Review Article

Current Concepts

SCHISTOSOMIASIS

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IN 1851, Theodor Bilharz described a parasitic infection (bilharzia) that would later be termed schistosomiasis. Currently, 200 million people in 74 countries have this disease; 120 million of them have symptoms, and 20 million have severe illness.[1] Schistosomiasis is caused by parasitic trematode worms (schistosomes) that reside in the abdominal veins of their vertebrate definitive hosts. The life cycle of the schistosome is depicted in Figure 1. Schistosomiasis is 1 of the 10 tropical diseases especially targeted for control by the Special Program for Research and Training in Tropical Diseases of the United Nations Development Program, the World Bank, and the World Health Organization.[4] The 54th World Health Assembly has set a goal of treating annually at least 75 percent of the school-age children who are infected with schistosomes and soil-transmitted helminths.[5]

Despite major advances in control and substantial decreases in morbidity and mortality, schistosomiasis continues to spread to new geographic areas.[6] Furthermore, there are reports of resistance to praziquantel, the mainstay of medical treatment. The majority of *Schistosoma haematobium*, *S. mansoni*, and *S. intercalatum* infections are found in sub-Saharan Africa. *S. mansoni* remains endemic in parts of Brazil, Venezuela, and the Caribbean. *S. japonicum* infection still occurs in China, Indonesia, and the Philippines, despite substantial and largely successful control measures. *S. mekongi* is found in Cambodia and Laos, along the Mekong River.[1] Accurate figures on the global status of schistosomiasis have been published[1] and are also available at http://www.who.int/ctd/schisto/epidemio.htm.

Environmental changes that result from the development of water resources and the growth and migration of populations can facilitate the spread of schistosomiasis.[6] For example, the construction of Diama Dam on the Senegal River led to the introduction of *S. mansoni* into Mauritania and Senegal. The movement of refugees and the displacement of populations resulted in the introduction of *S. mansoni* into Somalia and Djibouti. The presence of the Aswan Dam in Egypt has led to the virtual elimination of *S. haematobium* from the Nile Delta but has brought about the establishment of *S. mansoni* in upper Egypt. The Three Gorges Dam is currently being built on China's Yangtze River between two areas where schistosomiasis is endemic.[7] The Chinese Ministry of Health is currently evaluating the potential effect of the dam on schistosomiasis transmission.[7]

Figure 1 (facing page). Life Cycle of the Schistosome.

Five species of schistosoma are known to infect humans. Infection with *Schistosoma mansoni, S. japonicum, S. mekongi,* or *S. intercalatum* is associated with chronic hepatic and intestinal fibrosis. *S. haematobium* infection results in fibrosis, stricturing, and calcification of the urinary tract. All schistosoma infections follow direct contact with fresh water that harbors free-swimming larval forms of the parasite known as cercariae. Cercariae penetrate the skin of humans or, in the case of *S. japonicum,* humans and other mammalian hosts that act as reservoirs for infection. The cercariae shed their bifurcated tails, and the resulting schistosomula enter capillaries and lymphatic vessels en route to the lungs. After several days, the worms migrate to the portal venous system, where they mature and unite. Pairs of worms then migrate to the superior mesenteric veins (in the case of *S. mansoni*), the inferior mesenteric and superior hemorrhoidal veins (in the case of *S. japonicum*), or the vesical plexus and veins draining the ureters (in the case of *S. haematobium*). Egg production commences four to six weeks after infection and continues for the life of the worm — usually three to five years. Eggs pass from the lumen of blood vessels into adjacent tissues, and many then pass through the intestinal or bladder mucosa and are shed in the feces (in the case of *S. mansoni* and *S. japonicum*) or urine (in the case of *S. haematobium*). The life cycle is completed when the eggs hatch, releasing miracidia that, in turn, infect specific freshwater snails (*S. mansoni* infects biomphalaria species, *S. haematobium* infects bulinus species, and *S. japonicum* infects oncomelania species). After two generations — primary and then daughter sporocysts — within the snail, cercariae are released. Modified from Jordan et al.[2] and Waine and McManus.[3]

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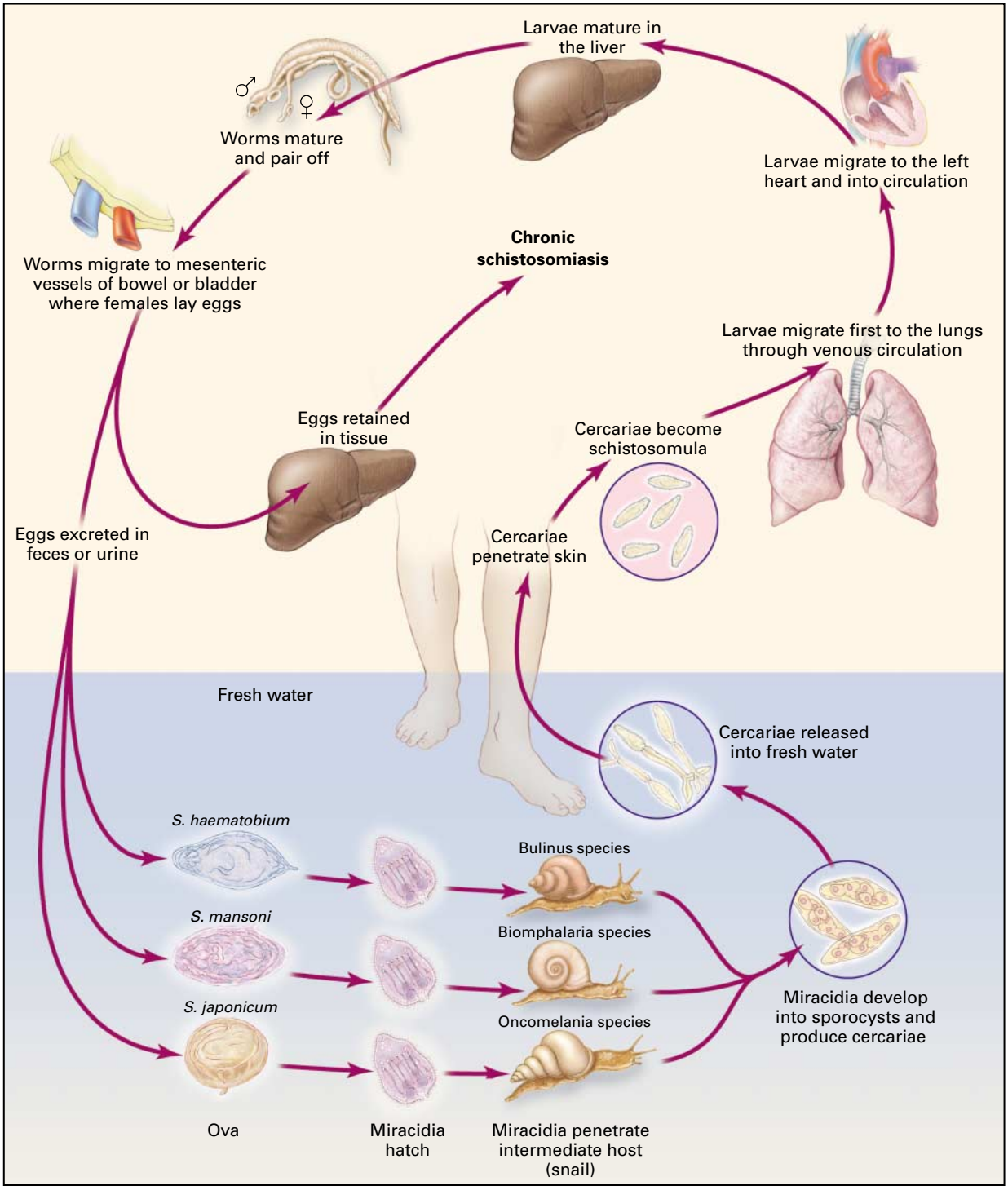

PATHOPHYSIOLOGY AND CLINICAL DISEASE

Immediate Manifestations

A maculopapular eruption may arise at the site of penetration by the cercarial (free-swimming larvae) form of the parasite. In migrants or tourists who become infected, skin reactions may develop within a few hours after infection. However, a rash may appear up to one week later. The dermatitis is similar to, but less severe than, swimmers' itch, which develops in sensitized persons when they are reinfected by species of schistosomes that do not colonize humans (usually the types that colonize birds).[8]

Acute Schistosomiasis

Acute schistosomiasis (Katayama fever)[9] is common in areas of high transmission rates. A history of contact with contaminated water 14 to 84 days before presentation is usual. Symptoms are thought to be mediated by the immune complex, and the majority of cases begin with the deposition of an egg into host tissues. Common symptoms include fever, headache, generalized myalgias, right-upper-quadrant pain, and bloody diarrhea. Respiratory symptoms have been reported in up to 70 percent of persons infected with *S. mansoni* but less frequently in those infected with *S. haematobium*.[10-12] Tender hepatomegaly is usually present, and splenomegaly occurs in one third of cases. Aseptic meningitis is rare. There may be radiologic evidence of interstitial pneumonitis. Not all patients shed eggs, but all have eosinophilia and most have positive serologic tests. Praziquantel works exclusively against adult worms, and therefore, repeated treatment or a prolonged course with 20 mg per kilogram of body weight per day has been used.[13,14] Oxamniquine has also been recommended.

Chronic Schistosomiasis

Gastrointestinal and Liver Disease

Schistosomiasis results from the host's immune response to schistosome eggs (Fig. 2) and the granulomatous reaction evoked by the antigens they secrete.[15] The intensity and duration of infection determine the amount of antigen released and the severity of chronic fibro-obstructive disease (Fig. 3). The granulomas destroy the ova but result in fibrotic deposition in host tissues. Most granulomas develop at the sites of maximal accumulation of eggs — the intestine and the liver (in the case of *S. mansoni* and *S. japonicum*) and the genitourinary tract (in the case of *S. haematobium*). However, periovular granulomas have been found in many types of tissue, including the skin, lung, brain, adrenal glands, and skeletal muscle.[16] The inflammatory response may assist the migration of eggs into the lumen of the gut or urinary tract.

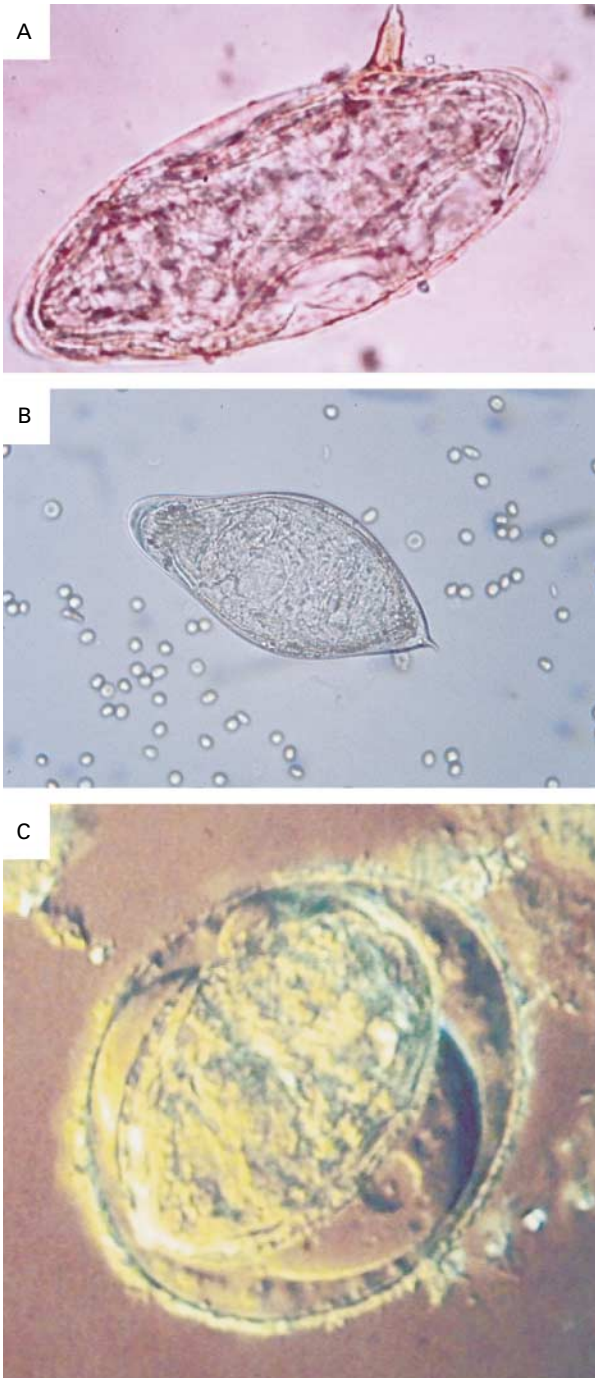

Figure 2. Morphology of the Eggs of the Three Key Schistosomes That Infect Humans.

The *Schistosoma mansoni* egg (Panel A, ×200) measures approximately 140 by 61 μm and has a prominent lateral spine. The *S. haematobium* egg (Panel B, ×100) is approximately 150 by 62 μm with a prominent terminal spine. Both are ovoid. The *S. japonicum* egg (Panel C, ×200) is round, has a lateral spine that is often obscured, and is smaller than the other two types of eggs (60 by 100 μm).

This possibility is supported by studies demonstrating that T-cell–deficient mice[17,18] and patients with advanced cases of the acquired immunodeficiency syndrome have significantly reduced egg output.[19]

Eggs retained in the gut wall induce inflammation, hyperplasia, ulceration, microabscess formation, and polyposis.[20-22] Colicky hypogastric pain or pain in the left iliac fossa is frequent. Diarrhea is common and may alternate with constipation. Diarrhea is particularly common in children, and its presence correlates strongly with schistosomiasis.[23] Occult (or sometimes visible) blood in the feces is usual. Severe chronic intestinal disease may result in colonic or rectal stenosis. Colonic polyposis may be manifested as a protein-losing enteropathy.[24] Inflammatory masses in the colon may even mimic cancer.[25] The relation between colorectal cancer and schistosomiasis has been debated for decades. If there is an increase in the risk of colorectal cancer, it is small.[14,26,27]

Eggs of *S. mansoni* and *S. japonicum* embolize to the liver, where the granulomatous inflammatory response induces presinusoidal inflammation and periportal fibrosis. Referred to as clay-pipe-stem fibrosis, this condition occurs in 4 to 8 percent of patients who have chronic infection.[16] It takes many years to develop and is associated with sustained heavy infection. Hepatomegaly reflects the presence of granulomatous inflammation and occurs early in the evolution of chronic disease.[28] Periportal collagen deposits lead to the progressive obstruction of blood flow, portal hypertension, and ultimately varices, variceal bleeding, splenomegaly, and hypersplenism. This periportal fibrosis can be seen on ultrasonography, computed tomography, or magnetic resonance imaging and is characteristic of schistosomiasis. Hepatocellular synthetic function is preserved until the very late stages of disease. Lobular architecture is retained, and nodular regenerative hyperplasia does not occur. Ultrasonography, in addition to clinical examination, is used to detect and quantify hepatosplenic disease on the basis of the criteria of the World Health Organization.[29-31] *S. haematobium* infection occasionally causes mild colonic or hepatic disease.[32]

Coinfection with either hepatitis B virus (HBV) or hepatitis C virus (HCV) and *S. mansoni* is associated with accelerated deterioration of hepatic function.[33,34] Alcohol-induced cirrhosis, HBV, or HCV can coexist with clay-pipe-stem fibrosis. The combination of chronic schistosomiasis caused by *S. mansoni* and HBV infection may result in a higher risk of hepatocellular carcinoma than that attributable to HBV alone.[33] In contrast, there does not appear to be a significant interaction between HBV and *S. japonicum* infection.[35] Egypt's mass campaigns of parenteral antischistosomal therapy (which ceased in the 1980s) contributed substantially to the high preva-

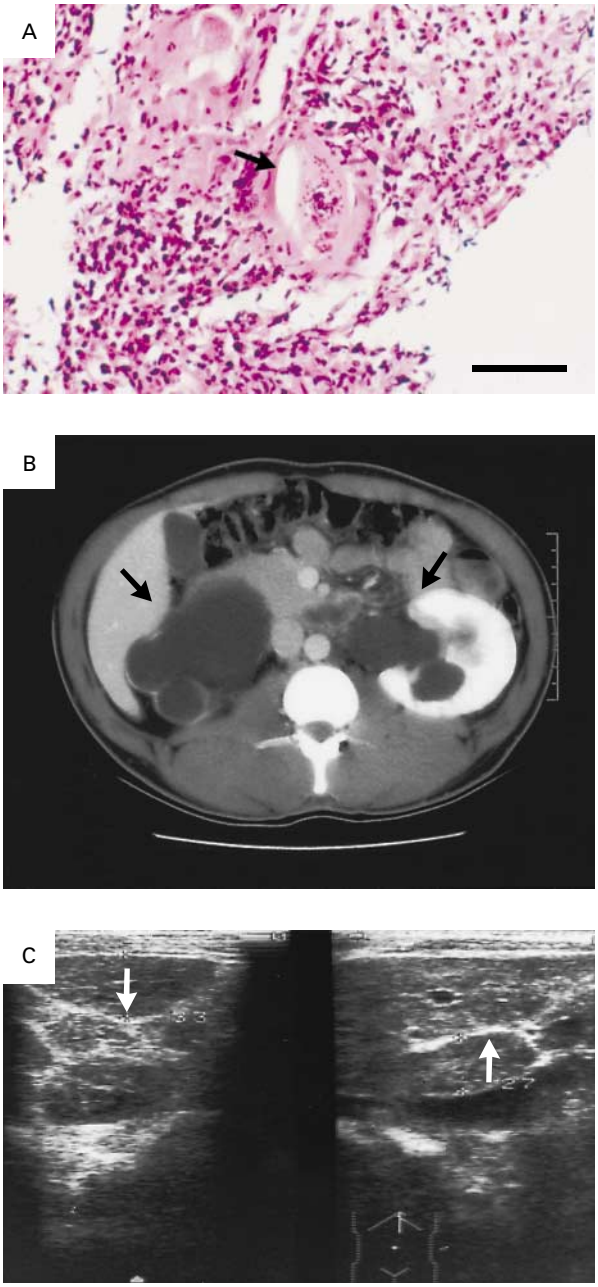

Figure 3. Clinical Findings in Two Patients Infected with Schistosoma Species.

Panel A shows loose granuloma formation surrounding a *Schistosoma haematobium* egg (arrow) in a bladder-biopsy specimen from a 27-year-old man with hematuria and left-sided loin pain who had *S. haematobium* eggs in his urine (hematoxylin and eosin, ×400). The black bar represents 100 μm. In Panel B, a computed tomographic scan of the abdomen of the same patient shows gross bilateral hydronephrosis (arrows) due to ureteric stricturing. The right kidney is atrophic and nonfunctional. In Panel C, an ultrasonogram shows gross hepatic fibrosis (grade 3) (arrows) in a 45-year-old man with severe hepatic schistosomiasis.

lence of HCV infection in that country because of the widespread reuse of needles.[36]

Genitourinary Disease

Urinary tract disease is a specific trait of infection with *S. haematobium*.[32] Hematuria is the first sign of established disease, appearing 10 to 12 weeks after infection. Again, chronic disease is caused by granulomatous inflammation that occurs in response to the deposition of eggs in tissue. Dysuria and hematuria are common in both early and late disease. Late manifestations also include proteinuria (often in the nephrotic range), calcifications in the bladder, obstruction of the ureter, renal colic, hydronephrosis, and renal failure. Secondary bacterial infection is frequent. On cystoscopy, sandy patches (areas of roughened bladder mucosa surrounding egg deposits) are often visible and are pathognomonic. Structural abnormalities of the urinary tract can occur in children.[37]

The association between *S. haematobium* infection and squamous-cell carcinoma of the bladder has been the subject of intense research and debate. Squamous-cell carcinomas of the bladder associated with *S. haematobium* tend to be well differentiated and to metastasize locally. In Egypt, squamous-cell carcinoma of the bladder accounts for 18 to 28 percent of all cancers, with an incidence of 10.8 per 100,000 population.[38,39] Male smokers appear to be at particular risk.[39] The association appears to be consistent in many sub-Saharan nations as well.[32] However, large autopsy series have failed to demonstrate a consistent association with a particular type of tumor,[40] and squamous-cell carcinoma of the bladder is prevalent in some countries that have a very low prevalence of *S. haematobium* infection or none at all. *S. haematobium*–associated bladder cancers are often associated with mutations of the *p53* and cyclin-dependent–kinase inhibitor 2 tumor-suppressor genes.[32] At present, there is sufficient evidence to conclude that *S. haematobium* has a role in causing some types of bladder cancer.

S. haematobium infection causes genital disease in approximately one third of infected women.[32,41] Isolated internal genital disease is less frequent. Vulval and perineal disease may be hypertrophic, ulcerative, fistulous, or wart-like and may be mistaken for other genital infections, particularly condylomata lata.[42] Tubal infertility may be a late complication. Vulval schistosomiasis may also facilitate the transmission of human immunodeficiency virus (HIV).[41,43]

Neurologic and Other Manifestations

Symptoms do not develop in all persons with egg deposits in the central nervous system. The mechanism of egg deposition is unknown. The presence of egg deposits may reflect either aberrant migration of worms or the embolization of eggs from a remote location.[8] Central nervous system schistosomiasis has been described in soldiers and aid workers serving in areas where schistosomiasis is endemic[44,45] and in tourists who have had relatively limited exposure to such areas. Focal or generalized tonic–clonic epilepsy is a typical presentation for *S. japonicum* infection with central nervous system involvement. Focal neurologic deficits may also occur.[46] Among groups of Chinese adults hospitalized with schistosomiasis, up to 4.3 percent have central nervous system disease.[14] The prevalence of epilepsy in communities where infections have occurred has been estimated at 1 to 4 percent — eight times as high as at base line.[14,45] Transverse myelitis is the most common neurologic manifestation of *S. mansoni* or *S. haematobium* infection. Treatment is largely supportive. Praziquantel is usually used, augmented by a course of corticosteroids and anticonvulsants. Lifelong use of anticonvulsants is rarely indicated.

Schistosome infection during childhood causes substantial growth retardation and anemia.[28,47,48] Successful chemotherapy leads to substantial but incomplete catch-up growth and improvement in hemoglobin levels. Infected children may also have cognitive impairment and memory deficits.[49] Schistosome infection appears to have adverse effects on both maternal health and the fetus. Unfortunately, praziquantel is listed in pregnancy category B (safe in animals but untested in humans). Many experts believe the risk–benefit ratio favors treatment, at least after the fourth month of gestation.

Infections in Travelers and Immigrants

Acute schistosomiasis is a problem for travelers, particularly those who visit Africa.[50] Swimming in Lake Malawi, Lake Kariba, and the Zambezi River has been particularly problematic. Hematuria and diarrhea are common early symptoms. Central nervous system disease, including transverse myelitis, is rare. Standard doses of praziquantel are curative. Although the average life span of a schistosome is five years, adult worms may live for decades. Immigrants from areas where schistosoma species are endemic can remain infected for 30 to 40 years.[51] Urinary schistosomiasis can be misdiagnosed as bladder cancer or chronic prostatitis. Hepatic or intestinal disease may be found in patients who present with anemia and chronic gastrointestinal bleeding. Schistosomiasis is not a notifiable disease in the United States or in many other developed countries, so there is no accurate information about infection rates among returned travelers and immigrants.

Susceptibility

HLA class I and class II antigens are associated with more severe manifestations of disease. For ex-

ample, HLA-B16 and Cw2 have been associated with *S. haematobium*–related bladder cancer among patients in Egypt.[52] HLA-DR and DQ alleles are associated with some protection against mild liver fibrosis, and some HLA-DP alleles are associated with protection against severe hepatic fibrosis.[53] Advanced hepatic fibrosis appears to be closely linked to the interferon-γ–receptor gene on chromosome 6q22–q23.[54] Another locus (SM1) is associated with resistance to reinfection with *S. mansoni* and is located on chromosome 5q31–q33.[55] A gene product of this locus may regulate the development of type 2 helper T cells.

DIAGNOSIS

The detection of schistosome eggs in feces or urine is diagnostic of schistosomiasis. The extent of shedding of eggs may fluctuate widely, and as many as three specimens may be required in some patients. *S. mansoni* or *S. japonicum* eggs may be observed in stool specimens of 2 to 10 mg with or without suspension in saline. The use of formalin-based techniques for sedimentation and concentration may increase the diagnostic yield.[56] Such techniques are useful in patients with few eggs, as in a returned traveler. The miracidium-hatching test has been used extensively by public health workers in China to rule out *S. japonicum* infection.[40] The test is initiated by the concentration of ova from feces through a nylon tissue bag and suspension in distilled water. Miracidia that hatch from ova are visualized microscopically, and their presence is diagnostic of infection. In patients with a typical clinical presentation but negative urine and feces specimens, a biopsy of bladder or rectal mucosa must be used for diagnosis. These are the most sensitive diagnostic procedures available.

The rapid, simple, and inexpensive Kato–Katz thick-smear stool examination requires 40 to 50 mg of feces and is widely used in field studies[57] and national control programs to determine the burden of eggs in feces. Several population-based studies have demonstrated that mean egg burdens correlate with the mean severity of disease.[58,59] However, it is generally unnecessary to quantify the egg burden in order to provide clinical care.

Antibody detection is useful in a few specific circumstances, but its use is limited because antibodies persist after parasitologic cure. A positive serologic test may be diagnostic in patients in whom there are no eggs, such as those with Katayama fever. Furthermore, serologic testing is useful in field studies for defining regions of low-level endemicity where individual patients have low egg burdens.[60,61] Serologic testing may also be useful in determining whether infection has reemerged in a region after an apparently successful eradication program. Commercially available immunodiagnostic kits are not as sensitive as multiple fecal examinations and are less specific.[62] Detection of circulating adult-worm and egg antigens is a promising technique that may eventually supersede traditional diagnostic methods. A recent development is an immunoblot assay for the detection of adult-worm antigen,[63] which reportedly has 95 percent sensitivity and 100 percent specificity.

Additional supportive laboratory evidence of schistosomiasis might include evidence of peripheral-blood eosinophilia, anemia (iron-deficiency anemia, anemia of chronic disease, or macrocytic anemia), hypoalbuminemia, elevated urea and creatinine levels, and hypergammaglobulinemia. Splenomegaly develops in some patients with pancytopenia.

Biochemical markers of hepatic fibrosis are currently a focus of research. Serum levels of procollagen peptide (types III and IV), the P1 fragment of laminin, hyaluronic acid, and fibrosin may be elevated in patients with severe hepatic fibrosis and can decrease after praziquantel treatment.[59,64,65] Persistent elevation of these levels after parasitologic cure suggests the presence of coinfection with HBV or HCV. The measurement of the N-terminal propeptide of type III procollagen, combined with the C-terminal propeptide of type IV procollagen and collagen VI, can be used to predict the risk of progressive hepatic fibrosis. A biopsy of the liver may be necessary in some patients with coinfection. Liver involvement in patients with schistosomiasis is often suggested by the characteristic appearance of the organ on abdominal imaging.

TREATMENT AND CHEMOPROPHYLAXIS

Praziquantel, a pyrazinoisoquinoline derivative, is the mainstay of treatment and a critical part of community-based schistosomiasis control programs. Since its discovery in the mid-1970s,[66] its safety and efficacy have ensured its widespread use. It is absorbed well but undergoes extensive first-pass hepatic clearance. Praziquantel is secreted in breast milk, it is metabolized by the liver, and its (inactive) metabolites are excreted in the urine. The drug's precise action on adult worms is unknown. It appears to cause tetanic contractions and tegumental vacuoles, causing worms to detach from the wall of the vein and die. In animal models, the presence of host antibodies has been shown to be critical for its efficacy.[67] Optimal therapy requires two to three doses of 20 mg per kilogram given six to eight hours apart with food. Community-based control programs usually treat patients with a single dose of 40 mg per kilogram. Higher doses are often used against *S. japonicum* (a total dose of 60 mg per kilogram). Reexamination of feces or urine one month after treatment is recommended in order to assess efficacy.

Praziquantel reliably cures 60 to 90 percent of patients and substantially decreases the worm burden and egg production in those who are not cured. Patients who continue to shed viable eggs should be re-treated with the same dose; the second treatment is usually successful. Hepatic fibrosis from *S. mansoni* infection[68,69] and *S. japonicum* infection[31,68] and the urinary tract disease from *S. haematobium* infection[37,68] may improve after successful treatment if reinfection is avoided. The efficacy of praziquantel is unaltered in patients who are coinfected with HIV type 1 (HIV-1).[70] Treatment of schistosomiasis caused by *S. mansoni* does not influence the load of HIV-1.[71] Corticosteroids may be useful adjuvant treatment for cerebral disease associated with features of surrounding edema apparent on radiology[46] or for severe Katayama fever. Oxamniquine is the only alternative to praziquantel for *S. mansoni* infection but has limited availability. Metrifonate is an alternative drug for *S. haematobium* infection but is no longer available commercially. We believe that these drugs should be maintained in international formularies in case widespread resistance to praziquantel emerges.

Praziquantel is a poor choice for chemoprophylaxis because of its short half-life (1 to 1.5 hours) and because it cannot kill schistosomula (the migrating larvae) that are 3 to 21 days old. Artemether, which is well known for its antimalarial activity, does kill schistosomula during the first 21 days in the body. Therefore, it should kill all immature schistosomula if it is given every two weeks.[72] In a trial involving residents of an area in southern China where *S. japonicum* is endemic, the drug was administered every 15 days throughout the transmission season at a dose of 6 mg per kilogram.[72] Acute cases were prevented and new infections were less than half as frequent as in the control group, and those that did occur were of lower intensity. Artemether is also active against the other schistosome species that infect humans.[73-75] Combining artemether with praziquantel appears to produce a synergistic killing of adult worms.[76] The prospects seem good for prophylaxis with artemether in high-risk groups in areas where schistosomiasis is endemic, such as flood relief workers, tourists, and fishermen.[73] The doses required are lower than those required for treatment of malaria, but it is unlikely that artemether would be used in areas where malaria is endemic because such use might lead to the selection of artemether-resistant *Plasmodium falciparum*.

Resistance to praziquantel may be emerging after nearly 20 years of intensive use. Hycanthone resistance in *S. mansoni* is well documented.[77] In regions of Egypt and Kenya where there has been heavy exposure to praziquantel, there are reports of *S. mansoni* and *S. haematobium* infections that are not responsive to multiple courses of treatment.[78,79] There is some laboratory evidence suggesting that these drug-tolerant worms may have altered tegumental architecture, which could limit the effectiveness of the drug.[78] So far, however, patients in many communities have undergone multiple courses of treatment over a period of 10 or more years without a demonstrable loss of efficacy.[80] Because worm reproduction in the mammalian host is sexual and the generation time is relatively long, resistance is likely to take many years to become an important clinical and public health issue.[80]

VACCINE DEVELOPMENT

The control of schistosomiasis requires large-scale population-based chemotherapy in addition to environmental and behavioral modification. It is difficult and costly to sustain such a program.[4] There is a need for a vaccine for long-term prevention. Schistosomula appear to be the primary source of the target antigens that are vaccine candidates. A high level of protection against *S. mansoni* infection has been attained in mice and a similar level of protection against *S. japonicum* infection has been attained in mice, buffaloes, and pigs when the animals were immunized with irradiated cercariae. Both type 1 and type 2 helper-T-cell responses may contribute to protection.[81]

Considerable efforts have been made to identify relevant schistosome antigens that may be involved in inducing protective immune responses, with a view to developing a recombinant-protein, synthetic-peptide, or DNA vaccine.[81] Coordinated laboratory and field research has identified a set of well-defined *S. mansoni* molecules with protective potential.[81] In recent phase 1 and 2 clinical trials involving human volunteers, a schistosome-derived molecule, the *S. haematobium* glutathione *S*-transferase (Sh28GST) (Bilhvax), was safe and demonstrated excellent immunogenicity.[82] In addition, recent studies in water buffaloes of the protection afforded by the *S. japonicum* antigens paramyosin (Sj-97) and GST-26 (Sj-GST26) have yielded encouraging results, and it may be feasible to develop a vaccine that blocks transmission for use in reservoir hosts.[62] Given the breadth of the international efforts to generate antischistosome vaccines, there is considerable optimism about possible future success.[83] However, these vaccines will be only one component of schistosomiasis control programs. Environmental modification of snail habitats and use of molluscicides are common methods of controlling the parasite but are expensive.

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