

# Schistosomiasis and its impact on the liver and gut

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## Summary

This in-depth overview provides detailed information on liver and intestinal schistosomiasis, including pathogenesis, clinical manifestation, diagnosis and treatment.

## Souhrn

**Jaterní a střevní postižení při schistosomiáze**  
Tento aktuální přehledový článek podává podrobný přehled problematiky jaterní

miasis, including pathogenesis, clinical manifestation, diagnosis and treatment.

a střevní schistosomiázy, včetně patogeneze, klinického obrazu, diagnostiky a léčby tohoto onemocnění.

**KEY WORDS:** SCHISTOSOMIASIS, BILHARZIOSIS, LIVER INVOLVEMENT, INTESTINAL INVOLVEMENT

**KLÍČOVÁ SLOVA:** SCHISTOSOMIÁZA, BILHARZIÓZA, JATERNÍ POSTIŽENÍ, STŘEVNÍ POSTIŽENÍ

## INTRODUCTION

Schistosomiasis is a chronic parasitic disease caused by a trematode blood fluke of the genus *Schistosoma* that belongs to the Schistosomatidae family [14]. Worldwide, it is estimated that more than 200 million people suffer from this disease and that it is responsible for more than 200,000 deaths every year [34,41].

Schistosomiasis has been known since time immemorial. The ancient Egyptians contracted the disease more than 4,000 years ago – 1900 B.C. (Fig. 1), and recorded it in the Kahun Papyrus [32]. In 1851, Theodor Bilharz discovered schistosoma from a human autopsy material in Cairo and described the relationship of the parasite to pathologic lesions. From 1910 to 1918, Leiper showed there were two species of schistosoma in Egypt and that they were transmitted by two different snails [50].

## GEOGRAPHIC DISTRIBUTION

There are 5 species of *Schistosoma* with a tendency to occur in restricted geographic patterns (Fig. 2). *Schistosoma mansoni* is most prevalent in certain tropical and subtropical areas

of sub-Saharan Africa, the Middle East, South America and the Caribbean. *Schistosoma heamatobium* infection is acquired in North Africa, sub-Saharan Africa, the Middle East and India. *Schistosoma japonicum* occurs only in Asia. *Schistosoma intercalatum* occurs in Central and West Africa while *Schistosoma mekongi* is restricted to Laos and Cambodia [39].

In Egypt following construction of the Aswan High Dam in the 1960s, a striking change in the geographic distribution of the two species of schistosoma (*S. mansoni* and *S. heamatobium*) occurred with an increasing prevalence of *Schistosoma mansoni* in the Nile Delta and concomitant decrease of *Schistosoma heamatobium* prevalence spreading from the Nile Delta into Upper Egypt. This

change was believed to be caused by less silt and by variability in the velocity and volume of water flow with a resultant shift in the relative abundance of the corresponding snail vectors (Fig. 3) [3,4,21,53].

The largest and latest epidemiological survey in Egypt mentioned the prevalence of *Schistosoma heamatobium* in Upper Egypt (where it is endemic) as being around 7.8 % while the prevalence of *Schistosoma mansoni* in Lower Egypt (where it is endemic) is around 36.4 % [29].

## SCHISTOSOMAL HEPATOPATHY

Schistosomal hepatopathy is the best-known form of the chronic disease and usually results from heavy *Schistosoma mansoni* infection [48].



**Schistosoma.**  
Copulating male and female trematodes.



**Figure 1**  
Ancient Egyptians contracted the disease.

### Pathogenesis

Gross anatomical features and a complex set of vascular changes characterize schistosomal hepatopathy as a peculiar form of chronic liver disease, clinically known as hepatosplenic schistosomiasis. It differs from hepatic cirrhosis, although clinical and pathological aspects may sometimes induce confusion between these 2 conditions [8]. The key pathogenetic products of schistosomes are the eggs while the adult worms play a minimal role. The egg contains a living embryo, secretes antigenic material which is released through ultramicroscopic pores in the shell and survives for three weeks after which the shell is breached and the remainder of the embryo is phagocytosed [68].

The egg antigens sensitize CD4 T cells resulting in a cell mediated immune response and granuloma formation. This acute granuloma is characterized by dense cellularity and maximum cytokine production. As the infection progresses into the chronic stage, cytokine production and cellularity decrease while the fibrotic components of the immunopathologic process increase (Fig. 4) [18,25,44].

On the vascular level, the portal fibrosis leads to intrahepatic portal vein obstruction and compensatory arterial hypertrophy that render the hepatic parenchyma vulnerable to ischaemic insult. This may lead to focal necrosis and focal post necrotic scars ending with schistosomal hepatopathy [8].

The mechanism of intrahepatic portal vein obstruction starts with damage of the muscular walls of the portal vein, dissociation of smooth muscle cells and then their transition toward myofibroblasts that behave as transient cells, some becoming fibroblasts and others disappearing, probably undergoing apoptosis [8,10]. Signs of focal collagen breakdown and

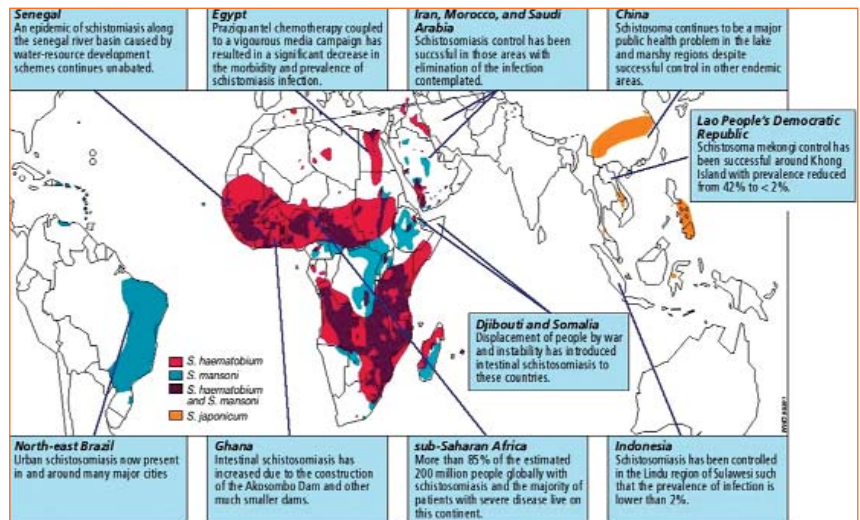


Figure 2  
Global distribution of schistosomiasis.

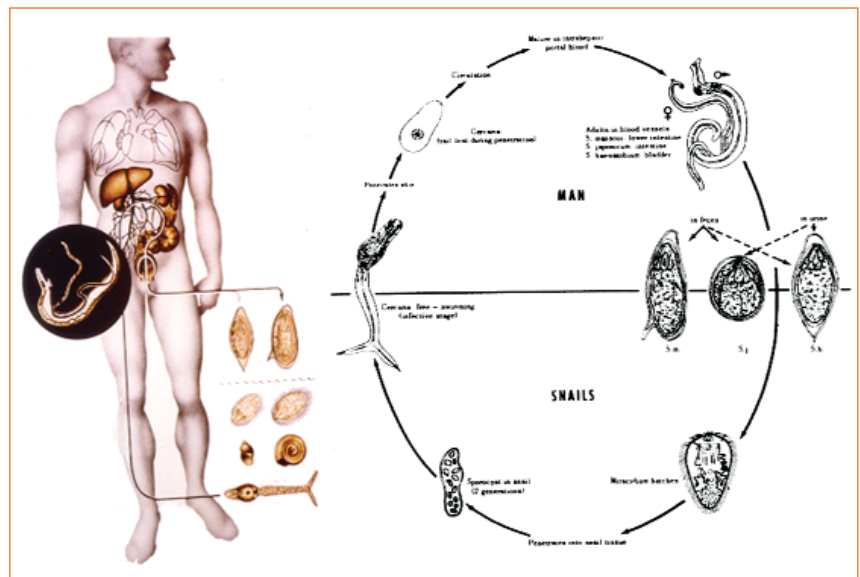


Figure 3  
Life cycle of schistosomiasis.

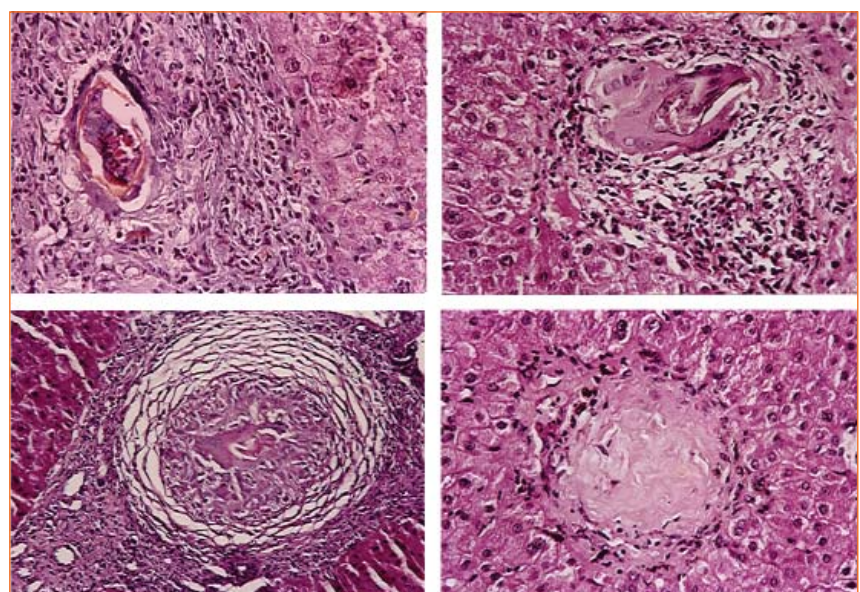


Figure 4  
Steps of schistosomal hepatic fibrosis.

resorption are frequently noted in portal fibrosis. This shows the dynamic state of equilibrium between the forces of synthesis and breakdown with a possibility of curing schistosomiasis and the associated hepatosplenic disease, which does not hap-

pen with hepatic cirrhosis [7]. Finally, it was noticed that schistosomiasis per se can cause a certain degree of chronic hepatitis, probably of a reactive nature [8].

All these events of egg deposition, granuloma formation and consequent fibrosis expansion of the portal spaces lead to the gross appearance of the cut surface of the liver as whitish fibrinous plaques (replacing portal spaces) on a background of normal looking parenchyma. One century ago, Symmers (1904) classically described this picture after performing autopsies in Egypt [63].

#### Clinical manifestations

It is usually admitted that the clinical presentation of hepatosplenic schistosomiasis markedly differs from that of cirrhosis. Although the signs and symptoms of portal hypertension and hypersplenism are dominant in schistosomiasis (Fig. 5), the counter part of hepatocellular failure is absent. However, some patients with schistosomiasis do evolve to an end stage of

the disease by exhibiting muscle waste, hypoalbuminemia, ascites and coma. These observations led to the concept of compensate and decompensate schistosomiasis to differentiate patients with the sole manifestations of portal hypertension from those who, in addition, presented signs of hepatocellular failure [8]. Ultrasound examination showed characteristic pictures of schistosomal periportal hepatic fibrosis (Figs 6-9).

#### Interaction with hepatitis viruses

Although some studies denied the presence of any special relationship between schistosomiasis and infection with hepatotropic viruses [9], many studies mentioned a totally different opinion.

Patients with hepatosplenic schistosomiasis were found to be 7–10 times more susceptible to co-infection with hepatitis B virus than healthy persons [9,27,73], exhibit chronic hepatitis on liver biopsy, manifest persistent antigenaemia [59] and suffer from a higher frequency of cell decompensation [12]. Similar interaction was also observed with viral hepatitis C [5,6,9,11,22,37,40,67].

The reasons for this interaction between schistosomiasis and hepatitis viruses include the direct stimulation of viral replication by soluble egg antigen [26], defects in cell mediated immunity [30] and the high exposure of schistosomal patients to repeated specific parenteral therapy, blood transfusion and non specific therapy [72]. Frank and others reported that the large reservoir of HCV infection in Egypt was primarily built during schistosomiasis control campaigns conducted 20–50 years ago by use of intravenously administered tartar emetic [36] and this occurred using improperly sterilized glass syringes [17,33,38,43,52].

#### INTESTINAL SCHISTOSOMIASIS

Intestinal schistosomiasis represents



Figure 5  
Schistosomiasis. Advanced hepatosplenomegaly and ascites.

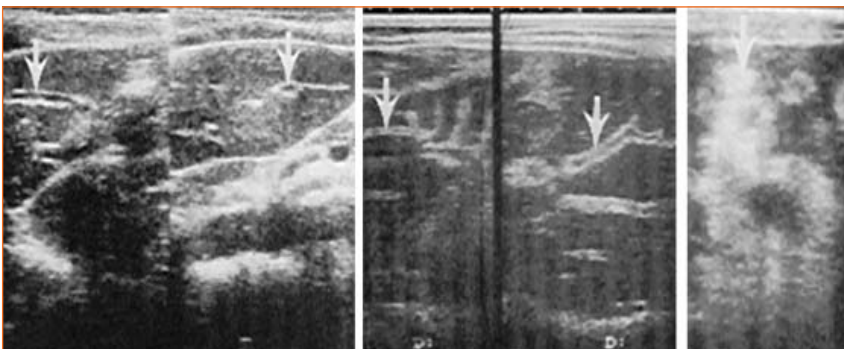


Figure 6  
Characteristic pictures of schistosomal periportal hepatic fibrosis on abdominal ultrasound.

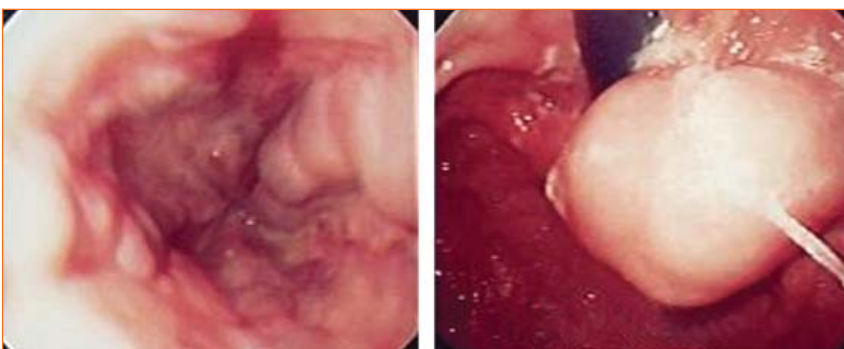


Figure 7  
Portal hypertension in schistosomiasis. Oesophageal varices and fundal varix.

another form of schistosomal affection. Among the spectrum of intestinal lesions, polyps are the commonest [45]. The presence of schistosomal colonic polyposis has been associated with increased morbidity and mortality [1]. Intestinal schistosomiasis is essentially due to *Schistosoma mansoni* infection [28] and it has been reported as well in some *Schistosoma haematobium* cases [13].

### Pathogenesis

Egg-laying worms are present in the intestinal micro-vasculature especially in the distribution of the inferior mesenteric venous plexus. In the large intestine, ova are mainly distributed in the loose submucosa, and to a lesser extent in the subserosa where infrequently multiple granulomas are formed. Subsequently, the muscularis mucosa becomes involved and the overlying mucosa is either denuded forming small superficial ulcers or undergoes hyperplastic changes. Sandy patches develop when the submucosa becomes densely thickened by fibrous tissue containing immense numbers of calcified eggs. The overlying mucosa becomes atrophic and acquires a granular dirty yellowish appearance [62].

The mechanism of polyp formation starts by deposition of schistosomal eggs in the superficial layers of submucosa where the connective tissue is loose, delicate, and not bounded superficially by firmer tissue. This allows the accumulation of large amounts of reactive cellular debris and vascular granulation tissue. In the submucosa, the eggs produce a cell mediated inflammatory response with granuloma formation and necrosis. As necrotic foci heal, fibrous connective tissue is formed and the adjacent muscularis mucosa becomes hypertrophied. The fibrous tissue in the submucosa and the hypertrophied muscularis mucosae form a barrier to the usual route of ova transit from the

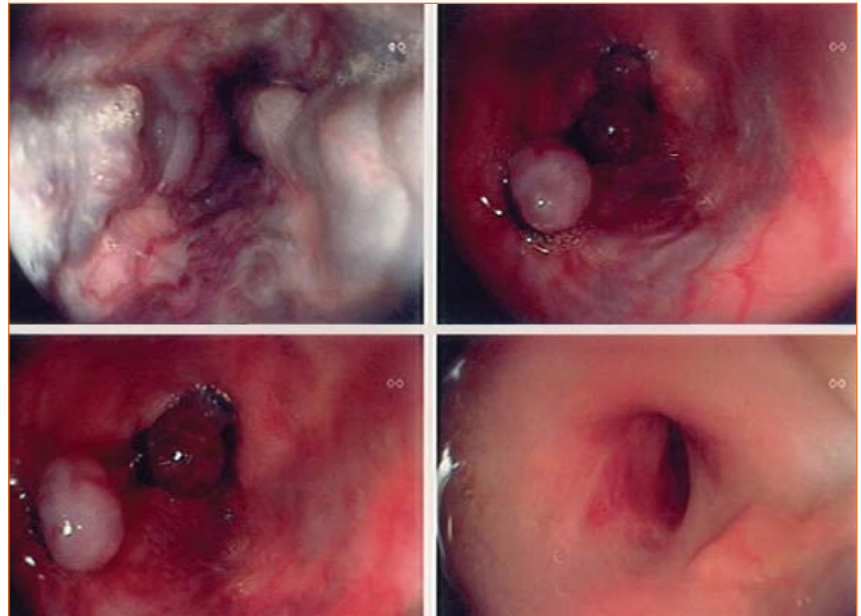


Figure 8  
Oesophageal varices. Steps of band ligation till eradication.

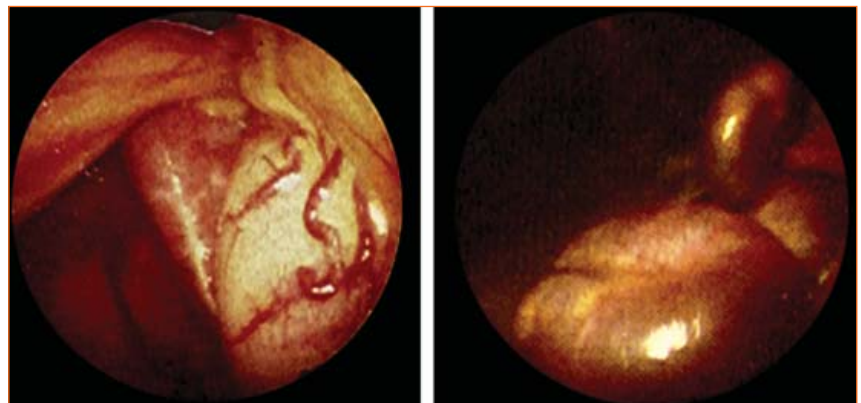


Figure 9  
Portal hypertension in schistosomiasis - laparoscopic pictures. Courtesy of Professor Shoukry Hunter.

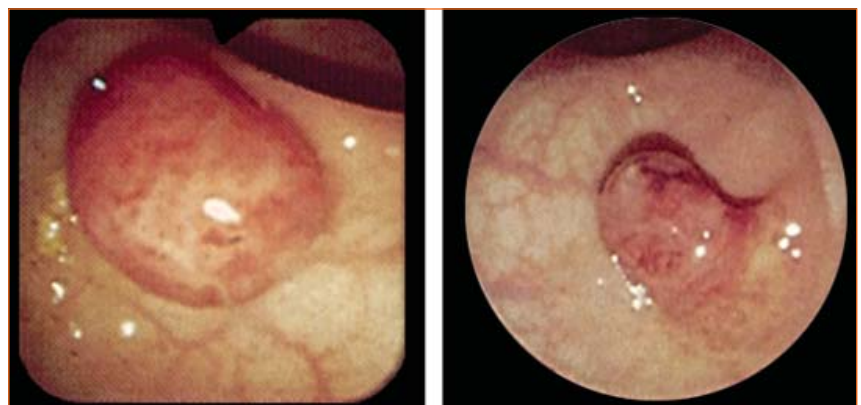


Figure 10  
Intestinal schistosomiasis. Solitary polyps.

mesenteric veins to the gut lumen. This entrapment of ova leads to a foreign body reaction with further inflammation and fibrosis. As this process continues, a nodule is formed

that elevates the hypertrophied muscularis mucosae and mucosa to form the earliest detectable polyp [13]. This mechanism can explain the main concentration of the *Schistosoma*

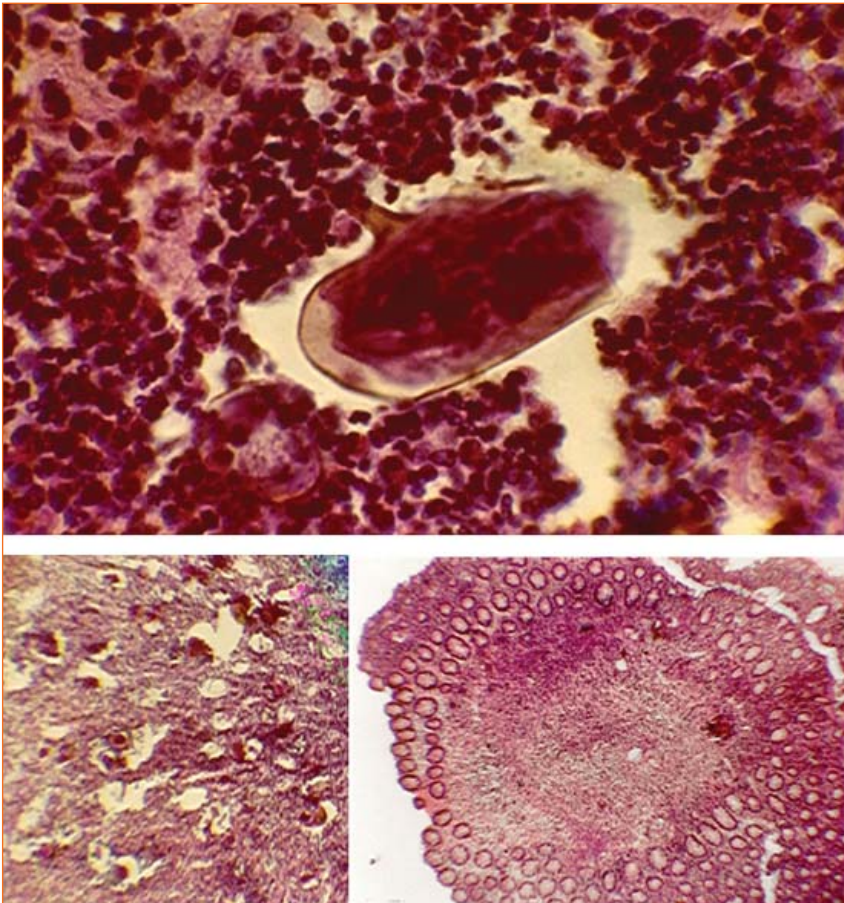


Figure 11  
Schistosomal egg granuloma and schistosomal polyp (histopathology).



Figure 12  
Nail clubbing in schistosomiasis.

*S. mansoni* ova in the polyps than in the adjacent mucosa and submucosa [55].

### Pathology

Polyps range in size from 2 to 20 mm and may be sessile, pedunculated or showing a cauliflower appearance. They are mainly concentrated in the distal colon, and they count from few to very numerous polyps. The covering

mucosa of the polyps is usually redder than the surrounding mucosa due to severe congestion and due to focal haemorrhages (Fig. 10). Ulceration is common in rectal polyps, the ulcerated areas appear dusky to blackish grey in colour caused by superficial haemorrhage, and are frequently secondarily infected [28,65].

Histologically, the typical polyp is composed of a stalk of fibrous con-

nective tissue projecting from the submucosa into the lumen and partially covered with mucosa. The overlying mucosa consists of distorted glands showing varied degrees of mucoid activity, mucinous degeneration, and adenomatoid hyperplasia. Focal areas of ulceration frequently interrupt the surrounding mucosa. Larger areas of ulceration may be replaced by granulation tissue. Mononuclear cells, eosinophils, and few polymorphonuclear leukocytes infiltrate the mucosa. The supporting tissue is composed of fibrous connective tissue and muscle derived from the muscularis mucosae. Blood vessels may be present in large numbers but diminish as fibrosis progresses. Viable and nonviable eggs are present in all polyps (Fig. 11) [56].

### Clinical picture

Schistosomal colonic polyposis mainly affects adult males, with an age ranging between 8 and 15 years. The primary symptoms present are usually tenesmus and the rectal passage of blood and mucus. Diarrhoea, abdominal pain, dyspepsia, and irreducible schistosomal papilloma protruding from the anus occur in some patients [1,24,57].

Malnutrition, weight loss, nail clubbing (Fig. 12), pitting peripheral oedema, and pericolic masses may also be present [1,13]. Other manifestations include iron deficiency anaemia, hypoalbuminaemia, protein-losing enteropathy, and rectal prolapse [35,58].

The presence of polyposis (Fig. 13) does not appear to predispose patients to the development of large bowel cancer [16] and many investigators even have rejected any relationship between schistosomiasis and colorectal carcinoma, although this view is debatable if we consider *Schistosoma japonicum* [31,54,70].

### DIAGNOSIS

Definite diagnosis of the disease depends on certain tools such as

microscopy and egg identification, serology and radiologic findings. Other non-specific findings include eosinophilia (in relation to stage, intensity and duration of infection), thrombocytopenia (from splenic sequestration) and anaemia (from chronic blood loss). Liver biochemical profile is usually normal [49].

Demonstration of parasite eggs in stool is the most common method used diagnosis of schistosomiasis and species identification. Concentration techniques improve the sensitivity of egg detection. To assess intensity of infection, quantitative sampling of defined amounts of stools (Kato Katz technique) is applied. Schistosomiasis can be diagnosed also by finding eggs in tissue biopsy specimens from rectal, intestinal and liver biopsies (Figs 14 and 15) [34,47,49,60].

Serologic tests can detect anti-schistosomal antibodies in serum samples, but none of the tests can distinguish between past and current active infection. However, a negative test can rule out infection in endemic population. Another drawback is that they remain positive for prolonged periods following therapy making them unreliable for post treatment follow up [49].

To solve these defects, techniques to detect parasite antigens, in sera and stools, have recently been developed and can identify current infection and its intensity [23].

Radiologically, abdominal ultrasonography plays an integral role in the diagnosis of hepatosplenic schistosomiasis. Imaging can show periportal fibrosis, splenomegaly, increased portal vein dimension and the presence of collateral vessels [2,48,71]. Ultrasonography helps to assess degree of periportal fibrosis by measuring portal tract thickness: Grade I if thickness is 3–5 mm, Grade II if it is 5–7 mm and Grade III if it is more than 7 mm. This method reflects the haemodynamic changes and provides a good esti-

mate of the clinical status of patients who have periportal fibrosis [2].

Concerning the presence of colonic polyps, sigmoidoscopy and radiography of the colon after barium enema with air insufflation are the main tools for their diagnosis [28].

### TREATMENT

The two main drugs used to treat *Schistosoma mansoni* are praziquantel and oxamniquine, with an upper hand for praziquantel [61]. Praziquantel is safe and tolerable and its adverse effects are generally mild, including dizziness, headaches, vomiting, abdominal pain, diarrhoea and pruritus. It can reverse early complications associated with schistosomal infections. Regression of periportal fibrosis and portal tract thickening has been documented. However, once late stage fibrosis and oesophageal varices have developed, therapy will not be effective in reversing these complications [49] and will be treated with propranolol and/or sclerotherapy or shunt procedures [34].



Figure 13  
Multiple schistosomal colonic polyposis (surgical specimen).



Figure 14  
Schistosoma. Circumoval precipitin test (CPT).

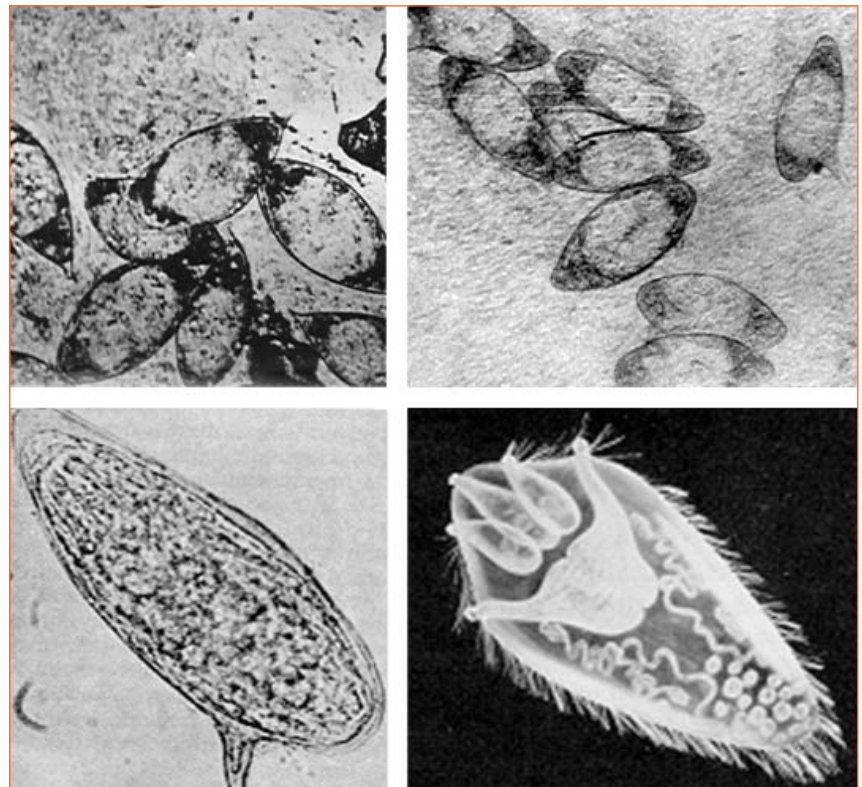
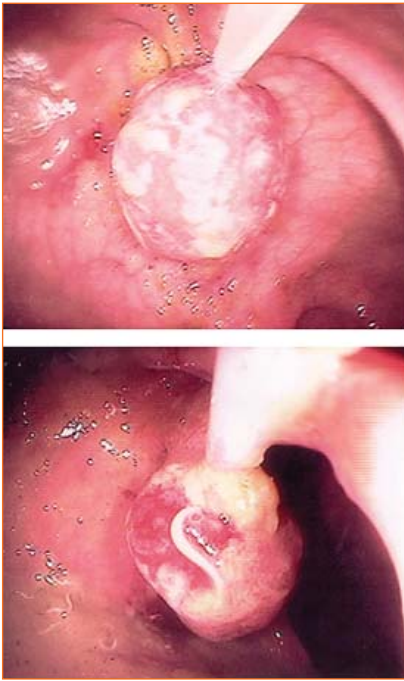


Figure 15  
Schistosoma. Fresh rectal biopsies - hatching ova.



**Figure 16**  
Schistosomal polyp of the large bowel.  
Steps of polypectomy.

Due to the extensive use of praziquantel for more than 10 years, recent evidences suggest that resistance to the drug may be developing. The classic phenotype of resistance is a significant increase in the 50% effective dose value of isolates retrieved from patients not responding to the drug, such phenotypes have been isolated from humans infected with *Schistosoma mansoni* [46]. This problem opened the door to a search for new drugs such as oleo-resin extract from myrrh of *C. molmol* tree (Mirazid®) that has been marketed since 2001, but different studies found a much lower cure rate compared to that with praziquantel and doubted its use for treatment [15,19].

Colonoscopic polypectomy is safe and effective and may be required along with medical therapy to achieve complete symptom relief and prevent complications (Fig. 16). All symptomatic or large polyps should be removed after pharmacologic treatment even before waiting for a complete parasitologic cure because they will not be resolved with medical treatment alone [42,57,66,69].

### VACCINATION

Clinical trials to develop an antischistosomal vaccine are still in progress. A recent study identified certain issues to facilitate its development and licensure as follows: identification of the human immunoprotective antigens and mechanisms, induction of the appropriate responses by adjuvant vaccines, understanding the effect of immunization on immunopathology, development of an improved serologic assay to determine worm burden, and generation of a fund to apply it primarily through a project [66].

### PREVENTION

Integral to any control programme is the need for sanitation and proper sewage control, as well as limiting access to infested fresh water and provision of a safe water supply. Programmes focused on eradication of snail species have been attempted. In general, this approach does not result in complete eradication and is difficult to sustain. Repopulation by snails can occur very rapidly. Educational programmes also have a role. Mass or targeted chemotherapy programmes are now frequently being employed in endemic areas to reduce the burden of infection. Programmes are frequently directed at treatment of adolescents since this age group has the highest intensity of infection. Community programmes generally use annual administration of praziquantel and this decreases transmission, prevalence and intensity of infection [20,51,64].

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