

## Schistosomiasis mansoni – Clinical features

L.C. Da Silva<sup>a,b</sup>, P.P. Chieffi<sup>b</sup> y F.J. Carrilho<sup>a</sup>

<sup>a</sup>Hepatology Unit. Department of Gastroenterology. Tropical Medicine Institute. University of São Paulo. School of Medicine. São Paulo.

<sup>b</sup>Immunopathology of Schistosomiasis Laboratory. Tropical Medicine Institute. University of São Paulo. School of Medicine. São Paulo. Brazil.

### ABSTRACT

In the present review, we will discuss the *Schistosoma mansoni* form, which is the most widely distributed schistosome in humans and is found both in the Old and New Worlds.

The main features of the natural history of mansonic schistosomiasis are reviewed, with emphasis on the clinical forms of the disease, their diagnosis and treatment.

**KEY WORDS:** *Schistosoma mansoni*. Mansonic schistosomiasis. Clinical features. Diagnosis. Treatment.

### INTRODUCTION

The human schistosomes or blood flukes are digenetic trematodes belonging to the *Schistosomatoidea* superfamily. The main species responsible for the clinical forms are *Schistosoma mansoni*, *S. hematobium* and *S. japonicum*. Other species that affect humans (*S. mekongi* and *S. intercalatum*) have limited geographic distribution in Asia and Africa, respectively<sup>1</sup>.

In the present review, we will discuss the *S. mansoni* form, which is the most widely distributed schistosome in humans and is found both in the Old and New Worlds<sup>2</sup>. Mansonian schistosomiasis is endemic in northeast Brazil, where it affects approximately 2.5 million people<sup>3</sup>. The decrease in the number of infected individuals in the last few decades and the geographic frontiers of schistosomiasis remain to be established in Brazil. The main reasons for this lack of epidemiological data are the presence of the snail *Biomphalaria* sp., which is susceptible to *S. mansoni* infection in nonendemic areas, and migration<sup>4</sup>. Nowadays, in some areas such as the Caribbean Islands, Venezuela and Suriname, the prevalence of *S. mansoni* is very low (under 1%)<sup>5</sup>. Some authors believe that this

might be due, at least partly, to the predatory action of some snails (e.g. *Thiara granifera*) or the *Biomphalaria glabrata*<sup>6,7</sup>. Such measures may be feasible in small areas, but not in our country where the *Biomphalaria* snails live in vast territories. In Brazil, an extensive *S. mansoni* control program based on treatment with oxamniquine and snail control resulted in a sharp decrease in hepatosplenic and other advanced forms of schistosomiasis<sup>5</sup>.

The basic life cycle of the parasite alternates between generations, with a sexual stage of adult schistosomes in the definitive vertebrate host (man) and an asexual stage in a molluscan host (*Biomphalaria*). A relatively short-lived and free-swimming stage, the miracidium, hatches from the egg found in human stool and infects the snail intermediate host, where it gives rise to sporocysts that produce numerous free-swimming cercariae. These are infective both to man and to other vertebrate hosts. After skin penetration the cercariae are known as schistosomula, which migrate to the lungs and then to the liver. After maturation, both the male and female worms migrate to the terminal branches of the mesenteric veins where each female produces 100-300 eggs per day. A considerable number of eggs pass into the lumen of the bowel and are discharged into the feces. Some of these eggs become trapped in the intestinal wall and the remaining eggs are carried by the portal blood to the liver.

Schistosomiasis is considered to be a «man-made disease» since humans are both the victims and the source of infection<sup>8</sup>. Insanitary habits among humans such as defecation in canal water and at the same time exposing themselves to this polluted water by bathing, swimming for recreation, washing utensils and clothes and other forms of contact characterize endemic areas<sup>8</sup>. Exposure to infection starts as early as at 6 months of age and maximal infection and severity occur in early childhood (10-14 years) followed by a progressive decrease. The lower prevalence in adults may be explained by lower exposure to contaminated water and to the development of acquired concomitant immunity<sup>8</sup>.

Environmental changes that result from the development of water resources and population growth and migration

Correspondencia: Dr. L.C. Da Silva.  
Rua Silva Correia, 153, ap. 41  
ZC 04537-040 São Paulo, Brazil  
Correo electrónico: fjcarril@usp.br

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can facilitate the spread of schistosomiasis. For example, the construction of the Diama Dam led to the introduction of *S. mansoni* into Mauritania and Senegal<sup>9</sup>.

### CLINICAL FORMS AND PATHOGENESIS

Liver disease in schistosomiasis results from the entrapment of eggs that are not excreted but instead lodge in portal venules that match the egg's smallest diameter, about 50  $\mu\text{m}$ <sup>1</sup>. Eggs in the liver remain viable for about 3 weeks and secrete products that elicit a characteristic initial response, the schistosome egg granuloma. In some persons with heavy infections, the final result of hepatic schistosomiasis is severe portal fibrosis (figs. 1 and 2). Advanced schistosomal hepatic fibrosis gives a gross appearance of greatly enlarged fibrotic portal tracts, described by Symmers in 1904 as resembling clay pipestems thrust through the liver, and now termed Symmers' pipestem fibrosis<sup>1</sup>. Schistosome infection can be divided into distinct stages. The prepatent stage begins with cercarial invasion and ends with initiation of egg laying. The patent stage coincides with schistosome egg production and can be further divided into acute and chronic schistosomiasis<sup>10</sup>.

#### Acute form (Katayama fever)

Acute schistosomiasis is due to a fresh infection. Clinical manifestations may be absent, particularly in individuals living in an endemic area<sup>11</sup>. Occasionally some individuals may develop the syndrome after an initial contact with water contaminated by *S. mansoni cercariae*. The most common manifestations are fever, chills, weakness, headache, anorexia, nausea, vomiting, and general malaise. Severe watery diarrhea, sometimes bloody stools, nonproductive cough, and rapid weight loss may develop. Occasionally, patients with acute schistosomiasis mansoni have been diagnosed as having typhoid fever, hepatitis, pancreatitis, miliary tuberculosis, myelitis and appendicitis<sup>12</sup>, only to be cured when the schistosomiasis has been discovered after a long search<sup>13</sup>. On the other hand, many patients have been erroneously diagnosed with schistosomiasis in endemic areas where this disease is common<sup>14</sup>. Hepatomegaly is virtually a constant finding and is frequently accompanied by slight right upper quadrant tenderness. Transitory generalized lymphadenopathy and splenomegaly frequently appear but there is no clinical evidence of jaundice. Laboratory examinations show leucocytosis with eosinophilia, which can reach 70% and slight changes in serum aminotransferase<sup>11,15</sup>.

Ultrasonographic studies are still scarce in patients with acute schistosomiasis<sup>12</sup>. Cesmeli et al reported the case of a patient with acute schistosomiasis who presented nodular liver lesions on abdominal ultrasound and computed tomography scan<sup>16</sup>. Such lesions, however, were not found by others<sup>17</sup>, suggesting that these sonographic features are uncommon<sup>12</sup>.

Acute schistosomiasis usually progresses to an asymptomatic period and eventually to the chronic forms<sup>11</sup>. In pa-

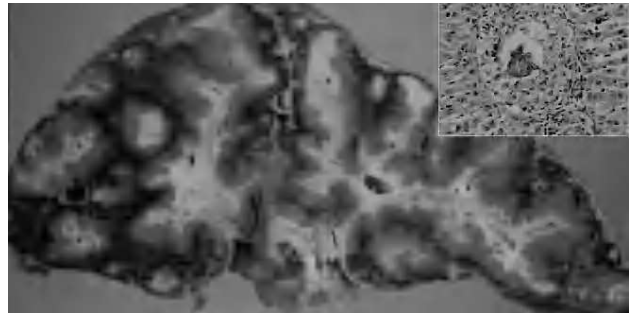


Fig. 1. Symmers' periportal fibrosis of the liver with *Schistosoma mansoni* showing an egg at the center of a granuloma (detail).

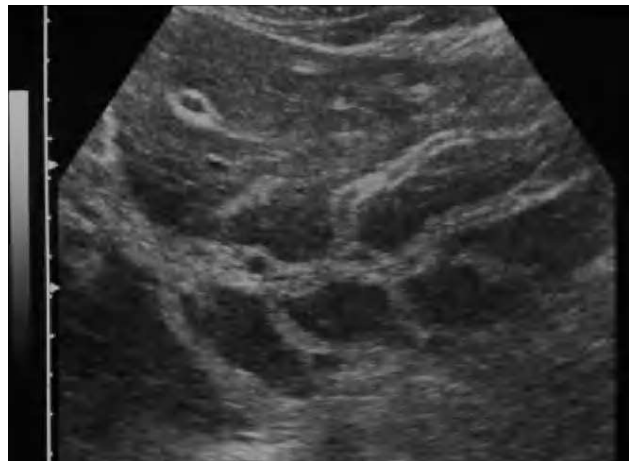


Fig. 2. Sonographic features of periportal fibrosis in schistosomiasis mansoni.

tients with acute schistosomiasis admitted to hospital because of the intensity of their symptoms, treatment should be started with corticosteroids, followed by schistosomides<sup>18</sup>. However, these situations are fairly uncommon.

#### Chronic forms

The life cycle of the parasite in the host, which begins with penetration of cercariae into the skin and ends with the adult worms lodging in the terminal branches of the portal vein, explains why *S. mansoni* can damage several organs other than the intestines and liver<sup>19</sup>. However these localizations are by far the most frequent.

#### Intestinal and hepatointestinal forms

Intestinal manifestations such as diarrhea and colicky pain are occasionally observed, but asymptomatic forms are more common.

A modulation of the egg granuloma is observed during the transition of the acute form to the chronic form: the exudative-necrotic granuloma of the acute phase becomes smaller and with fewer inflammatory cells and, consequently, it becomes less pathogenic to the liver cells<sup>5</sup>. Some authors believe that in patients with poor modula-

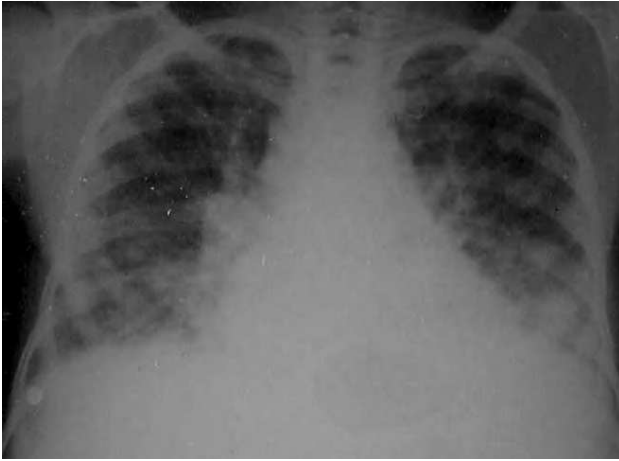


Fig. 3. «Dead worm pneumonitis» after chemotherapy in a patient with heavy infection.

tion of the granuloma, the disease tends to evolve to the hepatosplenic form<sup>20</sup>.

Because the intestinal form is frequently asymptomatic, the diagnosis is based on the finding of *S. mansoni* eggs in stools.

Schistosomotic intestinal polyposis is uncommon in Brazil<sup>5</sup> but frequently observed in Egypt<sup>21</sup>.

The subdivision into an intestinal form and a hepatointestinal form is not uniformly accepted<sup>5,22</sup>, but enlargement of the liver, mainly of the left lobe, may be seen in schistosomotic individuals living in highly endemic areas, and characterizes the hepatointestinal form<sup>2</sup>. Recently, our group has reported portal and splenic overflow in both the hepatointestinal and hepatosplenic forms of schistosomiasis<sup>23</sup>.

#### *Hepatosplenic form and portal hypertension*

**Pathophysiology.** The pathogenesis of the distinct stages of schistosomiasis and of its clinical manifestations is not well understood. Many authors agree that the egg granuloma is the main process causing tissue damage in organs such as liver, intestines, lung and pancreas. However, immunocomplexes derived from parasite antigens are responsible for special lesions such as glomerulopathy<sup>19</sup>.

Hepatic granulomas are initiated endovascularly and are presinusoidal, mostly at inlet venules or terminal portal venules. Following initial endothelial proliferation, the blood vessels rapidly become occluded with eventual obliteration of the lumen and displacement of hepatocytes by the developing granuloma<sup>24</sup>. Symmers' fibrosis of the liver, which may result in portal hypertension and congestive splenomegaly, occurs in individuals aged 6– to 20-years or 5–15 years after the onset of infection<sup>15</sup>. It is the most severe form and the most common cause of morbidity and death<sup>2</sup>. However, in heavily infected young patients there is a «noncongestive» phase of the disease with splenomegaly but without evident signs of portal hypertension. Data from Brazil show that in such cases, the spleen may become impalpable after adequate chemothe-

rapy<sup>2,19,25</sup>. A strong correlation between the hepatosplenic form and worm load in young patients has repeatedly been shown<sup>26</sup>. Furthermore, experimental studies suggest that massive infections during early periods of exposure to cercariae may be important. Failure of immunologic modulation of inflammatory reactions seems to play a role<sup>27</sup>. These and other factors (see below) explain the presence of hepatosplenic schistosomiasis in only a small percentage of patients with heavy worm burden<sup>19</sup>.

Hepatic periportal fibrosis is caused by the T cell-dependent granuloma that develops around schistosome eggs. Experimental models of infection have shown that granuloma and fibrosis are highly regulated by cytokines. However, why advanced periportal fibrosis occurs only in certain individuals is unknown. A study performed in 75 patients with no or mild fibrosis and in 24 patients with advanced fibrosis suggested that interferon (IFN)-gamma plays a key role in the protection of *S. mansoni*-infected patients against periportal fibrosis, whereas TNF-alpha may aggravate the disease<sup>28</sup>.

In some patients with heavy infection chemotherapy may produce a peculiar type of pulmonary lesion, «dead worm pneumonitis» (fig. 3), which has been attributed to a hyperergic pulmonary reaction to the products of dead worms.

The pathogenesis and pathophysiology of the hepatosplenic and other forms of *S. mansoni* infection are presented in figure 4.

It is now well established that some experimental models can reproduce a «pipe-stem» fibrosis. According to Andrade<sup>29</sup>, a peculiar pattern of vascular intrahepatic lesions, described later, seems to depend on 2 mechanisms: egg embolization, with a partial blocking of the portal vasculature, and the appearance of small portal collaterals along the intrahepatic portal system. The continuous lodging of newly arrived eggs into these thin and anastomosing blood vessels leads to vascular obstruction and periportal fibrosis<sup>30</sup>.

In more advanced cases, a thin septal fibrosis, which dissects the parenchyma in several directions, is observed. Its pathogenesis is not well established. The distribution of schistosomal antigen immunoglobulins and complement C3 was studied by our group using biopsy specimens of human liver from 21 patients with hepatosplenic schistosomiasis. The kinetics of the granuloma formation and IgG deposits along the sinusoidal wall were described.

The irreversibility of schistosomotic fibrosis has been seriously disputed. Experimentally, chemotherapy markedly decreases mortality in infected mice soon after treatment. Later, periportal fibrosis can undergo degradation in a way similar to that of periportal granulomas.

In a study based on family heredograms, Tavares-Neto and Prata<sup>31</sup> found a highly significant concentration of hepatosplenic forms among children from the same nuclear family, particularly when the mother was affected by the same clinical form of the disease. Furthermore, this clinical form is more frequent in whites than in blacks, even though Brazilian whites are more socially and economically advantaged. All these findings would point to a genetic component, which is not yet well characterized.

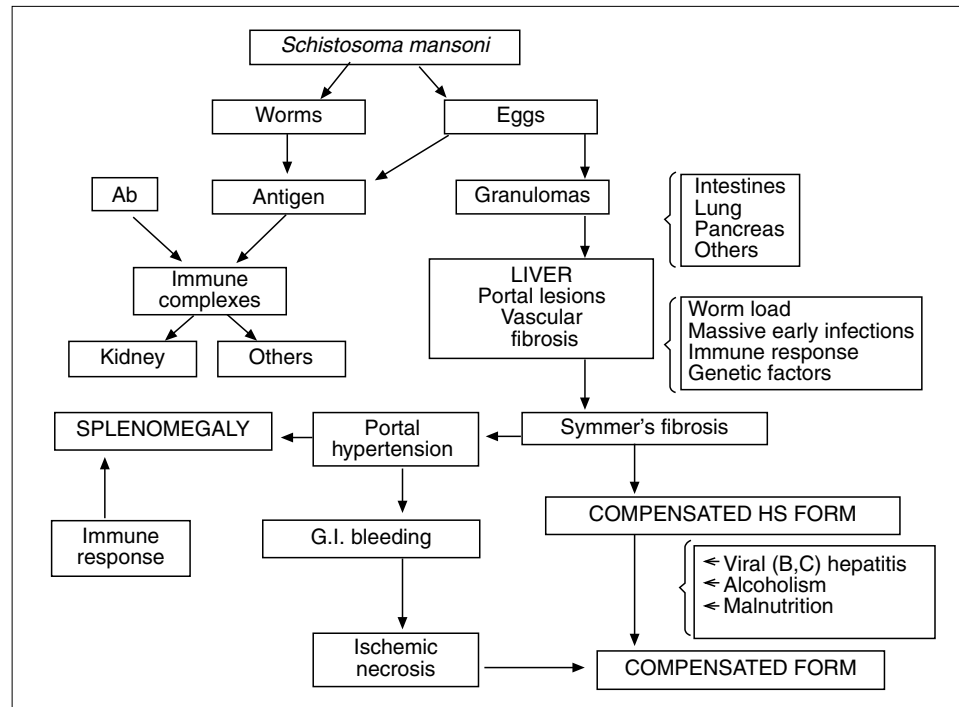


Fig. 4. Pathogenesis and pathophysiology of human hepatosplenic (HS) schistosomiasis (G.I.: gastrointestinal; Ab: antibodies).

– Association of schistosomiasis with viral hepatitis B and hepatitis C. In the last few decades, several authors have pointed out the role played by hepatitis B virus infection in increasing morbidity due to schistosomiasis<sup>32</sup>. It is generally accepted that *S. mansoni* infection alone does not lead to cirrhosis<sup>12</sup>. Liver biopsy studies have shown a significant increase in chronic hepatitis and hepatic decompensation in schistosomal patients with hepatitis B virus infection. According to Strauss<sup>33</sup>, the higher frequency of hepatitis B virus markers in the hepatosplenic form than in the hepatointestinal form is due to therapeutic measures in patients who seek medical care. This point of view is advocated by some authors<sup>34</sup>, but not by others<sup>32</sup>.

Seventeen cases of acute hepatitis C in previously infected patients with mansonian schistosomiasis were compared with 15 non-schistosomal control patients, also with acute hepatitis C. Spontaneous viral elimination was observed in 5 controls, but in none of the patients with schistosomiasis<sup>34</sup>. Furthermore, structural liver changes were more severe in patients with double infection and predominant Th 2 immune response. The relationship between hepatitis C virus infection and different clinical forms of mansonian schistosomiasis was investigated by Pereira et al<sup>35</sup>, who demonstrated that hepatitis C viral infection is an important pathogenic factor in decompensated forms of schistosomiasis.

– Hemodynamic features. Some intrahepatic angiographic changes are highly suggestive of hepatosplenic schistosomiasis<sup>19</sup>.

1. Hepatic veins. Hepatic veins are enlarged and there is a marked reduction of branching, along with a somewhat

pronounced arching of large branches<sup>36</sup>. In 50 patients studied by Mies et al<sup>36,37</sup> the gradient between hepatic vein wedged and free pressures was at the upper limit of normality ( $7 \pm 4.4$  cm H<sub>2</sub>O). In about 40% of patients, however, it was slightly raised: the gradient ranged from 8 to 17.5 cm H<sub>2</sub>O. These findings were in agreement with those reported by Coutinho<sup>38</sup>.

2. Intrahepatic pattern of the portal system. Contrast material injected into the portal system shows an intrahepatic pattern characterized by gross amputations of large branches and by the appearance of an intense network of small-caliber vessels around portal branches. These features were described by Bogliolo in 1957<sup>39</sup> and are known as «Bogliolo's sign» (fig. 5).

3. Extrahepatic portal system and portal pressure. Enlargement of splenic and portal veins is usually present. Portal pressure is raised to levels similar to those seen in liver cirrhosis. In an analysis of 20 scientific papers with 432 patients in whom portal pressure was measured by various methods, usually by intrasplenic puncture, Carneiro<sup>40</sup> found an average pressure of 33 cm H<sub>2</sub>O.

4. Hepatic artery. Angiographic studies have shown a reduced diameter of the hepatic artery, with thin, arched branches outlining vascular gaps (fig. 6). The tortuous aspect characteristic of liver cirrhosis is not observed<sup>41</sup>. Interestingly, increased hepatic arterial flow was demonstrated in infected hamster<sup>42</sup>. These findings suggest that the poor intrahepatic arterial vascularization demonstrated by selective arteriography in human hepatosplenic schistosomiasis is due to «functional deviation» of arterial blood to the splenic territory<sup>19</sup>. In advanced schistosomiasis, hypertrophy of the hepatic artery may be found<sup>43</sup>.

5. Liver blood flow. Total liver blood flow, measured by various methods, is normal<sup>44,45</sup>, suggesting that increased

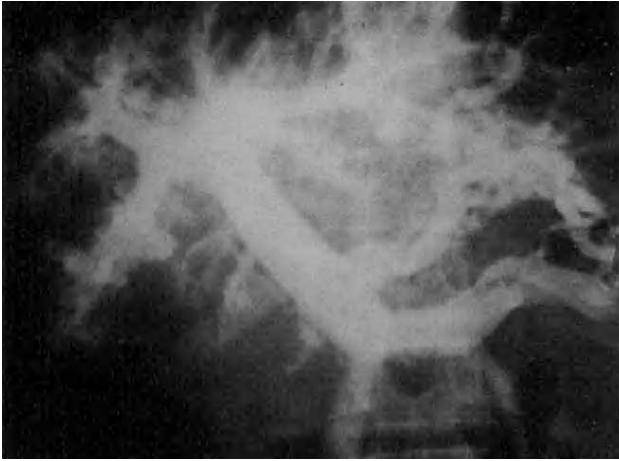


Fig. 5. Intrahepatic pattern of the portal vein characterized by gross amputations of large branches and by the appearance of an intense network of small-caliber vessels around portal branches (Bogliolo's sign).

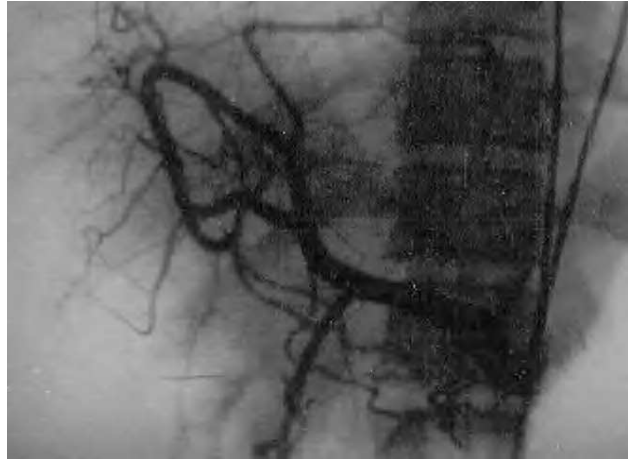


Fig. 6. Angiographic study showing reduced diameter of the hepatic artery, with thin, arched branches outlining vascular gaps.

portal blood flow is accompanied by a reduction of arterial blood flow<sup>44</sup> and that there is an interaction between portal and arterial blood flow<sup>46</sup>. As already shown, the diameter of the common hepatic artery increases after occlusion of the splenic artery by a balloon catheter<sup>47</sup> or after splenectomy<sup>48</sup> or selective portal decompression.

Some dynamic studies have demonstrated that high splenic blood flow may be responsible for the increased portal blood flow. The splenic component and the abundant network around portal branches («Bogliolo's sign») may predominate (hyperflow component) over the obstruction of the intrahepatic portal branches produced by parasitosis (presinusoidal block), at least in cases of severe splenomegaly<sup>2</sup>. However, ultrasound studies show that intense periportal thickening of the liver can be found in some patients without a palpable spleen, despite the presence of portal hypertension, probably as a consequence of spontaneous shunts<sup>49</sup>. Furthermore, schistosomal portal hypertension is not restricted to splenic hyperdynamic circulation. Mies et al<sup>50</sup> showed that despite small changes in sinusoidal pressure and liver function, schistosomal patients present with high cardiac index and low systemic vascular resistance compatible with a systemic hyperdynamic circulatory status similar to that of cirrhosis.

**Clinical and laboratory changes.** Hepatosplenic schistosomiasis can be clinically divided into compensated and decompensated forms. The latter is characterized mainly by muscular wasting, low serum albumin, and occasionally, chronic ascites. However, other causes, such as alcoholism, and hepatitis B and C virus infection, are frequently responsible for the decompensated form (fig. 4).

*S. mansoni* shows a wide range of clinical manifestations, varying from asymptomatic to highly symptomatic forms. Sometimes the disease is accidentally discovered, either by a routine stool examination or by findings of an enlarged liver or spleen on physical examination<sup>22</sup>.

The main symptoms of the hepatosplenic form are related to splenomegaly and hemorrhage. Spontaneous ascites is

uncommon and usually appears after an episode of bleeding or infection or in association with other liver lesions. Spontaneously appearing neuropsychiatric symptoms are very rare in hepatosplenic schistosomiasis, even with abundant collateral circulation. This syndrome is only seen after precipitating factors, mainly hemorrhage or infection.

In patients with compensated hepatosplenic schistosomiasis, arterial blood ammonia determination shows normal or slightly increased levels after hemorrhage or after an oral ammonium chloride load. This contrasts with the significant elevation of ammonia in compensated forms after portocaval anastomosis and in decompensated forms<sup>51</sup>. Anemia with delayed somatic and sexual development may be observed in young people. Spider nevi, gynecomastia, and palmar erythema are rare in uncomplicated schistosomiasis.

A hard, enlarged liver with a predominant increase of the left lobe is frequently palpable. The spleen is enlarged, and Symmers' fibrosis is one of the main causes of huge spleens in Brazil.

Leukopenia and thrombocytopenia are found in most cases of hepatosplenic schistosomiasis. Anemia is common but is also due to other mechanisms, such as malnutrition, ankylostomiasis, chronic bleeding, and hemolysis<sup>19</sup>.

In hepatosplenic schistosomiasis, the clotting defects are due to an impaired rate of protein synthesis by the liver or localized consumption coagulopathy, or both<sup>52</sup>. The relative role of these 2 factors is not well established. Some changes in plasma coagulation systems may be partially corrected by subcutaneous heparinization and mainly by splenectomy<sup>53</sup>.

– **Diagnosis.** Direct diagnostic methods are based on the demonstration of eggs or of miracidia. Eggs may be found in the stools by the Kato-Katz quantitative method<sup>54</sup>. The hatching test is a simple, cheap, and useful method, without the need for microscopy. Rectal biopsy is used in suspected cases with negative parasitological tests.

Immunologic methods, indirect immunofluorescence, indirect hemagglutination, and enzyme-linked immunoabsorbent assay (ELISA) give a high degree of positivity<sup>55,56</sup>. Serum precipitins have been demonstrated by immunodiffusion<sup>57</sup>; its low sensitivity was greatly increased by counter immunoelectrophoresis and enzyme-linked-immunoelectrodiffusion assay (ELIEDA)<sup>58</sup>.

Antibody titers are usually higher in the hepatosplenic form than in the hepatointestinal form. It is well known that antibody titers present an early and significant increase after chemotherapy as a consequence of worm death<sup>56</sup>.

One major diagnostic problem concerned the demonstration of periportal fibrosis, even with wedged liver biopsies. Fortunately, ultrasonography has become a reliable and sensitive method of detecting these lesions<sup>59</sup>.

– *Ultrasonography in schistosomiasis*. A review of the literature on the use of ultrasonography in schistosomiasis showed that ultrasonography can provide direct information on lesions in internal organs and can thus provide information about patterns of morbidity and regression of pathological changes after treatment<sup>60</sup>. The method is non-invasive and can be used under field conditions. However, the methodology used for ultrasonography has varied considerably so that valid comparisons between results obtained in different places or at different times are difficult to make<sup>60</sup>.

From the clinical point of view, periportal fibrosis, seen in ultrasonography as echodense areas along the portal vein (fig. 2), is an important diagnostic feature, and also indicates the possible existence of portal hypertension<sup>59</sup>. Until fibrosis reaches an advanced stage, thickened patches are typically scattered throughout the liver. Experience shows that the portal vein and the structures around it can best be visualized in the left liver lobule<sup>61</sup>.

A combined clinical sonographic classification of hepatosplenic schistosomiasis mansoni was proposed by Lambertucci et al<sup>49</sup> for use in field-based studies. In 741 individuals out of 892 (83%) living in an endemic Brazilian area who underwent physical and parasitological examination, splenomegaly was diagnosed by abdominal palpation in 71 patients (9.6%). By using abdominal palpation and ultrasound examination, 4 groups of individuals have been identified: (i) palpable spleen and intense periportal thickening in 9 individuals (1.2%); (ii) spleen not palpable and intense periportal thickening in 15 (2%); (iii) palpable spleen with light-to-moderate periportal thickening in 32 (4.3%) and (iv) palpable spleen with a normal liver on ultrasonography in 30 (4%). Based on these results, the authors<sup>49</sup> concluded that the definition of hepatosplenic schistosomiasis in field-based studies as the finding of *S. mansoni* eggs in the stools in an individual with splenomegaly is no longer acceptable.

According to recent studies, the parameters associated with variceal bleeding in patients with hepatosplenic schistosomiasis are endoscopic (variceal size, red signs, congestive gastropathy, and fundic varices) and ultrasonographic (portal vein diameter and periportal thickness)<sup>62</sup>. The most important combined parameters are

gastropathy and red signs, portal vein diameter and variceal size, and variceal size and gastropathy<sup>62</sup>.

A series of recommendations on qualitative and quantitative data obtained by ultrasonography in studies performed in Africa and Brazil were presented at a recent symposium on ultrasound in Schistosomiasis held in Minas Gerais, Brazil (Niamey-Belo Horizonte protocol). Imaging patterns of liver and portal hypertension assessment were analyzed<sup>63</sup>. These patterns were more recently reviewed<sup>64</sup> and include: non-specific minor thickening of the walls of portal branches («starry sky»); fibrosis of the peripheral portal branches or of the main portal system and of the right and left branches can occur alone or simultaneously.

Finally, in agreement with previous reports<sup>59,65,66</sup>, a Doppler ultrasonographic study by our group<sup>23</sup> showed that hepatic left lobe hypertrophy and right lobe atrophy are commonly observed in hepatosplenic schistosomiasis. Increased portal blood flow in patients with the hepatointestinal form of schistosomiasis, diagnosed by the absence of gastroesophageal varices and of splenomegaly and by the presence of hepatomegaly, as shown by our group<sup>23</sup>, would be unexpected. However, the possibility of low-grade portal hypertension not detected by clinical and ultrasonography in these patients cannot be ruled out<sup>49</sup>. In summary, our group showed that portal overflow may be found in both forms of schistosomiasis<sup>23</sup>.

#### *Extrahepatic schistosomiasis*

*Glomerulopathy*. The incidence of nephrotic syndrome and chronic renal failure is much higher in tropical than in temperate climates, suggesting that parasitic diseases, principally schistosomiasis, might be involved in the pathogenesis of glomerular disease<sup>67</sup>. A recent study conducted in a series of patients with schistosomal glomerulopathy allowed localization of schistosomal antigens in glomerular structures<sup>68,69</sup>.

The kidneys play an important role in the disposal of circulating antigens. In *S. mansoni* infection, circulating antigens derive from the adult worm (gut antigens) or from the schistosome eggs<sup>67</sup>. In hepatosplenic schistosomiasis the shunting of portal blood carrying the primary load of antigens into the systemic circulation is the main mechanism by which the liver may be excluded from processing the schistosomal antigens, which are then supplied to the kidneys in larger amounts<sup>67,70</sup>.

Earlier studies have suggested that mesangioproliferative glomerulonephritis and membranoproliferative glomerulonephritis type I are the more common forms of schistosomal glomerulopathy<sup>68,71,72</sup>. Clinically, patients with this disease may either be asymptomatic, with only minor urinary changes, such as proteinuria or hematuria, or may manifest a nephrotic syndrome that may evolve to end-stage renal failure<sup>69</sup>. The transformation of mesangioproliferative glomerulonephritis into membranoproliferative glomerulonephritis was demonstrated by De Brito et al<sup>73</sup>. Nephrotic syndrome seen in association with schistosomiasis presents with an increased plasma globulin con-

centration and normal cholesterol levels in one-third of affected patients<sup>12</sup>.

Notably, schistosomal antigens were demonstrated for the first time in the glomeruli of humans with active schistosomiasis mansoni for the first time in the transplanted kidney of a patient with focal and segmental glomerulosclerosis<sup>74</sup> and later by our group in patients with mesangioproliferative glomerulonephritis<sup>75</sup>. The outcome of treatment of nephrotic syndrome associated with hepatosplenic schistosomiasis with antischistosomal drugs, corticosteroids and immunodepressors, has been disappointing<sup>76</sup>.

**Pulmonary forms.** Pulmonary manifestations may be observed in the acute phase, but are far more common in the chronic phase. Besides the rare «pneumonias» produced by dead worms after chemotherapy<sup>77</sup>, pulmonary hypertension can be found in 13% to 16% of patients with hepatosplenic schistosomiasis and, more rarely (0% to 2%), cor pulmonale<sup>12</sup>.

Anti-schistosomal therapy usually has no effect, but is given to prevent further progression of the disease. Pulmonary embolism of dead worms may produce an abrupt increase in pulmonary pressure<sup>12</sup>.

**Other forms.** Other forms of schistosomiasis, including neuroschistosomiasis are clinically less important than those previously described. The course of *Salmonella* and *Escherichia* infections in patients with schistosomiasis is unusual; the infection becomes chronic with prolonged fever and blood cultures that remain positive for months<sup>15</sup>. These infections can only be cured by antischistosomal treatment.

#### Course and prognosis

The prognosis of hepatic schistosomiasis is good in the acute and hepatointestinal forms. The prognosis of the hepatosplenic forms depends on whether the liver disease is compensated or decompensated. Fortunately, most cases belong to the compensated form: the prognosis is better than that of patients with cirrhosis. Recovery after hematemesis is rapid and patients live longer<sup>2</sup>. Hepatic coma and ascites after hemorrhage are less frequent and easier to control. A few patients with severe liver failure have a poor prognosis, similar to those with cirrhosis<sup>19</sup>.

#### Treatment

**Treatment of helminthiasis.** Treatment of helminthiasis is indicated in all stages and clinical forms of mansonian schistosomiasis, but some patients with a very advanced form or with unrelated conditions or diseases may not tolerate chemotherapy.

There are two highly effective chemotherapeutic drugs: oxamniquine, with different doses in Latin America and Africa, and praziquantel. Both drugs are administered through the oral route.

A double-blind trial published by our group in 1986<sup>78</sup> showed that both drugs have the same efficacy for the

Brazilian strains of *Schistosoma*; however, praziquantel produces fewer neuropsychiatric symptoms. Furthermore, this drug is also effective against other species of *Schistosoma*.

As reported by the World Health Organization, praziquantel has become the most widely used of the antischistosomal drugs<sup>79</sup>. Praziquantel can also be safely given to patients with the compensated hepatosplenic form of the disease<sup>80</sup>. Cessation of egg-induced immunopathology is reflected by a return to normal of serum procollagen-III-propeptide and neopterin concentrations<sup>81</sup>.

#### Treatment of portal hypertension.

**Nonsurgical treatment of bleeding esophageal varices.** The management of patients with esophageal and gastric varices remains challenging, particularly when prophylactic procedures are considered<sup>82</sup>. Although high portal pressure and large varices are associated with an increased risk of bleeding, the literature is still not clear and the methods of measuring size and pressure are still controversial<sup>83</sup>.

Some endoscopic changes that are thought to indicate a high risk of bleeding include large varices, cherry-red spots, varices on varices, erosions on varices<sup>84</sup> and hypertensive gastropathy. These, and probably other endoscopic signs, including ultrasonographic changes, should be used to identify patients for prophylactic procedures, including drug therapy, sclerotherapy and surgery.

**1. Propranolol.**  $\beta$ -blockers such as propranolol have mainly been used for the management of portal hypertension in liver cirrhosis. Their utility in chronic schistosomiasis, however, is not well established. In a murine schistosomiasis model, the development of portal systemic shunting was decreased or prevented by oral propranolol through the reduction of flow and pressure in the portal system<sup>85</sup>.

A prospective study of 42 patients with at least one episode of gastrointestinal bleeding showed a significant reduction in episodes in treated patients when compared with a historical control<sup>86</sup>. Therefore, propranolol seems to protect patients with schistosomiasis against gastrointestinal rebleeding during the short period of time that precedes definitive surgical treatment. Indeed, oral administration of a single «blockade dose» may significantly decrease azygos blood flow<sup>86</sup>.

The same group showed that administration of propranolol corrects hyperdynamic circulation, aggravates pulmonary hypertension, does not alter portal pressure and reduces sectorial portal blood flows, especially of the azygos vein, with maintenance of total hepatic blood flow<sup>87</sup>.

A controlled trial with non-cirrhotic portal fibrosis patients, most of whom had schistosomiasis, showed that continuous oral propranolol treatment is effective in preventing recurrent upper gastrointestinal bleeding. Despite these favorable results with  $\beta$ -blockers, we wondered whether we could obtain good compliance over a long period of time<sup>82</sup>. Furthermore in some clinical trials, high

doses of propranolol were necessary for a good pharmacological results, hampering the clinical utility of the drug<sup>88,89</sup>.

2. Sclerotherapy of esophageal varices. In retrospective study of sclerotherapy of bleeding esophageal varices in schistosomiasis, varices were eradicated in nearly 70% of patients during a follow-up period lasting between 48 and 132 months. Sclerotherapy was effective in controlling rebleeding in 97% of the patients in the group who had previous portal hypertension surgery and in 73% of the group without previous portal hypertension surgery, with a smaller number of sclerotherapy sessions per patient in the former group; these differences were statistically significant<sup>83</sup>. Favorable results were also obtained by another group after emergency or elective endoscopic sclerotherapy<sup>90</sup>. A prospective non-randomized trial comparing elective sclerotherapy with a control group with a 5-year follow-up showed that the incidence of rebleeding was 28% and 45%, respectively. This difference was not statistically significant; however, mortality from rupture of esophageal varices was 3% in the sclerotherapy group and was 28% in the control group, which was a statistically significant difference<sup>91</sup>.

*Surgical treatment of portal hypertension.* The morphological, hemodynamic and clinical features previously described show that mansonic schistosomiasis is an excellent model for the study of portal hypertension and of surgery used to treat bleeding varices.

Until 1986, three major types of operations were used in Brazil<sup>41</sup>: (i) esophagogastric devascularization plus splenectomy (EGDS); (ii) Splenectomy with splenorenal shunt (SRS), and (iii) selective portal decompression (SPD) or distal splenorenal shunt (DSS).

In 1986 an article based on a prospective randomized trial was published by our group<sup>92</sup> comparing the results of the three surgical techniques. It became clear that SRS frequently produces portosystemic encephalopathy (39%); for this reason we interrupted this trial. Later, a long-term follow-up study (85.7 ± 33.1 months) was performed by the same group<sup>93</sup> in the same patients, excluding 9 patients (9.6%) who were lost to follow-up. This study showed that gastrointestinal tract bleeding occurred in 24.1% of the patients, without statistical differences among the three groups, but rebleeding due to varices was more frequent after EGDS. Hepatic encephalopathy was significantly greater after proximal SRS (39.3%) than after DSS (14.8%) or EGDS (0%). Lethality was also significantly higher after SRS (42.9%) than after DSS (14.8%) or EGDS (7.1%). Indirect hyperbilirubinemia was absent after EGDS and was more frequent after DSS (52%), although it was also present after SRS (29.6%). Because of the absence of encephalopathy and the low mortality rates, EGDS was demonstrated to be the best option<sup>93</sup>.

As emphasized by Conn<sup>94</sup> many questions remain unanswered. For example, would endoscopic sclerotherapy with splenectomy be as effective? Would esophagogastric devascularization without splenectomy be as effective?

Our study was initiated before endoscopy sclerotherapy,

variceal ligation,  $\beta$ -adrenergic blockade and transjugular intrahepatic portal-systemic shunt (TIPS) became established as viable forms of therapy in portal hypertension. In our Department of Gastroenterology, patients with schistosomiasis and bleeding esophageal varices are treated with esophagogastric devascularization with splenectomy and, if rebleeding occurs, with sclerosis of the varices<sup>19,95</sup>.

## REFERENCES

- Dunn MA. Parasitic Disease. In: Schiff ER, Sorrel MF, Madrey WC, editors. Schiff's Disease of the liver. Philadelphia: Lipincott-Raven; 1999. p. 1533-48.
- Da Silva LC. *Schistosomiasis mansoni* – clinical features. In: Okuda K, Benhamou J-P, editors. Portal Hypertension. Clinical and Physiological Aspects. Tokyo: Springer-Verlag; 1991. p. 309-18.
- Passos ADC, Amaral RS. Esquistossomose mansônica: aspectos epidemiológicos e de controle. Rev Soc Bras Med Trop 1998;31 Supl II:61-74.
- Chieffi PP, Waldman EA. Aspectos particulares do comportamento epidemiológico da Esquistossomose mansônica no Estado de São Paulo, Brasil. Cad Saúde Públ, Rio de Janeiro 1988; 3:257-75.
- Lambertucci JR, Serufo JC. Esquistossomose mansônica In: Gayotto LCC, Alves VAF, editores. Doenças do Fígado e Vias Biliares. São Paulo: Atheneu; 2001. p. 35.
- Giboda M, Malek EA, Correa R. Human schistosomiasis in Puerto Rico: reduce prevalence rate and absence of *Biomphalaria glabrata*. Am J Trop Med Hyg. 1997;57:564-8.
- Tsang VCW, Hillyer GV, Noh J, et al. Geographic clustering and seroprevalence of schistosomiasis in Puerto Rico. Am J Trop Med Hyg. 1997;56:107-12.
- El-Garen AA. Schistosomiasis. Digestion. 1998;59:589-605.
- Ross AGP, Bartley PB, Sleight AC, et al. Schistosomiasis. N Engl J Med. 2002;346:1212-20.
- Elliott DE. Schistosomiasis. Pathophysiology, diagnosis, and treatment. Gastroenterol Clin North Am. 1996;25:599-625.
- Coutinho AD, Domingues ALC. Esquistossomose mansoni. In: Dani R, Castro LP, editors. Gastroenterologia Clínica, 2nd ed. Rio de Janeiro: Editora Guanabara; 1988. p. 1361-86.
- Lambertucci JR, Serufo JC, Gerspacher-Lara R, et al. Schistosoma mansoni: assessment of morbidity before and after control. Acta Tropica. 2000;77:101-9.
- Neves J, Raso P, Pinto DM, Silva SP, Alvarenga RJ. Ischemic colitis (necrotizing colitis, pseudomembranous colitis) in acute schistosomiasis mansoni: report of two cases. Trans R Soc Trop Med Hyg. 1993;87:449-52.
- Lambertucci JR, Rayes AAM, Barata CH, Teixeira R, Gerspacher-Lara R. Acute schistosomiasis: report on five singular cases. Mem Inst Oswaldo Cruz. 1997;92:631-5.
- Prata A. Infection with *S. mansoni*. In: Jordan P, Webbe G, editors. Schistosomiasis. Epidemiology, treatment and control. London: William Heinemann; 1982. p. 105-27.
- Cesmeli E, Vogelaers D, Voet D, et al. Ultrasound and CT changes of liver parenchyma in acute schistosomiasis. Br J Radiol. 1997;70:758-60.
- Lambertucci JR, Pinto-Silva RA, Gerspacher-Lara R, Barata CH. Acute mansoni's schistosomiasis: sonographic features. Trans R Soc Trop Med Hyg. 1994;88:76-7.
- Lambertucci JR. Treatment of schistosomiasis: gathering stones together. Mem Inst Oswaldo Cruz. 1995;90:161-4.
- Da Silva LC, Carrilho FJ. Hepatosplenic schistosomiasis. Pathophysiology and treatment. Gastroenterol Clin North Am. 1992; 21:163-77.
- Rezende SA, Lambertucci JR, Goes AM. Role of immune complexes from patients with different clinical forms of schistosomiasis in the modulation of in vitro granuloma reaction. Mem Inst Oswaldo Cruz. 1997;92:683-7.
- Mohamed ARS, Mohamed AAK, Yasawy MI. Schistosomal colonic disease. Gut. 1990;31:439-42.



22. Da Silva LC, Pontes JF. Clinical aspects of schistosomiasis mansoni. In: Popper H, Schaffner F, editors. Progress in Liver Disease. New York: Grunne and Stratton; 1965. p. 243-52.
23. Vezozzo DCP, Farias AQ, Cerri GG, Da Silva LC, Carrilho FJ. Assessment of liver morphology and portal hemodynamics by Doppler ultrasound in the hepatosplenic and hepatointestinal forms of schistosomiasis mansoni in Brazil. To be published.
24. Smithers SR, Doenhoff MJ. Schistosomiasis. In: Cohen S, Warren KS, editors. Immunology of parasitic Infections. 2nd ed. Oxford: Blackwell; 1982. p. 527-607.
25. Bina JC. Influência da terapêutica específica na evolução da esquistossomose mansoni. Doctoral Thesis. Salvador: Faculdade de Medicina; 1977.
26. Coura JR, Conceição MJ. Correlação entre carga parasitária de *S. mansoni* e gravidade das formas clínicas em uma comunidade rural de Minas Gerais. Rev Soc Bras Med Trop. 1981; 14:93-7.
27. Colley DG, Garcia AA, Lambertucci JR, et al. Immune responses during human schistosomiasis: XII. Differential responsiveness in patients with hepatosplenic disease. Am J Trop Med Hyg. 1986;35:793-802.
28. Henri S, Chevillard C, Mergani A, et al. Cytokine regulation of periportal fibrosis in humans infected with *Schistosoma mansoni*: IFN-gamma is associated with protection against fibrosis and TNF-alpha with aggravation of disease. Immunology. 2002;169:929-36.
29. Andrade ZA. Pathogenesis of pipe-stem fibrosis of the liver (experimental observation on murine schistosomiasis). Mem Inst Oswaldo Cruz. 1987;82:325-34.
30. Andrade ZA. Evolution and involution of hepatosplenic schistosomiasis. Mem Inst Oswaldo Cruz. 1989;84 Suppl 1:58-75.
31. Tavares-Neto J, Prata A. Family occurrence of schistosomal hepatosplenomegaly and maternal effect. Rev Soc Bras Med Trop. 1989;22:13-8.
32. Lyra LG, Rebouças G, Andrade Z. Hepatitis B surface antigen carrier state in hepatosplenic schistosomiasis. Gastroenterology. 1976;71:641-5.
33. Strauss E. Hepatite e esquistossomose. In: Da Silva LC, editor. Hepatites agudas e crônicas, 3.<sup>rd</sup> ed. São Paulo: Sarvier; 2003.
34. Kamal SM, Rasenack JW, Bianchi L, et al. Acute hepatitis C without and with schistosomiasis: correlation with hepatitis C-specific CD4(+) T-cell and cytokine response. Gastroenterology. 2001;121:646-56.
35. Pereira LM, Melo MC, Saleh MG, et al. Hepatitis C virus infection in Schistosomiasis mansoni in Brazil. J Med Virol. 1995; 45:423-8.
36. Mies S, Mori T, Larsson EJ, et al. A veia cava inferior e as veias supra-hepáticas na esquistossomose hepatoesplênica. Estudo angiográfico. Rev Hosp Clin Fac Med São Paulo. 1980;35: 136-42.
37. Mies S, Mori T, Larsson EJ, Rosa P, Raia S. Hepatic vein in mansonic schistosomiasis. Angiographic and hemodynamic pattern. Gastroenterology. 1980;78:A1314.
38. Coutinho A. Hemodynamic studies of portal hypertension in schistosomiasis. Am J Med. 1968;44:547-6.
39. Bogliolo L. A esplenoportografia na esquistossomose mansônica hepato-esplênica, forma de Symmers. Rev Ass Med Brás. 1957;2:263-9.
40. Carneiro JL. A circulação colateral gastroesofágica após desconexão azigoportal [doctoral Thesis]. Vitória: Universidade Federal do Espírito Santo; 1979.
41. Raia S, Mies S, Macedo AL. Portal hypertension in schistosomiasis. Clin Gastroenterol. 1985;14:57-82.
42. Morgan JS, Groszman RJ, Rojkind M, Enriquez R. Hemodynamic mechanisms of emerging portal hypertension caused by schistosomiasis in the hamster. Hepatology. 1990;11:98-104.
43. Alves CAP, Alves AR, Abreu WN, Andrade ZA. Hepatic artery hypertrophy and sinuoidal hypertension in advanced schistosomiasis. Gastroenterology. 1977;72:126-8.
44. Raia S, Mies S, Macedo AL. Surgical treatment of portal hypertension in schistosomiasis. World J Surg. 1984;8:738-52.
45. Ramos OL, Saad F, Leser WP. Portal hemodynamics and liver function in hepatic schistosomiasis. Gastroenterology. 1964;47: 241-7.
46. Condon RE, Nyhus LM, Chapman ND, Harkins HN. Portal vein and hepatic artery interaction, studies in the isolated, perfused liver. Gastroenterology. 1962;43:547-56.
47. Silveira GSM. Circulação arterial e portal do fígado esquistossomótico após esplenectomia [doctoral Thesis]. Salvador – Bahia, Faculdade de Medicina, Universidade Federal da Bahia, Brasil, 1980.
48. Mies S, Larsson E, Mori T, Rosa P, Raia S. O sistema porta e as artérias hepáticas, esplênica e mesentérica superior na esquistossomose hepato-esplênica. Estudo angiográfico. Rev Hosp Clin Fac Med São Paulo. 1980;35:121-31.
49. Lambertucci JR, Cota GF, Pinto-Silva RA, et al. Hepatosplenic schistosomiasis in field-based studies: a combined clinical and sonographic definition. Mem Inst Oswaldo Cruz, Rio de Janeiro. 2001;96:147-50.
50. Mies S, Neto OB, Beer A, et al. Systemic and hepatic hemodynamics in hepatosplenic Manson's schistosomiasis with and without propranolol. Dig Dis Sci. 1997;42:751-61.
51. Warren KS, Rebouças G, Baptista AG. Ammonia metabolism and hepatic coma in hepatosplenic schistosomiasis: patients studied before and after portacaval shunt. Ann Intern Med. 1965; 62:1113-33.
52. Manoukian N, Borges DR. Prealbumin, prekallikrein and prothrombin in hepatosplenic schistosomiasis: increased turnover of the clotting proteins? Rev Inst Med Trop São Paulo. 1984;26: 237-40.
53. Borges DR, Pardini DP, Cheter L. Estudo, em portadora da esquistossomose hepatosplênica, da protrombina e da procalcireína: efeitos da heparinização e esplenectomia [carta]. Rev Assoc Med Brás. 1989;35:39-40.
54. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in Schistosomiasis mansoni. Rev Inst Med Trop São Paulo. 1972;14:397-400.
55. Mott KE, Dixon H. Collaborative study on antigens for immunodiagnosis of schistosomiasis. Bull World Health Organ. 1982;60:729-53.
56. Da Silva LC, Hoshino-Shimizu S, Kanamura H, et al. Serum antibody changes after chemotherapy of patients with schistosomiasis mansoni. A statistical analysis. Rev Inst Med Trop São Paulo. 1975;17:344-9.
57. Da Silva LC, Ferri RG. Immunodiffusion studies in human schistosomiasis mansoni I. Hepatointestinal and hepatosplenic forms. Rev Inst Med Trop São Paulo. 1965;7:1-6.
58. Pinon JM, Dropsy G. Étude de l'immunité humorale dans la bilharziose humaine. Interêt de l'ELIEDA (enzyme – linked – immuno – electro – diffusion assay). Bull Soc Pathol Exot. 1977;69:238-44.
59. Cerri GG, Alves VAF, Magalhaes A. Hepatosplenic schistosomiasis mansoni: ultrasound manifestations. Radiology. 1984; 153:777-80.
60. Hatz C, Jenkins JM, Ali QM, Abdel-Wahab MF, Cerri GG, Tanner M. A review of the literature on the use of ultrasonography in schistosomiasis with special reference to its use in field studies. 2. *Schistosoma mansoni*. Acta Trop. 1992;51:15-28.
61. Cairo Working Group. The use of diagnostic ultrasound in schistosomiasis—attempts at standardization of methodology. Acta Trop. 1992;51:45-63.
62. Martins RD, Szejnfeld J, Lima FG, Ferrari AP. Endoscopic, ultrasonographic, and US-Doppler parameters as indicators of variceal bleeding in patients with schistosomiasis. Dig Dis Sci. 2000;45:1013-8.
63. Richter J, Domingues AI, Barata CH, Prata AR, Lambertucci JR. Report of the second satellite symposium on ultrasound in schistosomiasis. Mem Inst Oswaldo Cruz. 2001;96(Suppl): 151-6.
64. Richter J, Hatz C, Haussinger D. Ultrasound in tropical and parasitic diseases. Lancet. 2003;362:900-2.
65. Homeida M, Abdel-Gadir AF, Cheever AW, et al. Diagnosis of pathologically confirmed Symmers' periportal fibrosis by ultrasonography: a prospective blinded study. Am J Trop Med Hyg. 1988;38:86-91.
66. Paranagua-Vezozzo DC, Cerri GG. Duplex hemodynamic evaluation of hepatosplenic mansoni schistosomiasis. Mem Inst Oswaldo Cruz 1992;87 Suppl 4:149-51.
67. De Brito T, Nussensveig I, Carneiro CRW, Silva AMG. *Schistosoma mansoni* associated glomerulopathy [editorial]. Rev Inst Med Trop São Paulo. 1999;41:269-72.
68. De Brito T, Nussensveig I, Carneiro CRW, et al. Glomerular detection of schistosomal antigen by immunoelectron micros-

- copy in human mansonii schistosomiasis. *Int J Surg Pathol*. 1999;7:217-25.
69. Nussenzeig I, De Brito T, Carneiro CR, Silva AM. Human *Schistosoma mansoni*-associated glomerulopathy in Brazil. *Nephrol Dial Transplant*. 2002;17:4-7.
  70. Da Silva LC, De Brito T, Camargo ME, De Boni DR, Lopes JD, Gunji J. Kidney biopsy in the hepatosplenic form of infection with *Schistosoma mansoni* in man. *Bull World Health Organ*. 1970;42:907-10.
  71. Sobh MA, Moustafa FE, Sally SM, Deelder AM, Ghoniem MA. Characterization of kidney lesions in early schistosomal-specific nephropathy. *Nephrol Dial Transplant*. 1988;3:392-8.
  72. Andrade ZA, Van Marck E. Schistosomal glomerular disease (a review). *Mem Inst Oswaldo Cruz*. 1984;79:499-506.
  73. De Brito T, Gunji J, Camargo ME, Penna DO, Da Silva LC. Advanced kidney disease in patients with hepatosplenic Manson's schistosomiasis. *Rev Inst Med Trop Sao Paulo*. 1970;12:225-35.
  74. Falcao HA, Gould DB. Immune complex nephropathy i schistosomiasis. *Ann Intern Med*. 1975;83:148-54.
  75. Hoshino-Shimizu S, De Brito T, Kanamura H, et al. Human schistosomiasis: *S. mansoni* antigen detection in renal glomeruli. *Trans Roy Soc Trop Med Hyg*. 1976;70:492-6.
  76. Martinelli R, Pereira LJ, Brito E, Rocha H. Clinical course of focal segmental glomerulosclerosis associated with hepatosplenic schistosomiasis mansonii. *Nephron*. 1995;69:131-4.
  77. Da Silva LC, Sette Jr H. Pulmonary and renal lesions after oxamniquine in patients with hepatosplenic schistosomiasis mansonii. *Gastroenterology*. 1978;74:A1118.
  78. Da Silva LC, Zeitune JMR, Rosa-Eid LM, et al. Treatment of patients with schistosomiasis mansonii: a double blind clinical trial comparing praziquantel with oxamniquine. *Rev Inst Med Trop Sao Paulo*. 1986;28:174-80.
  79. World Health Organization. Control de la Esquistomiasis: informe de un Comité de Expertos de la OMS. Serie de Informes Técnicos 728. Geneva, 1985.
  80. Da Silva LC, Sette Jr H, Christo CH, et al. Praziquantel in the treatment of the hepatosplenic form of Schistosomiasis mansonii. *Arzneimittelforschung*. 1981;31:601-3.
  81. Zwingenberger K, Richter J, Vergetti JG, Feldmeier H. Praziquantel in the treatment of hepatosplenic schistosomiasis: biochemical disease markers indicate deceleration of fibrosis and diminution of portal flow obstruction. *Trans R Soc Trop Med Hyg*. 1990;84:252-6.
  82. Da Silva LC. Portal hypertension in schistosomiasis: pathophysiology and treatment. *Mem Inst Oswaldo Cruz*. 1992;87 Suppl IV:183-6.
  83. Sakai P, Boaventura S, Ishioka S, Mies S, Sette Jr H, Pinotti HW. Sclerotherapy of bleeding esophageal varices in schistosomiasis. Comparative study in patients with and without previous surgery for portal hypertension. *Endoscopy*. 1990;22:5-7.
  84. Spence RAJ. Prevention of recurrent bleeding: nonshunting surgery. In: Okuda K, Benhamou JP, editors: *Portal Hypertension, clinical and physiological aspects*. Tokyo: Springer-Verlag; 1991. p. 533-47.
  85. Scarin SK, Grozmann RJ, Mosca PG, et al. Propranolol ameliorates the development of portal systemic shunt in a chronic murine schistosomiasis model of portal hypertension. *J Clin Invest*. 1991;87:1032-6.
  86. Mies S, Pereira MB, Orlando CD, Sette M, Raia S. Propranolol na prevenção da recidiva de hemorragia digestiva em pacientes com esquistossomose hepatoesplênica. *AMB Rev Assoc Med Bras*. 1988;34:24-8.
  87. Neto OB, Beer A Jr, Baia CE, et al. Systemic and hepatic hemodynamics in hepatosplenic manson's schistosomiasis with and without propranolol. *Dig Dis Sci*. 1997;42:751-61.
  88. Strauss E, Lacet CM, Honain NZ, Santos WR, Tramonti R, Albano A. Partial results of a controlled randomized trial comparing propranolol and sclerotherapy for the treatment of portal hypertension. *Dig Dis Sci*. 1986;31:131S.
  89. El Torabi H, El Amin AA, Shaeen M, Woda AS, Homeida M, Harron DN. Propranolol reduces mortality in patients with portal hypertension secondary to schistosomiasis. *Ann Trop Med Parasitol*. 1994;88:493-500.
  90. Maurizio R, Eugenio C, Roberto PR. Results of sclerotherapy for bleeding esophageal varices in patients with schistosomal liver disease. A retrospective study. *Hepatogastroenterology*. 2000;47:424-8.
  91. Cordeiro F. Variceal sclerosis in schistosomotic patients: A five-year follow-up study. *Gastrointest Endosc*. 1990;36:475-8.
  92. Da Silva LC, Strauss E, Gayotto LCC et al. A randomized trial for the study of the elective surgical treatment of portal hypertension in mansonii schistosomiasis. *Ann Surg*. 1986;204:148-53.
  93. Raia S, Da Silva LC, Gayotto LCC, Forster SC, Fukushima J, Strauss E. Portal hypertension in schistosomiasis: a long-term follow-up of a randomized trial comparing three types of surgery. *Hepatology*. 1994;20:398-403.
  94. Conn HO. A randomized comparison of three types of surgery in schistosomal portal hypertension: many fewer answers than questions [editorial]. *Hepatology*. 1994;20:526-8.
  95. Carrilho FJ, Chieffi PP, Da Silva LC. Prevention of Schistosomiasis. IASL-EASL Postgraduate course. Prevention and Intervention in Liver Disease. Madrid: Spain; 2002. p. 109-19.