



Pulmonary schistosomiasis

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Schistosomiasis, also named bilharziasis (after the German physician Theodore Bilharz, who worked in Egypt during the nineteenth century and was the first to discover the life cycle of the parasite), is one of the most prevalent infectious diseases in the world. It is endemic in more than 70 countries, mainly in the less developed countries, and is estimated to place approximately 20% of the endemic population at risk. The number of people affected is estimated to be 200 million [1].

The schistosomes are a group of trematodes (flukes), some of which are pathogenic to humans. The principal parasites that affect humans are *Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum*; less prevalent parasites are *Schistosoma intercalatum* in Africa and *Schistosoma mekongi* in the Far East. Fig. 1 presents the global distribution of schistosomal species. The most prevalent area for schistosomiasis is Africa, where *S haematobium* and *S mansoni* dominate.

In the recent decades, schistosomiasis has been gaining attention in the developed countries after increasing numbers of returning travelers have presented at medical facilities with various symptoms caused by schistosomiasis. In most cases, the disease was acquired in sub-Saharan Africa, and once back in the developed world, it becomes a medical challenge to Western doctors, who are less familiar with the disease.

The incidence of schistosomiasis among travelers can only be guessed at from circumstantial evidence. The Centers for Disease Control and Prevention and

the International Society of Travel Medicine keep a database—GeoSentinel—that collects data regarding morbidity among returning travelers from a network of 25 travel and tropical clinics around the world [2]. According to GeoSentinel, schistosomiasis is one of the ten leading causes of morbidity among travelers, accounting for 6% of the cases in sub-Saharan Africa. Other data point to schistosomiasis as being a significant cause for morbidity among travelers to Africa who had contact with bodies of fresh water. A study conducted at Lake Malawi, one of the major infected freshwater lakes, showed that there was a correlation between the rate of infection and the days of exposure, with an estimate of up to 90% infection rate of travelers who stayed longer than 7 days [3]. It is reported that 55% to 100% of travelers on rafting tours in African rivers became infected, most of whom were symptomatic [4–7].

The clinical picture of the disease in nonimmune travelers can be considerably different from that in the endogenous populations, which increases the challenge of diagnosis and management. The literature on the disease among travelers is scarce, and even less information exists on pulmonary involvement. This article focuses on the pulmonary manifestations of schistosomiasis.

Schistosoma life cycle

The life cycle of *Schistosoma* involves two hosts: humans and snails. An infected human sheds the schistosome eggs into fresh water via the urine or feces. Snails, the intermediate hosts, ingest the eggs that subsequently hatch and go through several cycles of multiplication. They are then excreted into the

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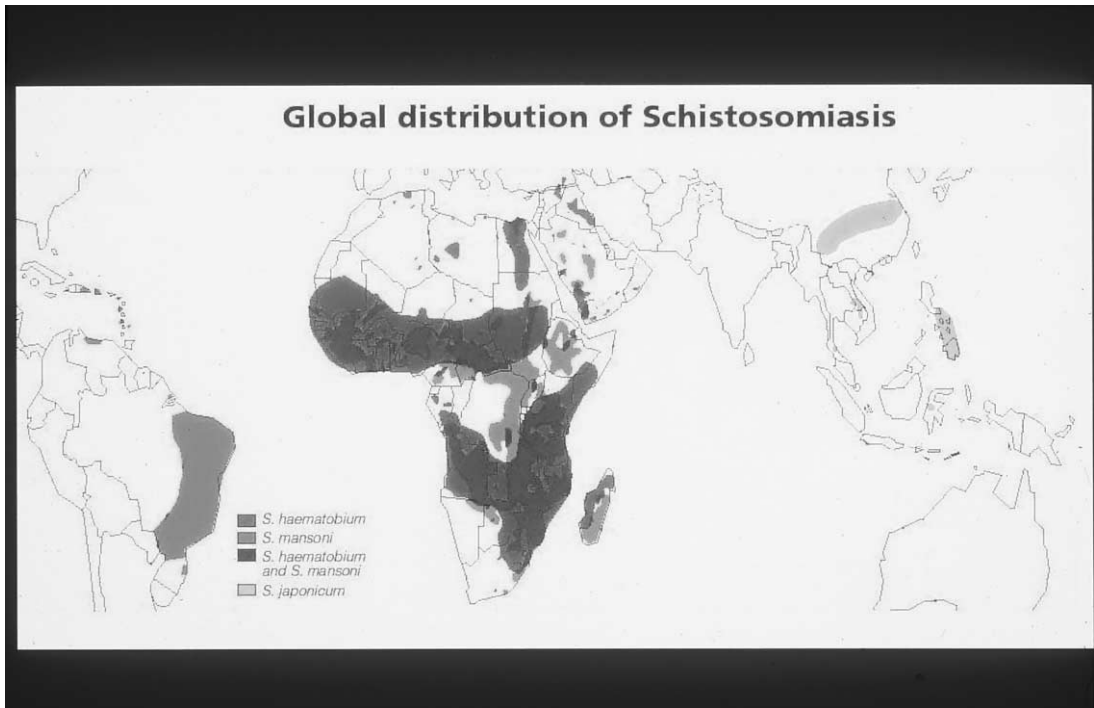


Fig. 1. Global distribution of *Schistosoma* species. Available at: www.who.int/ctd/schisto/epidemiio.htm. (See also Color Plate 1.)

water as cercariae, the infective form. Cercariae have the ability to penetrate human skin or, if ingested, penetrate the gut. People mostly become infected while swimming in contaminated water.

In the process of invading the human skin, the cercariae lose their tails and change into the juvenile form, called schistosomule. The schistosomule migrate first to the lungs and within 1 week reach the liver. After approximately 6 weeks, they mature into adult flukes that mate and descend via the venules to their final habitat: the vesicle beds in the case of *S haematobium* infection and the mesenteric beds in the case of *S mansoni* and *S japonicum*.

The life span of the adult fluke is a matter of controversy, but it is known to be several years and can be up to 30 years.

Most of the eggs laid by an adult fluke are excreted by the host (via urine in *S haematobium* and via the feces in other species). These eggs are important from a public health standpoint because they are the cause of the spreading of the disease. A few of the eggs remain in the host tissue and cause granuloma formation around them. These granulomas are what cause the clinical symptoms of schistosomiasis.

Clinical manifestations of schistosomiasis

The clinical manifestations can be divided into three major stages. (1) The first stage occurs within 24 hours after skin penetration by the cercariae and manifests as a pruritic papular rash (swimmer's itch; *Schistosoma* dermatitis). This symptom can occur also after infestation with a nonhuman schistosome and lasts less than 48 hours. (2) The second stage usually occurs 3 to 8 weeks after infection during the maturation of the adult fluke. This stage, termed "Katayama fever" or "toxemic schistosomiasis," is a febrile stage in which the infected patient may suffer from fever, malaise, headache, cough, arthralgia, hepatosplenomegaly, and marked eosinophilia. The fever can mimic malaria, with alternating spikes and chills.

This early postinfection period is the stage at which the schistosomule mature into the adult form. The adult flukes mate and start to lay eggs. One theory postulates that as the flukes begin to lay eggs, soluble antigens leak from the eggs into the blood stream. At this stage antibody production lags behind antigen release, and excess antigen prevails. This imbalance causes the immune complex disease, and because the antigen is soluble the effect is systemic. Recovery

takes place after antigen-antibody balance is achieved [8]. The author's data and other data show clearly that this syndrome may occur well before oviposition takes place [9–11]. The symptoms are probably the result of an immunologic reaction to various circulating antigens at different stages in the life cycle of the parasite. The clinical symptoms are a form of serum sickness or antigen-antibody complex disease [12].

This clinical phase is unique to nonimmune patients and rarely is seen in the endogenous population; it mainly affects travelers to endemic areas. The symptoms were originally described in Japan in the Katayama district, and it was first believed to occur only in *S japonicum* infection. It was later observed also in *S mansoni* [9,13] and *S haematobium* [10] infections, however.

The late stage, or chronic schistosomiasis, appears months to years after infection and results from granuloma formation around the schistosome eggs retained in the tissues. *S haematobium* infection affects the urinary system and may cause painless hematuria (usually terminal hematuria), dysuria, and later obstructive uropathy. It even may cause squamous cell carcinoma of the bladder.

Schistosoma mansoni and *S japonicum* affect the gastrointestinal system; infection may cause chronic diarrhea, abdominal discomfort, and colonic polypoidosis. Severe and long-standing infection may cause hepatic fibrosis (Symmer's pipestem fibrosis) with portal hypertension and splenomegaly.

During the oviposition stage, ectopic migration of the eggs can occur through the veins to tissues out of their usual habitats, such as the brain [14], spinal cord [15], and lungs [16].

Pulmonary involvement in schistosomiasis

Although the lungs are not an end organ in the life cycle of schistosome infection in humans, pulmonary pathology exists. For many years, pulmonary pathology was described mainly as a late complication of the infection. It recently has been recognized that pulmonary involvement also may occur in the early, acute stages [10,17]. Early-stage pulmonary involvement is unique to nonimmune patients, that is, populations never previously exposed to schistosomal infection, usually travelers from developed countries to endemic areas. Physicians who practice in Western countries who treat returning travelers are more likely to encounter pulmonary involvement in the early stages of infection rather than the later complications. Early and late pulmonary schistosomiasis are two different diseases with different clinical manifesta-

tions and different pathogenesis and pathology, not merely a difference in time of onset.

Early (acute) pulmonary schistosomiasis

Clinical manifestations

Early pulmonary manifestations occur usually 3 to 8 weeks after schistosome penetration [10,17]. Patients with pulmonary schistosomiasis reported shortness of breath, wheezing, and dry cough, mainly while recumbent. Reports show that in some cases the pulmonary symptoms coincided with febrile illness (Katayama fever) [18,19]. Most patients, however, presented several weeks after the fever had subsided. Almost all the patients could recall having had febrile disease before the onset of pulmonary symptoms, but the pulmonary symptoms continued for weeks after the fever subsided [10,17]. In this aspect, the clinical picture was different from that of the classic Katayama fever. The physical examination was usually unremarkable, although in some patients prolonged expiration was noted. Laboratory findings revealed significant eosinophilia, usually in a range of 30% to 50%, with mild leukocytosis [8,10,17], occasional abnormal liver function test results, and elevated IgE.

Based on the author's experience, pulmonary involvement can be divided into three types:

1. Symptomatic cases with radiologic findings (either chest radiograph or CT scan). The radiologic findings may be evident at presentation or, not uncommonly, may appear after antischistosomal treatment. In either case, cough may persist for several weeks despite the treatment.
2. Symptomatic cases without radiologic findings. In some patients, the clinical course is similar to the previous one, but radiologic findings (either chest radiograph or CT scan) are absent. This result may be caused either by the small dimensions of the findings, which makes them invisible by conventional methods, or their transient nature.
3. Asymptomatic cases with radiologic findings. Cases in which there are pulmonary findings without a current history of pulmonary symptoms are rare. The incidence of these cases is unknown, because radiology is usually not performed for asymptomatic patients. The author was able to identify such cases since chest radiographs were performed as part

of the evaluation of patients with suspected early schistosomiasis.

Pathogenesis

Pulmonary involvement in nonimmune patients occurs relatively early after infection and is reversible. Symptoms begin approximately 1 month after

exposure and, in the author's patients, the radiographic evaluations were performed even later—4 to 12 weeks after exposure. The infiltrates cannot be attributed to schistosomule migration through the lungs, which occurs typically 5 to 7 days after penetration, nor can they be attributed to granuloma formation around schistosomal eggs, because this process starts before oviposition is expected to take place. In

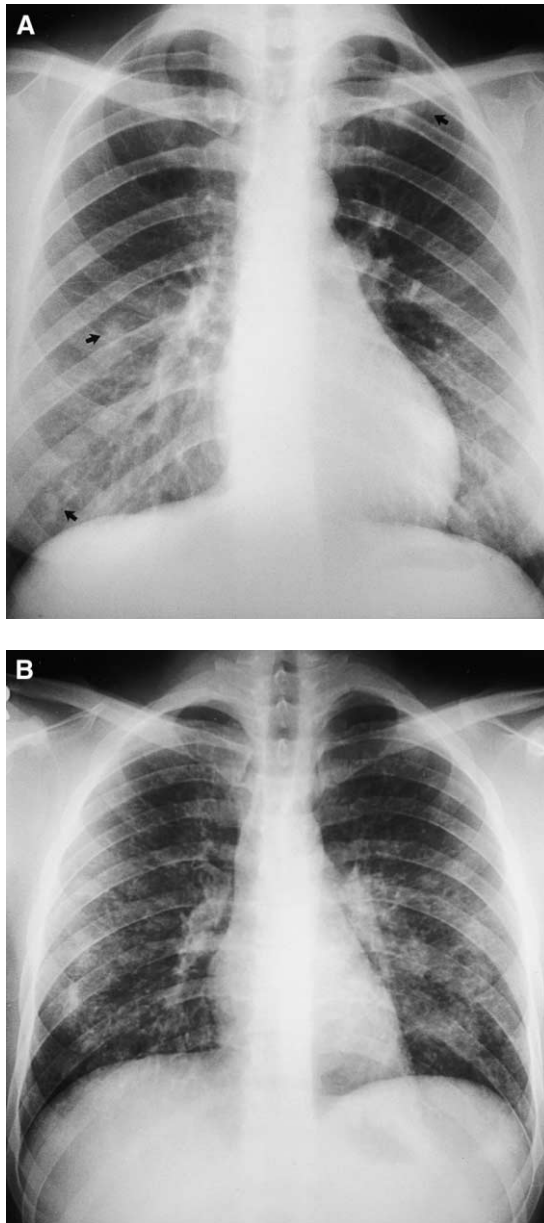


Fig. 2. (A) Chest radiograph that reveals several small round lesions in both lungs (*arrows*). (B) Chest radiograph that reveals diffuse, increased lung markings and prominent hilum with ill-defined nodules.

cases seen by the author and others, there was no correlation between clinical findings and egg burden, and eggs were not detected at the time patients presented with pulmonary symptoms [10,17,19]. The pulmonary findings were completely reversible, which would not occur if the pathologic condition were caused by granuloma formation around the eggs.

It is likely that the pulmonary pathologic status is immunologically mediated and similar to that seen in other forms of eosinophilic pneumonias, such as Loeffler's syndrome, in which the inciting agent exists elsewhere in the body (eg, intestine), but the eosinophils are sequestered in the pulmonary capillaries [20]. In cases in which transbronchial biopsy was performed, eosinophilic infiltration of the air spaces and eosinophilic abscesses were found [8,10]. Additional support to the immunologic theory is the observation that some of the patients developed radiologic findings only after antischistosomal treatment was initiated. Treatment is a known factor of antigenic stimulation [21] and may be accompanied by transient clinical deterioration, such as fever, skin rash, pulmonary function test abnormality, pleural effusion, and respiratory failure [8,22,23].

Katayama fever is also the result of an immunologic process that occurs in nonimmune patients 3 to 8 weeks after infection as a reaction to the circulating parasite antigen(s), just as in the afebrile pulmonary schistosomiasis described previously. The whole range of symptoms that occurs in nonimmune patients during the early stage of the infection, such as fever, urticaria, pulmonary manifestations, and eosinophilia, is part of the same immunologic process and can be assembled under the term "Schistosoma hyperreactive syndrome."

Imaging

The most common chest radiograph abnormalities observed were small, nodular lesions with ill-defined borders (Fig. 2A). Less common were reticulonodular patterns (Fig. 2B). Chest CT scans revealed more nodular lesions than were apparent on chest radiographs (Fig. 3A). In rare cases a bilateral, diffuse, ground glass pattern was demonstrated, with ill-defined nodules (Fig. 3B). Neither pleural effusion nor lymphadenopathy was evident. In approximately 25% of the author's cases, the radiographic abnormalities appeared only after praziquantel therapy [10,17].

Pathology

In view of the benign nature of early schistosomiasis, pathologic data are scarce. Only one report

other than that of the author's institution was found in the literature, which describes pulmonary pathologic condition based on transbronchial biopsies. Davidson et al [8] described a case of pulmonary symptoms in which reticulonodular densities appeared on chest radiograph 2 weeks after treatment. A transbronchial biopsy with 392 histopathologic sections showed alveolar exudate and interstitial infiltration by macrophages and eosinophils but failed to reveal any flukes or eggs. In the author's case, symptoms and radiologic findings (Figs. 2B, 3B) appeared before treatment; a transbronchial biopsy performed at that time (approximately 2 months after exposure in Lake Malawi) showed a picture compatible with eosinophilic pneumonia but also failed to reveal ova or parasite (Figs. 4A, B) [10].

Incidence

The incidence of pulmonary involvement in the early stages of *Schistosoma* infection is unknown. In several series of travelers with Katayama fever, coughing was reported in more than 40% of the infected persons [7,19,24]. In these series, radiographic evaluation was not performed. In a series the author and colleagues recently published, however, 8 out of 60 patients with schistosomiasis had pulmonary involvement with radiographic findings [10]. Because not all patients presented at the clinic at the onset of early symptoms, this finding suggests that pulmonary involvement may occur more commonly than previously recognized.

Diagnosis

In general, the diagnosis of early schistosomiasis in travelers still poses a challenge and must be based initially on clinical judgment. The traditional test of examining stool and urine for parasite eggs has low sensitivity. The sensitivity of stool or urine examinations, even when performed on three separate occasions, is limited by the sporadic passage of eggs by the adult flukes and the low fluke burden usually found in travelers. Rectal biopsy may, to some extent, increase the sensitivity of the test. It must be emphasized, however, that nonimmune patients may be acutely ill with pulmonary manifestation well before oviposition by the adult flukes has begun; thus stool or urine examinations performed at this time are unrevealing.

Serologic testing is potentially much more sensitive; however, it is not routinely used and is mainly performed in research laboratories. The sensitivity and specificity of the tests also vary according to the antigen

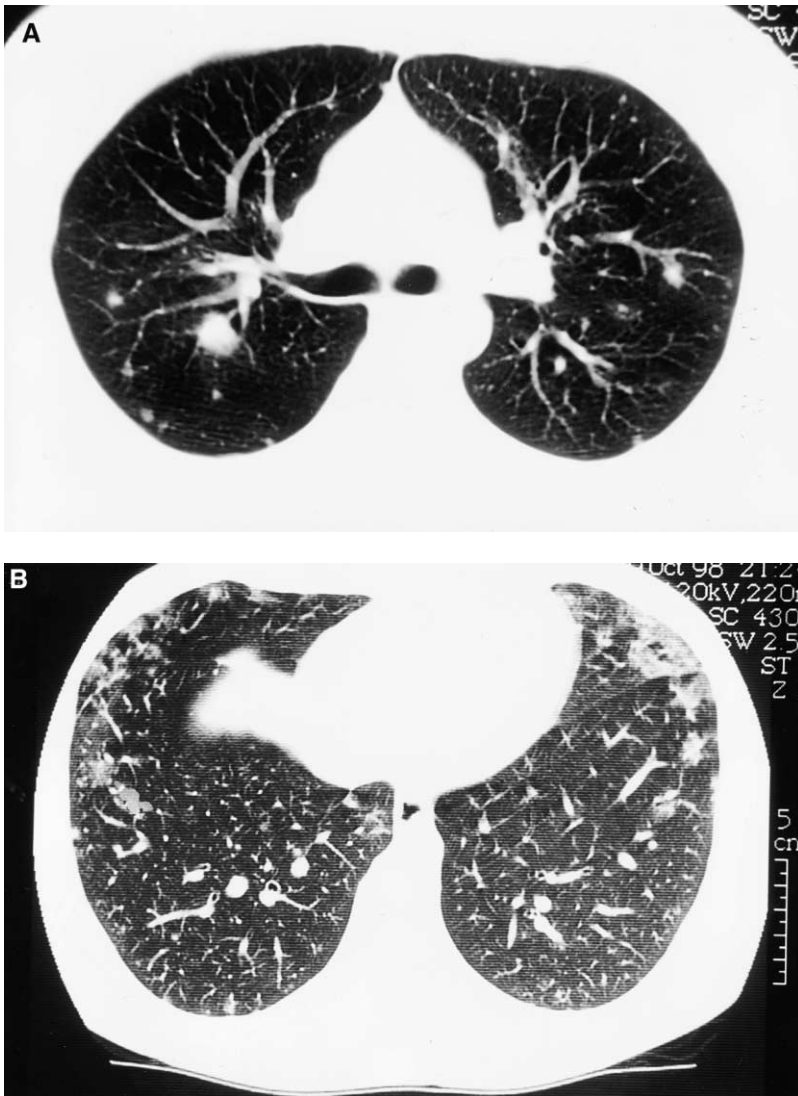


Fig. 3. (A) CT scan through the bifurcation of the trachea that shows multiple lesions of different sizes in both lungs. (B) CT scan through a point just above the diaphragm that shows diffuse ground-glass areas with some nodularity. The findings are mainly at the lung periphery.

used. The parasite laboratory at the Centers for Disease Control and Prevention uses Fast-enzyme linked immunosorbent assay (ELISA) as the initial step in diagnosis. Confirmation and speciation of positive ELISA results are performed with an enzyme-linked immunoelectrotransfer blot, which provides almost 100% specificity in confirming the presence of the *Schistosoma* species [3]. This method has proved to be highly sensitive and specific and usually yields positive results relatively early, 4 to 6 weeks after exposure. Other methods in other laboratories seem to

be less sensitive and specific and yield positive results at a later date.

A major limitation of the serology test is that it stays positive for many years despite efficacious treatment, which excludes it for use in confirming reexposure or evaluation of the success or failure of treatment.

For the clinician, the most important clue to obtain is a good travel history of the patient, especially regarding exposure to freshwater in endemic areas. The high eosinophilic counts that occur during the

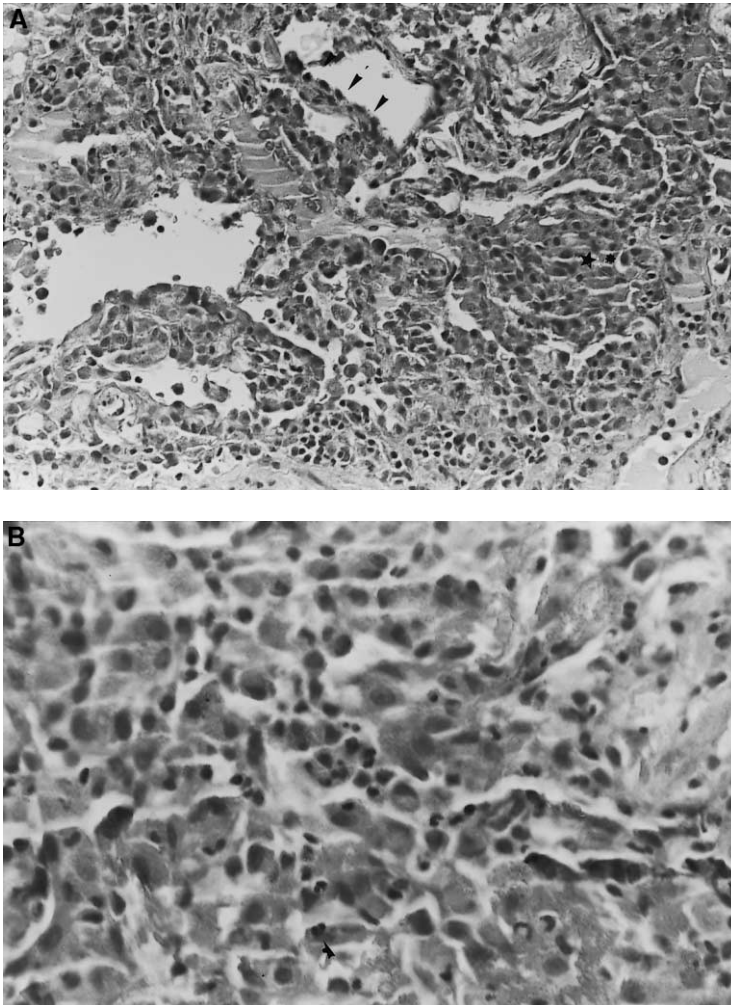


Fig. 4. (A) Transbronchial biopsy specimen that shows alveolar spaces (*asterisk*) filled with numerous eosinophils and macrophages, in association with an interstitial infiltrate, and hyperplasia of type II pneumocytes lining the alveolar septae (*arrowheads*). A focus of intraalveolar organization is seen in the right upper field. (Hematoxylin and eosin, $\times 200$). (B) A higher magnification of (A) demonstrates the intraalveolar infiltrate composed of numerous macrophages and eosinophils. (Hematoxylin and eosin, $\times 400$). (See also Color Plate 2.)

acute stage of the disease may be a useful indication for diagnosis.

Treatment

The drug of choice for treating all schistosome species is two doses of 20 to 30 mg/kg praziquantel given orally within 12 hours.

Praziquantel is an excellent and well-tolerated agent. It is known to be effective only against the adult fluke, however [25]. Its role in acute schistosomiasis has not been proved, because at that stage of the disease the fluke may not have matured fully.

Despite this limitation, many patients seemed to improve soon after receiving the drug. One cannot rule out that this result might have been caused by the self-limiting nature of the process rather than to praziquantel treatment [26].

Acute schistosomiasis is immunologic by nature, so corticosteroids may be effective therapy. Patients with severe manifestations either at presentation or after the treatment should receive a short course of steroids.

Some physicians recommend a repeat course of praziquantel several weeks after the first course because the first course may have been given too

early, when the fluke had not matured enough to be killed by the drug [19], or because the concomitant steroid may have reduced the blood levels of praziquantel [27].

Based on the pathophysiology of the disease at this stage, the treatment of early, acute schistosomiasis at presentation can be with corticosteroids alone followed by praziquantel several weeks later to ensure eradication of the adult flukes. Controlled studies that compare these options are difficult to perform because of the small numbers of patients seen at each clinic and because we do not have a good tool to assess eradication of the flukes.

New, promising antischistosomal drugs are the artemisinin derivatives. Artemether, a Chinese drug that originally was developed as an antimalaria agent, has been shown to have antischistosomal activity that uses a different mechanism than praziquantel. Artemether acts on the juvenile forms of the schistosome [28], in contrast to praziquantel, which on the mature form. Artemether may play a role in the future in treating the acute stage of *Schistosoma* infection.

Chronic pulmonary disease: late complication

Ectopic migration of schistosome eggs can reach the pulmonary beds. In the case of *S haematobium* infection, the final station of the adult flukes is in the perivesical plexus. From there the eggs laid by the mature flukes can be swept by the systemic venous system that drains the venous plexus to reach the lungs. As for *S mansoni* and *S japonicum*, their ova are swept with the portal blood flow and become lodged in the venules of the liver. There, the host immune system creates a granuloma around the eggs, which eventually can cause periportal hepatic fibrosis (pipestem fibrosis) and portal hypertension. As a result of portal hypertension, portacaval shunts are opened, which enables the schistosome eggs to be swept along until they become lodged in the lungs. In such cases, pulmonary involvement follows portal hypertension. Although this is the accepted explanation, reports have documented *S mansoni* eggs in lungs of patients without evidence of hepatic fibrosis [29].

In the pulmonary vasculature, the eggs trigger a granulomatous response that affects the intima and later the media wall of the arteries, which results in fibrosis, pulmonary hypertension, and, subsequently, the development of cor pulmonale.

The clinical expression of chronic pulmonary schistosomiasis can be divided to three groups [30]: a) asymptomatic cases with schistosomal eggs in the pulmonary beds, with or without granuloma forma-

tion; b) granuloma formation with pulmonary hypertension; c) granuloma formation with pulmonary hypertension and cor pulmonale.

It is still not clear whether all cases inevitably develop into cor pulmonale and whether such a progression is only a matter of time. Other explanations for the different pathologic response are (1) egg load (a higher density of fluke eggs may cause the progression to occur), (2) the rate at which eggs are released (if a low density of eggs is released over time, a less vigorous response from the immune system may result) [30], and (3) species-specific response as noted in a comparison of autopsy and clinical data. It was documented that although *S haematobium* is found at significant percentages in pulmonary beds, it causes much less cor pulmonale compared to *S mansoni* [31].

Clinical symptoms

The clinical symptoms in patients with chronic schistosomiasis are similar to those of patients with pulmonary hypertension and cor pulmonale: dyspnea, chest pain, fatigue, palpitation, and cough. As in cor pulmonale, signs of right heart failure are also evident. Pulmonary function tests may show some alterations, such as mild airway obstruction or decreased lung volumes, but these findings are non-specific [32,33]. Similarly, chest radiographs are not different from those of patients with pulmonary hypertension and cor pulmonale, which manifest as cardiomegaly and pulmonary arterial enlargement. Focal opacities in the lung parenchyma and radiographic findings that mimic tuberculosis or tumor have been reported [31].

Hepatosplenomegaly may be found because of portal hypertension that is secondary to infection with *S mansoni* or *S japonicum*. Cirrhosis of the liver is not part of the disease, because it affects the presinusoidal areas.

Pathogenesis

When the eggs reach the pulmonary beds, they either remain in the lumen or migrate to the lung tissue itself. Antigenic properties released by the eggs stimulate local lymphocytic reactions, which cause granuloma formation. The resulting granuloma and the fibrosis after it may lead to obliterative arteritis and, if extensive enough, to pulmonary hypertension.

Lung histologic status shows dumbbell-shaped interarterial and perivascular granulomas with local angiogenesis, which causes dilated and twisted vessels, called “angiomatoid” [34].

Diagnosis

Diagnosis should be based on demonstration of schistosome infection (ie, demonstration of eggs in stool or urine by direct microscopy or rectal/bladder biopsy).

Serology tests in these cases are not useful because they cannot differentiate between current infection and past exposure. Because most people with this pathologic condition are from endemic areas (residents or immigrants) and have a high probability of past exposure to schistosome, serology testing is not indicative. Indirect evidence of infection can be found by demonstrating hepatosplenic or genitourinary schistosomiasis by means of ultrasound or CT scans [16].

The usefulness of bronchoscopy and tissue biopsy for diagnosis has never been assessed systematically, but they are unlikely to be helpful because of the small amount of tissue obtained and the sporadic distribution of the granulomas [31]. There have been case reports in which open lung biopsy revealed the diagnosis [35,36], but this should not be adopted as protocol.

Sputum analysis for ova has a low yield. Polymerase chain reaction test of sputum already tested for filariasis [37] is a method currently under investigation for schistosomiasis with promising results (J. Hamburger, MD, personal communication, 2001).

Treatment

The drug of choice for schistosomal infection is praziquantel; however, when dealing with chronic infection with fibrotic sequela to granuloma formation, one may assume that the changes are irreversible. Several prospective studies have shown that praziquantel treatment reverses mild to moderate

changes in the liver and urinary systems [38,39]. No data exist regarding the effect of the drug on the pulmonary changes. There are several reasons in favor of this treatment, however. First, because the spectrum of side effects to the drug is mild, it is worth trying. The treatment is targeted at killing the adult flukes, stops the egg shedding and halts the progression of the disease. The author recommends that patients with chronic symptoms be given drug therapy, regardless of the severity of their symptoms. The dose should be the same as for early infection: two doses of 20 to 30 mg/kg over 12 hours. The physician should be aware that clinical deterioration also may occur after chronic infection and should be vigilant [8], although this is much less common compared to the nonimmune population.

Prevention

Control and prevention of the disease in the endemic countries is beyond the scope of this article. Among travelers to endemic areas, mainly Africa, prevention of the disease is primarily by avoiding contact with freshwater lakes or rivers (there is no risk of contracting schistosomiasis in salt water). The author's experience with travelers shows that this advice often is not followed, because water entertainment (such as diving in Lake Malawi or rafting on rivers in Africa) is too enticing.

Studies are searching for other protective measures. Using a repellent before swimming, such as DEET (N, N-diethyl-toluamide), the active ingredient for mosquito repellent, may give some protection [40].

Recent research has found Artemether, a Chinese antimalaria drug, to be active against the juvenile forms of schistosomes. It may play a role in treating

Table 1
Comparison between early and late schistosomiasis

	Acute pulmonary disease	Chronic pulmonary disease
Time of onset (after exposure)	Weeks (3–8)	Years
Population at risk	Nonimmune (mainly travelers)	Immune population residing in endemic areas
Pathogenesis	Immune-complex disease	Granuloma formation
Clinical manifestation	Cough, fever, eosinophilia	Pulmonary hypertension
Imaging	Pulmonary nodules	Pulmonary hypertension, cor pulmonale
Species specific	All species (most probably)	All species; <i>S. mansoni</i> more severe disease
Diagnosis	Mainly by means of serology; ova in stool/urine may be found	Demonstrating ova in stool/urine or in lung tissue; serology is not helpful
Treatment: steroid	Effective	Non-effective
praziquantel	Effective	effective
artemether	May play a role	Probably not effective
Outcome	Reversible	May be partially reversible

people soon after exposure, before clinical symptoms appear [28,41].

Summary

Schistosoma infection is one of the most common infectious diseases, limited in the past only to the endemic countries. With the enormous increase in migration and travel, we encounter more and more cases in developed, nonendemic countries. Although the disease has been known for many years from studies in the endemic countries, the new patient population of nonimmune travelers presents with a different clinical pattern that requires further investigation. One of the features of the disease in the nonendemic population is pulmonary involvement that seems to be much more common than previously suspected. The differences between the nonimmune population with the early pulmonary involvement and the population of endemic areas with late pulmonary involvement are summarized in Table 1. Clinicians in the Western countries have a higher chance of encountering the early (acute) form of the disease, although immigrants from endemic countries may present with late (chronic) schistosomiasis. In the differential diagnosis of pulmonary pathology, especially when accompanied by eosinophilia, schistosomal infection should be considered. The travel history of the patient is mandatory for an evaluation.

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