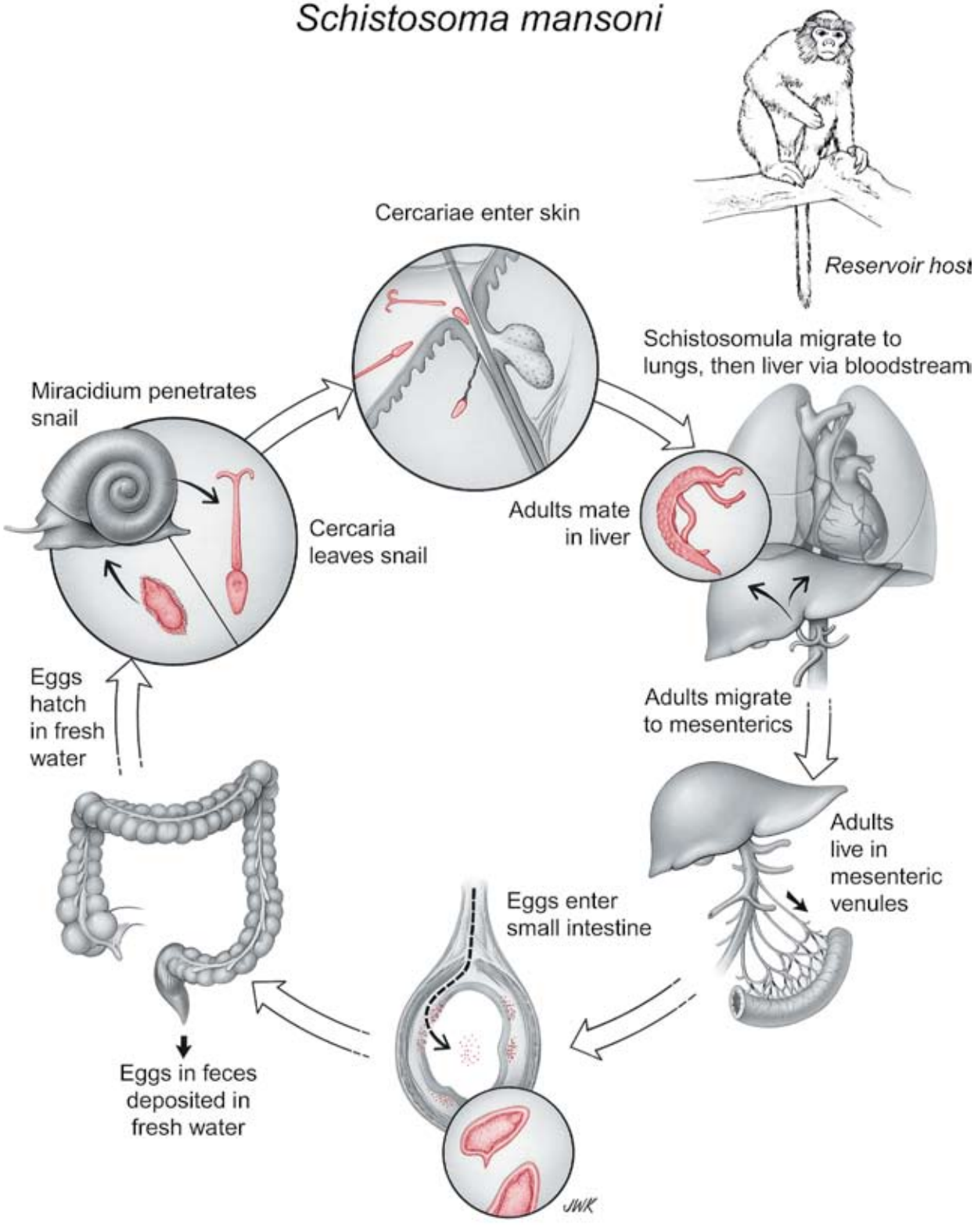
Figure 33.2. Scanning electron micrograph of adult schistosomes. Notice gynocophoral canal with female inside. Photo D. Scharf.

Schistosoma haematobium is prevalent in most parts of Africa and in some parts of the Middle East. Its aquatic intermediate host snails are in the genus Bulinus. There are no important reservoir hosts for this trematode species, although during an epidemic of the infection in the Omo River Valley of Ethiopia, the origin of the outbreak was traced back to monkeys.[1]

Schistosoma intercalatum occasionally infects people in Cameroon, Gabon, Equatorial Guinea, Central African Republic, Chad, and Democratic Republic of Congo.[2]

Schistosoma japonicum occurs in China, Malaysia, the Philippines, and, to a small extent, Indonesia. It has been eradicated from Japan as of 1977.[3] Its amphibious intermediate host snails are in the genus Oncomelania. In contrast to the other schistosomes, zoonotic transmission occurs on a regular basis.

Schistosoma mansoni



There are important reservoir hosts for *S. japonicum*, including water buffalo, cattle and pigs.[4] *S. mekongi,* a closely related species, is found in the Mekong River in southeast Asia. Some investigators consider this schistosome a member of the *S. japonicum* complex. There are no autochthonous infections in the United States with any of the above species of schistosomes because there are no appropriate species of intermediate host snails, and, most importantly, sanitary disposal of feces and urine is the general rule. However thousands of Caribbean and Southeast Asian immigrants may be infected, so clinicians who practice only in the United States must still be knowledgeable regarding this potentially life-threatening parasitic infection.

Historical Information

Ancient Egyptians believed that the advent of manhood was heralded by the appearance of blood in the urine, analogous to the onset of menstruation in women. Hematuria in males, in fact, represented a late manifestation of *S. haematobium* infection. Autopsies of mummies and microscopic examination of coprolites showed that schistosomiasis was quite prevalent throughout the lower Nile River valley more than 3,000 years ago. Bilharz, in letters to his friend and collegue, von Siebold, written between 1851 and 1853, described human cases of *Schistosoma haematobium*, a parasite of the venous plexus of the bladder, and whose eggs possessed a terminal spine. In 1902,

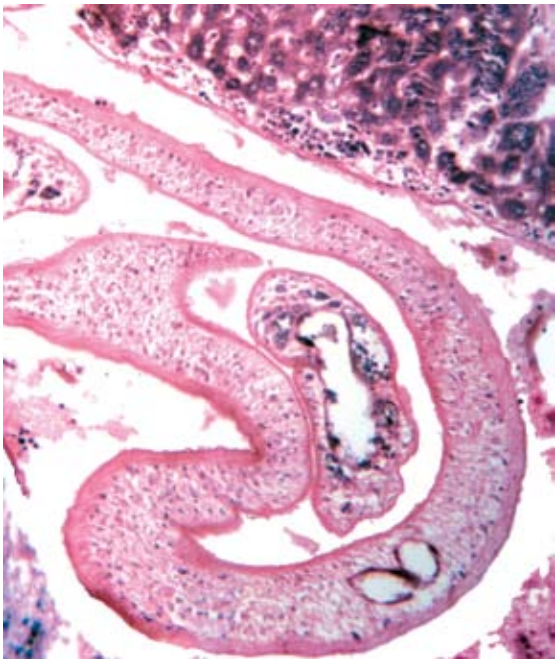


Figure 33.3b. Cross section of a pair of adult schistosomes *in situ* in a mesenteric venule.

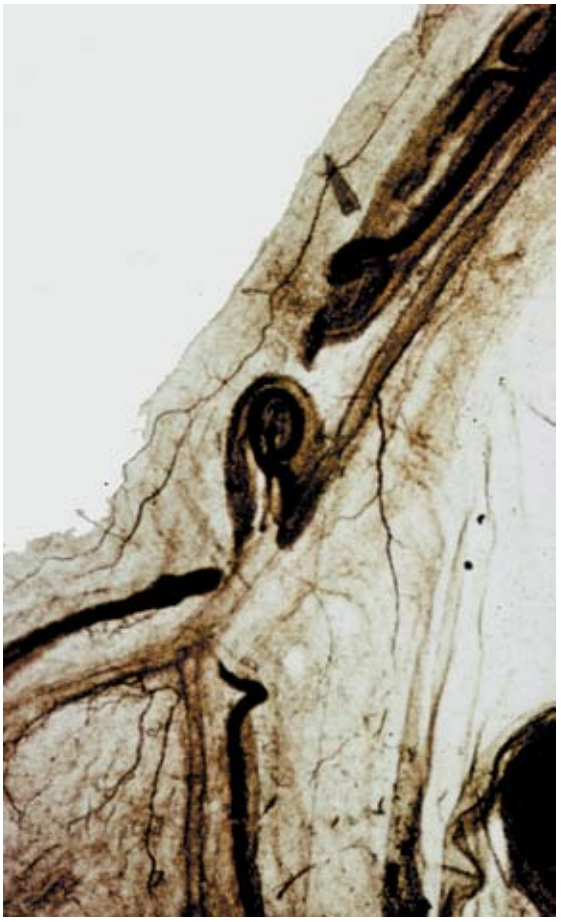
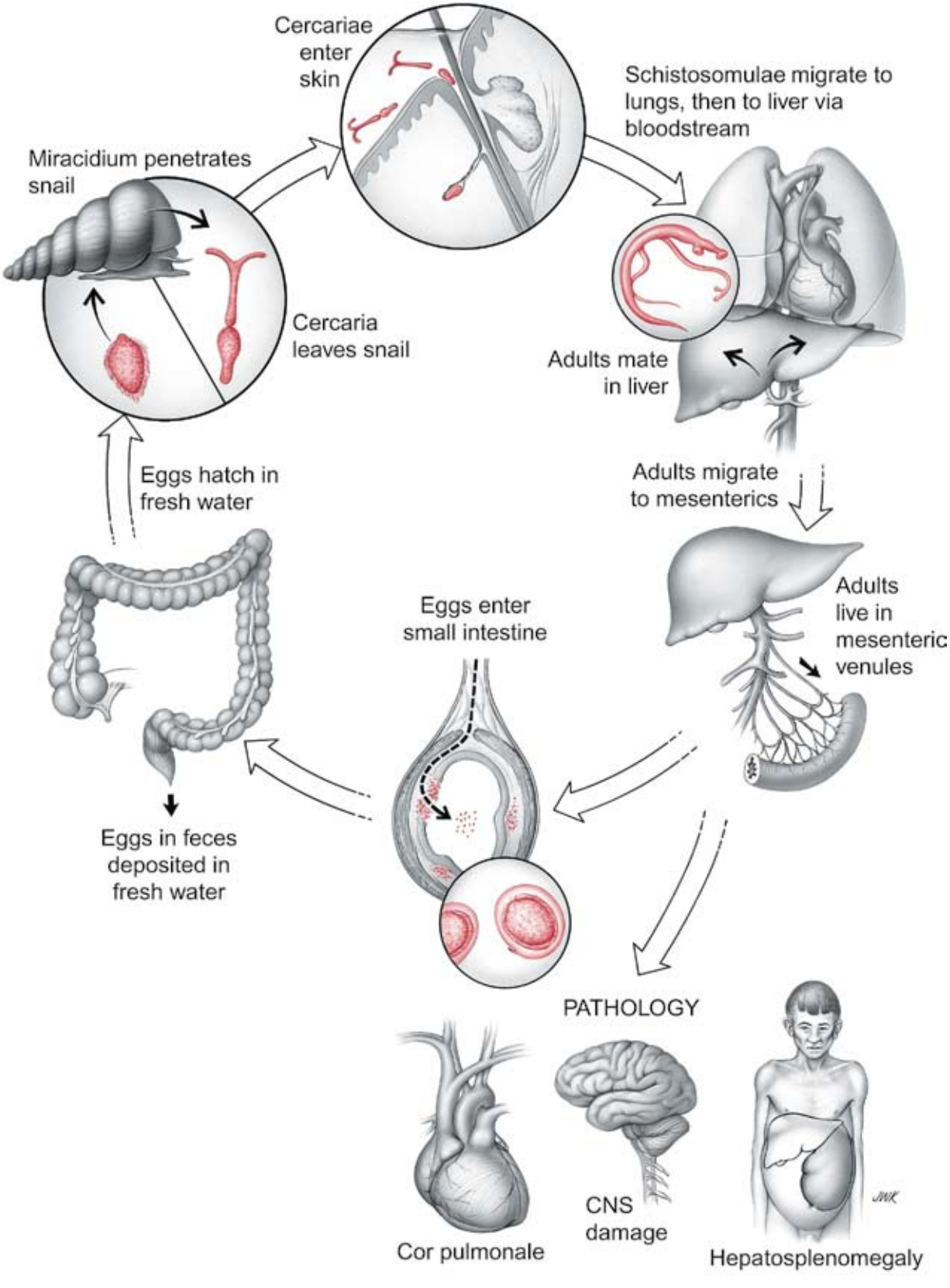


Figure 33.3a. Adult schistosomes *in situ*. The elongated worms appear dark due to the ingestion of hemaglobin.

Manson described a case of schistosomiasis in an Englishman who had traveled extensively throughout the Caribbean, and in whose stool, but not his urine, he found many eggs with lateral spines.[5] Sambon, in 1907,[6] recognized two blood flukes, on the basis of morphology and origin of the eggs in stool and urine. In tribute to Manson, Sambon named this new organism after him. Piraja de Silva, in 1908, also discovered *S. mansoni* in South America.[7] By 1918, Leiper[8] had conducted extensive investigations on schistosomiasis, and reported the life cycle of *S. mansoni*, in which he described its snail intermediate host, and morphology of the adult worms.

Katsurada, in 1904,[9] described *S. japonicum* adults from infected cats. Coincidentally, Catto, working in Singapore, described an identical adult worm in a patient who died of cholera.[10] He named it *S. cattoi*, but his publication was delayed, and the name *S. japonicum* was accepted instead. Earlier, in 1888, Majima[11] observed eggs of *S. japonicum* in a liver he examined at autopsy. He was unaware of the adult worms, but

Schistosoma japonicum



correctly ascertained that the eggs were responsible for the cirrhosis. Kawanishi, in 1904,[12] made the correlation between the clinical condition, Katayama fever (acute schistosomiasis), and the presence of *S. japonicum* adults, after finding eggs of this parasite in the stools of patients suffering from the acute phase of the infection. Fujinami and Nakamura in 1909,[13] and Miyagawa in 1912,[14] independently reported on the details of the life cycle. Miyairi and Suzuki, in 1914,[15] identified *Oncomelania spp*. snails as the vectors.

S. japonicum infection has had a major impact on the history of modern China. It is believed that Mao's troops were unable to launch an amphibious assault on Taiwan in the late 1940s because they developed Katayama fever while encamped along the Yangtze River. Later on during the great leap forward, Mao mobilized tens of thousands of peasants to either bury Oncomelania snails or even to remove them individually by hand.

Griesinger, in 1854,[16] described in detail the clinical disease and its pathology. He noted the relation of the infection to the involvement of the bladder and ureters. Leiper, in 1918,[8] described the life cycle of *S. haematobium*, its intermediate host, and its morphology. He also carried out experimental infections with *S. haematobium* in various indigenous animals of northern Egypt, and proved that rats and mice were susceptible.

Life Cycle

Schistosomes have separate sexes (Fig. 33.1); the female measures 15 mm in length, and the male is 10 mm long. Schistosome adults remain in copula (Fig. 33.2) during their life span, and live attached by their sucker disks to the endothelium of the veins (Figs. 33.3a, 33.3b) *S. mansoni* lives in the inferior mesenteric veins that drain the intestine, while *S. japonicum* and *S. mekongi* live in the superior mesenteric veins. *S. japonicum* adult worms can also find their way to the choroid plexus, the venules around the spinal column, and other ectopic locations. *S. haematobium* is found almost exclusively in the venus plexus that drain the urinary bladder. The routes by which adult schistosomes arrive at these sites is still considered controversial. Worms live 5-8 years, on the average, although some live as long as 37 years.[19] Schistosomes are facultative anaerobes, deriving energy primarily through the degradation of glucose and glycogen.

Figure 33.4. Egg of *Schistosoma mansoni*. Note lateral spine. 150 μm x 60 μm.

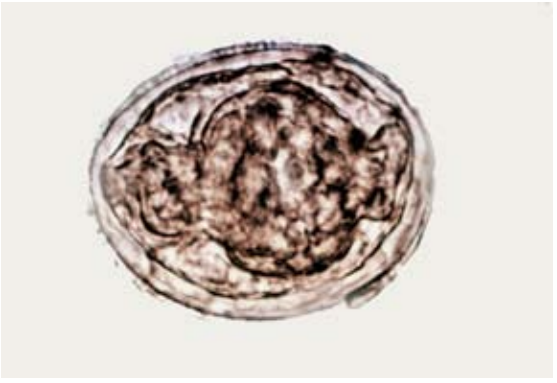


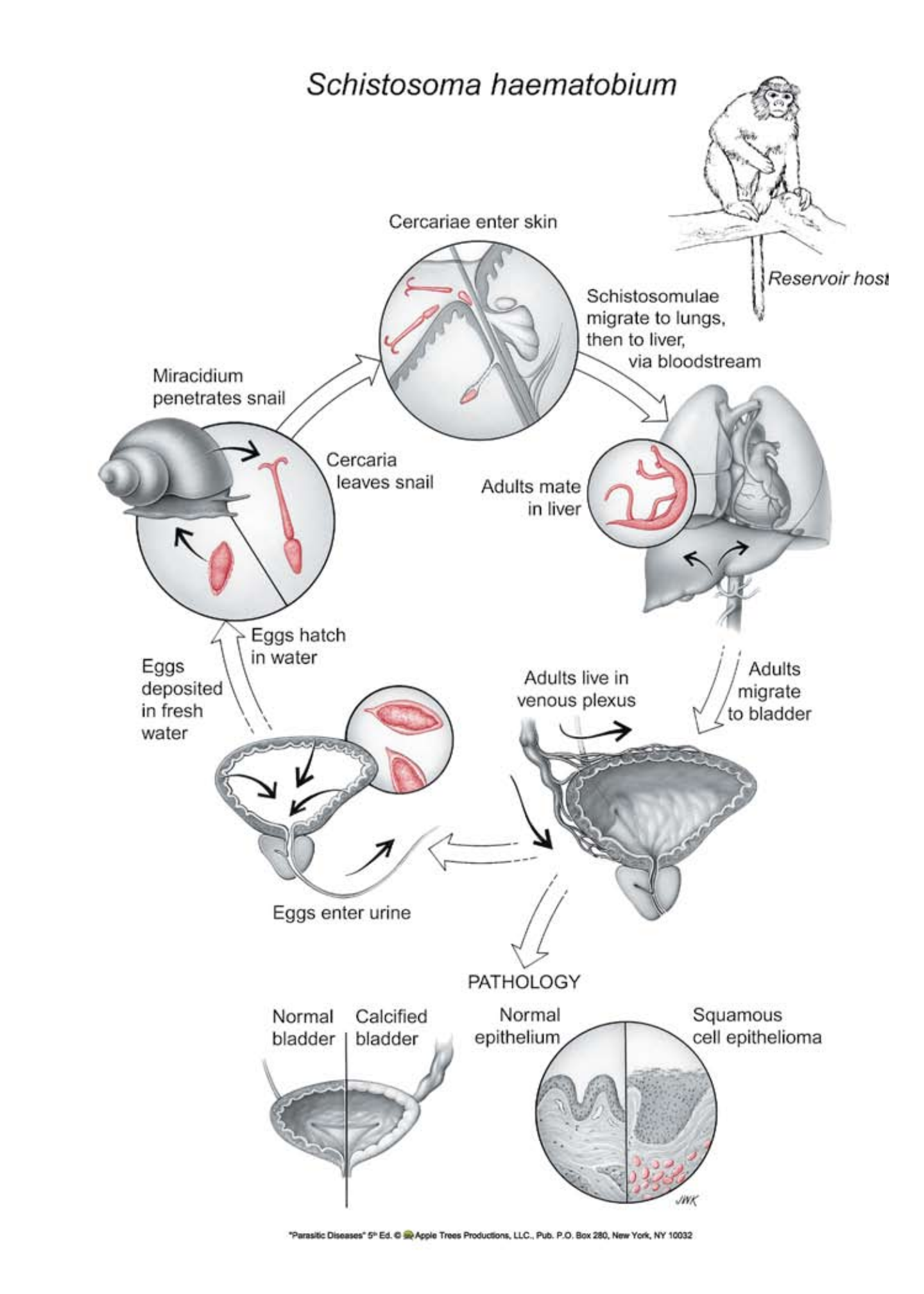
Figure 33.5a. Egg of *Schistosoma japonicum*. No spine can be seen. 85 μm x 60 μm.

Adult schistosomes utilize hemoglobin[16] as a primary source of amino acids, which is ingested into their blind, bifurcated gut. They employ a hemoglobinase,[18] digesting the globin portion of the molecule, and detoxifying the heme moiety into a pigment before it is regurgitated back into the blood stream. The female lies within the gynecophoral canal of the male (Fig. 33.2). This muscular, tegumental fold extends down both sides of the male, and may enable the female to feed on blood, by assisting in pumping blood into their esophagus. Single sex infections with females, or females experimentally separated from males, then re-introduced into the same host, do not produce eggs, presumably due to their inability to obtain a blood meal.

Free amino acids and glucose are transported across the tegument by active transport mechanisms. They store excess glucose as glycogen. The tegumental surface of male *S. mansoni* are covered with finger-like projections, termed "papillae", while male *S. haematobium* have more widely spaced, shorter, finger-like projections, termed "tubercles". The purpose(s) of these projections is not known. In contrast, males of *S. japonicum* and *S. mekongi* are smooth.

Females in copula lay eggs throughout their lives. The eggs of *S. mansoni* are oval, and possess a lateral spine (Fig. 33.4); those of *S. japonicum* and *S. mekongi* are globular and lack a spine (Fig. 33.5a, 33.5b); those

Schistosoma haematobium



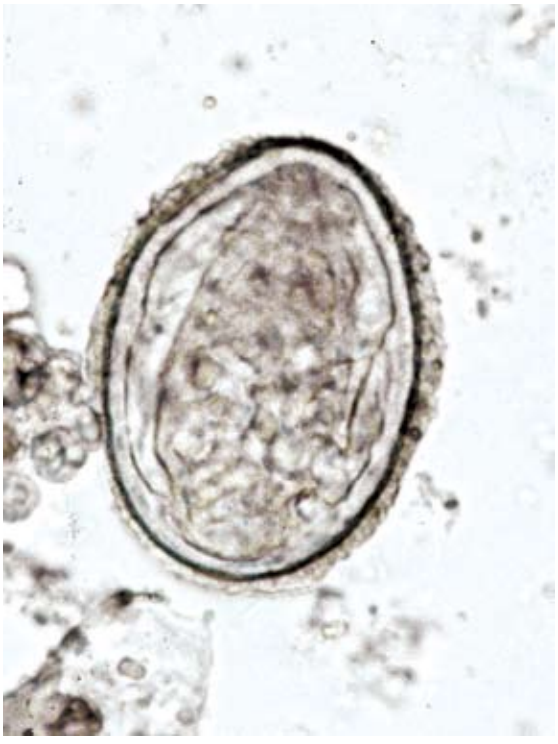


Figure 33.5b. Egg of *Schistosoma mekongi*. No spine can be seen. 65 μm x 50 μm.

of *S. haematobium* are oval, with a terminal spine (Fig. 33.6). *S. mansoni* females produce, on average, 300 eggs per day, while *S. japonicum* and *S. mekongi* shed some 1500-3000 eggs daily. Egg production of *S. haematobium* has not been determined. The eggs pass through the birth pore located above the posterior sucker. When the worm applies the sucker to the endothelial surface, the embryonated eggs secrete lytic enzymes, enabling them to enter the surrounding connective tissue. Eggs collect in the sub-mucosa (Fig. 33.7) before entering the lumen of either the small intestine, or for *S. haematobium*, the bladder.

When adult females raise their posterior suckers, eggs escape into the circulation, which carries them to the liver via the portal circulation. Nearly 50% of all *S. mansoni* eggs produced reach the liver. Eggs that reach the lumen of the small intestine are included in the fecal mass. Eggs of *S. haematobium* must traverse the wall of the bladder (Fig. 33.8) before exiting with the urine. In both cases, the egg's penchant for penetrating tissues causes the infected individual significant pathological consequences.

For the life cycle to continue, eggs in feces or urine must be deposited in fresh water. There, environmental cues trigger the larva stage, termed the miracidium, to hatch (Fig. 33.9). This ciliated, free-swimming stage (Fig. 33.10) seeks out its appropriate snail intermediate host, relying on a gradient of appropriate low molecular weight signal(s) emanating from the snail to do so. In essence, the snail becomes a chemical homing device for the parasite.

Upon finding the right snail (Fig. 33.11, 33.12), the miracidium enters the soft, fleshy parts, facilitated by a new set of proteolytic enzymes. The miracidium invades the snail's lymph spaces, and then its hepatopancreas.

A series of remarkable transformations then ensue, beginning with production of the sporocyst. This stage gives rise to daughter sporocysts, which, in turn, produce cercariae, the infectious stage for humans. During each stage of development, there is an increase in the number of individuals. A single miracidium of *S. mansoni* produces some 4,000 cercariae (Fig. 33.13). Throughout the process, the snail somehow manages to remain alive, even when it becomes infected with numerous miracidia. However, an infection that results in the production of more than 40,000 cercariae overwhelms the snail, and it dies. Each miracidium is either male or female, and the resulting cercariae are, also.

Cercariae exit from the snail aided by yet another set of proteolytic enzymes. Cercariae are positively phototropic and negatively geotropic. They accumulate at the surface of water, and swim about seeking their definitive host by following gradients of chemical cues, including linoleic acid, that emanate from human skin.

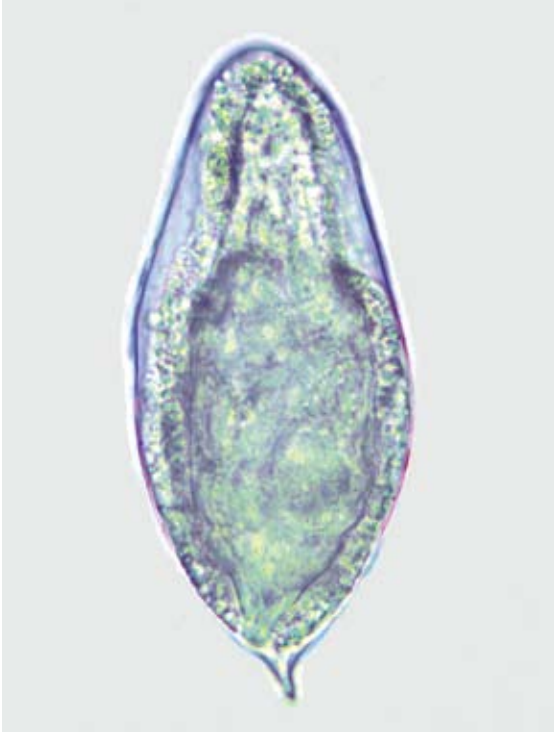


Figure 33.6. Egg of *Schistosoma haematobium*. Note terminal spine. 155 μm x 55 μm.

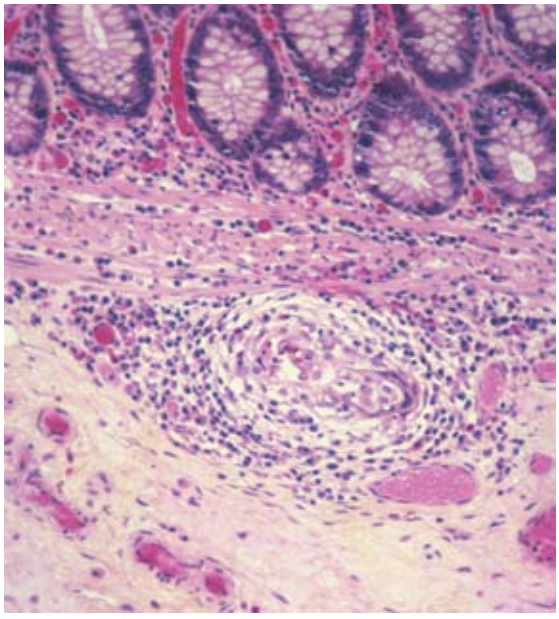


Figure 33.7. Schistosome egg in tissue of the small intestine. Note intense granuloma.

Cercariae must infect within 8 hours after emerging from its snail host; otherwise they exhaust their glycogen reserves and die.

Infection in the human host is initiated when the cercariae penetrate unbroken skin. With regards to *S. mansoni*, this step requires about 0.5 hour, but occurs much more rapidly with *S. japonicum*.[20] Skin penetration is usually through a hair follicle, and is facilitated by release of another set of proteases and eicasanoids.[21] Cercariae shed their tails, and rapidly transform within the dermal layer of skin into the schistosomula stage. After approximately 2 days, the schistosomulae migrate through the blood stream to the capillaries of the lung, where they remain for another several days. It is here that the immature worms acquire their ability to incorporate host serum proteins onto their tegumental surface. This "camouflage" has the profound effect of convincing the leukocytes that the worm is "self," enabling the parasite to live out a long, and prosperous life inside its new host. In addition, the worm possesses a β-2-microglobulin-like molecule that aids in confusing immune defense cells, particularly macrophages, in their attempt to recognize parasite antigens. Schistosomulae migrate from the lungs via the blood stream to the liver, where they mature to adult worms. Both sexes produce chemotactic agents that are mutually attractive, and eventually worms of opposite sex find each other in the vastness of the parenchymal tissue. They mate there, and migrate out into the mesenteric circulation. Egg production begins shortly thereafter. Other mammalian species, including baboons, rhesus monkeys, chimpanzees, mice, and rats, can be experimentally infected with the cercariae of *S. mansoni*. Few viable eggs are produced in the rat, however.

Cellular and Molecular Pathogenesis

Adult schistosomes usually do not cause significant pathological damage in the host. It is believed that the adult schistosome worm pair elicits remarkably little in the way of host immunopathologic responses as a consequence of unique antigen-masking properties. However, adult schistosomes living in the venous circulation have the capacity to harbor enteric bacteria affixed to their surface. This relationship can result in the introduction of enteric bacteria, such as Salmonella, directly into the bloodstream. As a result there is a well-described association between chronic schistosomiasis and so-called enteric fevers from non-typhoidal salmonellosis.[22]

In contrast to adults, the eggs produced by the worm pair result in profound immunopathologic responses. This phenomenon accounts for almost all of the pathology and clinical manifestations of schistosomiasis. For *S. japonicum* and *S. mansoni,* egg deposition occurs in the circulation of the small intestine and liver (Fig. 33.14) to produce intestinal and hepatic fibrosis, whereas *S. haematobium* egg deposition occurs in the circulation of the bladder to produce fibrosis leading to an obstructive uropathy. Heavy egg depo-

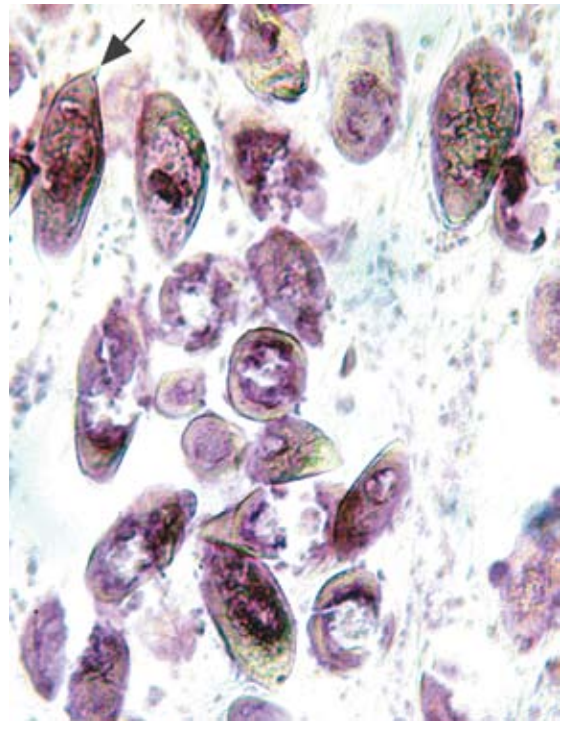


Figure 33.8. *S. haematobium* eggs in bladder wall. Note terminal spine (arrow).

sition occurs predominantly in individuals with large numbers of adult worms. Clinical illness caused by schistosomiasis generally occurs only in people who suffer from recurrent heavy worm burdens. Increasing evidence suggests that a component of this phenomenon depends on host genetic factors.[23] In this regard, the same genes specific for susceptibility to *Schistosoma mansoni* have been identified in people living in Africa and South America.[24] In a study in the Sudan, a specific gene locus was associated with advanced liver disease confirming epidemiologic observations of fibrosis occurring in families.[25] Furthermore, immunocompromised individuals with HIV shed fewer eggs in stool exams than similar individuals without HIV.[26] The soluble secretions from schistosome eggs, termed soluble egg antigens (SEAs), trigger host inflammatory and immune responses that result in granuloma formation,[27] and are T cell-dependent so as to include prominent Th2 components.[28] This Th2 bias can downregulate other host Th1 responses and result in altered patterns of host susceptibility to other infectious pathogens, possibly including the human immunodeficiency virus.[29, 30] The pathogenesis of granuloma formation also requires host-derived production of tumor necrosis factor.[31] The sizes of the granulomas vary with the age of the infection. In newly acquired infections, granulomas are large, causing displacement of normal tissue with fibrotic, epitheloid reactions. Over time, eggs elicit less and less volume of granulomatous tissue. This reaction appears to be under the regulation of IL-12.[32]

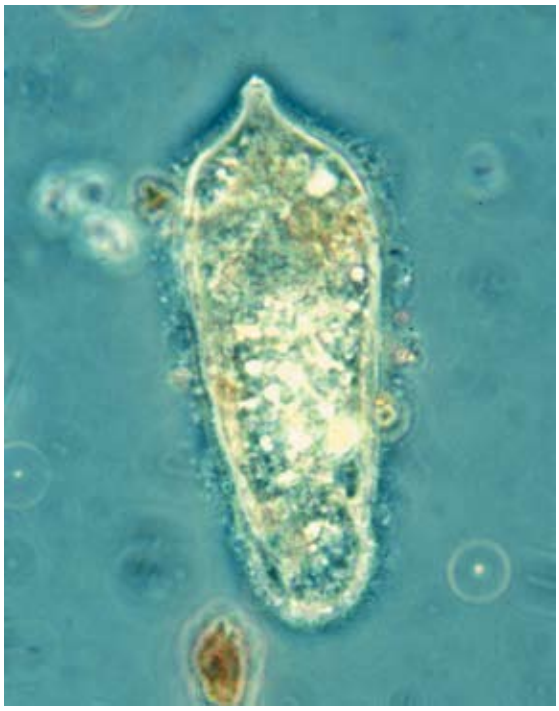


Figure 33.10. Miracidium of *S. mansoni*. Phase contrast.

Figure 33.9. Miracidium of *S. mansoni* caught in the act of hatching.

Granulomas form around eggs that collect in the intestinal wall and result in fibrosis. Erosion of the submucosa and villous tissue also occurs, presumably by the action of secreted proteolytic enzymes from the eggs. In heavy infection, gastrointestinal hemorrhage results from damage to the submucosa.

Eggs swept back into the liver block pre-sinusoidal capillaries, and induce granulomas there, as well. The presence of granulomas causes tissue fibrosis, and eventually leads to obstruction of the hepatic vasculature. Fibrosis of most of the portal areas incorporating the blood vessels leads to pipe stem fibrosis (Symmer's Fibrosis) (Fig. 33.15), and, ultimately, to portal hypertension. Clinically, this is manifest as hepatosplenomegaly, the extent of which is dependent partially on host major histocompatibility class II alleles.[33] Development of collateral circulation follows, including esophageal varices. Parenchymal liver cells remain unaffected by granulomas, and, hence, liver function remains normal.

Portal hypertension forces eggs to bypass the liver, and many are carried to the spleen, which becomes enlarged, further contributing to increased pressure in portal circulation. Infection with *S. japonicum* results in a greater number of granulomas and consequently greater morbidity because this species produces, on average, five to ten times more eggs than *S. mansoni*. Collateral circulation may also wash eggs into the lung

Figure 33.11. *Biomphalaria grabrata*, the most common intermediate snail host for *S. mansoni*.

capillary beds, occasionally leading to pulmonary fibrosis and consequent cor pulmonale.

Accumulation of *S. haematobium* eggs around the bladder and ureters leads to granuloma formation and fibrosis. In addition, calcification of dead eggs in the bladder wall (Fig. 33.16) results in rigidity of the bladder and subsequent increased pressure in the ureters and kidneys. The bladder epithelium develops pseudopolyps (Fig. 33.17), which can transform into squamous cell carcinoma in untreated patients (Fig. 33.18).

In some patients with long-standing disease (in all four types of schistosomiasis), deposition of immune complexes in kidneys can lead to basement membrane disease.[32]

Figure 33.12. *Oncomelania nosophora*, a snail intermediate host for *S. japonicum*.

Penetration of the skin by cercariae is dependent on the release of parasite-derived proteases and eicasanoids. The process of host entry typically causes no major reaction, but repeated exposure can lead to sensitization, and the development of a maculopapular rash (Fig. 33.19), characterized by IgE or IgG antibodies and an eosinophilic infiltrate. This is particularly true of accidental skin penetration by avian or bovine schistosomes. Many schistosomes specifically parasitic for animals can cause aberrant infections in humans. Avian schistosomes of the genera Austrobilharzia, Trichobilharzia, and Ornithobilharzia, and other mammalian schistosomes (*S. matthei* and *Schistosomatium douthitti*) are included in this group. The cercariae of these species cause a hypersensitivity skin reaction (cercarial dermatitis), known as “clam digger’s itch” or “swimmer’s itch” (Fig. 33.20).

Cellular and humoral responses to both penetrating cercariae and migrating schistosomula are a critical

Figure 33.13. Scanning electron micrograph of a cercaria of *S. mansoni*. Photo D. Scharf.

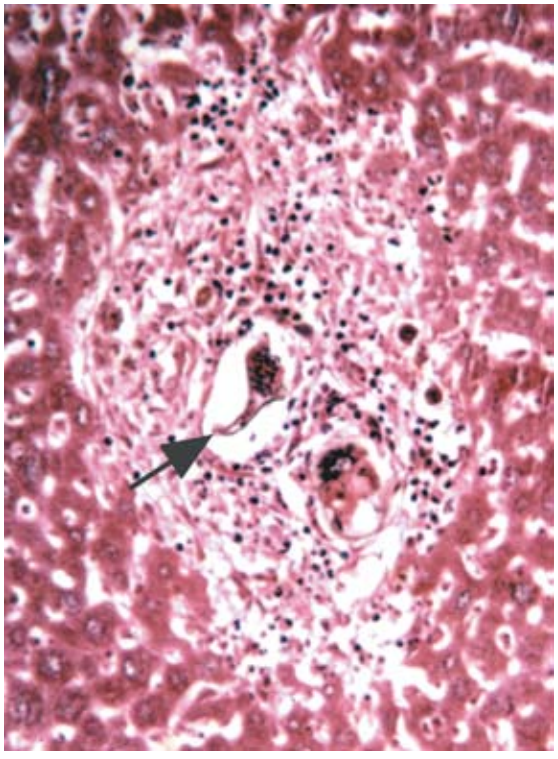


Figure 33.14. Granuloma in liver surrounding eggs of *S. mansoni*. Note the lateral spine (arrow).

component of naturally-acquired immunity to human schistosomiasis. This hypothesis derives from experimental evidence showing that cercariae attenuated by exposure to ionizing radiation (e.g., x-rays, gamma-rays or ultraviolet light), can penetrate skin and migrate through the tissues. In so doing they elicit protective immune responses, including IL-13.[35-37] These observations are the basis for an experimental vaccine in non-human primates. However, the cercariae must remain alive in order to secrete the antigens associated with vaccine protection. In humans living in endemic regions, this process may take years of exposure to cercariae. Until then, young children have a particular problem mounting an effective immune response to invading schistosomulae. The mechanism by which children during their early years of exposure to cercariae and invading schistosomulae are susceptible to the parasite but then become resistant over time is unclear. One widely held hypothesis is that young children respond initially to the parasite by producing IgG4 blocking antibodies.[38] It has been suggested that blocking antibodies delay the development of protective IgE that is needed for the resistance to infection that older people have in endemic areas.

Exploiting the current understanding of Th1 and Th2 immune responses elicited by different candidate antigens is the means by which vaccine researchers are attempting to bring a product to the field. Animal protection studies have used the protein paramyosin with good results in a mouse model although the mechanism of protection is still under study.[39] Studies in the Philippines in a population with risk of exposure to *S. japonicum* demonstrated that individuals with predominantly Th1 cellular immune responses appeared resistant to initial infection.[40, 41]

Clinical Disease

As in other helminth infections, clinical disease resulting from schistosomes usually occurs only in heavily-infected individuals. The clinical manifestations of acute schistosomiasis occur predominantly in *S. japonicum* and *S. mansoni* infections. This condition is sometimes known as “Katayama fever”. The classical disease attributed to schistosomiasis occurs during chronic infections. Chronic infection with *S. haematobium* can also lead to squamous carcinoma of the bladder.

Acute schistosomiasis (Katayama fever)

The dramatic clinical manifestations of Katayama fever occur most commonly in new immigrants who experience intense levels of exposure to either *S.*

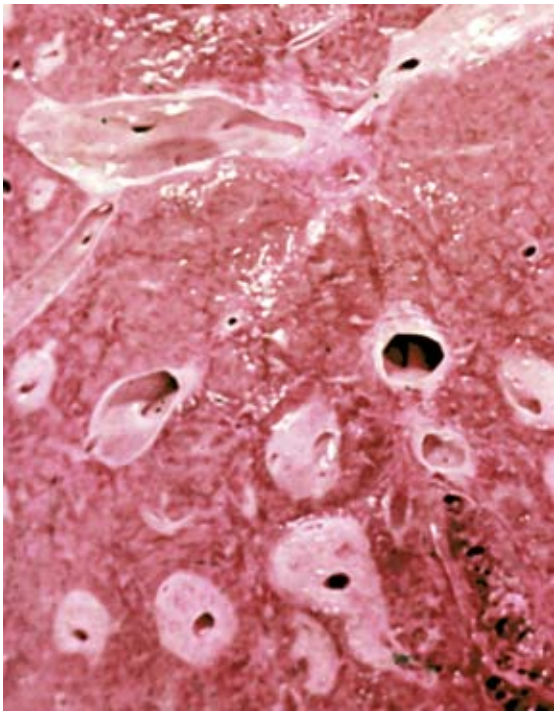


Figure 33.15. Pipe stem fibrosis in liver due to heavy infection with *S. mansoni*. Note normal liver tissue next to fibrotic vessels.

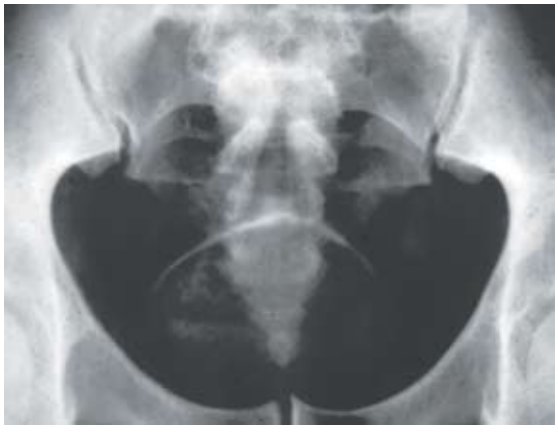


Figure 33.16. X-ray showing calcified dome of the bladder due to chronic infection with *S. haematobium.*

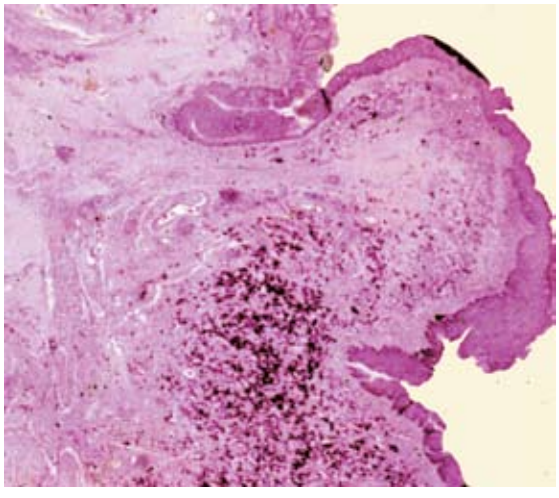


Figure 33.17. Histological section of bladder with pseudopolyp due to chronic infection with *S. haematobium.*

japonicum or *S. mansoni* cercariae. The name reflects the early descriptions of this syndrome in the Katayama Valley of Japan. The symptoms are often dramatic and appear approximately 4-8 weeks after initial exposure, when adult worm pairs begin releasing their eggs in the tissues. Some investigators believe that Katayama fever resembles some of the manifestations of serum sickness. There is also a clinical resemblance to typhoid fever. Patients experience hepatosplenomegaly and lymphadenopathy as well as an impressive eosinophilia. The affected individual is frequently febrile and has flu-like symptoms including cough and headache. At this stage of the illness, schistosome eggs may not yet have appeared in the feces.

Chronic schistosomiasis

This manifestation of infection occurs as a consequence of many years of progressive injury resulting from chronic egg deposition in the tissues and the resulting granuloma formation (Fig. 33.21). The injury has an immunopathological basis. In the case of *S. japonicum* and *S. mansoni* infection, the injury occurs when eggs are deposited in the wall of the intestine and in the liver parenchyma. With *S. haematobium,* injury occurs in the bladder. The extent of injury depends on chronic worm burden, so chronic schistosomiasis occurs predominantly in individuals who are predisposed to repeated heavy infections.[38] Generally speaking, heavy infections occur only in less than one-fourth of a given population under conditions of heavy exposure to cercariae, where up to 10% of individuals develop periportal fibrosis.

S. japonicum and *S. mansoni* infections result in chronic intestinal and hepatic dysfunction. Children with intestinal schistosomiasis develop intermittent abdominal pain, sometimes accompanied with bloody diarrhea. The blood loss and ulceration of intestinal schistosomiasis may result in iron deficiency and anemia. This may explain why chronic schistosomiasis during childhood can result in physical growth retardation similar to that described for intestinal nematode infections. Stunting becomes most prominent at the age of peak intensity (usually between 8 and 20 years).[42] It is partly reversible by specific anthelmintic therapy.[43]

Hepatomegaly results from portal fibrosis. Splenomegaly follows, and in advanced cases, the spleen may fill much of the left side of the abdomen. The patient may also develop symptoms of hypersplenism. Portal obstructive disease due to schistosomiasis is similar to other causes in that it leads to hematemesis from ruptured esophageal varices. As a result of portal hypertension, and the consequent development of a collateral circulation, schistosome eggs are washed into the lungs, where they induce granulomatous inflammation, leading to obstructive disease culminating in cor pulmonale. As noted above, long standing infections can cause nephrotic syndrome, resulting from the deposi-

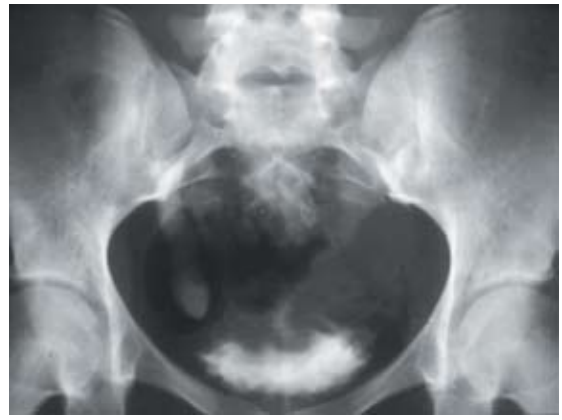


Figure 33.18. X-ray of bladder with a squamous cell tumor induced by *S. haematobium* eggs.

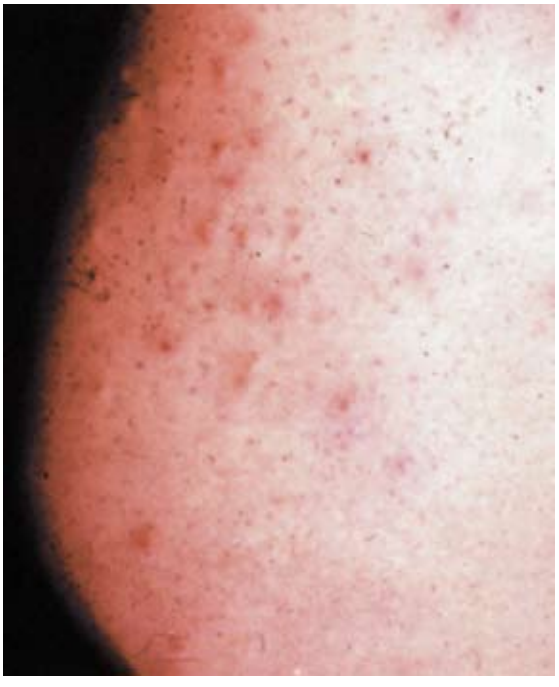


Figure 33.19. Thigh of a child suffering from a maculopapular rash ("swimmer's itch") due to the cercariae of a schistosome species that normally infects birds.

tion of immune complexes onto the glomerular membrane.

S. haematobium, unlike the other three major schistosomes, causes involvement of the urinary tract, which is characterized by an inflammation to the eggs as they are deposited in the wall of the bladder. Patients with chronic *S. haematobium* infection develop hematuria as well as symptoms that mimic urinary tract infections such as dysuria and increased urinary frequency. Over time the inflammatory changes in the bladder can result in fibrosis that can lead to an obstructive uropathy. This sometimes results in hydronephrosis or hydroureter. The resulting urinary stasis can sometimes lead to secondary bacterial urinary tract infections that may exacerbate the scarring and fibrosis.

Bladder carcinoma

A unique type of bladder carcinoma occurs in regions where *S. haematobium* is endemic. In contrast to adenocarcinoma, the most common type of bladder cancer in industrialized countries, some patients with chronic *S. haematobium* go on to develop squamous cell carcinoma. Squamous cell carcinoma is the most common type of bladder cancer in parts of Egypt as well as elsewhere in Africa. Possibly over time the *S. haematobium* eggs function as a human carcinogen that elicit metaplastic changes in the bladder.[44]

CNS schistosomiasis

Rarely, all three schistosomes induce focal inflammatory reactions within the central nervous system, caused by deposition of eggs in the spinal cord and the brain.[45] *S. mansoni* and *S. haematobium* are more likely to do so in the spinal cord, and *S. japonicum* in the brain. Inflammation due to eggs may result in focal transverse myelitis and encephalopathy.

Diagnosis

Definitive diagnosis is made by microscopically identifying schistosome eggs in stool or urine (Figs. 33.4, 33.5a, 33.5b, 33.6). If a single stool examination is negative, concentration of a specimen collected over a 24-hour period is required, because the number of eggs in stool can be few. Quantitative egg counts are sometimes useful for epidemiologic studies attempting to determine infection intensities. For light infections, or in patients from whom egg excretion is intermittent and from whom eggs cannot be found in stool, a rectal biopsy can be carried out (Fig. 33.22). The tissue is squashed between two microscope slides and examined under the low-power lens of a microscope. It is helpful to refer to the specimen as a "rectal snip," rather

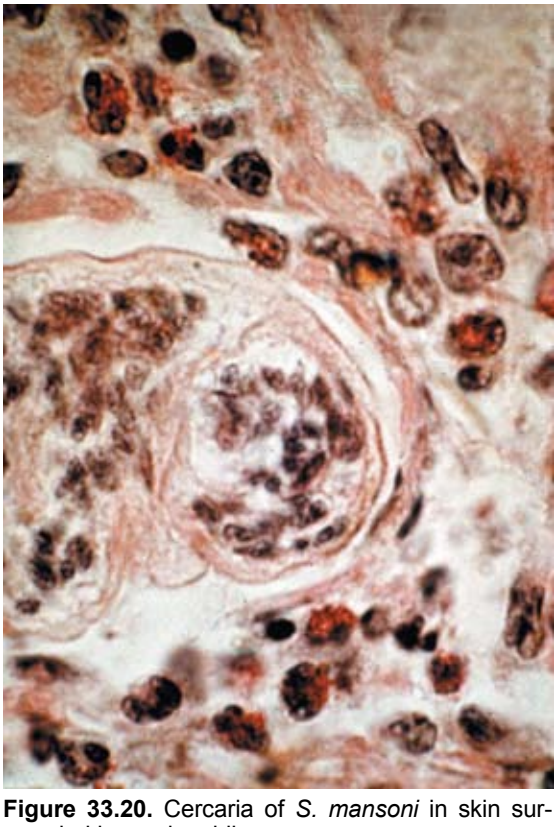


Figure 33.20. Cercaria of *S. mansoni* in skin surrounded by eosinophils.

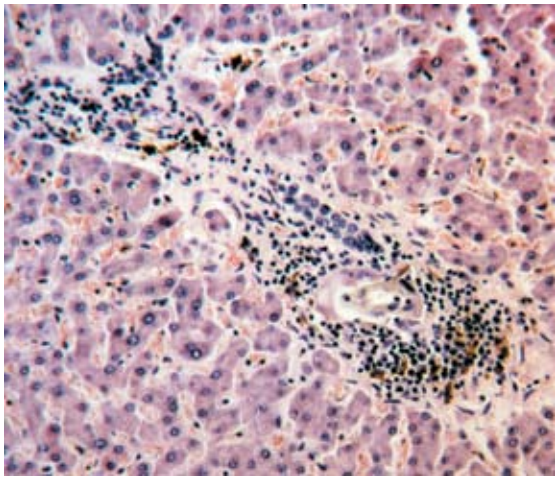


Figure 33.21. Granuloma surrounding an egg of *S. mansoni* in liver tissue.

than a biopsy, to preclude its fixation and subsequent sectioning, which would make identification of eggs more difficult.

Urine is examined for the presence of eggs of *S. haematobium*. The urine sample should generally be collected close to noon, when egg excretion is usually maximal. Urine may have to be concentrated by sedimentation to reveal the few eggs present. *S. haematobium* eggs may also be seen in stool and rectal snip specimens, but their numbers are typically small in these samples.

As an alternative to the current methods of diagnosis, two schistosome antigens known as CCA and CAA that circulate in the bloodstream of infected patients have been identified.[46] The detection of these antigens may someday provide the basis of a fingerstick dot-ELISA assay for the diagnosis of active infections.A positive serological test to detect anti-schistosomal antibodies is indirect evidence of infection, and cannot distinguish current from past infection, or light versus heavy infection. Indirect immunofluorescence, ELISA, and circumoval precipitin tests are available. The reactions are positive in nearly all infected individuals. The ELISA test is particularly useful for conducting epidemiologic surveys or in recent travelers.

Portable ultrasound imaging has been shown to be clinically useful in the diagnosis of schistosomiasis. Ultrasound can define the extent of Symmer's fibrosis in patients with *S. mansoni* or *S. japonicum* infections, while the chronic obstructive changes associated with *S. haematobium* infection can also be detected.[47]

Treatment

Praziquantel is the drug of choice for most species of schistosomes. This drug is well-tolerated, is associated with few side effects (nausea, epigastric pain, dizziness, and general malaise), has a very high therapeutic index, and a single dose is usually sufficient to kill all adult worms. Praziquantel allows for calcium ion influx across the tegument resulting in spastic paralysis and at higher doses, the worm tegument develops blebs and is unmasked, and is now susceptible to immune attack by the host.[48] In younger patients praziquantel may also reverse some of the pathology associated with Symmer's fibrosis.[49] There is evidence that part of its effectiveness is due to synergism with the host's humoral immune response.[50] Because it is effective in a single dose, it has been used in control programs (see below). In patients with CNS schistosomiasis, administration of the drug may elicit inflammation that may temporarily exacerbate pathology and worsen symptoms similar to that described in patients with neurocysticercosis. It is not recommended for pregnant patients.

Praziquantel is now available for $0.30 and the World Health assembly has endorsed community treatment of school-age children in endemic areas. Resistance has not occurred to any appreciable degree although this must be monitored closely.

Alternatives to praziquantel are limited in use due to a higher frequency of adverse reactions and differences in spectrum of activity. Oxamniquine is an alternate drug with good anti-parasitic activity. In some regions, oxamniquine is as effective as praziquantel for the treatment of infections with *S. mansoni*, and metrifonate is effective for the treatment of *S. haematobium* infections.[51] The anti-malarial drug artemether has been studied in China as a chemprophylactic agent in patients who anticipate high levels of exposure to *S. japonicum* and *S. mansoni* cercariae

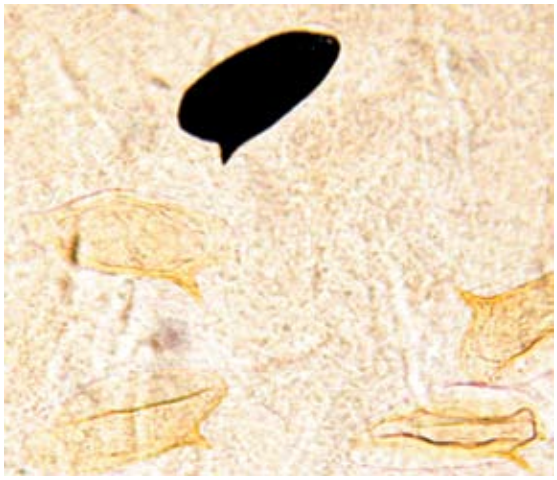


Figure 33.22. Biopsy of rectal tissue revealing eggs of *S. mansoni*. Note calcified egg, indicating that the infection was chronic.

Figure 33.23. Lake Nasser and the Aswan High Dam in Egypt. Photo S. Musgrave, astronaut *extraordinaire*.

during seasonal floods.[52] Chemoprophylactic activity of artemether was present but lower against *S. haematobium*.[53] The efficacy of praziquantel is enhanced when combined with artemether[54] and the combination might prevent the emergence of resistance to praziquantel when used in widespread and repeated community treatment.

Treatment should be carried out only in patients with active schistosome infections. Portocaval or splenorenal shunts should be avoided in untreated schistosomiasis, because they increase the probability of eggs reaching the lungs. If such a shunt is mandated by the intensity of portal hypertension, it should be carried out only after treating with any of the above mentioned drugs.

Prevention and Control

Schistosomes' success in carrying out their life cycles is dependent upon complex ecological interactions with a wide variety of invertebrate and vertebrate host species. Hence, they appear to have numerous weak points in their quest to complete their life cycles. Numerous control programs have attempted to take advantage of these "weak points." Control programs in the Middle East and North Africa have nearly succeeded in schistosome elimination while programs in China and Brazil have also achieved remarkable success.[55, 56] The prospects for less-developed countries remain dismal because of a lack of adequate resources committed to health in general.

Prevention of schistosomiasis by individuals requires that they never come in contact with infested fresh water. This suggestion is impossible to carry out in much of the world because of many complex economic, cultural, and behavioral patterns. In addition, it may be necessary for many people to be in contact with fresh water for agricultural or other food-gathering purposes. Temporary visitors to endemic areas, however, can heed the advice to avoid potential sources of infection. Dam-building in Africa has helped increase the spread of schistosomiasis (Fig. 34.23).

Control of schistosomiasis at the community level has been directed at (1) eradication of snail vectors with molluscacides, and biologic agents[57]; (2) public health education; (3) sanitation,[58] or other engineering interventions concerning fresh water supplies; and (4) chemotherapy with praziquantel and oxamniquine. Control of *S. japonicum* is complicated by the occurrence of reservoir hosts, such as water buffalo and cattle, in many regions of Asia, particularly in China. The true extent of horizontal transmission from these animal reservoir hosts to people is not known.

Studies in endemic areas have shown that while praziquantel is effective at treating large populations, there is a high rate of post-treatment reinfection. This necessitates frequent administration of the drug, although this tactic is frequently not possible in poor, developing rural areas.[59] Therefore, control of the infection with anthelminthic drugs alone is difficult. There is also concern about the emergence of praziquantel drug resistance.[60]

Candidate antigens under study as potential vaccine candidates were largely discovered over 10 years ago. An *S. haematobium* vaccine has completed safety testing in humans.[61] Paramyosin combined with other peptides to prevent *S. mansoni* infection is likely to be the first candidate tested.[62] Human testing is needed to evaluate the experimental evidence from murine models.[63]

To learn more about the ecology of snail intermediate hosts important to the maintenance of schistosome infections in humans, as well as control programs that take advantage of their biology, see www.medicalecology.org/water/schistosomiasis/schistosomiasis.htm.

References

1. Fuller GK. Lemma A. Trinidad H. Schistosomiasis in Omo National Park of southwest Ethiopia. Am J Trop Med Hyg 28:467-471. 1979.
2. World Health Organization. Weekly Epidemiol Rec 64:171. 1989.
3. Minai M. Hosaka Y. Ohta N. Historical view of schistosomiasis japonica in Japan: implementation and evaluation of disease-control strategies in Yamanashi Prefectur. Parasitol Int. 52:321-6. 2003
4. Hotez PJ. Feng Z. et al. Emerging and re-emerging helminthiases and the public health of China. Emerg Infect Dis 3:303-310. 1997.
5. Manson P. Report of the case of bilharzia from the West Indies. BMJ 2:1894-1895. 1902.
6. Sambon LW. New or little known African entozoa. J Trop Med Hyg 10:117. 1907.
7. Piraja de Silva MA. Contribucao para o estudo da schistosomiasena Bahia. Brazil Med 2:281-283. 1908.
8. Leiper RT. Researches on Egyptian Bilharziosis. John Bale Sons and Danielsson. London. 1918.
9. Katsurada F. The etiology of a parasitic disease. Iji Shimbun 669:1325-1332. 1904.
10. Catto J. Schistosoma cattoi, a new blood fluke of man. BMJ 1:11-13. 1905.
11. Majima T. A strong case of liver cirrhosis caused by parasitic ova. Tokyo Ig Za 2:898-901. 1888.
12. Kawanishi K. A report on a study of the “Katayama disease” in Higo-No-Kuni. Tokyo Ig Za 18:31-48, 1904.
13. Fujinami K. Nakamura H. Katayama disease in Hiroshima prefecture: route of infection, development of the worm in the host and animals in Katayama disease in Hiroshima prefecture (Japanese blood sucking worm disease-schistosomiasis japonica). Kyoto Ig Za 6:224-252. 1909.
14. Miyagawa Y. Uber den Wanderungsweg des *Schistosomum japonicum* von der Haut bis zum Pfortadersystem und uber die Korperkonstitution der jungsten Wurmer zur Zeit der Hautinvasion. Zentralbl Bakteriol Parasit Lnfekt 66: 406-417. 1912.
15. Miyairi K. Suzuki M: Der Zwischenwirt der *Schistosoma japonicum* Katsurada. Mitt Med Fakultat Kaiserlichen Univ Kyushu 1:187-197. 1914.
16. Griesinger W: Klinische und anatomische Beobachtungen uber die Krankheiten von Aegypten. Arch Physiol Heilk 13:528-575. 1854.
17. Lawrence JD. The ingestion of red blood cells by *Schistosoma mansoni*. J Parasitol 59:60-63. 1973.
18. Chappell CL. Kalter DC. Dresden MH. The hypersensitivity response to the adult worm proteinase, Smw32, in *Schistosoma mansoni* infected mice. Am J Trop Med Hyg 39:463-468. 1988.
19. Vermund SH. Bradley DJ. Ruiz-Triben E. Survival of *Schistosoma mansoni* in the human host: estimates from a community-based prospective study in Puerto Rico. Am J Trop Med Hyg 32: 1040-1048.1983.
20. Ruppel A. Chlichlia K. Bahgat M. Invasion by schistosome cercariae: neglected aspects in *Schistosoma japonicum*. Trends Parasitol. 20:397-400. 2004.
21. Cohen FE. Gregoret LM. et al: Arresting tissue invasion of a parasite by protease inhibitors chosen with the aid of computer modeling. Biochemistry 30:11221-11229. 1991.
22. Gendrel D. Kombila M. Beaudoin-Leblevec. Richard-Lenoble D. Nontyphoidal salmonellal septicemia in Gabonese children infected with Schistosoma intercalatum. Clin Infect Dis 18:103-5, 1994.
23. Webster JP. Do hosts and parasites coevolve? Empirical support from the schistosoma system. Am Nat.164 Suppl 5:S33-51. 2004.
24. Chiarella JM. Goldberg AC. et al. Absence of linkage between MHC and a gene involved in susceptibility to human schistosomiasis. Brazil J Med Biol Res 31:665-70. 1998.
25. Dessein AJ. Hillaire D. et al. Severe hepatic fibrosis in *Schistosoma mansoni* infection is controlled by a major locus that is closely linked to the interferon-gamma receptor gene. Am J Hum Genet. 65:709-21. 1999.
26. Karanja DM. Boyer AE. et al. Studies on schistosomiasis in western Kenya: II. Efficacy of praziquantel for treatment of schistosomiasis in persons coinfected with human immunodeficiency virus-1. Am J Trop Med Hyg. 59:307-11. 1998.
27. Warren KS. The pathology of schistosome infections. Helminth Abstr Ser A 42:591-633. 1973.
28. King CL. Xianli J. et al. Mice with a targeted deletion of the IgE gene have increased worm burdens and reduced granulomatous inflammation following primary infection with *Schistosoma mansoni*. J Immunol 158:294-300. 1997.
29. Pearce EJ. Caspar P. et al. Down-regulation of Th1 cytokine production accompanies induction of Th2 responses by a parasitic helminth, *Schistosoma mansoni*. J Exp Med 173: 159-166. 1991.
30. Curry AJ. Else KJ. et al. Evidence that cytokine-mediated immune interactions induced by *Schistosoma mansoni* alter disease outcome in mice concurrently infected with *Trichuris muris*. J Exp Med 181:769-774. 1995.
31. Haseeb MA. Shirazian DJ. Preis J. Elevated serum levels of TNF-alpha, sTNF-RI and sTNF-RII in murine schistosomiasis correlate with schistosome oviposition and circumoval granuloma formation. Cytokine. 15:266-9. 2001.
32. Wynn TA. Development of an anti-pathology vaccine for schistosomiasis. Ann New York Acad Sci 797:191-5. 1996.
33. Secor WE. del Corral H. et al. Association of hepatosplenic schistosomiasis with HLA-DQB1*0201. J Infect Dis 174:1131-5. 1996.
34. Watt G. Long GW. et al. Prevalence of renal involvement in *Schistosoma japonicum* infection. Trans R Soc Med Hyg 82: 339-342.1991.
35. Bickle QD. Andrews BJ. et al. Resistance against *Schistosoma mansoni* induced by highly irradiated infections: studies on species specificity of immunization and attempts to transfer resistance. Parasitol 90:301-312. 1985.
36. Mangold BL. Dean DA. The role of IgG antibodies from irradiated cercaria-immunized rabbits in the passive transfer of immunity to *Schistosoma mansoni*-infected mice. Am J Trop Med Hyg 47: 821-829,1992.
37. Dessein A. Kouriba B. et al. Interleukin-13 in the skin and interferon-gamma in the liver are key players in immune protection in human schistosomiasis. Immunol Rev. 201:180-90. 2004.
38. Acosta LP. McManus DP. et al. Antigen-specific antibody isotype patterns to *Schistosoma japonicum* recombinant and native antigens in a defined population in Leyte, the Philippines. Am J Trop Med Hyg. 70:549-55. 2004.
39. Kojima S. Nara T. et al. A vaccine trial for controlling reservoir livestock against schistosomiasis japonica. In Tada, I Kojima S and Tsuji

M (eds), Proceedings of the 9th International Congress of Parasitology. Bologna, 489-494. 1998.
40. Acosta LP. Waine et al. Immune correlate study on human *Schistosoma japonicum* in a well-defined population in Leyte, Philippines: II. Cellular immune responses to *S. japonicum* recombinant and native antigens. Acta Trop. 84:137-49. 2002.
41. Acosta LP. Aligui A. et al. Immune correlate study on human *Schistosoma japonicum* in a well-defined population in Leyte, Philippines: I. Assessment of 'resistance' versus 'susceptibility' to *S. japonicum* infection. Acta Trop. 84:127-36. 2002.
42. McGarvey ST. Aligui G. et al. Child growth and schistosomiasis japonica in northeastern Leyte, Philippines. I. Cross sectional results. Am J Trop Med Hyg 46:571-581. 1992.
43. Stephenson LS. Latham MC. et al. Single dose metrifonate or praziquantel treatment in Kenyan children. II. Effects on growth in relation to *Schistosoma haematobium* and hookworm egg counts. Am J Trop Med Hyg 41:445-453. 1989.
44. Hodder SL. Mahmoud AA. et al. Predisposition to urinary tract epithelial metaplasia in *Schistosoma haematobium* infection. Am J Trop Med Hyg. 63:133-8. 2000.
45. Scrimgeour EM. Gaidusek CD. Involvement of the central nervous system in *Schistosoma mansoni* and *S. haematobium* infection. Brain 108:1023-1038.1985.
46. van Dam GJ, Wichers JH. et al. Diagnosis of schistosomiasis by reagent strip test for detection of circulating cathodic antigen. J Clin Microbiol. 42:545 61. 2004.
47. Ultrasound in Schistosomiasis (Hatz C. Jenkins JM. Tanner M, eds). Acta Tropica 51:1. 1992.
48. Greenberg RM. Are Ca2+ channels targets of praziquantel action? Int J Parasitol. 35:1-9. 2005.
49. Homeida MA. Tom JE. Nash T. Bennett JL. Association of the therapeutic activity of praziquantel with the reversal of Symmer's fibrosis induced by *Schistosoma mansoni*. Am J Trop Med Hyg 45:360-365. 1991.
50. Brindley PJ. Sher A. The chemotherapeutic effect of praziquantel against *Schistosoma mansoni* is dependent on host antibody response. J Immunol 139:215-220. 1987.
51. King CH. Lombardi G. et al. Chemotherapy-based control of schistosomiasis haematobia. II. Metrifonate vs. praziquantel in control of infection-associated morbidity. Am J Trop Med Hyg 42:587-595. 1990.
52. Xiao SH. Tanner M. Artemether in the chemopropylaxis against schistosomiasis in China. Parasitol. Today. 2000.
53. Utzinger J. Chollet J. et al. Effect of combined treatment with praziquantel and artemether on *Schistosoma japonicum* and *Schistosoma mansoni* in experimentally infected animals. Acta Trop. 80:9-18. 2001.
54. Ngoran EK. Utzinger J. et al. Randomized, double blind placebo controlled trial of oral artemether for the prevention of patent S. hematobium infections. Am J Trop Med Hyg, 68; 24-32. 2003.
55. Engels D. Chitsulo L. Montresor A. Savioli L. The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta Trop. 82:139-46. 2002.
56. Jordan P. Schistosomiasis research to control. Am J Trop Med Hyg 26:877-885. 1977.
57. Jobin WR. Brown RA. et at. Biological control of *Biomphalaria glabrata* in major reservoirs of Puerto Rico. Am J Trop Med Hyg 26: 1018-1024.1977.
58. Unrau GO. Individual household water supplies in rural St. Lucia as a control measure against *Schistosoma mansoni*. Bull WHO 52:1-8. 1975.
59. Olveda RM. Daniel BL. et al. Schistosomiasis japonica in the Philippines: The long term impact of population based chemotherapy on infection, transmission and morbidity. J Infect Dis 174:163-72. 1996.
60. Herwaldt BL. Tao LF. et al. Persistence of *Schistosoma haematobium* infection despite multiple courses of therapy with praziquantel. Clin Infect Dis 20:309-15. 1995.
61. Capron A. Capron M. Dombrowicz D. Riveau E. Vaccine strategies against schistosomiasis: from concepts to clinical trials. Int Arch Allergy Immunol Jan 124:9-15. 2001.
62. Pearce EJ. Progress towards a vaccine for schistosomiasis. Acta Trop. 86:309-13. 2003.
63. Bergquist R. Al-Sherbiny M. Barakat R. Olds R. Blueprint for schistosomiasis vaccine development. Acta Trop. 82:183-92. 2002.