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PROGRESS IN ASSESSMENT OF MORBIDITY DUE TO *SCHISTOSOMA MANSONI* INFECTION: A REVIEW OF RECENT LITERATURE[1]

CONTENTS

[1] This bibliographic review is one of a series of documents (WHO/SCHISTO/83.68-69-70-71, 87.91, 88.95) which have been prepared by the Schistosomiasis Unit of the WHO Parasitic Diseases Programme (PDP) and which are intended to provide up-to-date information on technical aspects of schistosomiasis control. According to the advances in technology and as experience accumulates in national control programmes, these documents will be revised. Inquiries and comments may be directed to Chief, Schistosomiasis and Other Trematode Infections, Parasitic Diseases Programme, World Health Organization, 1211 Geneva 27, Switzerland.

1. INTRODUCTION

Schistosoma mansoni has a wide geographical distribution including 53 countries in Africa, the eastern Mediterranean, South America and the Caribbean. The disease is mainly due to eggs deposited in host tissue by the adult female worms which induce inflammatory and fibrotic lesions in the host organs: mainly in the intestine, liver and lungs. In communities with both high prevalence and intensity of infection, schistosomiasis due to S. mansoni is usually a public health problem. Of all schistosomes, S. mansoni has been the most extensively investigated because of its wide distribution and the availability of suitable animal models. The scientific literature on S. mansoni is voluminous and there has been considerable progress in research on morbidity and control. However, some aspects of pathogenesis and the relationship between certain types of morbidity and S. mansoni infection remain controversial.

This document reviews the literature on the assessment of morbidity due to S. mansoni infection published mainly in the past 12 (1976-87) years. It emphasizes topics for which there is no general consensus and is oriented to inform clinicians and epidemiologists about the current state of our knowledge of disease due to infection with the parasite. The study design, particularly the lack of an appropriate control group, and the diagnostic techniques used may limit the stated conclusions. Furthermore, classification of S. mansoni infection in clinical investigations by qualitative or insensitive diagnostic techniques is to be regarded as unsatisfactory. It should be noted that in clinical investigations a single quantitative examination may also be insufficient to classify adequately the intensity of infection in an individual. The reader is encouraged to consult the original articles.

2. PATHOLOGY

2.1 Pathogenesis

An average daily egg output of female S. mansoni has been estimated to be about 300 eggs in many textbooks and other sources. However, higher daily egg production of S. mansoni females has been estimated by Cheever & Duvall (88) in grivet monkeys (529-658 eggs/female daily) and Damian & Chapman (105) in baboons (1107 $\pm$ 258 eggs/female daily) after single exposure to S. mansoni cercariae. The eggs are laid in the branches of portal and mesenteric veins and over 50% of these remain within the host organs (382). Several days after oviposition the eggs mature and can remain viable in the host tissue for up to 11-14 days (268, 304). The cephalic glands in living miracidia secrete soluble antigens through pores of the egg shell whereas immature eggs without cephalic glands do not (347). The antigenic constituents stimulate an extensive host immunological response and egg granulomas are formed (167, 304). The morphological aspects of the peri-ovular granuloma in humans are similar to those in experimental animals suggesting that similar mechanisms are involved. Thus, the results from the extensive animal experiments may be used to explain the pathology of egg granulomas in man (167).

Increasing intensity of infection was not associated with as significant a decrease in granuloma size in S. mansoni-infected mice as compared with S. japonicum-infected mice (85). No relationship between intensity of the infection and the volume of granulomas was observed in another experiment (89). However, yet another study showed that granuloma size both in lung and liver was significantly smaller in mice exposed to 200 S. mansoni cercariae than that in mice exposed to 25 cercariae at 8 weeks after infection (393). On the other hand, in S. mansoni-infected mice, the size of egg granuloma, which may reach 100 times the volume of the egg, decreased with increasing duration of infection (387). The mean volume of new granulomas from mice 20 weeks after infection was about one-fourth that of 8 weeks after infection (380). There have been no autopsy studies in the past decade which confirm these experimental findings regarding the modulation of granuloma size.

In a comparative analysis of autopsies, the mean diameter of liver granulomas around S. mansoni eggs with intact miracidia was 227 μm in Egypt, but 236 μm in Brazil. Granulomas in the lung, only measured in the Brazilian cases, had an average diameter of 260 μm (216).

The cell populations of the granulomas differ according to the immune status of the host and the duration of the infection. They consist mainly of eosinophils, lymphocytes, large mononuclear cells including macrophages, epithelioid cells, fibroblasts, and a few neutrophils (149, 268). Other cells, such as basophilic mononuclear cells, plasma cells, multinucleated giant cells and mast cells, were rarely seen (268). The egg granuloma has been shown to be the source of a fibroblast-stimulating factor and may play a role in regulating hepatic fibrosis in S. mansoni infection (402). As the formation of egg granulomas is the major factor responsible for development of severe disease, the characteristics and evolution of these granulomas continue to be important topics of research.

Various disease mechanisms associated with S. mansoni infection have been identified in different experimental animals as well as in man (42, 87, 118, 286, 379, 386). The delayed type of hypersensitivity in granuloma formation is a major pathological change associated with the infection (122, 275, 387, 390). Following sensitization with soluble egg antigens, only delayed footpad swelling was seen in S. mansoni-sensitized mice (382). It is now generally agreed that the egg granuloma is primarily a T-lymphocyte-mediated host response to egg deposition (84, 123, 379, 380, 382, 385, 387). Simultaneous sensitization of animals with lymph nodes or spleen cells taken from S. mansoni-infected animals amplified the granulomatous reaction (373, 386). New granulomas formed in the chronic stage of infection are much smaller than those seen in the early stage. In the experimental lung and liver granuloma models, the granulomatous reaction is subject to modulation depending on the duration of the infection; the modulation mechanism is also cell-mediated (380, 382, 387). This effect has been shown, however, to be due not only to suppressor T-lymphocyte activity, but also to antibody-mediated blockade (384). The modulation can be transferred by splenic T-lymphocytes from infected mice to recipient mice infected recently (373, 387). Measures that inhibit cell-mediated immunological reactions, such as niridazole treatment, irradiation, neonatal thymectomy and lymphocyte-antiserum injection, significantly suppress the inflammatory reaction of granulomas in animals (379, 382, 384, 385, 386). Suppression of cell-mediated immunity in man with S. mansoni infection also results in suppression of granuloma formation (195). However, the condition of the eggs which did not elicit reactions was not reported. It seems unlikely that specific antibody is necessary for the formation of granulomas per se. However, antibody or antigen-antibody complexes may be involved in the granuloma modulation (379).

A significant increase in eosinophil counts both in bone marrow and peripheral blood is an outstanding feature in schistosomiasis (247). Since the development of a monospecific anti-eosinophil serum (AES), the role of eosinophils in the immunity and pathogenesis of S. mansoni infection has been widely studied (114, 221, 247, 280, 369, 384). Eosinophils constitute up to 50% of the granuloma cells and are responsible for destroying the retained schistosome eggs (268, 280) as demonstrated by co-culturing schistosome eggs and eosinophil-rich materials in vitro as well as by experiments in vivo in mice (208, 246, 280). When infected mice were treated with AES, there was a significant retention of schistosome eggs in the tissue, increased morbidity and mortality, and a marked delay in egg destruction in the lungs. These effects could not be found in the infected mice treated with other antisera, e.g., anti-neutrophil serum or anti-thymocyte globulin (280). The effect of eosinophils is dependent on the participation of complement, either alone or combined with antibody (221). In vitro study showed that the schistosomula-killing capacity of eosinophils from S. mansoni-infected patients was greater than that for uninfected subjects; thus S. mansoni infections lead to changes not only in the level of eosinophilia but also in the ability of eosinophils to resist the parasite (109). An increase in the half-life of mature eosinophils in patients with S. mansoni has been reported (215).

2.2 Factors influencing morbidity

In schistosomiasis endemic areas, people living under similar environmental conditions and probably with comparable frequencies of water contacts show different degrees of morbidity. Several factors that may contribute to pathogenesis in man have been investigated.

2.2.1 Intensity of infection

Faecal egg counts are now accepted as the best available indirect measurement of actual worm load. Clinical, epidemiological and pathological studies support the relationship between intensity of S. mansoni infection and severity of the disease (34, 90, 112, 232, 275, 383). However, this correlation is useful for population studies but may not be reliable for evaluating individuals. While heavy S. mansoni infection is probably the most important factor in the development of Symmers' fibrosis (90, 216), other factors may be important as clinical disease can be seen in individuals with very low stool egg counts, and not all persons with heavy infections have hepatosplenomegaly (173, 216).

2.2.2 Strain of parasite

As different techniques develop it is recognized that S. mansoni is a complex of parasites. Ten polymorphic gene loci have now been reported in S. mansoni (238). Variations in morbidity due to different strains of S. mansoni have been reported in the past. In a recent study, different levels of acquired immunity and different responses to antischistosomal drugs were observed in 2 geographical strains of S. mansoni (303).

2.2.3 Race

The effect of race on the development of severe disease was studied by Bina et al. (62) by investigating autopsy records and comparing faecal egg counts among children and clinical manifestations of the disease among whites, mulattos and blacks in Brazil. The authors concluded that there was strong evidence of a greater resistance in black people to development of severe forms of the disease, while intensity of infection and prevalence rates were similar in the 3 racial groups. Furthermore, although Brazilian black subjects showed the same intensity of schistosomal infection and the same prevalence as white subjects, the former did not develop hepatic schistosomiasis (303). In St Lucia, a higher proportion of East Indian persons presented with hepatosplenomegaly compared with black persons (210).

2.2.4 Blood type

Among patients in Brazil with untreated S. mansoni infections, Camus et al. (77) found that those with blood group A had a higher frequency of hepatosplenic disease than those with blood group O who were more likely to develop a milder form of the disease. Hepatic schistosomiasis was previously reported to be more common in individuals with blood group A than in those with group O (303). These observations were confirmed by Pereira et al. (292) in Brazil who compared 280 subjects with hepatic schistosomiasis with a control group; a positive relationship between genetic factors and the evolution of S. mansoni infection in man was suggested.

However, El-Masri & Sharfi (138), after comparing the distribution of ABO blood groups in 187 persons with hepatosplenic schistosomiasis and in normal control subjects in Sudan, reported that no significant difference could be found. Furthermore, the blood groups were not significantly different between patients with and without rupture of gastro-oesophageal varices. In Swaziland, where both S. haematobium and S. mansoni are endemic, Trangle et al. (368) reported a significantly increased frequency of blood group B among schoolchildren infected only with S. mansoni.

2.2.5 Genetic predisposition

Possible genetic factors with regard to histocompatibility antigen (HLA) haplotype influencing the pathogenesis of disease and susceptibility to infection in human schistosomiasis were suggested by Abdel-Salam et al. (5, 6). Egyptian children with asymptomatic S. mansoni infection (46 cases), schistosomal hepatosplenomegaly (88 cases) and schistosomal colonic polyposis (29 cases) were compared to a control group of 345 healthy age- and sex-matched subjects. Thirty-two antigens of the HLA series were studied. The results showed that hepatosplenomegaly was associated with the presence of 2 HLA antigens, HLA-A1 and B5, and colonic polyposis with the presence of HLA-B5 and B8. In individuals with asymptomatic infections a significant association was found with antigen CW2; and the presence of this antigen is associated with a lower hypersensitivity response to schistosome eggs, and hence less clinical disease (6). A statistical increase in number of individuals with HLA-A1 and B5 in hepatic schistosomiasis with oesophageal varices was also reported (1). In another study by Kamel et al. (217), it was shown that HLA-B5 was significantly more frequently associated with schistosomal polyposis than with hepatic schistosomiasis and that HLA-B5 was no more prevalent in patients with hepatic schistosomiasis than in those with intestinal disease.

Other genetic predisposition has been considered in the development of hepatic schistosomiasis. Patients with alpha-1-antitrypsin deficiency have been reported to have a predisposition to develop hepatic cirrhosis, but alpha-1-antitrypsin deficiency was not observed to be associated with hepatosplenic schistosomiasis (172).

2.3 Disease in different organs

2.3.1 Liver

Symmers' original description of the hepatic pathology in schistosomiasis as clay pipestem fibrosis is still valid. However, as liver parenchymal function is virtually normal, the term cirrhosis is no longer used (112, 275, 384). The liver may be enlarged, of normal size or even slightly shrunken. Liver enlargement tends to be more significant in the left lobe than the right (304). The outer surface of the liver is sometimes nodular, and the cut surface showing wide bands of fibrosis around portal tracts is characteristic and cross-sectionally resembles the stems of a number of clay pipes from different directions (275). The liver parenchyma between fibrotic areas is well preserved and lobular architecture is not usually disturbed (145). The basic vascular lesion is localized mainly in the connective tissue around the intrahepatic portal vein and its ramifications causing chronic granulomatous pylephlebitis and peripylephlebitis (303). Eggs are seen in the granulomas with inflammatory infiltrate containing eosinophils. Schistosomal pigment, similar to malarial haemozoin, may be present. At autopsy, focal necroses or regenerative nodules have been recorded in a few cases due to intra-hepatic thrombosis or severe ischaemia after massive gastrointestinal bleeding (303, 304), and piecemeal necroses and other appearances of chronic active hepatitis were also noted in some cases (23, 134).

In a series of autopsies performed in Cairo, Egypt, Kamel et al. (216) found that hepatic fibrosis other than Symmers' fibrosis was unrelated to the presence or intensity of S. mansoni infection. Their findings were also in agreement with earlier work done in Brazil on the relationship between the intensity of infection and Symmers' fibrosis at autopsy. In these studies, using the same techniques, 37% of Brazilians and 36% of Egyptians with Symmers' fibrosis harboured more than 160 worm pairs. However, heavy S. mansoni infections are not always associated with Symmers' fibrosis; in 10% of Brazilians and in 6% of Egyptians without liver fibrosis comparably high numbers of worms were found.

Most reviewers have concluded that in hepatic schistosomiasis, total blood flow in the liver remains within normal limits in most patients (57, 112, 258, 381, 382), but the mechanism remains controversial. Portal hypertension is caused by changes that affect both the portal system and the hepatic artery. These reviewers considered that

an increase in the arterial supply (shown by an increase in the size and number of hepatic arterial branches) compensates for the diminished portal blood flow due to portal hypertension (57, 112, 275, 304, 382). At autopsy contrast injected into the portal system demonstrated a rich capillary network around the portal branch which was completely arterial in origin and communicated with the portal vein (303, 304). In agreement with previous autopsy studies by injecting casting material into intrahepatic vessels, Ibrahim et al. (203) demonstrated that the main portal branches were normal, and only the lesser branches, i.e., branches of the fourth order, were narrowed. However, in clinical studies other investigators (258, 259, 309) found that in S. mansoni infection, hepatic arterial atrophy, rather than proliferation of capillaries of arterial origin existed, and a reduced arterial blood flow was compatible with an increased portal blood flow, thus maintaining the hepatic blood supply. There is therefore no complete agreement between clinical and post-mortem studies on the arterial origin of the hepatic capillary network. The portal blood flow is increased in massive splenomegaly because an enlarged spleen requires a greater blood supply which in turn would increase portal hypertension due to a presinusoidal block (309).

Hepatic fibrosis evolves from an excessive accumulation of collagen in the liver (387). In theory, this accumulation may result from proliferation of collagen-synthesizing cells, increase in collagen biosynthesis by existing cells, or deficiency in collagen degradation (123). Animal experiments demonstrated that the amount of collagen in the liver increased rapidly in parallel with egg granuloma formation (384). Fibrotic liver in S. mansoni-infected mice contained 20 times more collagen compared with normal controls (126). In murine schistosomiasis, co-culture of inflammatory cells with liver fibroblasts has shown that the degree of stimulation increased from 2- to 10-fold compared with that of control fibroblasts. This proliferative activity may be attributed to fibroblasts (125). In human hepatic schistosomiasis Dunn et al. (124) have shown remarkably increased collagen content and marked collagen synthesis compared with control tissue in wedge-liver biopsy specimens. Intrahepatocellular collagen develops in the human schistosomal liver and possibly originates in the hepatocytes themselves (167). Free proline, a substrate for collagen synthesis, is increased in schistosomal liver both in mice and humans (124, 126). Host cells seem to be the source of newly formed proline (126). However, collagenolytic activity in the liver of S. mansoni-infected mice is greatly increased (358). The collagen types formed in S. mansoni infection are I, III and basement-membrane-like (V), similar to other forms of liver fibrosis (123).

At an ultrastructural level, the entire hepatic lobule is involved in human hepatic schistosomiasis (176). Investigations in Brazil using wedge hepatic-biopsy (20 patients) and needle-biopsy (2 patients) specimens in advanced schistosomiasis with episodes of haematemesis, showed definite pathological changes in Disse's spaces (176, 177). The vascular pole of the hepatocytes showed diminution of microvilli replaced by irregular cytoplasmic projection. The hepatovascular barrier was modified and the endothelial lining of the sinusoid was often composed of 2 or 3 layers and appeared poorly fenestrated. The endothelial cells were oedematous. Disse's spaces became wider than normal. The irregular cytoplasmic projections of the hepatocytes, together with cell debris and collagen fibres, entirely filled the Disse's spaces. IgG deposits were demonstrated in Disse's spaces (177). All these modifications provide a barrier between hepatocytes and blood circulation and have been asserted, although as yet unproven, to interfere with hepato-vascular exchange (177).

2.3.2 Spleen

In most individuals with hepatic schistosomiasis the spleen is increased in size. Splenomegaly results from chronic passive congestion and hyperplasia of the reticulo-endothelial system (23, 304). Nodular-type lymphoma was occasionally encountered in enlarged spleen with S. mansoni infection in Brazil (23). The average spleen weight in 6 autopsy cases with Symmers' fibrosis in Egypt was 1.2 kg (216); in another report from Brazil, it was 1.1 kg (309). On angiographs, the splenic artery was large and tortuous with an average diameter of 9.8 $\pm$ 2.5 mm, and that of the splenic vein

was 18.7 ± 3.9 mm, significantly larger than normal (10 ± 2.5 mm) (309). At autopsy casting material injected into the splenic vein filled the splenic arteries showing massive arteriovenous shunts in cases of advanced hepatic schistosomiasis with splenomegaly (203).

2.3.3 Intestine

The main intestinal lesions due to S. mansoni infection are colonic polyposis and focal fibrosis and inflammation (275).

In 400 consecutive autopsies in Cairo by Cheever et al. (91) schistosomal colonic polyps were found in 26 (6.5%), whereas elsewhere outside Egypt polyps were not common (23, 134, 318, 399). A direct relationship between schistosomal polyposis and the intensity of infection was reported. S. mansoni infection was associated with colonic polyposis and was the cause of death in 3 heavily infected subjects (91). Within the polyps the concentration of S. mansoni eggs was much higher than elsewhere in the intestine suggesting that focal oviposition occurred over a period of time. Eggs were more numerous in the mucosa and submucosa than in the muscular layers. Histologically, the polyps were inflammatory lesions with glandular proliferation and destruction. However, no adenomatous change was observed. The authors concluded, "schistosome infection, excluding the local reaction to eggs, was not related to acute or chronic colitis, nor to colonic cancer nor colonic ulcers" (91).

Although S. mansoni eggs may be deposited in large numbers in the small intestine (90), severe small-bowel disease due to S. mansoni infection has been only rarely found (91, 399). In contrast to the early stage of schistosomiasis, a shift in egg deposition from colon to the small intestine was noted with the appearance of Symmers' fibrosis and portal hypertension, and the tissue egg burden was found to be high in the small intestine at autopsy studies both in Brazil and in Egypt (90). However, even in these cases, the pathology in the small intestine was not as severe as in the large bowel (23, 90)

2.3.4 Lung and heart

Pulmonary hypertension and cor pulmonale induced by pulmonary arteritis as a result of S. mansoni egg deposition have been well documented in the literature (22, 205, 275, 304, 334). Such pathological effects are due to collateral circulation in patients with liver fibrosis and portal hypertension which provides direct access of eggs to the lung (12, 275, 321). Despite the same mechanism in S. japonicum infection with extensive collateral porto-caval shunt and the frequent finding of egg deposition in the lung at autopsy, pulmonary hypertension and cor pulmonale have been much less frequently reported than in S. mansoni infection (204, 401, 405). In S. haematobium infection, the access of eggs to the lung via the vena cava is more direct; however, both pulmonary arteritis and cor pulmonale are rare complications (91, 275, 400). Although several explanations for these phenomena were given (91, 387, 389), none has been proven.

The pathology of cor pulmonale due to S. mansoni was described in detail by Sadigursky & Andrade (321) in 32 autopsies of hepatosplenic schistosomiasis in Brazil. Apart from use of conventional histological techniques, the lungs were investigated by serial sectioning and by plastic vascular casting. Hypertrophy of the right ventricle and a significant pulmonary conus were characteristic in every patient. Periovular granulomas were seen only in a few cases at the cut surface, and the most important lesions were microscopic. Fibrin precipitation and endothelial cell hyperplasia obstructing the pulmonary arteries and arterioles were the main changes. Plexiform lesions included tortuous and twisted newly formed vessels that ended up as capillaries in the alveolar tissue. Vascular casts revealed the plexiform lesions to be purely arterial with a glomeruloid appearance. No evidence of vascular shunts was seen. Myocardial involvement was rare (180).

In a single case report, a large tumour-type lung lesion measuring 5 cm in diameter on X-ray film, proved to be a solitary bilharzioma after lobectomy of the affected lung (361).

2.3.5 Kidney

Renal lesions in S. mansoni infection were first reported in the 1960s. The histopathology was described by Andrade & Queiroz (28) in 1968 as thickening of the basement membrane and proliferation of mesangial cells in a few patients who died from hepatosplenic schistosomiasis. Further studies have suggested that liver disease with portal hypertension is a prerequisite for the development of the glomerular changes; it is almost exclusively in the hepatosplenic form of the disease that the glomerulopathy has been observed (46, 47, 116, 304, 315, 371). The porto-systemic collateral circulation diverts the schistosome immune complexes which are usually eliminated by the liver and its Kupffer cells and subsequently these immune complexes are trapped in the glomerular capillary walls, activating complement and causing glomerular damage (348, 371, 372). By interfering with proper clearance of immune complexes, Van Marck et al. (372) reported that partial ligation of the portal vein in experimental animals significantly increases the amount of immunoglobulin deposits in glomeruli. Now there is little doubt that the schistosomal glomerulopathy is mediated via the glomerular deposition of immune complexes (29, 379). By direct or indirect immunofluorescence techniques, glomerular deposits of IgM, IgG, IgA, IgE, C3, C1q and fibrogen were demonstrated by several investigators in infected animals (116, 277, 372) and in biopsy or autopsy material (72, 197, 245, 348) from hepatosplenic schistosomiasis patients infected with S. mansoni. Moriearty & Brito (270) found that IgG obtained from elutes of human kidney tissue infected with S. mansoni produced specific indirect immunofluorescent reactions to the gut and tegument of adult S. mansoni. Furthermore, S. mansoni antigen was identified in the glomeruli in mice by El-Dosoky et al. (133) and Van Marck et al. (372) and in human biopsy and/or necropsy materials by Hoshino-Shimizu et al. (197) and others (310, 348). Circulating anodic antigen (CAA), but not soluble egg antigen (SEA), is probably the major responsible antigen (133, 348).

The main histological changes in the glomeruli are seen in the mesangium and basement membrane, showing membrano-proliferative glomerulonephritis or focal glomerulonephritis (29, 47, 274, 315). Mesangial hypertrophy consists of cell proliferation and an increase of mesangial matrix. Leukocyte infiltration is mild or absent (29, 72, 116, 245). Changes in capillary basement membrane are less prominent (47, 371), but thickening and splitting of the basement membrane, associated with capillary-wall collapse (315), are reported. The degree and extent of glomerular changes differ from one case to another. Usually segmental changes are seen. Electron microscope studies have shown the presence of electron-dense deposits in the mesangial areas and along the basement membrane (29, 315).

In S. mansoni infections with glomerular changes, diffuse amyloid deposits in the glomeruli have been reported (49, 274, 283, 375), especially in those infections associated with Salmonella infection (48, 49, 351). Barsoum et al. (49) have found amyloid deposits in 10 out of 60 renal biopsies obtained from patients with nephrotic syndrome and schistosomiasis. The distribution was segmental, mainly mesangial, although amyloid was also found around the tubules, in the renal vessels or in the interstitium (49, 283). In some cases, the amyloidosis was generalized and also seen in the liver, spleen, heart and lungs (283). In contrast, no relationship between schistosomiasis and renal amyloidosis was observed by Sadigursky & Andrade (320) in 245 autopsies in Egypt. No significant difference in frequency of renal amyloidosis was observed between infected and uninfected groups from Egypt. Furthermore, in 53 cases of hepatosplenic schistosomiasis from Brazil, no renal amyloidosis was found. On the other hand, deposition of eggs in the kidney has rarely been reported and is not considered to be the basis of the renal pathology (301).

The relationship between schistosome infections and glomerulopathy was reviewed recently by Barsoum (46).

2.3.6 Central nervous system

Schistosomes or their eggs may reach the central nervous system through anastomoses of the valveless vertebral plexus of Batson with the visceral pelvic veins or

haemorrhoidal vein (231, 295, 329). It has also been suggested that eggs reach the brain through arterial embolization and through a retrograde venous route (295). The lesions in the central nervous system are mainly caused by the eggs, although adult S. mansoni worms were found at autopsy inside the vessels in the cerebral leptomeninges in one case (267) and within subarachnoid veins of the spinal cord in two others (121, 237).

In spite of a considerable number of case reports, in comparison with the enormous population infected. In Puerto Rico, among 1095 consecutive autopsies in persons above 5 years of age, 14.8% had evidence of S. mansoni infection, but only 3 had central nervous system involvement: cerebral granulomas without symptoms in 1 case, and lesions in the spinal cord presenting clinically as transverse myelitis in the other 2 (250). On the other hand, Pittella & Lana-Peixoto (295) reported from Brazil that among randomly selected autopsy cases with hepatosplenic schistosomiasis, 12 (26%) out of 46 showed S. mansoni eggs in the brain. The authors suggested that the brain was frequently affected in severe cases of hepatosplenic schistosomiasis due to S. mansoni. In reviews of the published literature, it appeared that most cases of cerebral schistosomiasis due to S. mansoni were seen in the hepatosplenic form of the disease (294, 295). However, among the 12 cases with S. mansoni eggs in the brain, only 1 had had a convulsive disorder; in the other cases no symptoms were related to cerebral schistosomiasis. Furthermore, 11 of these 12 cases had concurrent cardiopulmonary schistosomiasis (295).

Eggs of S. mansoni have not been observed in the brain as often as have those of S. haematobium (333). Myelopathy due to S. mansoni has most frequently been reported in acute schistosomiasis and less frequently in hepatosplenic schistosomiasis (333). More cases of S. mansoni infection associated with myelopathy have been reported than with S. haematobium infection (304, 329, 333).

Eggs may be present in the central nervous system with little or no histological reaction (7, 295). Usually, a slight inflammatory reaction surrounding the eggs with the presence of lymphocytes, epithelioids and macrophages, vasculitis, granulomas, oedema of the adjacent tissue, and focal astrocytosis were seen (7, 294, 333); rare findings were tumours (41, 264), subarachnoid haemorrhage (301), choroiditis (296) and massive spinal-cord necroses (307). The lesions may extend from the leptomeninges deep into the nervous tissue via vascular channels. Arteritis with fibrinoid necroses, and thickening and destruction of vascular wall were sometimes observed (294). The eggs and granulomas in the brain were found mainly in the leptomeninges, cerebral and cerebellar cortex and pons (294, 295), although involvement of other parts of the brain and widespread distribution were also reported (333). Any part of the spinal cord can be involved, but more often the lower thoracic and lumbar cord (93, 95, 130, 198, 231, 237, 264, 307, 340, 376). In 78% of cases, myelopathy occurred in the conus medullaris showing intramedullar granulomas. Multiple nodules on the surface of the spinal cord were noted in a few cases. Cauda equina involvement was recorded, sometimes with congestion and oedema of the nerve roots (333).

2.3.7 Other ectopic lesions

Cutaneous lesions caused by ectopic deposit of S. mansoni eggs are rare. Lesions of the abdominal wall, especially the para-umbilical, and of the scapular and shoulder regions have been reported (19, 242). Early lesions show multiple, small rounded or oval papules, without symptoms (19) or they may be slightly pruritic (242). Older lesions appear to aggregate forming nodules with a granular appearance.

Genital organ involvement in S. mansoni infection is not rare in Egypt. Of the total S. mansoni eggs recovered at autopsy in Egypt 24% were in genitourinary organs (90). In another study, S. mansoni infection accounted for 4% of total female genital schistosomiasis whereas S. haematobium accounted for the remainder (7). The

first case of placental schistosomiasis was reported in Brazil by Viggiano & Leite (378) in 1978: S. mansoni-egg granuloma in the placenta and a pair of coupled adult S. mansoni in the uteroplacentary vein were identified; stool examination also showed S. mansoni eggs. Four other cases of placental involvement with S. mansoni eggs were reported later from Brazil (64): 3 of the pregnancies resulted in stillbirth, 1 in a normal newborn. Egg granulomas were found in the placenta of all 4 cases, and adult schistosomes were detected in 2: a pair of worms in the intervillous spaces and a single worm in a decidual vein. No evidence of fetal infection by S. mansoni was found by stool examination in 1 and organ examination in 3 stillborn fetuses. The inflammatory lesions in the placenta were considered to cause fetal death.

An extensive granulomatous reaction in a testicle associated with S. mansoni adult worms and numerous egg deposits was reported recently in Brazil (40). The testicle was enlarged, 9 cm in the greatest dimension, with a firm, nodular lesion, and a malignant testicular tumour was suspected before operation. Examination of the excised testicle showed large egg granulomas and in the pampiniform venous plexus 3 pairs of S. mansoni worms were found. Two other cases of testicular schistosomiasis were also confirmed by the findings of S. mansoni egg granulomas in testicular masses after operations (76, 162). Adenocarcinoma of the prostate associated with local heavy S. mansoni egg deposition was reported (17).

An aortic aneurysm associated with S. mansoni infection was described recently (374). Extensive deposition of eggs in the left upper lobe of the lung extended into the adjacent pleura and aortic sheath, causing endarteritis and obliteration of the vasa vasorum of the aorta and formation of the aneurysm. Surgical intervention was successful.

2.3.8 Endocrine glands

A wide range of potential interactions between schistosomiasis and endocrine functions has been suggested (see 3.3.2.2), supported mostly by experimental studies (228). Results of a few experimental studies on the morphological and functional changes of the endocrine glands have been reported (184, 363, 364, 365).

3. CLINICAL PRESENTATIONS

Human disease associated with S. mansoni infection evolves according to age at initial exposure, re-exposure and intensity of infection as well as other factors (see section 2.2). Morbidity studies both in the community and in hospital patients in recent years have added more information on this spectrum.

3.1 General description

Earlier clinical studies based on hospital findings or reports from individuals had their limitations because they often dealt with symptomatic patients and hence were biased towards the severe form of the disease. The need for community-based studies on schistosomiasis was emphasized by the World Health Organization for assessment of its public health impact (398). During the past decade, a series of cross-sectional and community-based studies on the prevalence and intensity of S. mansoni infection, and their relationship with clinical disease have been carried out in Botswana (20), Brazil (43, 44, 96, 97, 99, 182, 232, 343), Egypt (10, 131, 302), Ethiopia (190, 234, 297), Kenya (34, 345), Liberia (196), Puerto Rico (92, 191), Saudi Arabia (175), Sudan (282) and Zaire (179).

The distribution of schistosomiasis in any population is directly related to water-contact patterns. In rural endemic areas, the infection rates are usually higher in males than in females. Intensity of S. mansoni infection increases during the first couple of decades of life and thereafter decreases. Both peak prevalence in communities and the highest intensity of infection are usually seen in the 10-19 year age group (Table 1; 271, 297, 342, 357).

Several studies showed, and it is widely accepted, that most persons with S. mansoni infection are symptom-free (92, 192, 302, 304) and severe clinical manifestations are seen in a relatively small proportion of patients with persistent or heavy infections (34, 96, 246, 275, 343). However, in a heavily endemic village in Zaire with a population of 547 and a prevalence rate of 96%, a mean stool egg count of 791 eggs per gram (epg) in infected persons was found, in contrast to a mean stool egg count of 39 epg in a comparable control village with a lower prevalence of 19%. Symptoms, such as abdominal pain, bloody diarrhoea, and fatigue, were reported by most of the villagers in the heavily endemic village, whereas in the village with the lower prevalence, frequencies of complaints of the symptoms were very low (179). Several studies confirm that the frequency and severity of clinical appearance are positively correlated to the intensity of infection (34, 44, 96, 232, 275, 282, 343).

The relationship between symptoms and signs and S. mansoni infection is shown in Table 2. Most of the studies showed a significant correlation between either visible or occult blood in stool and S. mansoni infection. Four (34, 175, 179, 345) and 3 (179, 282, 356) studies respectively showed that abdominal pain and diarrhoea were also correlated with infection. In Zambia, the blood in stool had the highest specificity (94.9%) and positive predictive value (85.3%) for S. mansoni infection compared with other symptoms (355).

In the evaluation of studies on the relationship between the symptoms and intensity of S. mansoni infection, differences between age groups must be taken into consideration. As pointed out by Arap Siongok et al. (34), some symptoms may be related to age rather than intensity of infection. Data from an age-comparable control group without the infection are required to assess this correlation.

Studies from Brazil (232), Egypt (10), Kenya (34), Zaire (179) and Zambia (75, 356), where prevalence rates and intensity of infection were high, showed significant correlation between intensity of infection and hepatomegaly, whereas other studies from Ethiopia (192), Kenya (345), Liberia (196), Saudi Arabia (175) and Sudan (282) failed to show such a correlation, although the intensity of infection in these countries was not low. Splenomegaly seems to be less correlated with schistosome infection (10, 75, 192, 345), although in children the correlation may be significant (98, 232, 271, 392).

The estimated life-span of the adult S. mansoni worm has been derived from: (a) extrapolation of follow-up data on infected persons (171, 377), (b) cross-sectional epidemiological studies (388), and (c) case report (81). A mean life-span of adult S. mansoni of 3.3 years was estimated by Goddard & Jordan (171) based on data collected in St Lucia from periodic determination of stool egg counts in 625 individuals infected with S. mansoni over 5 years. Vermund et al. (377) estimated survival of S. mansoni in the human host from a community-based prospective study in Puerto Rico from 1972 to 1981. Three different cohorts were studied: (a) 27 persons with 10 consecutive stool examinations in each of 3 years, (b) 7 persons with 10 consecutive examinations in each of 4 years, and (c) 528 persons examined once yearly for 6 years. The average estimated life-span of S. mansoni was 5.5, 37.0 and 35.0 years in each cohort, respectively. In the absence of transmission, substantial egg output by the worms can be expected to persist for a decade or more. Life-span of 5-10 years was estimated by Warren et al.; in individual cases, i.e., infected persons who had left an endemic area, eggs were still passing in the stool up to 20 years after infection (388). In 1 person as long as 37 years outside the endemic area, viable eggs were shown on rectal biopsy snip (81).

Observations of working men in endemic areas suggest that heavy, but not light, S. mansoni infection has a negative effect on working capacity. Among 194 Sudanese cane cutters, those who were infected had significantly lower haemoglobin levels compared with those who were uninfected. On the other hand, 6 types of submaximal response to exercise were similar both between infected and uninfected persons as well as between infected individuals with and without hepatosplenomegaly. The efficiency was similar between the uninfected group and the infected group (94). Working capacity between S. mansoni

infected and uninfected male labourers, 60 persons in each group, in a tin mine in Zaire showed no significant difference as estimated by submaximal worktests, Monark bicycle ergometer and double Master step-test (370). In another study done in the Sudan, physiological responses to exercise were not different between uninfected villagers and villagers with light infections. However, physical working capacity was impaired in those with very heavy infections (> 2000 epg) in comparison with those with comparatively lighter infections (< 1000 epg). The authors concluded that only heavy infections with S. mansoni had an adverse effect on physical working capacity (38). The 24-h energy expenditure was found to be negatively associated with the stool egg count (37). An analytic study among an agricultural population in St Lucia showed that S. mansoni infection had a negative effect on productive potential, and daily earnings among the infected persons were reduced by 15% (391).

3.2 Acute phase

Several investigators have studied the acute phase of S. mansoni infection, i.e., Katayama syndrome, the infection being acquired in Brazil (163), Egypt (155), Ethiopia (206, 408), Mali (352), Puerto Rico (193) and Saudi Arabia (263). Most of the subjects were tourists or visitors from non-endemic countries or areas who had been in contact with infested water for 1 day to 2 weeks. Several reports reaffirmed the commonly held belief that the acute form of S. mansoni infection is seldom observed in endemic populations, and visitors to endemic areas appeared to be more likely, or, as some authors considered, exclusively susceptible to develop the acute symptoms (145, 163, 263, 275, 352, 408). However, Farid et al. (155) held that, regardless of whether persons are visitors or native inhabitants, any initial contact with S. mansoni cercaria-infested water by non-immune individuals can lead to the acute disease, even if the exposure is minimal and the infection is light.

Cercarial dermatitis, or "swimmer's itch", is considered to be more frequently associated with non-human than with human cercarial penetration (71, 304). In acute disease associated with S. mansoni, dermatitis after exposure to infested water was reported in some cases (193, 263). Itching started within an hour after contact, followed by a papular erythema which lasted up to 24 h or several days. The condition is due to hypersensitivity reactions of both the immediate and delayed types (390).

The incubation period of the Katayama syndrome ranges from 4 to 87 days, but is generally between 3 and 7 weeks (163, 193, 352, 408). However, since the period of exposure was from a few days to several weeks, the period of incubation cannot be precisely determined. In one report from Puerto Rico (193), exposure dates of a group of 26 persons were linked to a specific weekend event and the date of onset of symptoms of acute schistosomiasis was known. The mean incubation period (exposure to onset of fever) was 31.8 days (range, 13-52 days). Seven of the 26 patients had incubation periods of less than 3 weeks. Although it is generally accepted that in a small proportion of the infections acute symptoms can start before egg deposition by the female worms (193, 352, 408), in most cases symptoms usually intensify when egg laying is initiated (275). Symptoms last for a few weeks to several months and gradually abate without therapeutic intervention (275). Among people living in endemic areas the acute phase may pass imperceptibly (303). During the acute phase of S. mansoni infection, death is exceptional (304).

The main clinical manifestations of the acute infection include fever (intermittent or remittent, with peaks in the late evening), rigor, sweating, headache, general muscular pain, unproductive cough, abdominal pain, diarrhoea, urticaria, focal oedema, lymphoadenopathy and loss of weight. On physical examination, the liver is usually tender and enlarged, with or without a slightly enlarged and soft spleen.

Leukocytosis with a high percentage of eosinophils (10% up to 75%) is common (155, 206, 263, 352, 408). Eosinophilia is a conspicuous and constant feature which aids in the diagnosis. Lymphocyte-subset analyses show elevated levels of T4 and T8 subsets (163). The erythrocyte sedimentation rate (ESR) is usually high (263, 352, 408). Serum concentrations of IgM, IgE and IgG are elevated whereas IgA is normal (155, 193, 230). The titres of species-specific anti-schistosome antibody in serum are also markedly elevated (155, 163, 193, 263). Fourteen (93%) of 15 persons with the acute infections showed elevated ^{125}I-Clq-binding immune complex, and in the chronic phase the immune complex could be detected in 2 of 11 persons (230). Using competitive inhibition enzyme-linked immunosorbent assay (ELISA), circulating schistosome antigen was detected by Hayunga et al. (188) as early as 1 week after heavy infection in experimental mice. Nash et al. (276) reported that serological responses to schistosome-specific antigens can differentiate patients in the acute phase from those in the chronic phase. Comparatively higher IgM antibody and lower IgG levels were seen in the former and comparatively lower IgM and higher IgG levels were seen in the latter compared with healthy individuals. Liver function tests showed slightly higher levels of serum glutamic oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), alkaline phosphatase (AKP) and lactic dehydrogenase (LDH) (193, 263, 408). Serum globulin levels were also high (263, 304). Renal function tests including blood urea nitrogen, urine sediment, and protein were normal in 26 Puerto Rican patients and no evidence of renal disease was found (193). Faecal egg counts depend on the time of examination after infection. They are often high, although low faecal egg counts in the acute syndrome are not rare (193, 206, 408).

3.3 Chronic phase

After the clinical manifestations of the acute infection subside, those infected can be symptom-free and evolve to the chronic phase (275). Most chronic infections are seen in asymptomatic inhabitants in endemic areas. These persons lack marked hypersensitivity to S. mansoni and do not present an acute clinical syndrome in the face of chronic re-exposure (186, 246, 275, 303, 304). S. mansoni eggs are present in the stool and the egg excretion is relatively stable (45). The typical population distribution of S. mansoni infections is an example of a truncated form of the negative binomial, i.e., heavy infections (more than 100-800 epg of faeces depending on the endemic area) are usually seen only in a small portion of the infected population (74). Asymptomatic infection may become symptomatic after recurrent exposure and reinfection or with continuous long-term egg deposition without treatment.

There is disagreement as to whether egg production of S. mansoni is influenced by a density-dependent factor (86, 254, 394), i.e., the number of eggs in faeces per worm pair decreases as the number of worm pairs in a person increases, as seen in some other intestinal helminth infections (183). Patients with hepatosplenic schistosomiasis usually have fewer epg of faeces per worm pair than persons with earlier-stage chronic disease (86).

Morbidity is related to the intensity of the infection (273) and appears to vary from one geographical area to another, being related to the parasite, the host, and the environment (145). Among those with symptoms different categories have been suggested: the so-called intestinal, hepatointestinal, hepatic, hepatosplenic and splenic schistosomiasis (145, 304, 318). This clinical division is arbitrary (304) as, in any S. mansoni infection, intestinal and hepatic pathology invariably coexist although in some individuals one or the other may be predominant. Even in the clinical classification of hepatosplenic schistosomiasis, the spleen may not be palpable.

General symptoms related to chronic S. mansoni infection, which may disappear after treatment, are weakness, fatigue, irregular bowel movement, abdominal pain and blood in stool (303). However, most of the controlled epidemiological field studies have failed to link infection with these symptoms and signs except for blood in the stools (Table 2; 246). Infected subjects usually enjoy a normal life and work efficiently unless the infection is quite heavy, or complications coexist, or until the disease becomes

well-advanced. In a population-based morbidity study in Qalyub, Egypt, although the intensity of infection was high (10-3580 epg of stool), clinical morbidity was not as striking as that seen in S. haematobium infection in the same area (302).

3.3.1 Intestinal disease

Since adult S. mansoni worms favour the inferior mesenteric vein radicals, egg deposition occurs most commonly in the large intestine, especially the rectosigmoid colon (346). The small intestine is comparatively less affected. Stomach involvement is rare and was diagnosed by the peroral suction biopsy technique in only 3 (3.3%) out of 90 subjects with S. mansoni infection and hepatosplenomegaly (147).

3.3.1.1 Small intestine

Two cases of duodenal disease diagnosed by gastroscopy and biopsy have been reported (360, 397). Both patients complained of epigastric pain and one patient presented with dark-coloured stool and vomiting "coffee ground" material. A sessile polyp, 1 x 1 cm in size, located in the duodenal bulb was seen in one (360), and a number of white papular lesions on the duodenal mucosa were revealed in the other (397). Granulomas containing S. mansoni eggs were identified by microscopy.

Jejunal biopsy using the Crosby Capsule was performed in 17 Sudanese with active S. mansoni infections and 13 uninfected control subjects (159). In 4 out of the 17 infected persons, S. mansoni eggs were seen in the lamina propria without granulomas. Although there were significant histological changes in the villous structure (significant shortening and broadening) and eosinophil infiltration in the schistosome-infected group, the authors considered it unlikely that egg deposition significantly affected nutrient absorption because the parasite eggs occupied only a small area of small intestine. In Brazil 8 of 11 small-bowel biopsies in infected individuals with abnormal faecal fat excretion showed S. mansoni eggs and granulomas in the muscularis mucosae (306).

A case of iron deficiency anaemia with eosinophilic gastroenteritis induced by S. mansoni infection was reported by Hesdorffer & Ziady (189) in South Africa. Gastric and duodenal biopsies showed an eosinophilic mucosal infiltrate consistent with eosinophilic gastroenteritis. However, S. mansoni eggs were identified only in the rectosigmoid mucosa associated with eosinophilic infiltrate. The authors suggested that the infection produced eosinophilic gastroenteritis which resulted in gradual blood loss leading to an iron deficiency anaemia. After oxamniquine treatment, the patient made a full recovery. In Zimbabwe, a boy with malabsorption syndrome presented with diarrhoea, anaemia, hypoalbuminaemia, emaciation and peripheral oedema. Biopsies of the jejunum, rectum and liver revealed S. mansoni infection. After treatment with praziquantel, the patient recovered fully (225). The authors suggested that the protein-losing enteropathy was caused by the infection.

Large granulomatous lesions of the bowel due to S. mansoni infection may cause intestinal obstruction. In Puerto Rico a granulomatous mass, 8 x 10 cm in size, was found in the ileocaecal region at surgery having been misdiagnosed as colonic carcinoma. The patient had peritonitis with intestinal obstruction. Microscopic examination of the mass showed multiple granulomas containing Schistosoma eggs (207). A pseudo-tumoural form of S. mansoni infection involving the small bowel was also reported in 3 Brazilian children (65); intramural lesions of the ileum were seen in 2 children and in the third child only the serosa of the jejunum was involved. In an adult an abdominal mass in the ileocaecal region presented with radiological features of lymphoma, and after treatment with praziquantel the size of the mass was significantly reduced (406).

3.3.1.2 Large intestine

Colonic polyposis is a common intestinal complication of schistosomiasis in Egyptian farmers (2, 139, 141, 346). In a report of 77 selected infected subjects without

controls in Egypt, rectocolonic polyposis was absent in 12% (302). The disease causes significant morbidity and some mortality (2, 399). On the other hand, it is rarely seen in the Western Hemisphere and other parts of Africa including the endemic countries neighbouring Egypt, such as the Sudan (150, 318, 399, 407, 409). The high prevalence of schistosomal colonic polyposis in Egypt is difficult to explain. Several factors, such as intensity and duration of infection, host genetics, concomitant S. haematobium infection, and even parasite strain differences are suggested (139, 318, 409); none has been confirmed. At autopsy, Cheever et al. (90) have shown colonic egg burden not to differ between samples from Egypt and those from Brazil.

Most of the patients with colonic polyposis are young men, usually about 30 years of age or less (2, 60, 139, 346). The most common site of polyps was in the sigmoid, then in descending order, rectum, descending transverse and ascending colon (Table 3).

Several reports of polyps surgically removed or removed by colonoscopic polypectomy have been published. The size and shape of the polyps varied from pin head to grapelike collections (60) of 2-20 mm in diameter with an average size of 8 mm (409). They were pink-tan to beefy red in colour, sometimes with ulcerations covered with greyish-green membrane (60, 346, 409). In most of the patients, polyposis was multiple. In a series of 404 polyps removed by colonoscopic polypectomy from 20 patients who all had multiple polyps except one patient with a single polyp, as many as 51 polyps were removed from a single patient (59). Small polyps are sessile and the less-common larger polyps may be pedunculated (407, 409). A pedunculated polyp with a 15 mm stalk in the transverse colon was reported from a Puerto Rican woman (407). In schistosomal polyposis the colonic wall may be diffusely thick and in some cases the lumen was locally narrowed with colonic obstruction (60). High densities of eggs can usually be found in the mucosa and submucosa of colonic polyps (139, 346) and adult worms have been found in polyps (409). Patients with greater numbers of polyps also had higher worm burdens as evidenced by stool egg count (139). No adenomatous hyperplasia has been reported (346) and no correlation between histology, anatomical location or geographical distribution of colon cancer and schistosomiasis due to S. mansoni infection has been established (407).

The main symptoms of intestinal polyposis are bloody diarrhoea, abdominal pain, and tenesmus (Table 4). In a hospital series of 108 cases reported by El-Masry et al. (139) in Cairo, all patients complained of moderate to severe diarrhoea with an average of 9 bowel movements per day. On examination, abdominal tenderness along the course of the descending colon and sigmoid may be elicited (304) and a tender abdominal mass usually in the left iliac fossa. Barium enema and fibreoptic colonoscopy showed these masses to be clusters of polyps or paracolonic fibrosis (60, 139). Pallor, emaciation, dehydration, dependent oedema, ascites, clubbing of fingers are common in the patients (59, 139, 141). Hepatic fibrosis and splenomegaly in schistosomal colonic polyposis are usually less marked than in patients with mild colonic involvement (60, 139). Due to severe bloody diarrhoea, iron-deficiency anaemia, hypoalbuminaemia and hypokalaemia may result (60, 139, 346, 409).

Colonic polyposis can be diagnosed by sigmoidoscopy, colonoscopy and barium enema with air contrast (58, 141, 409). The finding of eggs in a biopsy specimen is suggestive of schistosomal aetiology. Antischistosomal drug treatment is effective in reducing symptoms and correcting anaemia and hypoalbuminaemia as well as reducing or causing complete regression of the polyps (2, 139, 409).

Rectocolonic calcification in association with S. mansoni and S. haematobium infection was found in 4 Egyptian men by abdominal radiography. Many calcified eggs of both parasites were shown in the submucosa (157).

In the Sudan a field study of 114 patients with S. mansoni infection showed low rates of colonic disease as found by sigmoidoscopy (318). Rectosigmoid polyps were found only in 4 (3.5%) and mucosal ulcers in 6 (5.3%). Other findings consisted of mucosal oedema and petecheal haemorrhage. Biopsies confirmed schistosomal eggs and granulomas.

A large, ulcerating mass in the caecum, suggestive of a carcinoma, was seen together with a polyp in a migrant from Suriname, who complained of abdominal cramps, bloody diarrhoea and tenesmus. Biopsy of the mass showed granulomatous lesions with numerous S. mansoni eggs. The patient also had many small polyps in the sigmoid, descending and transverse colon (150). A low frequency of pseudotumours in the large bowel associated with S. mansoni has been reported in Madagascar (101). Although the large bowel is the fifth most common site of cancer its association with schistosomiasis has not been investigated there.

Among 1600 surgical specimens from appendicectomies in Dammam, Saudi Arabia, where both S. haematobium and S. mansoni are endemic, 26 (1.6%) had schistosome eggs (331). The species identification was not reported. The egg deposits were attributed to acute appendicitis in 19 patients, and in the remaining 7, eggs were accompanied by fibrosis without inflammation.

3.3.2 Hepatic disease

3.3.2.1 Hepatosplenomegaly

The enlargement of the liver and the spleen in S. mansoni infection develops insidiously. In endemic communities, hepatomegaly in childhood has been correlated with the intensity of infection, specifically in most children with more than 800 S. mansoni epg of faeces. After persistent infection and an evolving pathological process, hepatic enlargement is clinically recognized in the second or third decades of life (120, 145). Males are usually more frequently affected than females owing to the heavier exposure of males to infested water (349). Almost all people with hepatic schistosomiasis also have intestinal lesions, but intestinal symptoms may not be prominent.

Patients may be asymptomatic until the disease is well advanced or haematemesis occurs. They may complain of a left hypochondrial mass, causing discomfort, a dragging sensation, and abdominal fullness (303, 304). In the early stages, the liver is enlarged, smooth, firm and without tenderness on palpation. Enlargement of the left lobe is usually predominant. As the disease progresses, the liver becomes larger, hard and nodular. With further evolution of the disease, the size of the liver may decrease. However, a small shrunken liver as observed in postnecrotic or end-stage alcoholic cirrhosis is rarely seen (123).

Splenomegaly is caused by passive venous congestion in the portal circulation and reticuloendothelial hyperplasia due to antigenic stimulation (123, 145). Egg granulomas may occasionally be found, but the spleen is not the site for extensive egg deposition (123). In most cases liver and spleen enlargement evolve in parallel (167). The spleen may sometimes become greatly enlarged extending down across the umbilicus level, or fill most of the abdomen (112). It is usually firm and smooth on palpation. The splenic notch may be palpable when it is very large (112). S. mansoni infection has been reported to be the most common cause of gross splenomegaly in Zimbabwe (395).

3.3.2.2 Other symptoms and signs

Additional symptoms and signs seen in hepatic disease are haematemesis, melaena, ascites, pallor, low-grade fever, ankle oedema, collateral periumbilical varices (112, 303, 304, 309). Symptoms suggesting severe hepatic insufficiency, such as jaundice, spider angiomas, palmar erythema, gynaecomastia, and altered hair distribution are rarely reported. Hepatic encephalopathy is unusual in hepatic schistosomiasis (112, 145, 246, 303). Death from hepatic failure in S. mansoni infection is rare (123), with the exception of those cases complicated with hepatitis B infection which leads to decompensated hepatosplenic disease (15, 123, 145, 385).

Hepatosplenomegaly in childhood has been associated with retardation of growth and infantilism (79, 399) and retarded bone age (79); in adults, amenorrhoea, earlier menopause, infertility and loss of libido are not unusual (145, 362). Endocrine changes

are attributed to hypopituitarism (145, 166, 362). Sucupira & Pupo (353) have shown that serum levels of growth, thyroid and luteinizing hormones are normal and have concluded that delayed puberty and short stature may be related to malnutrition. In hepatic disease, humoral hypersensitivity usually occurs, associated with a depression of cellular immunity (102).

3.3.2.3 Ascites

The main causes of ascites in the late stage of hepatic schistosomiasis are portal hypertension and hypoalbuminaemia. However, when synthesis of albumin in the liver is normal, the presence of portal hypertension alone is probably not sufficient to cause ascites (123). Intestinal lymphangiectasis and protein-losing enteropathy were seen in some patients with ascites (145). Ascites has been observed to occur or to increase shortly after an episode of bleeding (145). The frequency of ascites among S. mansoni-infected individuals in rural communities is very low (196). However, in hospital series, patients with ascites account for a considerable proportion among those with hepatic disease due to schistosomiasis; the figures of 15%, 33%, 40% and 45% of ascites were reported by Prata (303), De Cock (112), De Cock et al. (113) and Abdurrahman et al. (11) respectively. The prevalence of ascites associated with schistosomiasis apparently varies in different geographical areas. In Egypt, it is common and schistosomiasis is the most common of all causes of ascites (338); but in Brazil, it usually appears after upper gastrointestinal bleeding and responds well to treatment (303).

3.3.2.4 Oesophagogastric haemorrhage

Upper gastrointestinal bleeding from varices is the most frequent consequence of schistosomal hepatic disease (304, 399). Oesophageal varices demonstrated by barium meal and oesophagoscopy are found in 80% of persons with hepatic disease due to schistosomiasis. The varices are mainly at the lower third of the oesophagus and sometimes at the fundus of the stomach (303). Among 77 persons with high intensity of S. mansoni infection in Qalyub, Egypt, 6 (8%) had a history of haematemesis (302). In a hospital in Cairo 4.8% of out- or in-patients with S. mansoni infections were reported to be suffering from haematemesis and melaena (144). In a hospital series in Nairobi 50% of patients with hepatic schistosomiasis gave a previous history of haematemesis or melaena at least once (112, 113); the age of patients in this series ranged from 13 to 40 years with an average of 25 years. Portal hypertension is the most important risk factor for oesophagogastric haemorrhage and this risk is generally proportional to the portal vein pressure (304). Haemorrhage is unlikely in individuals whose portal vein pressure is less than 10 mm Hg above inferior vena cava pressure (112). The spleen is usually markedly enlarged in patients with upper gastrointestinal bleeding (113).

Haematemesis may occur suddenly without warning or it may be preceded by asthenia or gastric discomfort (303). The blood loss is usually large so that the patients present with hypothermia, somnolence, thirst, sweating, pallor and shrinkage of the enlarged spleen. The following day, fever and coffee-ground faeces, or tarry stools, depending on extent of the haemorrhage, can be observed. Melaena is rare without haematemesis. Oedema and ascites may appear a few days after heavy blood loss (303, 304). The initial bleeding may be fatal, but in most cases multiple recurrent episodes are characteristic (123).

The sequelae of oesophagogastric bleeding depend on the amount of haemorrhage, liver function status and general condition, and prompt treatment. The usual cause of death is exsanguination (246, 275), but in general, the bleeding is not fatal (381). Even if the haematemesis is severe, patients whose liver function is compensated have a low mortality rate and do not develop hepatic coma (112, 384). They have either normal or slightly raised blood ammonia levels after bleeding (381, 384, 387). However, severe haemorrhage with shock may bring about a sudden drop in the oxygen supply to the hepatic cells which may result in fairly extensive liver necrosis. Recently, repeated episodes of severe haemorrhage have been suggested to cause post-necrotic hepatic cirrhosis superimposed on the portal fibrosis (167). However, no autopsy studies have confirmed this.

3.3.3 Laboratory findings

The only abnormal laboratory findings in chronic infections may be peripheral eosinophilia and a mild increase of serum globulin and IgG. In hepatosplenic schistosomiasis, the classic findings of hypersplenism are also associated with a higher serum globulin and IgG, and a lower serum albumin level. Endocrine function may be abnormal in advanced cases.

3.3.3.1 Haematology

(1) Eosinophilia: Peripheral eosinophil counts have been reported for 292 Sudanese with chronic S. mansoni infections seen at the endemic disease clinic in the Khartoum Civil Hospital excluding those with other concomitant parasitic infections (and without a control group) (325). Peripheral eosinophilia was reported in 57% of these patients (166 of 292) and 22% of them (64 of 292) had an eosinophil count of more than 1000/mm^3; 43% (126 of 292) of these patients had a normal eosinophil count (less than 400/mm^3). In South Africa, eosinophilia was seen in 81% of those with only intestinal disease and 71% of those with hepatic disease (243). Patients with eosinophilia excreted significantly more eggs in the stool than those without (325, 326, 369) and high eosinophilia occurred in cases with heavy S. mansoni infection (32, 326). However, another report by Pope et al. (302) has described no consistent relationship between degree of eosinophilia and intensity, or clinical type, of S. mansoni infection. Arafa et al. (32) reported that in S. mansoni infection, eosinophilia was proportionally related to hepatic, but not splenic, enlargement. Eosinophilia is usually mild, and sometimes moderate, in chronic schistosomiasis in comparison with the acute disease (304, 326). However, eosinophilia as high as 71% has been recorded (325). The total leukocyte counts of most infected persons are within normal limits. Leukopenia probably due to hypersplenism may be seen in persons with gross splenomegaly and mainly the neutrophils are affected (304). Leukocytosis, if present, is generally moderate and consists predominantly of lymphocytosis (302).

(2) Anaemia: In a community-based study, anaemia was uncommon and only seen in 12% of infected persons, all with high S. mansoni egg excretion (302). However, in hospital series, anaemia has been reported more frequently. It was more often in association with hepatic (92%) than with intestinal (26%) disease (243). Lower haemoglobin levels in males with hepatic schistosomiasis were significantly related to egg count (326). Anaemia is usually microcytic and hypo- or normo-chromic (145, 304). The life span of the red blood cells may be diminished and reticulocytosis may be seen (303).

(3) Hypersplenism: Hypersplenism in S. mansoni infection is uncommon (145). However, in a few cases of advanced hepatic disease, definite hypersplenism is present with granulocytopenia, anaemia and thrombocytopenia. The bone marrow is hyperplastic, and the production of red cells and leukocyte precursors is always increased. However, the maturation of the granulocyte series is checked after developing into band cells. Thrombocytogenetic activity is diminished (303). The haematological abnormality usually responds to splenectomy, especially the peripheral cytopenias (145, 303).

3.3.3.2 Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) in chronic schistosomiasis is increased, although not as strikingly as in the acute phase. A positive correlation between ESR and stool egg count has been reported (326). The mean ESRs were 15, 20 and 39 mm at the end of an hour in 3 different infection intensity groups, namely, 1-100, 101-400 and over 400 epg of stool. The ESR was also significantly elevated in patients with hepatic, as compared with the intestinal, form of the disease.

3.3.3.3 Liver function

S. mansoni infection causes periportal fibrosis and porto-systemic collateral circulation whereas liver parenchymal function is preserved (384). Liver function

remains relatively normal if no complications, such as bleeding from oesophageal varices, malnutrition and hepatitis, are superimposed (385).

(1) Protein metabolism: Total serum protein is usually within the normal range (249, 323). Hypoalbuminaemia, which is more commonly seen in hepatic disease, severe colonic polyposis or after haematemesis, is compensated by hyperglobulinaemia (349). Most persons with intestinal disease have a normal serum albumin level but in hepatic disease the average albumin level is considerably lower (136, 303). This disease is attributed to synthesis reduction, plasma volume increase or intestinal loss (303). Although the serum globulin level in both intestinal and hepatic disease may be significantly elevated, it is much higher in the latter (243, 326). Alpha-1 and gamma globulin levels are usually increased (323). A marked elevation of the beta globulin fraction has also been reported in hepatic disease due to schistosomiasis (322). Indices of thymol turbidity and zinc sulfate turbidity tests are elevated in hepatic schistosomiasis because of the high globulin levels (151).

(2) Serum enzyme levels: Changes in serum enzyme activities have been reported. In a population-based study, Pope et al. (302) found that, although elevation of hepatic enzymes (AKP, GOT, GPT) was not uncommon, the extent of the rise in enzyme activities was quite small. Serum GOT was within normal range in schoolchildren with S. mansoni infection, but serum AKP was slightly elevated (243). However, in hospital series, Mansour et al. (249) reported that GOT and AKP were commonly elevated in both groups with intestinal and hepatic disease, whereas serum monoamine oxidase (MAO) and gamma-glutamyl transferase (GGT) were elevated mainly in those with hepatic schistosomiasis. Glutamic dehydrogenase and alanine aminotransferase levels were not significantly different from normal controls in both groups.

(3) Others: Serum bilirubin levels are generally normal except in patients with decompensated hepatic schistosomiasis (326). Higher levels have been reported in hepatic (10 ± 21 µmol/l) than in intestinal disease (4 ± 17 µmol/l) (243). The urinary urobilinogen level may be altered in hepatic disease (303). Increase in retention of sulfobromophthalin may be occasionally observed in hepatic schistosomiasis (145). Normal serum cholesterol levels were reported in 92 persons infected with S. mansoni in a community (without controls) (302). Prothrombin indices were lower in hepatic (86%) than in intestinal disease (94%) (243). The mean value of serum histamine was significantly higher in patients with ascites and with oesophageal varices than in those without (135).

The correlation between abnormal laboratory findings and the clinical form of the disease was more significant than with stool egg counts (326). This same study suggested that haematological and biochemical changes are influenced not only by the intensity of S. mansoni infection, but also by other factors such as splenomegaly, hypersplenism, portal hypertension and its sequelae, and upper gastrointestinal bleeding.

3.3.3.4 Gastrointestinal function

Both gastric-acid secretion and volume were significantly lower in 19 patients with hepatic schistosomiasis than in normal controls (137). After intravenous infusion of histamine, the maximum acid output was significantly lower than in the control group (70, 137). In another study of 50 persons with hepatic schistosomiasis, 23 (46%) had low gastric-acid secretion (146). However, fasting levels of plasma gastrin in hepatic disease were not lower than in control subjects. The diminished gastric secretion remains unexplained (70).

The exocrine function of the pancreas was assessed in 36 patients with hepatic schistosomiasis (158). The study group had a remarkably lower bicarbonate concentration than the control group. The authors concluded that exocrine pancreatic function as indicated by bicarbonate secretion is impaired in hepatic schistosomiasis.

Small intestine function was observed in 50 Egyptian patients with hepatic schistosomiasis (349). The low D-xylose excretion in a 5-h urine specimen and an increased amount of fat in 24-h stool suggest small-bowel malabsorption. Intestinal fat absorption in S. mansoni infection was assessed in 21 Brazilian patients by faecal measurement of triolein and oleic acid excretion (306). Two patients had normal faecal excretion of oleic acid and elevated faecal excretion of triolein; 10 patients had elevated faecal excretion of both oleic acid and triolein. Only 2 of 17 had normal small-bowel X-radiographs. The 2 patients with the most rapid intestinal transit times and abnormal small-bowel X-ray patterns had the highest oleic acid faecal excretion. The authors suggested the possibility of selective malabsorption of certain nutrients in schistosomiasis due to S. mansoni.

3.3.3.5 Endocrine function

(1) Thyroid: Thyroid function is normal in hepatic schistosomiasis (79, 253). A significant reduction in total serum thyroxine (T4) was found only in patients with non-schistosomal cirrhosis but not in those with hepatic schistosomiasis (253). Serum T4, serum tri-iodothyronine (T3) uptake and free thyroxine index in 17 men with hepatic schistosomiasis did not differ significantly from controls. There was no correlation between these values and serum protein levels or other liver function tests (151).

(2) Parathyroid: No significant change in the levels of both total and ionized calcium in persons with S. mansoni infection was seen by estimating these levels before and after intravenous infusion of calcium gluconate (323). Seventy-four schistosomiasis patients were divided into 3 groups: those without hepato- or splenomegaly, those with hepatic disease without ascites, and those with hepatic disease with ascites. In the last group the level of serum calcium was significantly lower than and the level of serum phosphate significantly higher than those in the 2 former groups with schistosomiasis as well as in a control group without schistosome infection. The authors believed that hypocalcaemia and hyperphosphataemia in the group with ascites is likely to be due to hypoparathyroidism (187).

(3) Pancreas: Data on involvement of the pancreas in S. mansoni infection are inconsistent (323). In a study among 50 Egyptian patients with ascites the mean value of fasting blood glucose was higher than that of controls, but the difference was not statistically significant. The mean level of blood glucose 2 h after glucose intake was significantly higher than that of controls, and 14 patients had a rise less than 20 g/dl at 30, 60, 90 and 120 min after glucose intake (349). These abnormalities were suggested to be due to alteration of both liver and pancreatic function. A significantly higher value of immunoreactive insulin and immunoreactive proinsulin in hepatic schistosomiasis than in controls was reported from Egypt (323). However, another report from the Sudan showed that although fasting blood glucose levels were low, or in the lower limits of the normal range, blood insulin levels were not high in 8 hepatic schistosomiasis patients, and a slow return of blood glucose to the fasting level after a glucose load was recorded in most of the patients (354). In another series in Egypt, glucose tolerance was impaired in 50% of 44 patients with hepatic schistosomiasis whereas hyperinsulinaemia and increased free fatty acid were present in almost all these patients (166).

(4) Adrenal gland: The information on the interaction between S. mansoni infection and the adrenal glands is limited. No recent data on histopathological examination in human infection have been published. Urinary 17-ketosteroid levels were low and a decrease in urinary corticoids and plasma cortisol in patients with schistosomiasis was noted; a primary defect of the adrenal cortex was suggested (323).

(5) Gonads: Signs of secondary feminization such as gynaecomastia, testicular atrophy, palmar erythema and spider angiomas may be, although rarely, seen in hepatic schistosomiasis. The serum levels of oestrone, oestradiol and oestriol in 30 males with the hepatic disease were determined by Rizk et al. (314). Serum oestrone and oestriol levels were significantly higher than those of normal controls whereas the levels of serum oestradiol were normal or slightly decreased. The increase of serum oestrone and

oestriol was suspected to be due to an increase of the peripheral conversion of adrenal and testicular androgens whereas the decrease of oestradiol may be attributed to an altered rate of conversion of testosterone to oestrone via oestradiol. In the series studied by Cavaliere et al. (79) including 5 males and 6 females between 14 and 20 years of age with hepatic schistosomiasis and delayed growth, serum testosterone or oestradiol levels were abnormally low. However, serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) of the anterior pituitary gland were normal but the serum level of somatomedin-C was low. The authors concluded that malnutrition, hepatic schistosomiasis, in association with decrease of serum sex steroids and somatomedin-C concentration were responsible for growth failure and delay of puberty in the patients. However, the role of the pituitary gland in S. mansoni-induced growth delay has not yet been fully studied. El-Ridi et al. (143) reported recently that serum testosterone levels in 14 adult male patients with S. mansoni and/or S. haematobium infections (4.62 ± 0.46 ng) were lower than in 11 normal control subjects (6.38 ± 0.58 ng) although statistically not significant ($P>0.05$). However, in 15 patients with schistosomal hepatic disease, the serum testosterone level (2.6 ± 0.29 ng) was found to be significantly lower than in those without hepatic disease and in healthy controls ($P<0.01$).

3.3.3.6 Electrolytes and trace elements

Hathout et al. (187) reported that significant hypocalcaemia and hyperphosphataemia were found only in hepatic schistosomiasis with ascites. Hypomagnesaemia was found both in ascitic and non-ascitic patients, although it was more marked in the latter group. The authors suggested that this change was due to high aldosterone secretion and hypoparathyroidism.

Various changes in the levels of serum trace elements have been described in S. mansoni infection. In a review of Egyptian experience, low plasma zinc and serum magnesium and an increase in plasma copper levels in infected persons were recorded (323); the degree of the increase in plasma copper levels correlated with severity of the disease. In another report on patients with hepatic schistosomiasis, levels of serum zinc were significantly lower, serum copper was significantly higher, whereas levels of magnesium were similar, compared with healthy controls (4). In advanced schistosomiasis with encephalopathy or hepatic coma, serum magnesium and zinc levels were significantly lower, whereas serum copper levels, contrary to findings in compensated hepatic disease, were lower than in controls. The authors suggested that in compensated hepatic disease the capacity of the liver to remove copper from serum was impaired, whereas in liver failure the liver cells failed to synthesize ceruloplasmin, the main copper-carrier protein.

3.3.3.7 Immunoglobulins

At post-mortem in Egypt, serum immunoglobulin and complement C3 and C4 levels in hepatic schistosomiasis were reported by Sherif et al. (336). The mean concentrations of IgG, IgM and IgA were all increased significantly compared with normal controls. The highest IgG level was 6120 mg/dl. The mean levels of C3 and C4 were significantly lowered. In 20 Egyptian patients with hepatic schistosomiasis with giant splenomegaly, serum levels of IgG and IgM were found to be significantly increased whereas those of IgA were almost unchanged. Two weeks after splenectomy, IgG decreased to 89% of the presplenectomy level. However, no statistically significant changes in IgM and IgA levels were detected after splenectomy (165). In another series of 67 adult Egyptian males with schistosomiasis, 34 with hepatosplenomegaly and 33 without, the levels of IgG, IgM and IgA were increased in both groups. However, IgG levels were the highest among those with hepatomegaly. Serum IgG levels were significantly higher in patients both with (2620 mg/dl) and without (2160 mg/dl) hepatosplenomegaly compared with healthy controls (322). In 23 patients from Zambia with S. mansoni infection and giant splenomegaly, the levels of IgG were unusually high (3790 ± 2200 mg/dl) and the levels of IgM were high as well (370 ± 300 mg/dl) (239). Camus et al. (78) reported that IgG levels increased in parallel with intensity of infection in different forms of

schistosomiasis. However, in the series published by Salih et al. (327), although no relationship was established between the levels of immunoglobulins and intensity of infection, patients with splenomegaly had higher IgG and IgM levels.

Serum IgE levels were significantly higher in 17 out of 22 patients with S. mansoni infection (7 with the intestinal form and 15 with the hepatointestinal form) in Brazil, the highest level being 12 650 IU/ml (IgE upper normal limit = 700 IU/ml) (255).

In 20 Egyptian patients suffering from schistosomal colitis, a significant increase in the levels of IgG, IgM and IgE was recorded whereas those of IgA and IgD showed no statistically significant change (319).

Serum levels of specific IgG, IgM and IgE were determined by Lunde & Ottesen (240) using an enzyme-linked immunosorbent assay (ELISA) with SEA from S. mansoni in individuals with acute or early infections and chronic infections. Titres of anti-SEA IgG were similar in both groups. Specific anti-SEA IgM was found in sera of all persons with acute or early infections, but only in 2 of 10 persons with chronic infections. Anti-SEA IgE was found in 11 of the 13 with acute or early infections; sera from all but one of the chronically infected persons were negative for anti-SEA IgE antibody. On the other hand, Feldmeier et al. (161) detected anti-adult worm IgE by ELISA in 84% of chronic cases infected with S. mansoni.

3.3.4 Cor pulmonale and post-treatment pneumonia

No specific symptoms have been correlated with the presence of S. mansoni eggs in the lung until pulmonary hypertension and cor pulmonale are present (12, 22, 304). The diagnosis may only be made incidentally (194).

Guimaraes (180) reported haemodynamic data and observations on the blood gases and respiratory function in 141 cases with hepatosplenic schistosomiasis from 2 endemic areas in Brazil. Pulmonary hypertension was documented in 13.0% (19 of 141) and cor pulmonale in 2.1% (3 of 141). In 17 (89.4%) of 19 patients with pulmonary hypertension, the mean pulmonary arterial pressure was between 20 and 40 mm Hg, indicating benign pulmonary hypertension. In a series of 37 schistosomiasis patients from Côte d'Ivoire only 8 had evidence of pulmonary arterial hypertension (>30 mm Hg) of whom 6 had only S. mansoni infection and 2 had only S. haematobium infection (58).

The clinical presentation of cor pulmonale in S. mansoni infection resembles that due to other causes of pulmonary hypertension (304). Progressive dyspnoea on exertion, weakness, giddiness and palpitations are the main complaints. Mental clouding followed by loss of consciousness is occasionally seen (7, 304). Cyanosis is rare and, if it is encountered, pulmonary arteriovenous or portopulmonary shunts may be present (7, 181, 399). The patients may ultimately progress to decompensation with congestive heart failure. Sudden death with cardiovascular collapse has been reported (367).

In advanced cases of cor pulmonale due to S. mansoni infection, aneurysmal dilatation of the pulmonary artery and its main branches and right ventricular hypertrophy are shown on roentgenography (7, 12, 160). Fine mottling in the lung field can occasionally be seen (12). Electrocardiograms usually show right ventricular hypertrophy and strain and right axis deviation (7, 293, 304).

Post-treatment pneumonia in S. mansoni infection after treatment with oxamniquine has been reported mainly among children aged 4-12 years (110, 290). On X-ray examination, pulmonary changes consisted of bronchopneumonitis, pneumonitis and pulmonary congestion. The alterations were transitory starting within 3 days after treatment and recovery occurred within 15 days (290). Pulmonary function tests suggested restrictive physiology. Bronchoalveolar lavage and transbronchial biopsies showed a prominence of eosinophils and eosinophilic pneumonia (110). In the same patients, after oxamniquine was interrupted, praziquantel treatment did not induce such reactions (110). Post-treatment pneumonia after oxamniquine was further confirmed by Pedroso et al. (291)

in a double-blind trial in 77 S. mansoni-infected children between 6 and 14 years of age. Bronchopneumonitis with typical radiological alterations was seen in 7 (17.5%) of 40 patients in the oxamniquine-treated group, but in none of 37 in the placebo group.

3.3.5 Cerebral involvement and myelopathy

In active schistosomiasis transverse myelopathy may occur. It may be successfully treated with antischistosomal drugs with or without corticosteroids or it may result in permanent paraplegia.

The clinical presentations of cerebral and spinal involvement due to S. mansoni infection have been reviewed (323). In more than half of the reported cases with cerebrospinal involvement diagnosis was confirmed by the demonstration of S. mansoni eggs in the brain or spinal cord (41, 63, 95, 108, 168, 170, 231, 237, 250, 289, 294, 295, 296, 301, 307, 317, 329). In the other half presumptive diagnosis was based on clinical and laboratory findings supported by the outcome of treatment with antischistosomal drugs (63, 93, 130, 198, 222, 231, 235, 237, 250, 264, 284, 289, 328, 329, 333, 340, 376).

In Benghazi, Libya, where both S. mansoni and S. haematobium are endemic, the incidence rate of central nervous system involvement due to schistosome infection in 1983-84 was 0.2 per 100 000 persons aged 15 years and above (308). Most of the histologically proven cases (i.e., S. mansoni eggs deposited in the brain) did not reveal cerebral symptoms (294, 295, 296, 333). Neurological symptoms occasionally appear during the Katayama syndrome. Along with fever and eosinophilia, the patients variously presented headache, vomiting, positive Kernig's sign, delirium, stupor, speech, visual and sensory disturbances, weakness of extremities, hemiplegia, incontinence, general epileptic seizures, etc. (235, 250, 333), as observed in encephalomeningitis. Usually, when the Katayama syndrome subsides, or after specific treatment, the central neurological symptoms disappear (235, 333). The major symptom in chronic schistosomiasis with cerebral involvement is epilepsy without other abnormal signs (170, 235). Rarely, tumoural lesions in the cerebral cortex (168) or cerebellum (41), cerebral (333) or subarachnoid haemorrhage (301) and choroiditis (284, 296) were reported.

Myelopathy due to S. mansoni infection both histologically proven (63, 95, 121, 231, 237, 250, 307, 317, 332) and presumed (63, 93, 130, 198, 231, 237, 264, 328, 332, 340, 376) has been reported more frequently in the literature than has brain involvement. In a retrospective study in an endemic area of Tanzania, of 100 consecutive cases of paraplegia, biopsy evidence of S. mansoni eggs in the spinal cord was found in 1 case, and in another 5 there was presumptive evidence of S. mansoni being responsible for the paraplegia (332). The clinical features of schistosomal myelopathy are not specific. Three forms of clinical presentation were suggested: myelitis either by patchy lesions in the spinal cord or focal granulomatous mass in the conus medullaris or medulla (93, 95, 108, 130, 198, 231, 264, 289, 317, 328, 339), radiculitis (63, 328), and anterior spinal artery occlusion (340). Characteristically, the illness starts with pain in the lumbar region and lower limbs, followed by weakness of the limbs leading to flaccid paralysis and sensory loss (93, 108, 130, 198, 231, 237, 307, 317, 340, 376); quadriplegia may be present if the cervical spine is involved (264). Tendon reflexes in the lower limbs usually cannot be elicited, and dysfunction of the bladder sphincter is more frequently seen than of the rectal sphincter. The paraplegia may develop over 24 h, but a few days to 1 week after onset of symptoms is usual (93, 130, 198, 237, 307, 333, 340). On rare occasions, it may evolve slowly over 1-2 months (108, 231, 317) to 2 (231) to several years (333).

In laboratory examinations, the cerebrospinal fluid (CSF) is clear, with a slight increase in lymphomononuclear cells (93, 168, 236, 307, 328, 376), an increase of eosinophils (235, 236) and elevated protein concentration (93, 108, 198, 307, 328, 376). CSF changes were not related to clinical aspects of the disease (328). Antibodies to eggs and the adult worms of S. mansoni in CSF have been detected (93, 236).

Funduscopic examination in 50 individuals with hepatosplenic schistosomiasis was reported by Oréfice et al. (284). In 5 persons, yellowish-white translucent nodules of

various sizes were seen in the choroid and were confirmed by fluorescein angioretinography in 3 cases, all without clinical complaints. As S. mansoni egg granulomas have been shown to occur in the choroid of a patient with the hepatosplenic disease (296), the authors believed that the choroidal nodules were S. mansoni egg granulomas.

Myelography has revealed various defects including (a) a partial or complete block of the spinal fluid (108, 333), (b) a filling defect in the spine (264, 317), (c) a mass in the conus medullaris and, (d) swelling of the lower cord and conus medullaris by metrizamide myelogram (237). Computerized tomography (CT) scan showed swelling of the conus medullaris, enlargement of the spinal cord (198, 237) and cerebral foci of contrast enhancement in areas with schistosomal granuloma (168, 170). All the above-mentioned examination techniques are of value, but definite diagnosis is established only by tissue biopsies at surgery or autopsy.

Khalil et al. (222) have examined 25 patients with hepatosplenic disease (without comparable controls) and showed cortical atrophy in 9 (36%). Three (12%) of these patients also had central atrophy of the brain by CT scans. S. mansoni infection is a significant factor for the presence and severity of cerebral atrophy which occurs at a much earlier age (9 $\pm$ 3.4 years) in persons with the infection than in those without (16 $\pm$ 4.2 years).

There have been several reports of successful recoveries after treatment of cerebral or spinal schistosomiasis with antischistosomal drugs (130, 237, 264, 317, 376). Some authors have used corticosteroids alone without apparent effect on the course of the disease (198, 231, 301).

3.4 Ultrasonography

Hepatic imaging is a newer method of investigation in the diagnosis and study of hepatic schistosomiasis. The sonographic features of schistosomal periportal fibrosis were first described by Abdel-Wahab et al. (8) and are pathognomonic (8, 145, 200). Ultrasound examination is inexpensive, safe, simple and noninvasive and may be a valid alternative to liver biopsy when the latter is impracticable (145).

In hepatic schistosomiasis the normal echogenicity of the portal vein and its ramifications is replaced by densely echogenic bands. The echogenic bands of the periportal fibrosis are seen as tubular shadows when the scanning is along the long axis, or round to oval when it is across the axis of the intrahepatic portal veins, having a characteristic and fairly constant central sonolucent area. They are present in every patient (8, 33, 156, 200). The bands measure 15-20 mm centrally and 10-12 mm peripherally (156). The hepatic sonographic features are characteristic of portal tract thickening from schistosomal fibrosis. Similar echogenic bands were not seen in alcoholic cirrhosis or hepatitis (8, 145). When patients with histologically proved schistosomal periportal fibrosis were examined by ultrasound, all showed the characteristic appearance. However, although it is generally believed that the sonographic features of schistosomiasis are characteristic, their absence cannot exclude the disease (200). In an area not endemic for schistosomiasis the sensitivity of ultrasound in detecting portal hypertension was reported as 79.7% and the specificity as 100% (67).

The liver and spleen size can be measured by ultrasonography. The patency of the portal, splenic and other veins can also be evaluated in almost all cases of hepatic schistosomiasis (8, 33). Numerous abnormalities associated with portal hypertension could be demonstrated, such as oesophago-gastric varices, recanalization of the umbilical vein and the presence of porto-systemic shunts (100, 119, 169, 213, 218). Comparison between portal- and splenic-vein diameters and portal pressure measured transplenically showed a close correlation (3, 145). Portal hypertension in hepatic schistosomiasis may be assessed quantitatively by the use of sonography and subjects with oesophageal varices were associated with larger diameters of portal and splenic veins (3). Portal-vein

thrombosis could also be demonstrated by ultrasonography in patients suspected of having this affection (218, 256). Ultrasonographic findings may give clues to help clinicians to distinguish presinusoidal causes of portal hypertension from obstruction at the sinusoidal or postsinusoidal level (218). Thickening of the wall of the gallbladder, which is not a rarity in hepatic schistosomiasis, can also be shown by sonography (80).

The enlarged spleen shows homogeneous echo-density throughout the parenchyma. No differential diagnosis could be made between splenomegaly in schistosomiasis and that caused by other diseases (33).

Sonography of pancreatic schistosomiasis in a young girl was reported by Bahakim et al. (39). She suffered from fever, abdominal pain, anaemia, hepatosplenomegaly and eosinophilia. Stool examinations for schistosome eggs were negative. Abdominal ultrasound revealed an oval mass, 5 x 7 x 5 cm in front of the portal veins suggesting an enlarged pancreas. The portal veins were judged to be thickened and echogenic. On exploratory laparotomy egg granulomas were found in the pancreas and schistosomiasis of the pancreas was diagnosed and treated.

3.5 Complications

3.5.1 Viral hepatitis

The relationship between hepatitis B virus (HBV) and S. mansoni infection is a subject of controversy.

Reports from Egypt (142, 145, 404), Kuwait (18), Malawi (265) and Sudan (107) have indicated that rates of HBV antigenaemia were significantly higher in S. mansoni-infected persons, especially in those with hepatosplenic schistosomiasis (241), than in the uninfected control groups (Table 5). A higher prevalence of HBsAg has also been found in patients with hepatosplenic schistosomiasis compared to those with hepatointestinal disease (241, 303). In Egypt, persons with S. mansoni infection showed a significantly higher frequency of HBsAg and anti-HBs than those with S. haematobium infection (142).

It is generally accepted that S. mansoni infection alone does not lead to cirrhosis or chronic active hepatitis. Interaction between HBV and S. mansoni infection was suggested to cause a more serious form of chronic liver disease (18, 53, 404). Histological examination of repeated liver biopsies by Bassily et al. (50) suggested that morbidity in S. mansoni-infected individuals with chronic HBV infection was more severe compared with HBV infection in other populations. Other reports with autopsy or liver biopsy studies have shown a significant increase of chronic hepatitis and hepatic decompensation (27, 30, 241) and even cirrhosis (132) in S. mansoni-infected subjects. Orcein stains with HBsAg deposits in liver cells in patients with S. mansoni infection were common (244).

Among the suggested reasons as to why S. mansoni-infected subjects are more vulnerable to HBV infection or have a higher HBV prevalence rate, the following have been cited: (a) impaired cell-mediated immunity which reduces host resistance (53, 55, 142, 145, 311, 313), (b) low socioeconomic condition which increases the risk of exposure (142), (c) repeated parenteral treatments in the past with intravenous or intramuscular antischistosomal drugs and, in a few hospital cases, frequent blood transfusions (53, 142, 404), and (d) diffuse fibrosis which has been cited as an optimal milieu for viral replication in hepatocytes (53, 404). However, the mechanisms underlying the persistence of HBV antigenaemia in schistosomal patients remain obscure and speculative (279).

On the other hand, the positive relationship between HBV and S. mansoni infection has been questioned by a few investigators. In a longitudinal field survey in an area with a 50% prevalence of S. mansoni involving 324 villagers, Hyams et al. (202) could not find a statistically significant association between S. mansoni and HBV infections. During a 30-month study period no difference was seen between the individuals who

acquired HBsAg or anti-HBs in S. mansoni-infected and noninfected groups. Other investigations reported similar conclusions (35, 132, 199, 229).

Whereas the relationship between HBV and S. mansoni infection is controversial, consensus has been reached on one point that is that HBV infection is always high in hepatic schistosomiasis due to S. mansoni, although most of the reported cases were hospital series (18, 27, 30, 35, 107, 241, 366). Repeated parenteral administration of drugs including antischistosomal drugs to these patients may contribute a part of the HBV infection (53, 107, 142, 404). No consensus has been reached on the mechanism of interaction between HBV infection and hepatic schistosomiasis: whereas some believe that HBV infection causes early-stage schistosomiasis (intestinal disease) to develop to the advanced stage (hepatic or even decompensated hepatic disease), others believe that hepatic schistosomiasis leads to a greater susceptibility to HBV infection (35, 50, 241, 404). However, when HBV infection and hepatic schistosomiasis are associated, the prognosis is poor. HBV infection modifies the pathology of the schistosomal liver and frequently causes chronic active hepatitis; moreover, liver function deteriorates and compensated hepatic disease tends to become decompensated (27, 50, 404). Hepatic failure is not infrequently seen in these cases.

Although most published studies have endorsed a positive correlation between S. mansoni and HBV infection, the study populations were mainly hospital patients or patients who sought treatment at clinics. Further observations with well-designed, community-based studies in different S. mansoni-endemic areas are necessary to clarify the relationship between these two infections.

3.5.2 Salmonella infection

The frequent association of Salmonella spp. with schistosome infection has long been recognized (7, 304, 399). The bacteria are found in the tegument or in the intestinal tract of S. mansoni adult worms (69, 257, 399, 403). The role of schistosomes as a source and vehicle of salmonella infection has been suggested, and sera from patients with hepatosplenic schistosomiasis due to S. mansoni infection were found to have reduced antibody activities against Salm. typhi and Salm. choleraesuis compared with healthy controls (7).

These concomitant infections are characterized by prolonged fever, significant hepatosplenomegaly (281, 316, 324), eosinophilia with or without leukocytosis (304, 316), and persistently positive blood cultures for Salmonella (304, 316, 324, 399). Effective treatment of schistosomiasis alone deprives the salmonellae of favourable foci for growth and may eliminate both infections (278, 304, 337, 399, 403). On the other hand, antibiotic treatment alone, either with chloramphenicol or ampicillin, cured Salmonella infections without relapses in patients with schistosomiasis according to Rocha et al. (316) in 11 cases and Salih et al. (324) in 21 cases.

3.5.3 Other bacterial infections

Other concomitant bacterial infections such as Escherichia coli should not be neglected. Teixeira et al. (359) reported 2 cases of prolonged E. coli bacteraemia associated with S. mansoni infection, 1 of which was cured by treatment with hycanthone alone. Farid et al. (154) reported 5 patients with E. coli bacteraemia associated with S. mansoni infection in whom febrile attacks lasted 2-12 months. Presumptive diagnosis of chronic salmonellosis had been made and failure to respond to chloramphenicol treatment was recorded before hospital admission. E. coli was cultured both from the urine and blood during a febrile attack in all 5 patients with hepatosplenomegaly and S. mansoni eggs in their stools. E. coli isolated from urine or blood was resistant to chloramphenicol. Clearance of bacteraemia was achieved by treatment with co-trimoxazole or amoxycillin. After the patients became afebrile, antischistosomal drugs were successfully given.

3.5.4 Hepatic encephalopathy

Coma is a rare complication of hepatic schistosomiasis (112, 246, 385). Hepatic schistosomiasis is characterized by haemodynamic alterations with normal liver architecture and hepatocellular function, and on this basis alone, one would not expect persons with S. mansoni infection to develop encephalopathy and other symptoms of hepatic failure (123). However, in endemic areas patients with hepatic schistosomiasis do have these findings. Several hypotheses have been advanced:

(1) Association with HBV infection. A high proportion of hospital patients in Brazil (majority) and Egypt (13 out of 28) with decompensated hepatic schistosomiasis showed histological evidence of coexisting chronic active hepatitic cirrhosis (123, 335) and a high percentage of hepatitis B surface antigenaemia was recorded. It has been suggested that an undefined immunological abnormality in hepatic schistosomiasis may predispose the patients to a greater risk of severity of concomitant HBV infection (123).

(2) Abnormal immune response of the liver cell to schistosomal antigens. It has been proposed that the appearance of chronic active hepatitis in S. mansoni infection might not be due to HBV infection but might be the consequence of delayed hypersensitivity to schistosome antigens or autoimmunity of the liver cells (167).

(3) Severe haemorrhage. Repeated or severe oesophago-gastric bleeding may cause sudden lowering of the oxygen supply to the liver parenchyma leading to postnecrotic cirrhosis (167).

(4) Malnutrition. Although malnutrition may provide benefit to the host by diminishing egg output and granuloma formation (14, 381), severe malnutrition itself may worsen the already existing hepatic injury and lead to liver failure (385).

(5) Portal systemic shunt. Warren (381, 384) showed that after porto-caval shunt, a high proportion of individuals with hepatic schistosomiasis but with compensated liver function developed chronic portal systemic encephalopathy after haematemesis, and their liver function tests including ammonia tolerance became abnormal.

3.5.5 Renal diseases

The frequent association of glomerular disease with S. mansoni infection, especially with hepatosplenic disease, has been well documented in the literature since the 1960s (371). In 100 consecutive patients with hepatosplenic schistosomiasis in Brazil, renal involvement was reported in 15% by Rocha et al. (315). Persistent proteinuria of varying degrees was noted in 15 of these patients including 6 persons with hypertension and 9 with nephrotic syndrome. The evolution of the glomerular disease is insidious and probably takes years to become clinically apparent. Patients are asymptomatic until the renal disease is well advanced and the diagnosis is confirmed by biopsy and laboratory examinations.

On the other hand, an epidemiological study in Brazil by Lehman et al. (233) on the prevalence of proteinuria in the community in an S. mansoni-endemic area showed only limited morbidity. No correlation between schistosomal hepatosplenomegaly and proteinuria was found, although proteinuria was related to S. mansoni infection. However, a later field study from Brazil by Bina et al. (61) showed that significant proteinuria was detected in 24.7% of 89 individuals with hepatosplenic schistosomiasis but in only 4.6% of 86 persons with mild or asymptomatic schistosomiasis. Whether intensity of S. mansoni infection has an effect on the occurrence of schistosomal glomerulopathy is still controversial (46, 61).

In patients with both hepatosplenic schistosomiasis and glomerular disease, proteinuria is the most common and, frequently, the only clinical manifestation (47). Before the nephrotic syndrome appears, there is no distinct clinical picture, and even once the disease is well established, clinical findings are not as consistent compared to

those for the nephrotic syndrome due to other glomerular diseases (29, 47, 127). Advanced renal failure has been reported (348) but is considered to be rare (24). The mortality rate of the nephrotic disease associated with S. mansoni infection has not been documented. In concomitant infection with Salmonella sp., 2 patterns of clinical and histological renal involvement have been described (47). In the first, there was no oedema or hypertension, minimal proteinuria and normal levels of serum proteins and immunoglobulins except for an elevated IgA concentration. Although glomerular filtration was normal, ability of tubular concentration was reduced. Clinically, the histology showed advanced interstitial infiltration and fibrosis with glomerular pathology. The second and more frequent pattern resembled classic acute glomerulitis.

The outcome of treatment of the nephrotic disease associated with hepatosplenic schistosomiasis due to S. mansoni with antischistosomal drugs, corticosteroids and immunodepressors has been disappointing (29, 48, 285). Even with clinical improvement, follow-up renal biopsies usually show no regression of the lesions (29, 48), although a few cases that responded well to treatment have been reported (127). On the other hand, antischistosomal drugs have no deleterious effect per se on renal function (29). Some authors suggest that when patients with hepatosplenic schistosomiasis present with the nephrotic syndrome, the renal lesion is usually too far advanced and is, therefore, irreversible. Hence, early detection of changes in renal function in S. mansoni-infected persons and prompt treatment are necessary (127).

Although our understanding of schistosomal nephropathy due to S. mansoni infection has improved, many questions remain to be answered. The prevalence, morbidity and mortality of nephrotic disease in endemic populations, the clinical course of the disease, the nature of the antigen or antigens involved in the disease, the immunological factors involved in pathogenesis, and effective treatment of the disease, require further investigation (29, 348).

3.5.6 Neoplasia and S. mansoni infection

The role of S. mansoni infection in the aetiology of cancer has been debated.

In the earlier literature, Andrade & Abreu (21) reported from Brazil that hepatosplenic schistosomiasis was associated with follicular lymphoma of the spleen in 8 out of 863 patients whose spleens had been surgically removed. Later, Paes & Marigo (288), also from Brazil, added 6 cases among 714 with splenomegaly due to S. mansoni. The authors considered that the association was not coincidental. However, elsewhere no such association has been reported.

Whether or not S. mansoni infection plays a role in the pathogenesis of hepatocellular carcinoma has been controversial (73, 82, 106, 129, 214, 262). The co-carcinogenicity of S. mansoni infection in mice was established experimentally (82, 164). Experimental studies have been completed with both S. mansoni (214) and S. japonicum (262) infection in mice treated with the carcinogen N-2-fluorenylacetamide (2-FAA). A significant increase in incidence of hepatocellular carcinoma was observed during a 40-week period in the group given schistosome infection plus 2-FAA compared with the group treated with 2-FAA alone. No hepatoma was discovered in schistosome-infected control groups. Schistosome infection may act as a promoter, and the liver cell proliferation in response to the egg deposition increases the susceptibility of liver cells to carcinogens (73). On the other hand, no geographical association of liver carcinoma and S. mansoni infection has been documented (129), and in autopsy series from Brazil, Puerto Rico, Egypt and Mozambique, hepatomas were almost equally distributed in uninfected and S. mansoni-infected patients (82).

Although patients with inflammatory bowel disease have an increased risk of developing colorectal cancer (128, 396), and chronic colitis, with or without polyposis, is common in S. mansoni infection, the association of S. mansoni infection with colon cancer seems to be coincidental in Egypt, elsewhere in Africa, and in the Western hemisphere (83).

3.5.7 Malnutrition and S. mansoni infection

The influence of S. mansoni infection on nutrition, including faecal nutrient loss, anaemia, growth, physical fitness, etc., was reviewed recently by Stephenson (350). The conclusions vary depending on the endemic areas, subjects, intensity of infection, sampling and study designs. The author emphasized the methodological difficulties of this type of study. A large sample size is needed to detect small differences in nutritional status. These investigations are important in estimating to what extent a community may benefit by the control of schistosomiasis.

Significantly decreased levels of serum vitamin A, carotenoids, carnitine and albumin have been reported in S. mansoni-infected hospital patients in Egypt, especially in persons with intestinal polyposis (260, 261). Nutritional supplements without treatment of S. mansoni infection resulted in significant improvement of the serum indices. Elevated serum and urine amino-acid levels were seen in hepatic schistosomiasis in Egypt as compared with healthy controls. These findings were attributed to impaired liver function (148). Since the sample sizes were relatively small and the subjects in the reports were selected, these studies do not validly support a causal relationship between S. mansoni infection and the reported nutritional deficiencies.

A few field studies assessing haemoglobin levels, physical fitness, working capacity in relation to S. mansoni infection, especially intensity of the infection, have been discussed (see section 3.1).

Although it is generally believed that malnutrition may promote the development of disease due to S. mansoni infection, animal experiments have shown the opposite. Malnutrition in experimental animals has a protective effect on the host associated with a decrease of both egg output and granuloma size (14, 381). Using the oogram method described by Pellegrino et al. (American journal of tropical medicine and hygiene, 2: 201, 1962), Akpom (13) has demonstrated that in experimentally infected mice, a depressive effect of malnutrition on reproductive capacity of the schistosome as evidenced by 3 parameters: viability, maturation, and stage of maturation of S. mansoni eggs. Since the viable schistosome egg is the main cause of pathology and since egg production can be inhibited by malnutrition of the host, "the net effect of malnutrition on schistosomiasis seems to be amelioration of the disease" in the experimental model (15).

3.5.8 Musculoskeletal involvement

An association between parasitic infections other than S. mansoni and reactive arthritis has been suggested by a few investigators (56, 66). Atkin et al. (36) have reported symmetrical inflammatory polyarthritis in a patient with active S. mansoni infection; symptoms disappeared after chemotherapy for schistosomiasis. After that, the authors carried out a detailed clinical investigation in 96 selected individuals with active S. mansoni infection and 72 to 75% had musculoskeletal complaints. Unexpectedly, inflammatory musculoskeletal disease was frequent: 16 had only an inflammatory peripheral polyarthritis but 47 presented with the combination of both arthritis and enthesitis, and nine suffered from enthesitis alone. The patients complained of joint pain and morning stiffness lasting for 0.5-2.0 h. The average age of schistosomiasis patients with arthritis was significantly higher, and the duration of schistosomal infection was significantly longer, than those without arthritis. The most affected joints were interphalanges, metacarpophalanges, wrists, knees, ankles and metatarsophalanges. Joints were tender and warm but not red. Synovial hypertrophy was noted in several patients and the viscosity of the synovial fluid was reduced with a high white cell count (7000-38 000/ml), predominantly polymorphonuclear leukocytes. Bacterial culture of the fluid was negative and no radiological abnormalities were found in the affected joints. The authors concluded that the inflammatory joint disease seems likely to be due directly or indirectly to active S. mansoni infection. However, the immediate and follow-up effects of treating the S. mansoni infection were not investigated. Recently, Greenfield et al. (174) reported a patient with S. mansoni infection and immune