

# Trematodes

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# Trematodes

## Introduction

The trematodes are flatworms which are of great importance in tropical pathology. They may affect various organs. They have at least two suckers, one oral and one ventral (*Heterophyes* has three). The oral sucker surrounds the mouth. The intestinal system has a blind ending. They have no blood circulation. Oxygen is absorbed by diffusion. Most trematodes are hermaphrodites and thus possess both male and female genitalia. They have a cirrus (penis). The function of the Laurer canal is unclear, but it is probably a vestigial vagina. Cross-fertilization and self-insemination are both possible. There are exceptions, e.g. schistosomes have separate sexes. After leaving the ovary, the eggs are fertilized and subsequently surrounded by yolk in the ootype (an extension of the vitelline duct). Several concentric eggshells are formed. The eggshells then undergo a chemical reaction, a kind of tanning process, which makes them tough and harder. In this way the egg acquires its typical form, and becomes more resistant to conditions in the outside world, which are often unfavorable.

## Localisation

<b>Intestinal lumen</b>	Large intestinal fluke ( <i>Fasciolopsis buski</i> )
	Small intestinal flukes ( <i>Metagonimus</i> , <i>Heterophyes</i> )
<b>Lungs</b>	Lung fluke ( <i>Paragonimus</i> )
<b>Bile ducts</b>	Large liver flukes ( <i>Fasciola hepatica</i> and <i>F. gigantica</i> )
	Small liver flukes ( <i>Opisthorchis</i> , <i>Clonorchis</i> , <i>Dicrocoelium</i> , <i>Amphimerus</i> )
<b>Blood vessels</b>	Blood flukes ( <i>Schistosoma</i> sp.)

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## Intestinal flukes

Various trematodes are found as adult worms in human intestines. Examples are *Fasciolopsis buski*, *Metagonimus yokogawai*, *Heterophyes heterophyes*, *Echinostoma* sp., *Gastrodiscoides* sp. Most

infections are asymptomatic or provoke vague abdominal symptoms. Only in severe infestations (high worm load) are there likely to be signs of malabsorption. Eosinophilia is common. Diagnosis can only be made by examining the faeces for parasites. As a general rule most of these infections can easily be treated with praziquantel.

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## Lung flukes

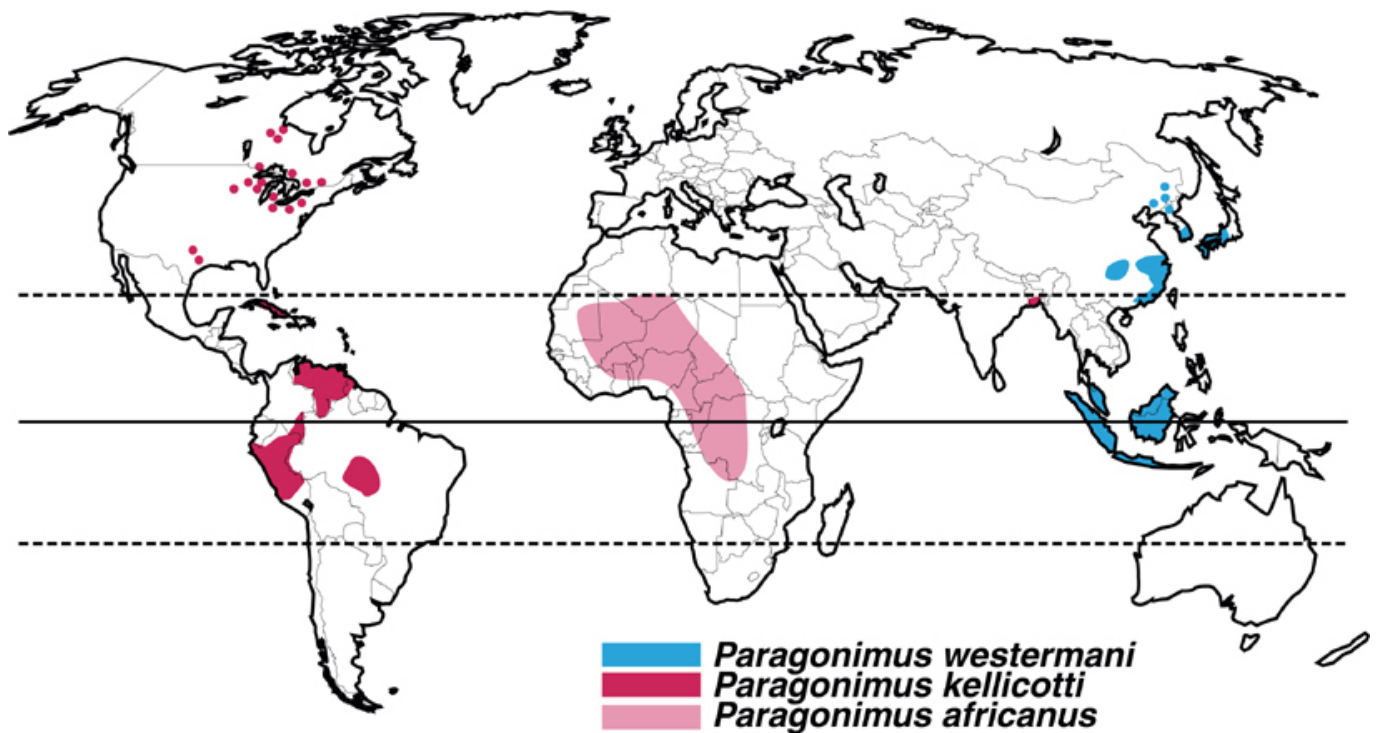
### Paragonimus sp.

#### Summary

- Transmission via eating infected crabs and crayfish
- Symptoms resembling pulmonary tuberculosis or chronic bronchitis
- Sometimes ectopic localization
- Diagnosis via detection of eggs in sputum

#### General

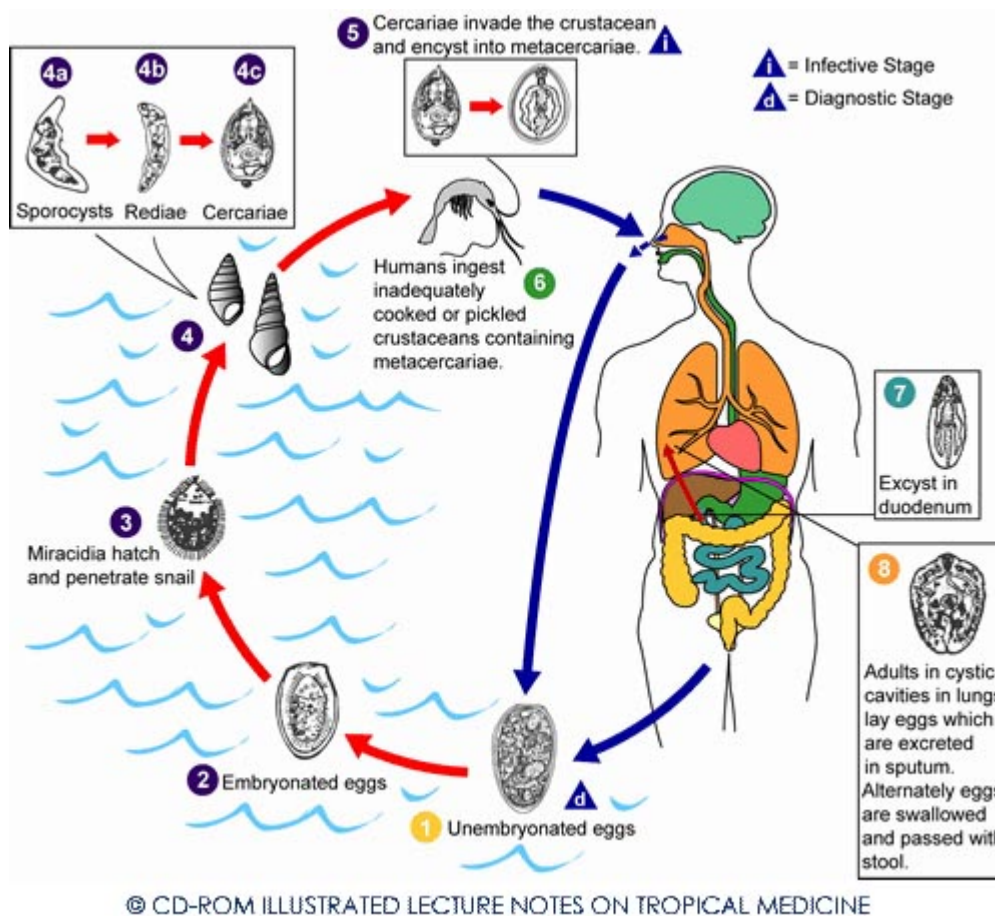
The parasite occurs in Southeast Asia and the Far East, in Central and West Africa. In America its distribution is limited to Central America and the north of South America. Usually *P. westermani* is reported, but there are a number of other species which can cause infection in humans (*Paragonimus africanus*, *P. bangkokensis*, *P. heterotremus*, *P. hueitungensis*, *P. kellicotti*, *P. mexicanus*, *P. miyazakii*, *P. ohirae*, *P. philippinensis*, *P. sadoensis*, *P. skrjabini*, *P. uterobilateralis*).



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Map showing areas endemic for *Paragonimus westermani*, *P. kellicotti* and *P. africanus*. Copyright ITM

## Life cycle



*Paragonimus westermani*, life cycle. Courtesy of CDC, Division of Parasitic Diseases.

*Paragonimus westermani*, life cycle. Courtesy of CDC, Division of Parasitic Diseases.

Adult worms live in the lungs. Eggs pass to the outside with the sputum. If sputum is swallowed, eggs may also be found in faeces. Once in the outside world and in water, miracidia (first-stage larvae) emerge from the eggs. They penetrate snails, where they undergo a transformation. After 3 to 5 months cercariae (second-stage larvae) leave the snail and penetrate crabs. Here the cercariae develop into metacercariae (third-stage larvae). It is this form which is infectious for the definitive host. Paragonomiasis is a zoonosis of carnivorous animals. Humans are only an exceptional host. They become infected by eating raw fresh-water crabs and river crayfish which contain infectious metacercariae. Excystation occurs in the duodenum. The larvae bore through the intestinal wall and migrate via the abdominal cavity and diaphragm to the lungs. There they develop into adult worms. The worms form a cavity 1 to 4 cm in diameter. Egg-laying begins 8 to 10 weeks after infection. The worms may also migrate to ectopic sites. An individual generally carries  $\leq 20$  worms, which can

persist within humans for 20 years. Paragonimus got its name from the shape with 'gonads at the side'.

## Clinical aspects

Mild infections are asymptomatic. In the acute stage (invasion and migration of the larvae) there may be diarrhoea, abdominal pain, urticaria and eosinophilia. This is followed by fever, thoracic pain, cough, dyspnoea and malaise. The chronic illness resembles chronic bronchitis and TB. There is spasmodic cough (especially after exertion) with expectoration of blood stained sputum, as well as dyspnoea sometimes with wheezing and pleural pain. When the parasite is located in an ectopic site (brain, peritoneal cavity, liver, subcutaneous region, etc.), causing an eosinophilic abscess, the symptoms depend on the place where the worms are.

## Diagnosis

Diagnosis is by detecting the eggs. The eggs often need to be concentrated (e.g. mix sputum + water + potassium hydroxide, then centrifuge and examine the sediment). Differential diagnosis includes tuberculosis of the lungs, Loeffler's syndrome, pulmonary abscess, chronic bronchitis, melioidosis, histoplasmosis, coccidioidomycosis, lung carcinoma and lung metastases. If sputum is swallowed, eggs may also be found in the faeces. Serology has a sensitivity and specificity > 90 percent.

## Treatment

Praziquantel 75 mg/day for 3 days is very effective. Triclabendazole is an alternative. In cases of cerebral localization higher doses must be given but only under the protection of steroids due to the risk of epileptic fits secondary to perilesional oedema.

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# Liver flukes

## Summary

- Small liver flukes: eating infected fish leads to cholangitis, icterus, eosinophilia, cancer of the bile duct
- Large liver flukes: eating contaminated plants leads to cholangitis, icterus, eosinophilia

## Small liver flukes: *Clonorchis*, *Opisthorchis* and *Metorchis*

*Opisthorchis viverrini* and *Clonorchis sinensis* (= *Opisthorchis sinensis*) occur in Asia. Eggs eliminated in the bile and faeces are taken up by snails. After further development in these animals, they leave the mollusk and penetrate freshwater fish (metacercariae). Humans become infected by eating raw fish such as carp. After the larvae are released in the duodenum, they migrate directly via the main bile duct to the intrahepatic bile ducts. Thus, there is no tissue passage. The parasites are approximately 1 to 2 cm long and can live for 20 years. Dogs and cats form a reservoir.

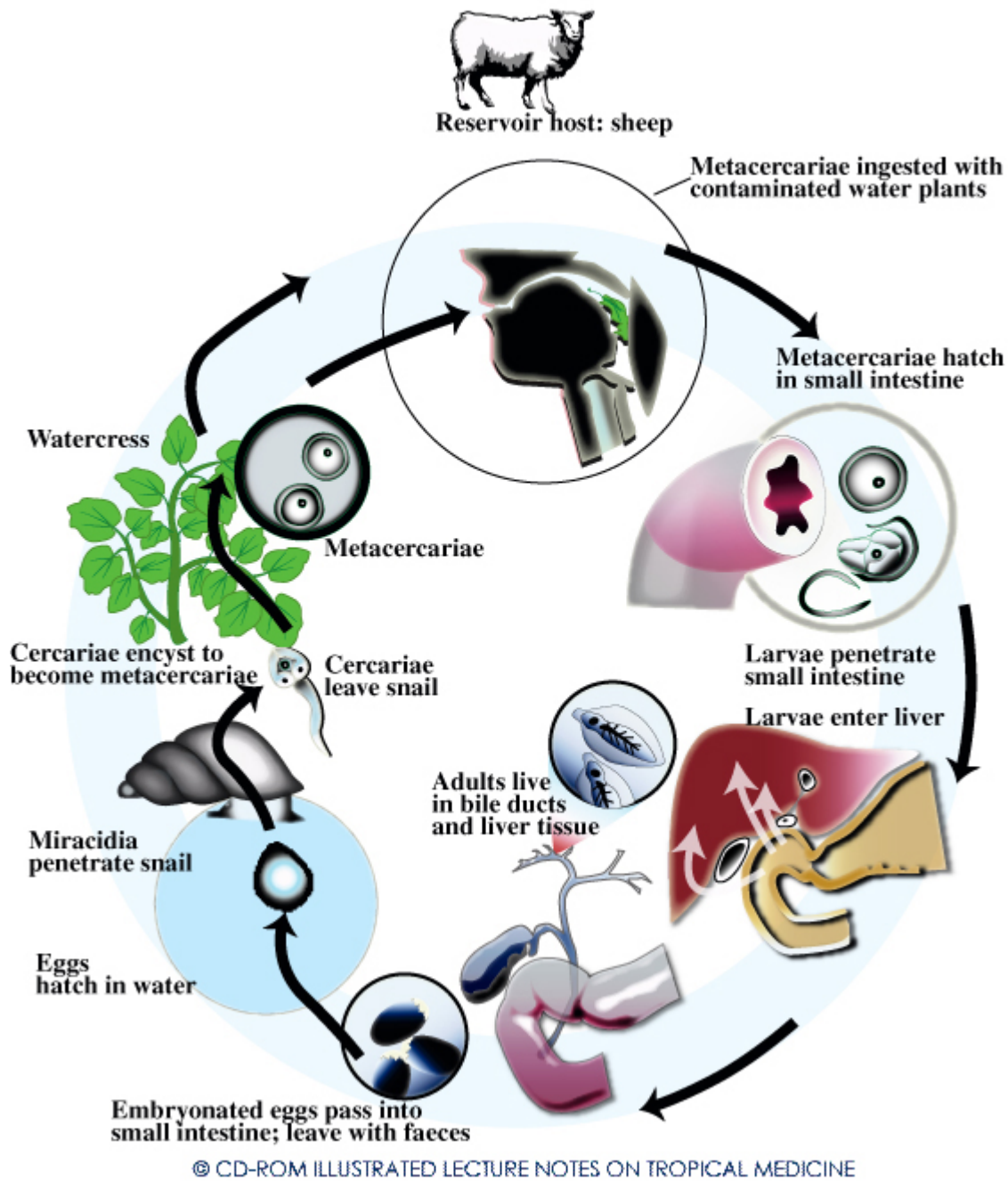
There may or may not be symptoms, depending on the worm load and location of the worms. Intermittent pain may occur around the liver which is sometimes enlarged. If bacterial superinfection occurs, febrile suppurating cholangitis results. If impaction with obstruction of the main bile duct occurs, there will be progressive icterus. In long-existing cases of infestation with *Clonorchis sinensis*, secondary biliary cirrhosis and carcinoma of the bile duct (cholangiocarcinoma) may develop. The diagnosis is made by detecting eggs in the faeces. A concentration technique is necessary. However, if bile duct is obstructed, no eggs can be detected. Sometimes duodenal intubation is necessary (aspiration of bile containing eggs). Serology may be helpful. The treatment consists of **praziquantel**. A new drug, tribendimidine, appeared very promising for both *Opisthorchis* and *Clonorchis* in recent phase 2 trial.

## Large liver flukes: *Fasciola hepatica* and *F. gigantica*

### General



## *Fasciola hepatica*



*Fasciola hepatica*, life cycle. Copyright ITM

Infection with these large liver flukes is quite wide-spread among animals. For example, *Fasciola hepatica* causes liver rot in sheep. The encapsulated larvae (metacercariae) are found on all kinds of

plants such as water cress (*Nasturtium officinale*), etc. After infected plants have been consumed the larvae are released in the small intestine, migrate within the hour through the intestinal wall to the peritoneal cavity and then bore through the liver capsule about 5 days later. After further migration in the liver, they reach the bile duct after approximately 7 weeks and remain there, laying their eggs. These are transferred via the bile to the intestine, and then excreted with the faeces. A single liver fluke can lay up to 20,000 eggs a day but usually produces smaller numbers. It should be noted that fertilized eggs can be produced by a single liver fluke (they are hermaphroditic).

Eggs often remain viable for months and can overwinter. Survival for more than 2 years has been demonstrated at a temperature of 2°C. Fierce heat and drying out kills the eggs. At a temperature of approximately 25° C (the optimum temperature) eggs develop in about three weeks. There is much variation in the rate at which eggs are released, which is an advantage to the parasite, since a particular habitat will remain infectious over longer periods. Under the influence of specific stimuli a 130 µm long larva (miracidium) emerges from the egg. This is covered with cilia and is immediately mobile in water. It can easily swim for hours. The larva has eye spots and is highly phototropic (it swims towards the light). This prevents the larva from wasting time and energy exploring the bottom of the pond, where the intermediate host (usually *Lymnaea trunculata*) is not to be found. This is unlike *F. gigantica* where the miracidium actively swims away from light to find *L. natalensis*, which lives deeper down. If the larva does not find the correct snail within 24 hours its glycogen reserves are exhausted and the larva dies. If a miracidium arrives some 15 cm from a snail, there is pronounced chemotaxis and the larva swims directly to the host and penetrates it. The next development takes place within the snail. These snails can survive long periods of drought (via aestivation) and long-term cold (via hibernation). Inside the snail, the miracidium develops into a sporocyst and then into rediae, a stage named after the Italian physician Francesco Redi (1688). The rediae measure approximately 1-3 mm, are mobile and may cause significant damage in the snail (if the infection is severe the snail dies). After 4-7 weeks the first cercariae emerge from the rediae; they measure 250-350 µm and leave the snail. The cercariae swim around in the water, to encyst within 2 hours on particular plants. Each cercaria then changes into a metacercaria (plural metacercariae). Due to the amplification phase in the snail, a single egg can produce 4000 metacercariae. Metacercariae can survive for more than a year on pasture. They are destroyed by heat and drought (the effect of long hot summers).

## Clinical aspects

Symptoms are present mainly during the migration period: fever, pain in the liver region, hepatomegaly, urticarial, eosinophilia. After this period symptoms are generally mild or absent. Sometimes there is cholangitis and obstructive jaundice. If raw goat's or sheep's liver is eaten, adult

worms can sometimes attach to the throat, resulting in local irritation (halzoun).

## Diagnosis

The diagnosis is made by detecting the eggs in faeces or duodenal aspirate (eggs appear approximately 12 weeks after infection). Repeated specimens are often necessary in view of the small number of eggs which are produced daily. If an individual has eaten infected sheep's liver, he/she can have eggs in the faeces, although no real infection occurs (spurious infection). Ultrasound or CT scan of the liver may show a clustering of hypo reflective or hypo dense tunnels in the liver parenchyma (these are inflamed bile ducts). Sometimes it is possible to actually visualize the moving worms. Via laparoscopy, one can sometimes find slowly migrating worm tracts. The specificity of serology is lowered by cross-reactivity with other helminths.

## Treatment

The therapy is problematical at present.

- Praziquantel is not sufficiently active.
- **Triclabendazole (Fasinex®, Egaten®) 10 mg/kg taken in one dose** together with a fatty meal is becoming the treatment of choice. Triclabendazole-resistant *F. hepatica* strains are already known in cattle.
- Nitazoxanide is an alternative drug. The dose is 500 mg BD for 1 week.
- Artemisinin may become an alternative. Worm burden reductions of 99-100% were observed with a single dose of the drug.

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## Blood flukes

## Schistosomiasis

### Summary

- Schistosomiasis (or bilharziasis): infection with small blood flukes
- *S. haematobium*, *S. mansoni*, *S. japonicum* are the most common
- *S. intercalatum* (closely related to *S. guineensis*) and *S. mekongi* are of regional importance

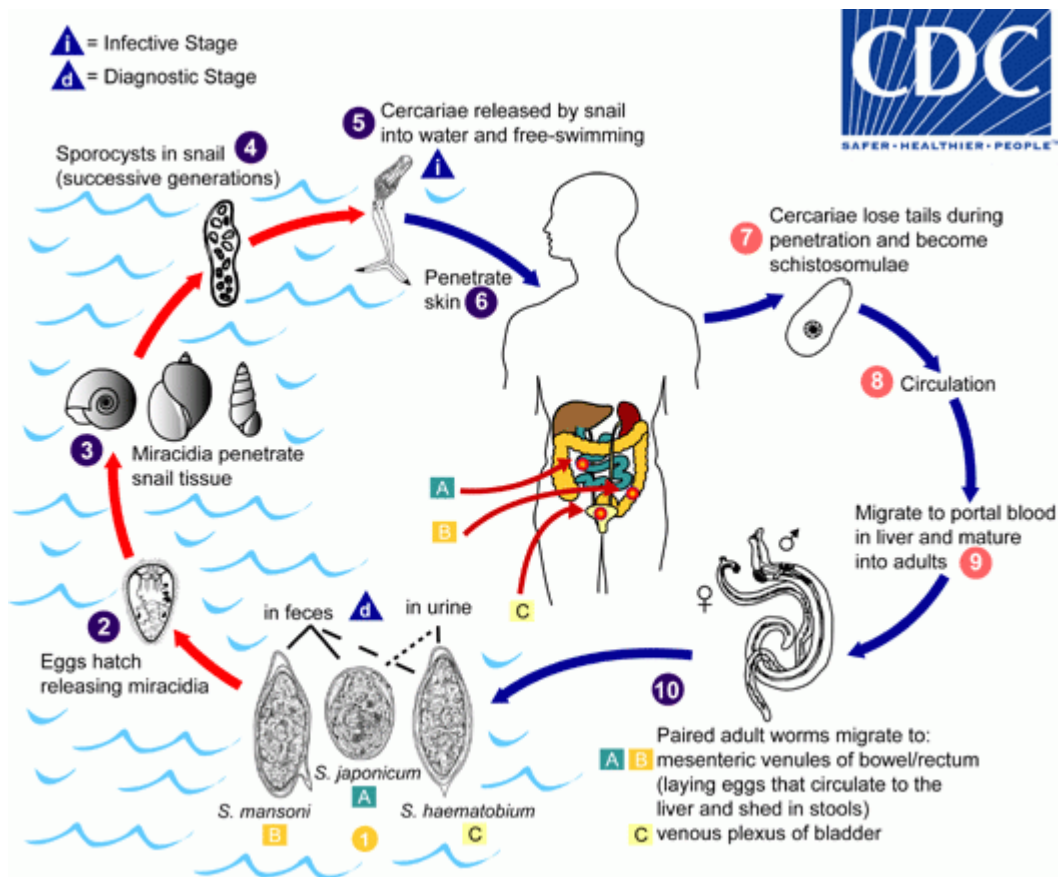
- Hybrid species (*S.bovis-S.haematobium*) are occasionally found in humans
- Certain species of fresh water snails are intermediate host
- Transmission via skin contact with fresh water containing larvae (cercariae) released by intermediate host.
- Mainstay treatment with praziquantel, active against adult worms only. Artemisinin derivatives are active against immature schistosomes
- Symptoms depend upon worm load (number of worms), anatomical location of parasites, duration of infection and host immune system reactions.
- Short-lasting pruritus after transcutaneous infection is possible (swimmer's itch)
- Acute schistosomiasis syndrome or "Katayama syndrome" a few weeks to months after primary infection (beginning of egg production). Fever, cough, influenza-like symptoms, abdominal pain, hypereosinophilia, splenomegaly.
- Ectopic localizations with e.g. neurological lesions may occasionally occur after primary infection, but also during chronic infection
- Chronic lesions due to *S. mansoni* and *S. japonicum*: abdominal discomfort, bloody diarrhea, hepatic fibrosis with portal hypertension, esophageal varices, ascites, hepatosplenomegaly – no risk for colon carcinoma
- Chronic lesions due to *S. haematobium*: hematuria, hydronephrosis, renal insufficiency, genital lesions, right heart decompensation due to pulmonary hypertension secondary to lung fibrosis. Increased risk for bladder carcinoma.

## General

The infection was first described by Dr. Theodore Bilharz (1825-1862) when he was working in the Kasr-el-Aini hospital in Cairo. Schistosomiasis or bilharziasis (this terminology should be abandoned) is a disease caused by flatworms (trematodes or flukes). There are 3 main species which infect humans: *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*. There are a few other species that infect humans, but these are less widespread: *S. mekongi* and *S. intercalatum*. Approximately 200 million people throughout the world are infected, a minority of whom are severely infected.

Both males and female worms have two suckers. The more anterior one surrounds the mouth. Bilharz mistakenly took the two suckers for two mouths and thus called the worm Distomum ("two mouths"). Five species of schistosomes are known to infect humans and lay eggs (complete their life cycle). Infections with *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* are associated with intestinal lesions and chronic hepatic fibrosis. *S. haematobium* infection mainly results in fibrosis, strictures and calcification of the urinary tract.

## Life Cycle



Schistosomiasis Life Cycle. Source CDC

Eggs reach the outside world via the faeces or urine. Each egg contains a larva that possesses numerous cilia. In a fresh microscopic preparation, a larva can be seen moving in the egg. If an egg reaches fresh water, the larva (synonym miracidium) is released. If the eggs do not reach the water, the larvae die rapidly, except in the case of *S. japonicum*. The latter can survive for up to 80 days outside the body (importance for hibernating). After swimming around for a while, a miracidium penetrates a snail (each parasite species is restricted to its own range of host snails). After two generations in the snail in the form of primary and later daughter sporocysts, a very large number of larvae each with a bifurcated tail, known as cercariae, is released. There is asexual proliferation in the snail, therefore one miracidium can produce up to 100,000 cercariae (etymology Gr. "kerkos" = tail). Cercariae live for 48 to 72 hours. Infection is acquired via skin contact with contaminated water. These larvae can actively penetrate the skin in 3 to 5 minutes. Cercariae penetrate the skin of humans or, in the case of *S. japonicum*, humans and other mammalian hosts that act as reservoirs for

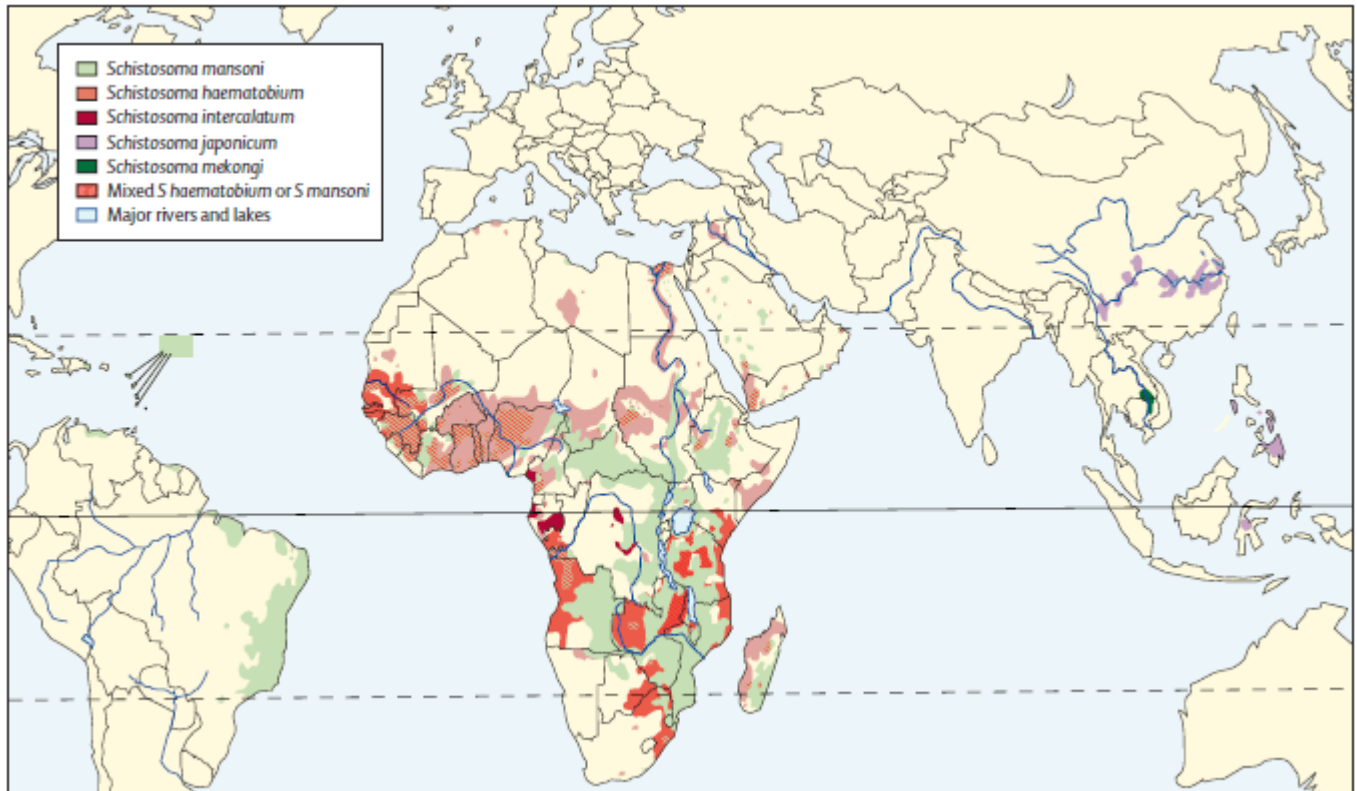
infection.

Once in the human body, the cercariae lose their bifurcated tail and develop further into schistosomula. After migration through the dermis and the lungs, they reach the liver. Copulation occurs in the blood vessels of the liver (in contrast to other trematodes, schistosomes are not hermaphroditic but have separate sexes). Afterwards, the worms migrate upstream to their final destination: the superior mesenteric venules in the case of *S. mansoni*, the inferior mesenteric and superior hemorrhoidal venules in the case of *S. japonicum*, or the vesical plexus and veins draining the ureters in the case of *S. haematobium*. Egg production starts (300 to 3000 per day, depending on the species) four to six weeks after infection. The eggs mature in approximately one week and remain alive for 3 weeks (longer in the case of *S. japonicum*). The eggs contain a miracidium that is motile (cilia). The movement can be seen in fresh microscopic preparations. The adult worms are not carried away by the flow of blood because they are attached to the vascular wall with two suckers per worm. The short, wide male contains the longer thinner female in a sort of groove, the gynaecophoric canal. It was previously thought that this was a single animal with a split body. This continuous “embrace” led to the parasite’s name [schistos = split; soma = body]. The male is approximately 10 mm and the female 20 mm long. The mean life span of the adult worms is 3 to 7 years, but some can survive for up to 20 years. The theoretical reproduction potential of one schistosome pair is up to 600 billion schistosomes. For *S. haematobium* and *S. mansoni*, humans are the most important reservoir. *S. japonicum*, however, is predominantly a parasite of animals (water buffalo, dog, pigs, etc).

## Geographical distribution

<i>S. mansoni</i>	Africa, Middle East, South America	GI-tract, mostly colon	( <i>Biomphalaria</i> sp)
<i>S. haematobium</i>	Africa, Middle East	Urinary tract	( <i>Bulinus</i> sp)
<i>S. intercalatum</i>	Central Africa	GI-tract, mostly rectum	( <i>Bulinus</i> sp)
<i>S. japonicum</i>	Southeast Asia and Far East	GI – small intestine	( <i>Oncomelania</i> sp)
<i>S. mekongi</i>	Mekong basin	GI-tract	( <i>Tricula</i> sp – syn. <i>Lithoglyphopsis</i> )





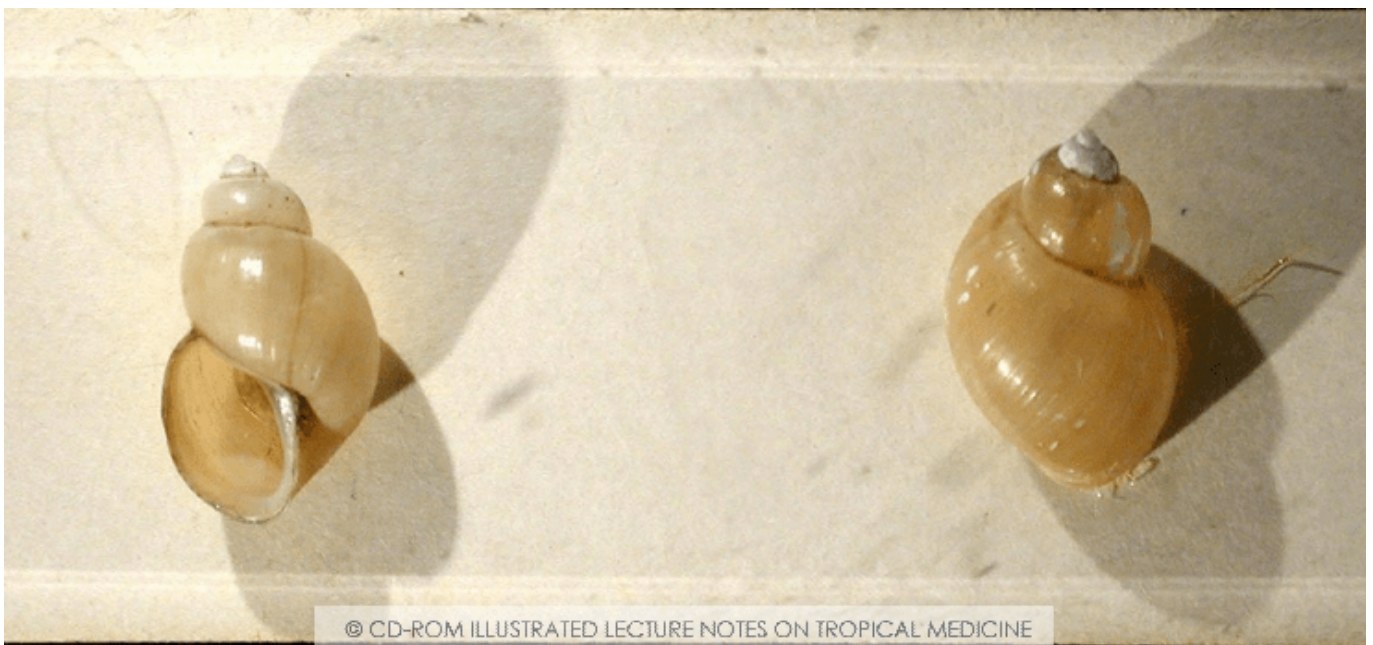
Global distribution of countries where human schistosomiasis is transmitted. Source Bruno Gryseels and colleagues

## Vector

Each *Schistosoma* species has its own snail species as a vector: see table above. These snails require well-defined ecological conditions to thrive. The average temperature plays a role. If it is too cold, the snails cannot proliferate. There is thus practically no transmission above 1800 meters, where the water temperature is too low. Some snail species resist periods of long-term drought. This explains the occurrence of schistosomiasis in locations where there is only abundant water during the rainy season. At these sites, there is naturally no transmission during the dry season.



*Biomphalaria alexandrina*. This snail can harbor *Fasciola gigantica* and *Schistosoma mansoni* (bilharzia). Copyright ITM



Snails. *Bulinus truncatus* / *Bulinus africanus*, host for *Schistosoma haematobium*, bilharzia. Copyright ITM



## Hosts

<i>S. mansoni</i>	principally humans, also baboons and rodents
<i>S. haematobium</i>	principally humans, rarely monkeys
<i>S. intercalatum</i>	only humans
<i>S. japonicum</i>	animals: water buffaloes, dogs, cats, rats, pigs, etc., also humans
<i>S. mekongi</i>	dogs, sometimes humans

## Immunologic aspects of schistosomiasis.

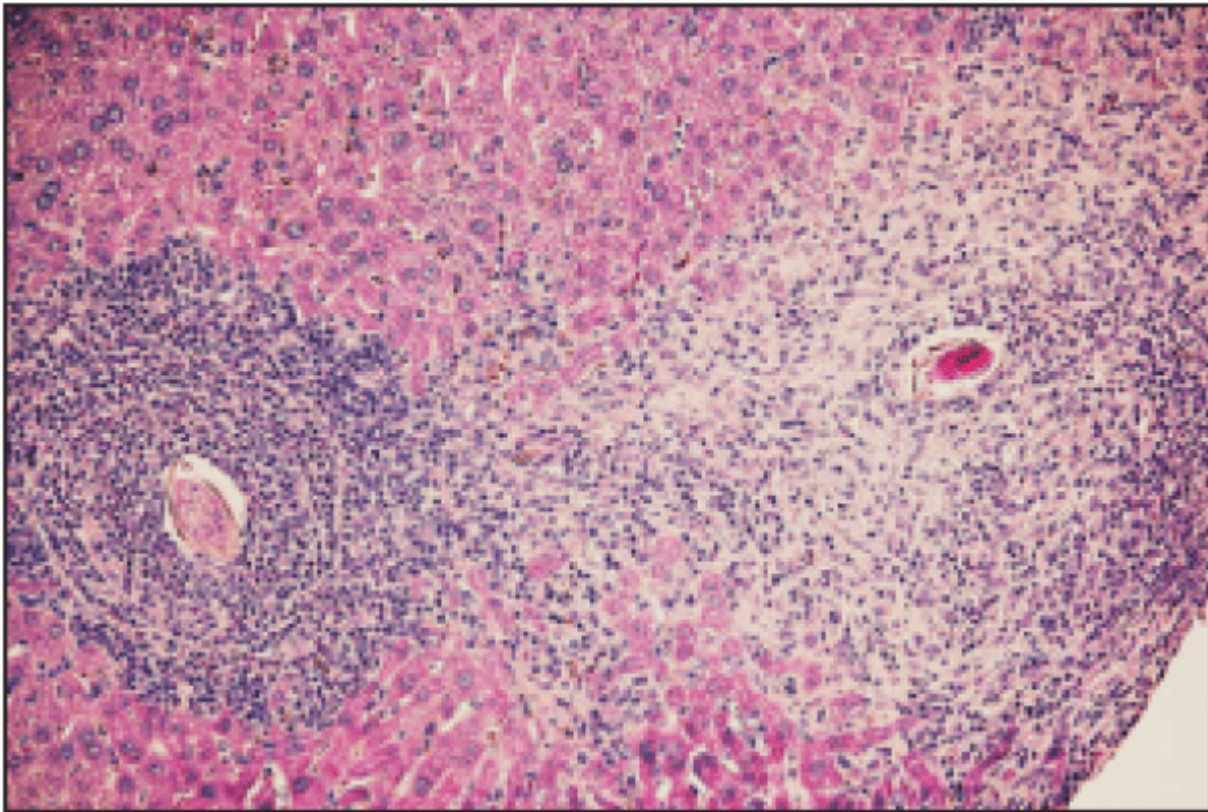
Longstanding epidemiological and clinical observations indicate that people living in endemic areas acquire some form of immune resistance after years of exposure. However it is not clear if true immunity is acquired or if the reduction in number of infections can be explained by reduced water contact after adolescence.

Comparative studies of reinfection after curative treatment have demonstrated that children are far more susceptible than adults and that these differences cannot be explained by quantified water contact patterns. Numerous studies in humans and in animal models suggest that acquired immunity would be mediated by IgE against larval and adult worm antigens, which stimulate eosinophils to release cytotoxines targeting schistosomulae.

Cellular immune responses against eggs and the enzymes they release are responsible for most schistosomiasis-related pathology. The granulomatous reactions around the eggs are orchestrated by CD4 T-cells and involve eosinophils, monocytes and lymphocytes. A shift from a predominantly  $T_H1$  reaction in early stages of the infection to a “modified”  $T_H2$  profile in chronic infections would account for the regression of the granulomas and their replacement by collagen. This has important implications for targeted mass treatment. Heavily infected children often present with non-fibrotic hepatomegaly due to its  $T_H1$  nature, and this pathology is usually reversible upon treatment. Likewise in early urinary schistosomiasis, haematuria seen in children promptly disappears after treatment with praziquantel.

## Clinical aspects

## Pathophysiology



*Schistosoma mansoni* egg-induced granulomas in the liver of an infected mouse. Eggs are roughly 120–180  $\mu\text{m}$  long, 45–70  $\mu\text{m}$  wide. From The Lancet

Pathology depends on the stage of the infection. Chronic symptoms are related to the total worm load (= number of worms in the body). Usually, light infections are asymptomatic. The likelihood of symptoms increases with an increase in the degree of infection. Sometimes parasites are found at ectopic sites (e.g. spinal cord), in which case there can be severe consequences, even in mild infections. Most people in endemic areas acquire some immunity over the course of the years. Many adults exhibit few signs of infection. This immunity is directed towards new infections, against schistosomula. Adult worms are covered in an unusual skin (“tegument”) that displays few parasite proteins on its outer membrane. As a result, the immune system usually takes little notice of the adults. In addition, certain human molecules, such as those which determine blood type, can stick to the surface of the worms, further shielding the parasite from the immune system. The immunological reaction directed towards the eggs produces cytokines which induce a host Th-2 immune response, leading to an eosinophilic granulomatous reaction, responsible for most pathology.

**Clinical, Swimmer's itch.** A local cutaneous itch can occur where cercariae penetrate. Slight erythema and pruritic papules develop, but will disappear spontaneously. This is well known with *S. mansoni*, *S. haematobium* and with *S. japonicum*. The itch is more frequent and violent in infections with animal schistosomes, probably because the cercariae die after penetration in humans (e.g. avian schistosomiasis, which also occurs in areas with a moderate climate).

**Acute schistosomiasis (or “Katayama fever”)** is caused by primary infection with schistosomes and represents a hypersensitivity reaction to maturing schistosomules (and probably also to antigens released from the eggs). It usually occurs 3 to 8 weeks after initial infection, It can be mild or severe, with one more of the following symptoms: fever, general discomfort, abdominal pain, diarrhea, vomiting, flu-like syndrome with muscle and joint pain, severe dry cough, wheezing, urticaria and sometimes lymph node enlargement and hepatosplenomegaly. There is nearly always a marked eosinophilia of  $> 1000/\mu\text{L}$ . Katayama fever is less frequent and milder in *S. haematobium* infections.

## Diagnosis and treatment of acute (symptomatic) schistosomiasis

- Katayama fever tends to occur in patients who are not previously exposed, although in the case of *S. japonicum* this syndrome can also occur on re-infection.
- History of recent exposure, freshwater contact in endemic area  $< 10$  weeks before symptom onset.
- Respiratory disorder and/or abdominal discomfort with fever and hypereosinophilia (DD trichinellosis, fascioliasis, filariasis, *Strongyloides* hyperinfection, etc.). Acute schistosomiasis is the most common cause of fever with hypereosinophilia in travelers returning from endemic areas, almost exclusively after a stay in sub-Saharan Africa.
- Eggs usually only appear in the faeces or urine after 6 to 12 weeks. Failure to detect eggs thus does not rule out acute schistosomiasis.
- Serum antibody tests may turn positive from 6 weeks after infection, but often much later.
- In acute schistosomiasis, the performance of PCR based genomic tests and of soluble schistosome antigen tests in blood and urine is still a research object.
- Treatment of acute schistosomiasis consists of steroids in the acute symptomatic phase, and additionally with praziquantel once symptoms are subdued with steroids. Repeat the course of praziquantel after a 3-4 months. Praziquantel is only active against adult worms.

## Ectopic localisations

Central nervous system schistosomiasis occurs by ectopic worm or egg dissemination via the bloodstream through retrograde venous flow into the Batson vertebral epidural venous plexus, which

connects the portal venous system to the spinal cord and cerebral veins. When eggs and/or adult worms cause lesions of the spinal cord, transverse myelitis (principally *S. haematobium* and *S. mansoni*) or brain lesions (principally *S. japonicum*) ensue. These take the form respectively of spastic paraparesis and CVA or space-occupying lesion (hemiplegia, epilepsy, etc...). Urgent treatment consists of steroids for several weeks to months to limit the local inflammatory reaction. Treatment with praziquantel has to be given while continuing steroids. Sometimes eggs can reach the skin, where they can cause papular dermatitis. This rare condition can only be diagnosed by biopsy. Even rarer is localization in the vocal chords, with nodules and hoarseness.

In acute schistosomiasis, a form of localized hypersensitivity encephalopathy may occasionally occur and requires steroids for effective initial treatment.

## Symptoms in chronic infections

### General

The live larvae (miracidia) in the eggs excrete proteolytic enzymes that digest the surrounding tissues. In this way, eggs can reach the rectal lumen or the bladder after their migration through the intestinal mucosa (*S. mansoni* and *S. japonicum*) or the bladder mucosa (*S. haematobium*). In general 50% or less of the eggs are eliminated with the faeces or urine. The remaining eggs either die locally or are transported with the venous blood until they reach the liver or another organ where the blood vessels become too small for their further passage. At this point the eggs and digestive juices which they secrete can cause local inflammation. The lesions of chronic schistosomiasis can be explained almost exclusively by the local inflammatory reaction to these eggs (formation of granulomata containing numerous eosinophils). Inflammation granulomata can reach up to 100 x the size of the original egg. Fibrous thickening and loss of elasticity of the tissues occurs. If massive infestation is present pseudopolyps occur in the intestine or bladder. The symptoms in chronic schistosomiasis differ according to the location.

### Intestinal lesions

Diarrhoea sometimes with some blood and mucus, can be caused by *S. mansoni* and *S. japonicum*. Pseudopolyps can occur in the colon. There is no increased incidence of intestinal cancer. In severe chronic infections, fibrosis of the intestine can occur. *S. mekongi* and *S. intercalatum* are also found in the intestine but usually does not cause severe pathology.

## Hepatosplenic schistosomiasis

When *S. mansoni* eggs are carried in the portal venous bloodstream as far as the liver they cause a physical obstruction of the bloodstream. Local inflammation around the eggs exacerbates this. The result is increased pressure in the portal circulation (portal hypertension). Clinically it takes the form of:

- Collateral circulation with oesophageal varices and increased venous markings on the abdominal skin, principally around the navel (umbilicus), the so-called “caput medusa”. Eggs can also reach other organs subsequently via this collateral circulation (lung).
- Ascites is a late sign.
- Because the eggs obstruct the branches of the portal venous system and fibrosis occurs around these foreign bodies, periportal fibrosis develops. This is also known as Symmers pipestem fibrosis which is seen years later in the course of the infection. The white fibrotic bands in the liver are in fact long and hollow like pipestems (in the center is a branch of the portal vein). Liver function remains surprisingly well preserved for a long time (normal blood coagulation, no severe hypoproteinemia, no hepatic encephalopathy, no gynaecomastia). This stands in contrast with chronic aggressive hepatitis B and alcoholic cirrhosis. *S. japonicum* lesions are usually more severe because the worms produce ten times more eggs per day (3000 as opposed to 300) than *S. mansoni*. People with severe, chronic infections often die from bleeding from oesophageal varices.

## Renal and urinary tract lesions

*S. haematobium* eggs lie grouped together in the bladder wall and surrounding organs (rectum, prostate, vagina, cervix, ovaries). This leads to the formation of very small (sandpaper-like) to a few mm large fleshy polyps and ulcerations. *S. haematobium* infection is a cause of genital lesions which are often mistaken for “warts”. The lesions in the urinary tract cause blood to be passed in the urine. In endemic areas this occurs typically in children of school age. The severity of the haematuria and proteinuria is related to the degree of infection. Ureteral strictures occur mostly in the distal third (mainly in the intravesical part). Ureteral obstruction can occur with resultant hydro-ureter and hydronephrosis. Because of the impairment of the normal anatomical relations vesico-ureteral reflux can also occur. Initially these lesions are still reversible. *S. mansoni* can give rise to a deposition of immune complexes in the kidney leading to glomerulonephritis. This happens in about 0.5% of cases usually in those with severe infections. In *S. haematobium* schistosomiasis the bladder wall can thicken. This resembles the thickening that can occur in tuberculous cystitis, chronic interstitial cystitis, radiation cystitis, chronic chemical cystitis or as a result of muscular hypertrophy with



obstruction due to prostatic hypertrophy or neoplasia or with a neurogenic bladder. At a later stage in bladder schistosomiasis, calcification of the dead eggs in the bladder wall occurs which is clearly visible on X-ray film.



Bladder calcifications due to *Schistosoma hematobium*

### Bladder carcinoma

In highly endemic areas of *S. haematobium*, there is an increased incidence of bladder carcinoma. This is manifested around the 4th or 5th decade of life. It principally involves a highly malignant squamous cell carcinoma which can occur anywhere in the bladder wall (in contrast to transitional cell carcinoma that occur later in life and is located principally in the trigonum). There may be a relationship with increased carcinogen concentrations (DNA alkylating nitrosamines) due to frequent bladder infections with nitrate-reducing bacteria, due to smoking tobacco or due to the local production of nitrosamines via activated macrophages.

## Late consequences

After severe chronic infection, the following serious problems can occur:

- Reduced bladder capacity.
- Increased incidence of bladder carcinoma, especially in tobacco smokers.
- Lesions of the female genitalia with cervical erosions, papillomatous lesions, sterility, increased risk of ectopic pregnancy and sexually transmitted diseases such as HIV.
- Lesions of the male genitalia e.g. localization in the ductus spermaticus.
- Irreversible obstruction of the urinary tract with hydro-ureter and hydronephrosis.
- Renal stones can form. Recurrent bacterial urinary infections are frequent, including *Salmonella*.
- Nephrotic syndrome can occur, as well as hypertension.
- Finally, chronic renal insufficiency may ensue.
- Remember that chronic glomerulonephritis can be caused by *S. mansoni* which is localized in the intestines (and eggs in the liver); This is secondary to the deposition of immune complexes in the renal glomeruli.

## Cardiac and pulmonary lesions

*S. haematobium* eggs can reach the systemic circulation and only rarely reach the portal circulation. This parasite is not a cause of hepatosplenomegaly. These eggs then reach the lungs. The same can happen with severe portal hypertension when *S. mansoni* or *S. japonicum* eggs reach the lung via the collateral circulation. Inflammation occurs in the lungs resulting in fibrosis and pulmonary hypertension. Right heart failure then occurs with development of cor pulmonale with congested jugular veins, peripheral edema and congested swollen liver. It used to be common in Brazil and Egypt but less so in recent years.

## Association with other infections

Patients with schistosomiasis (*S. mansoni*, *S. haematobium* and *S. japonicum*) are at increased risk of being *Salmonella* carriers. These bacteria are found in the intestinal tract of the worm. Urinary schistosomiasis often results in recurrent bacterial urinary tract infections.

Genital schistosomiasis is an independent risk factor for HIV infection since eggs can induce inflammation leading to development of ulcerative lesions in the female reproductive tract.

## Diagnosis

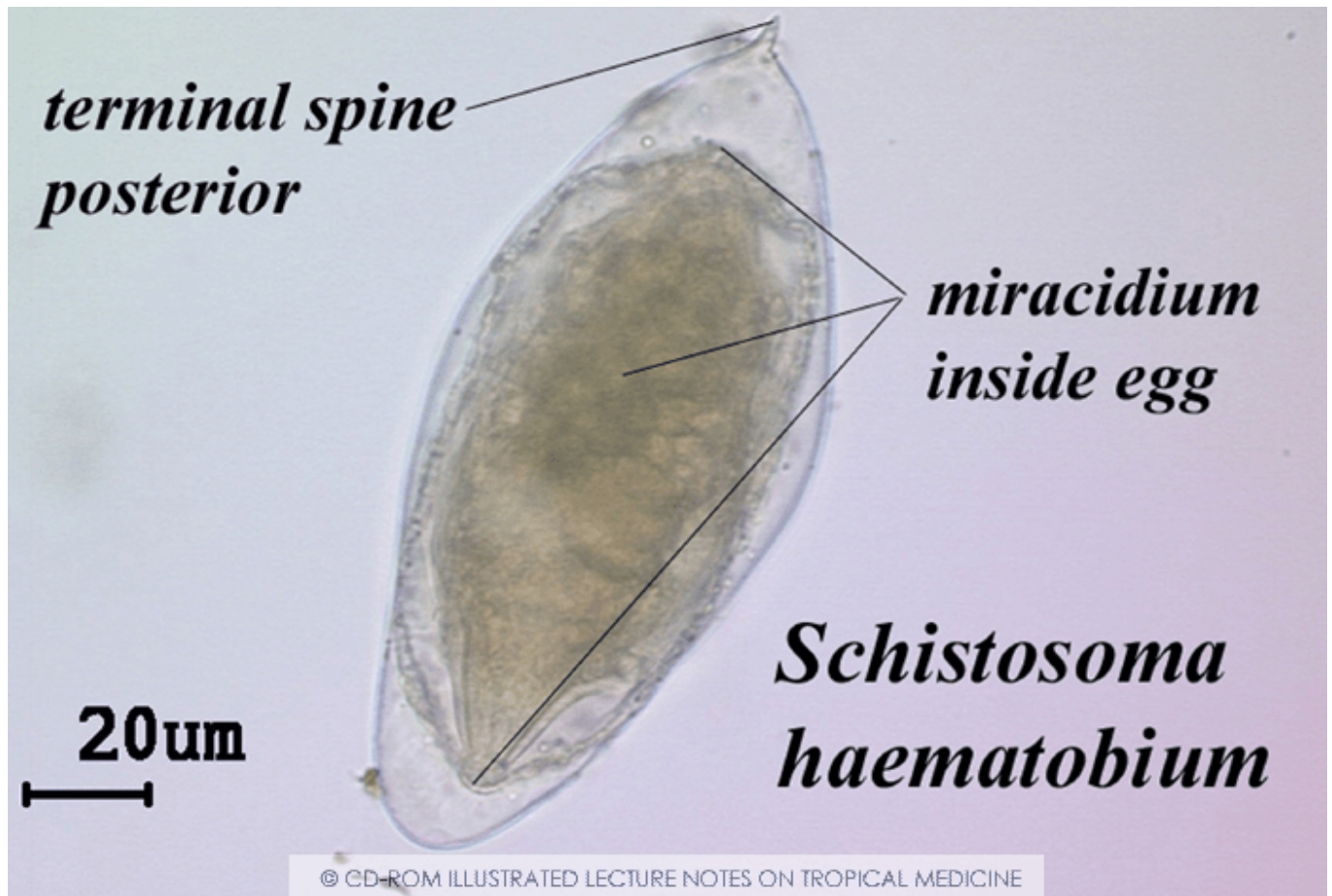
### Microscopy

The definitive diagnosis is established by the detection of eggs in the stools or urine with or without concentration techniques. The weight of a stool specimen that can be examined by direct microscopy is approximately 2 to 4 mg. In view of the small volume, egg excretions of up to 100,000 eggs per day can be missed. Only severe infections are detected in this way. The Kato-Katz method (cellophane impregnated with glycerol and malachite green) uses a larger quantity of stool (25 to 50 mg). The method is simple and more sensitive but more cumbersome. Low-grade infections can still be missed. Concentration of ova in faeces or urine can be done by a range of techniques.



*Schistosoma mansoni* egg with a large lateral spine. Copyright ITM





*Schistosoma haematobium* egg with terminal spine. Copyright ITM

The **sensitivity** of the laboratory tests can be problematic. It is dependent on the quantity of sample which it is feasible to routinely examine. A sample of 10 ml **urine** is equivalent to approximately 1/100 of the daily production and thus theoretically makes it possible to detect even a mild infection if it is assumed that at least 100 eggs/worm pair/day are found in the urine. With more than 50 eggs/10 ml there is almost always (microscopic) hematuria and proteinuria and this number has therefore been taken as the accepted threshold for distinguishing between mild and more severe infections. A **stool** smear by contrast, examines only 2 mg out of a total quantity of feces which for an adult in a tropical environment, may be estimated as 200-400 g/day. In this case therefore only 1/100,000 – 1/200,000 of the daily quantity of stool excreted is examined.

The severity of infection is reflected by the egg load. In *S. mansoni* infection, egg loads of less than 100 eggs per gram feces (epg) are considered mild and severe infections have more than 400 epg. A

mild infection is equivalent to more than 5 eggs/Kato smear. For this reason the WHO recommends the Kato method with which it is possible to examine 25 to 50 mg of stools, sufficient to discover all severe infections. It is however clear that even with this technique many milder infections are missed. It is important that a positive smear always indicates an infection which is already fairly severe.

There are several other flotation and sedimentation concentration methods which allow detection of lighter degrees of infection. For instance the FLOTAC stool concentration method is about 10 times more sensitive for *S. mansoni* egg detection than the Kato-Katz. The sensitivity is also affected by fluctuations in the quantity of eggs in the excreta. This is the case for excretion of *S. haematobium* eggs which peaks around midday. Specimens taken between 10 a.m. and 2 p.m. are therefore optimal for examination. During the evening hours and the night elimination falls to a minimum. This periodicity is the result of contractions of the muscle wall of the bladder which itself is affected by drinking/meals and exercise and not by the production of eggs (which occurs continuously). In the case of intestinal schistosomiasis this systematic factor has little if any importance.

An additional source of error is that the elimination of eggs in the same person can vary considerably from day to day, making the individual diagnosis more difficult. The consequence is that a negative parasitological examination even with sensitive techniques is only of limited value. In a severely infected person, on average high egg loads are found and only rarely low egg loads. The opposite is true for people with low worm loads. Taking fecal specimens on different days is better than examining several smears from 1 stool.

## Serology

Serology based on the detection of antibodies, does not distinguish between active and previous infections. Positive serological tests with low titers which cannot be confirmed parasitologically probably indicate either (1) an old, cured infection, (2) an infection with a very low worm load, (3) an infection by worms of a single sex or (4) cross-reactivity with other worm species. Antibodies are usually detectable before eggs are detectable.

## Antigen detection

Circulating antigen detection tests (circulating anodic and cathodic antigen CAA and CCA) have been developed, as a means to detect schistosomiasis. Antigen can be detected in serum as well as in urine (in urine also for *S. mansoni*). Many research groups are evaluating such antigenic tests in the tropical fields under rapid test formats (RDT) based on lateral flow immunochromatography. A

recently developed CCA dipstick test (in urine) has been consistently found much more sensitive in detecting infection with *S. mansoni* than conventional stool microscopy (Kato-Katz concentration).

## Polymerase chain reaction

PCR based molecular techniques are currently being developed for population surveys and for clinical use. Due to sophistication and costs this technique is still restricted to research and reference labs. The sensitivity and specificity of different formats and sequence targets are being evaluated.

## Medical imaging

Complications can be detected by means of ultrasound (e.g. hydronephrosis). The degree of liver involvement can also be determined echographically. This may be of epidemiological importance for example in control programs. Ultrasound is the only possible technique for establishing a non-invasive sensitive and specific diagnosis of hepatic lesions in hepato-intestinal schistosomiasis. The lesions are pathognomonic and can even be seen in children with surprisingly low egg excretion. There is a clear relationship between the presence of ultrasound lesions and the mean excretion of eggs.

Symmers hepatic fibrosis can become symptomatic in later life when the parasite load has become low and it can even be difficult to detect that there is an infection. Clinical differences between cirrhosis and Symmers hepatic fibrosis are relative: youth of the patients, more pronounced splenic enlargement in Symmers hepatic fibrosis, general health preserved for longer even after hematemeses, hepatic enlargement predominantly of the left liver lobe.

Bladder calcifications may be visible on a standard radiograph of the abdomen and on CT-scan.

## Biopsy

**Rectal snip or rectal biopsy** consists in removing 1 to 3 fragments of superficial tissue with biopsy forceps under endoscopic control from sites where small hemorrhages or other suspicious lesions are seen. These tissue specimens are placed between two glass slides and examined immediately in a drop of water without fixation. Histological examination has a lower diagnostic yield as the section of tissue examined is much thinner. The sensitivity of a rectal snip is good and curiously, better for *S. haematobium* than for *S. mansoni*. In travel medicine this examination is more sensitive, particularly in the case of *S. haematobium* than examination of the urine or stools because the patients involved are mainly adults with a low worm load with few eggs. Rectal snip detects eggs that have accumulated over a period of weeks, months or years under the rectal mucosa. The distinction

between dead and living eggs is important. When living eggs are examined immediately after sampling in an unstained biopsy the moving cilia of the miracidia can easily be seen. The rectal biopsy technique is not used so often in endemic areas where attention is directed particularly to children. Rectal snip data are not quantitative.

**Other biopsies:** Needle biopsy or surgical biopsy of the liver cannot confirm the diagnosis in all cases and is dangerous in patients with a bleeding tendency. Cystoscopy can be used to visualize bladder lesions. Eggs are found in bladder biopsies and sometimes in cervix or skin.

## Treatment

### Praziquantel (Biltricide®)

Praziquantel (PZQ) is the first choice treatment. The standard dose is one 600 mg tablet per 15 kg or 40mg/kg body weight. Usually it is given as a single dose but doses can be taken 4 to 6 hours apart to minimize side-effects. A single dose reduces the parasite load by more than 80%. Treatment cost is low and makes repeated mass treatment an attractive option to reduce the parasite load.

Praziquantel kills the adult worms not the immature schistosomules or the eggs. Praziquantel is undoubtedly the most effective medication with the fewest side-effects for the treatment of all species of schistosomes. The drug seems less effective in regions of West Africa where there has been a recent invasion of the parasite possibly due to rapid re-infections. Diminished sensitivity or resistance to praziquantel are other possibilities but not a major issue so far. Apart from its activity against all human schistosomes including *S. mekongi*, *S. intercalatum* and *S. mattheei*, praziquantel is also very effective against most infections due to trematodes (except *Fasciola*) and cestodes but not roundworms. There are no contra-indications and no major toxicity has been reported. It may be given in hepatic insufficiency. The drug however is not recommended during the first three months of pregnancy. Side-effects include abdominal pain, vomiting, diarrhea and fever; probably caused by the reaction to the dead worms. In very severe infections cases of rectorrhagia are observed. In patients with a hemorrhagic diathesis, this could be dangerous. There is a major risk if cysticercosis is present in the region since serious complications (seizures) can occur as a consequence of the death of cysticerci in the CNS following administration of the medication. In spinal and cerebral schistosomiasis, praziquantel always follows prolonged corticosteroid treatment.

Praziquantel has no effect on eggs and immature worms. Tissue-dwelling eggs can be excreted for several weeks after treatment. During the same period prepatent or newly acquired infections can become productive. The preferred timing of follow-up is therefore 4-6 weeks after initial treatment to

kill the meanwhile matured schistosomes. Katayama fever is primarily treated with corticosteroids to suppress the hypersensitivity reaction and with praziquantel to eliminate matured worms.

**Other drugs used in the past** (and still available in some countries) for schistosomiasis

- Niridazole (Ambilhar®)
- Metrifonate (Bilarcil®)
- Oxamniquine (Vansil®)

Praziquantel has become however the first-choice treatment everywhere in the world. Some of these second-line drugs might become important again if resistance to PZQ would emerge.

**It should be also noted** that the artemisinin derivatives have “preventive” effect on *S. mansoni* and *S. japonicum* (being mostly active on schistosomulae). Mefloquine is another antimalarial drug with some partial efficacy on *Schistosoma* larvae and adult worms (all species). Several small studies have demonstrated short-term reduction of egg load with both drugs in particular when they are combined. Whether these drugs can be used in addition to praziquantel for schistosomiasis treatment or prevention (in malaria-free areas or in returning exposed travelers) still remains to be thoroughly studied before any new recommendation can be made.

## Prevention

The main objective for schistosomiasis control is the **reduction of morbidity** which is based on the reduction of the worm load. No vaccine is yet available. Attention is focused on detection and treatment and vector control. Mass treatment can be undertaken with yearly administration of praziquantel (treat everyone without screening). Selective treatment of infected people can also be carried out following active screening. Treatment can be restricted to a particular group (e.g. all schoolchildren or children from specific school years). Passive screening (all those people who attend a health center) is also possible. Control of morbidity should not be seen separately from **control of transmission**.

Health education is not effective if it is not associated with an improvement in sanitary conditions in the district. The avoidance of contact with contaminated water is only possible if there is an alternative. Hence the importance of a technical infrastructure and its maintenance (washing areas, showers, toilets, footbridges over canals etc). It is obvious that these are only meaningful if they are accepted and used. The erection of numerous bridges over canals and the use of water pumps (drinking water, washing areas) reduce contact with potentially contaminated water. Water pumps

should be of a design that allows inexpensive local repairs to be made.

It is also possible to try to **control the vectors**. Snails like mud and the presence of water plants. If there is a large amount of deep shadow in places where the vectors are present, the latter will have less food (snails eat algae and plants, which are dependent on photosynthesis). No shadow at all, however, will reduce egg production. Control of water plants and vegetation involves infrastructural changes. Covering over irrigation channels can limit snail populations. Cleaning of canals or the use of concrete for irrigation canals can be useful. Snail control by chemical molluscicides cannot be sustained in the long-term (too expensive and too much collateral ecological damage). The efficacy of biological control of the vector still needs to be demonstrated. The use of certain plants with a molluscicidal effect is being studied, e.g. the soapberry Endod (*Phytolacca dodecandra*).

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