The Trematodes

Cellular and Molecular Pathogenesis

Adult schistosomes usually do not cause signifi-

cant 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 proper-

ties. 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 Salmo-

nella, directly into the bloodstream. As a result there is

a well-described association between chronic schisto-

somiasis and so-called enteric fevers from non-typhoi-

dal salmonellosis.22

**Figure . .** 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 glyco-

gen 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 penetra-

tion 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 tegumen-

tal 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 confus-

ing immune defense cells, particularly macrophages,

in their attempt to recognize parasite antigens. Schis-

tosomulae 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

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 schisto-

somiasis. For *S. japonicum* and *S. mansoni,* egg depo-

sition occurs in the circulation of the small intestine and

liver (Fig. 33.14) to produce intestinal and hepatic fibro-

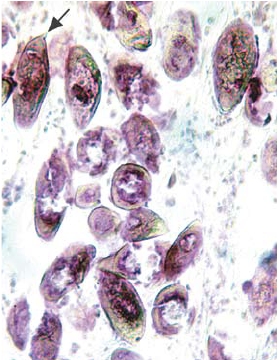
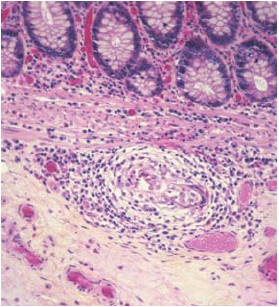
sis, whereas *S. haematobium* egg deposition occurs

in the circulation of the bladder to produce fibrosis

leading to an obstructive uropathy. Heavy egg depo-

**Figure .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 phenom-

enon depends on host genetic factors.23 In this regard,

the same genes specific for susceptibility to  *Schisto-*

*soma 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, immu-

nocompromised 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 inflamma-

tory 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 down-

regulate other host Th1 responses and result in altered

patterns of host susceptibility to other infectious patho-

gens, possibly including the human immunodeficiency

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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, granulo-

mas 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 . 0.** Miracidiumof*S.mansoni*.Phasecontrast.

**Figure . .** 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 sub-

mucosa 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-sinusoi-

dal capillaries, and induce granulomas there, as well.

The presence of granulomas causes tissue fibrosis,

and eventually leads to obstruction of the hepatic vas-

culature. Fibrosis of most of the portal areas incorpo-

rating the blood vessels leads to pipe stem fibrosis

(Symmer’s Fibrosis) (Fig. 33.15), and, ultimately, to

portal hypertension. Clinically, this is manifest as hepa-

tosplenomegaly, the extent of which is dependent par-

tially 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



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brane disease.32

Penetration of the skin by cercariae is dependent

on the release of parasite-derived proteases and eica-

sanoids. 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 antibod-

ies and an eosinophilic infiltrate. This is particularly true

of accidental skin penetration by avian or bovine schis-

tosomes. Many schistosomes specifically parasitic

for animals can cause aberrant infections in humans.

Avian schistosomes of the genera Austrobilharzia,

Trichobilharzia, and Ornithobilharzia, and other mam-

malian 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 penetrat-

ing cercariae and migrating schistosomula are a critical

**Figure . .** *Biomphalaria grabrata*, the most

common intermediate snail host for *S. mansoni*.

capillary beds, occasionally leading to pulmonary fibro-

sis 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 pseudopol-yps (Fig. 33.17), which can

transform into squamouscell carcinoma

in untreated patients (Fig. 33.18).

In some patients with long-standing disease (in all

four types of schistosomiasis), deposition of immune

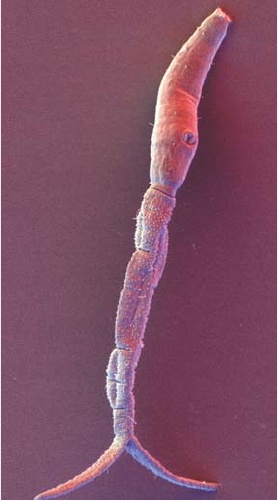
complexes in kidneys can lead to basement mem-

**Figure . .** *Oncomelania nosophora*, a snail inter-

mediate host for *S. japonicum*.

**Figure . .** Scanning electron micrograph of a

cercaria of *S. mansoni*. Photo D. Scharf.



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are attempting to bring a product to the field. Animal

protection studies have used the protein paramyo-

sin 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 pre-

dominantly 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 manifesta-

tions of acute schistosomiasis occur predominantly in

*S. japonicum* and *S. mansoni* infections. This condition

is sometimes known as “Katayama fever”. The classi-

cal disease attributed to schistosomiasis occurs during

chronic infections. Chronic infection with *S. haema-*

*tobium* can also lead to squamous carcinoma of the

bladder.

**Figure . .** 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 experi-

mental 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 obser-

vations 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 cer-

cariae 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 protec-

tive 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

Acute schistosomiasis

(Katayama fever)

The dramatic clinical manifestations of Katayama

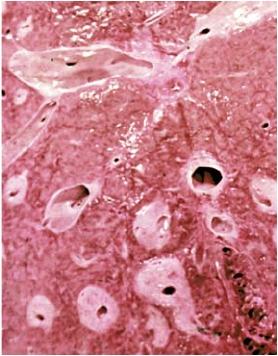
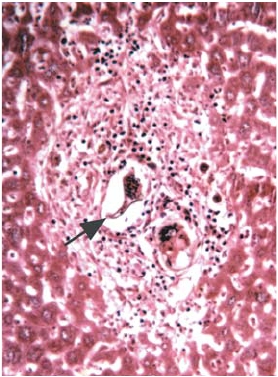
fever occur most commonly in new immigrants who

experience intense levels of exposure to either *S.*

**Figure . .** Pipe stem fibrosis in liver due to heavy

infection with *S. mansoni*. Note normal liver tissue

next to fibrotic vessels.



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**Figure . 6.** X-ray showing calcified dome of the

bladder due to chronic infection with *S. haematobium.*

**Figure . .** Histological section of bladder with pseu-

dopolyp 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 eosino-

philia. 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 con-

sequence of many years of progressive injury result-

ing 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. haema-*

*tobium,* injury occurs in the bladder. The extent of injury

depends on chronic worm burden, so chronic schisto-

somiasis 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 develope intermittent abdomi-

nal pain, sometimes accompanied with bloody diar-

rhea. The blood loss and ulceration of intestinal schis-

tosomiasis may result in iron deficiency and anemia.

This may explain why chronic schistosomiasis during

childhood can result in physical growth retardation sim-

ilar 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. Spleno-

megaly 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 rup-

tured esophageal varices. As a result of portal hyper-

tension, and the consequent development of a collat-

eral circulation, schistosome eggs are washed into the

lungs, where they induce granulomatous inflammation,

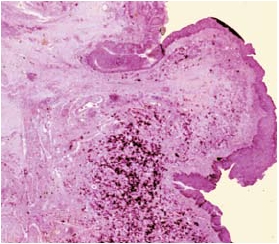
leading to obstructive disease culminating in cor pul-

monale. As noted above, long standing infections can

cause nephrotic syndrome, resulting from the deposi-

**Figure . 8.** X-ray of bladder with a squamous cell

tumor induced by *S. haematobium* eggs.



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CNS schistosomiasis

Rarely, all three schistosomes induce focal inflam-

matory 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

**Figure . .** Thigh of a child suffering from a maculo-

papular rash (“swimmer’s itch”) due to the cercariae of

a schistosome species that normally infects birds.

tion of immune complexes onto the glomerular mem-

brane.

*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 hema-

turia as well as symptoms that mimic urinary tract infec-

tions 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 uropa-

thy. This sometimes results in hydronephrosis or hydro-

ureter. 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

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 exam-

ined under the low-power lens of a microscope. It is

helpful to refer to the specimen as a “rectal snip,” rather

**Figure . 0.** Cercaria of *S. mansoni* in skin sur-

rounded by eosinophils.

