



PROGRESS IN ASSESSMENT OF MORBIDITY DUE TO
SCHISTOSOMA JAPONICUM INFECTION: A REVIEW OF RECENT LITERATURE^a

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1. INTRODUCTION

Of all the schistosomes that infect man, Schistosoma japonicum is considered to cause the most serious disease. Infection with this parasite is endemic in China, the Philippines, Japan and Indonesia. Although schistosomiasis due to S. japonicum remains a public health problem, its significance as a cause of morbidity and mortality is decreasing. Moreover, the epidemiological and morbidity patterns of the infection are changing. During the past decade, research on pathogenesis, pathology and clinical presentation has confirmed the sequelae of the infection, but the relationship between some types of morbidity and S. japonicum infection is still the object of controversial opinions. This review has emphasized literature published mainly in the past decade which reflects a diversity rather than a consensus of opinion on the morbidity of S. japonicum infection. In contrast to the previous WHO/SCHISTO review on morbidity due to S. haematobium (WHO/SCHISTO/87.91) and the forthcoming one on S. mansoni (WHO/SCHISTO, in preparation), the present review includes a greater number of references to studies on experimental pathology since information on the human pathology of the disease is limited. Chinese literature that has not been previously reviewed elsewhere in English publications is also partly included. Furthermore, the limited literature on S. mekongi has been reviewed.^a

Interpretation of the clinical and pathological literature on schistosomiasis is, for the most part, limited owing to the design of the studies reported. There is moreover a generalized lack of appropriate control data. Current and future clinical investigators who may read this document should be aware of these limitations. For instance, schistosomiasis due to S. japonicum is one of many causes of liver disease or other types of morbidity in endemic areas, and therefore the rates of such diseases in S. japonicum cases must always be assessed in relation to their rates in a comparable control population. Furthermore, the classification of disease should not rest on clinical assessment alone but also on histological evidence and examination results by X-ray, ultrasound or computerized tomography (CT) as these may contribute to specificity of the diagnostic classification.

The present review is concerned with the literature list since 1976. However, there are some classic investigations in English that should be consulted as these are essential to the analysis and interpretation of the current literature. They are:

Kane, C.A. & Most, H. Schistosomiasis of the central nervous system. Experiences in World War II and review of literature. Archives of neurology and psychiatry, 59: 141-183 (1948); a general review of central nervous system involvement.

Most, H., Kane, C.A., Lavietes, P.H., Schroeder, E.F., Behn, A., Blum, L., Katzin, B. & Hayman, J.M. Schistosomiasis japonica in American military personnel: clinical studies of 600 cases during the first year after infection. American journal of tropical medicine, 30: 239-299 (1950); a descriptive paper on acute schistosomiasis with follow-up.

Sulit, Y.S.M., Domingo, E.O., Dalmacio-Cruz, A.E., de Peralta, D.S. & Imperial, E.S. Parasitic cirrhosis among Filipinos. Philippine Medical Association journal, 40 (Suppl.): 1021-1028 (1964); this is the only adequate description in English of pipestem fibrosis in S. japonicum infection .

^a Bruce, J.I. & Sornmani, S., ed. The Mekong schistosome. White Lake, Michigan, USA, pp. 1-282, 1980.

Ostrea, E.M. & Marcelo, F.B. Relationship between pulmonary schistosomiasis japonica and cor pulmonale. Acta Medica Philippina, 2: 68-77 (1965); this is an important publication on cor pulmonale in S. japonicum infection.

von Lichtenberg, F., Sadun, E.H., Cheever, A.W., Erickson, D.G., Johnson, A.J. & Boyce, H.W. Experimental infection with Schistosoma japonicum in chimpanzees. American journal of tropical medicine and hygiene, 20: 850-893 (1971); Sadun, E.H., von Lichtenberg, F., Erickson, D.G., Cheever, A.W., Bueding, E.E. & Anderson, J.S. Effects of chemotherapy on the evolution of schistosomiasis japonica in chimpanzees. American journal of tropical medicine and hygiene, 23: 639-661 (1974); these classic studies in the chimpanzee showed a morphological pipestem fibrosis essentially identical to that found in man.

2. CURRENT EPIDEMIOLOGICAL SITUATION OF SCHISTOSOMA JAPONICUM INFECTION IN ASIA

S. japonicum infection is confined to the Far East: China, the Philippines, Japan and Indonesia. In addition, a zoophilic strain of S. japonicum that infects only lower animals and has not been shown to infect man occurs in Taiwan (45). In the Mekong delta in the Lao People's Democratic Republic and Kampuchea, S. mekongi, which is morphologically similar to S. japonicum, was found in man in the 1960s (79) and was recognized as a new species in 1978 (181). In Thailand and Malaysia, a number of persons infected with Schistosoma have been reported and S. japonicum-like eggs have been observed in faeces, tissue biopsies or at autopsy (79).

China represents the largest endemic area of S. japonicum infection. The disease is endemic mainly in areas along the Yangtze river and to the south of the river basin. These areas include 348 counties in 10 provinces, the Shanghai Municipality and the Guangxi Autonomous Region (121). In the 1950s, 10 million persons were estimated to be infected (121) and the snail habitats covered a total area of 14 billion square metres (155). In 1981, after extensive control efforts had been carried out for over 25 years, the respective figures for number of infected persons and snail habitat area had dropped to 705 000 persons and 2.9 billion square metres (155). By the end of 1983, of the 348 former endemic counties, 56 were in the surveillance phase, 191 in the consolidation phase and 101 in the attack phase (118). The prevalence and intensity of the infection have significantly decreased and transmission is at a low level in most of the endemic areas of China. However, in some swamp and lake regions and a few mountainous areas, transmission remains uncontrolled and acute cases are not infrequent (118,230).

In the Philippines, schistosomiasis is found in six of the 13 main islands, i.e. Luzon, Mindoro, Samar, Leyte, Mindanao and Bohol, covering 25 provinces in the southern and eastern part of the country with some 700 000 infected individuals and more than four million persons exposed to the risk of the infection (79). The National Schistosomiasis Control Commission was created in 1965 and with the assistance of many international agencies and private foundations, it has been carrying out schistosomiasis studies and control programmes (63,135). Although transmission persists, incidence and prevalence as well as intensity of the infection have decreased in some areas as a result of effective control measures (162).

In Japan, there were formerly five endemic areas: four in Honshu and one in Kyushu. As a result of an intensive control programme, only a few small snail colonies now exist and no new human infections have been reported since 1978 (179). It was estimated that in 1986 about 100 000 patients with chronic schistosomiasis remained in Japan (133).

In Indonesia, schistosomiasis is localized in two limited foci in Lake Lindu valley and Napu valley in Central Sulawesi. It was estimated that 6500 to 7000 persons were at risk of infection and about 2500 to 4000 persons had an active infection (79). A pilot control project for schistosomiasis has been under way since 1975 in the Lindu valley and

prevalence rates among the human population as well as among rats and snails have decreased (79,153,174).

Zoonotic S. japonicum infections have a great impact on the epidemiology and control. In endemic areas in China, 31 mammalian species have been found naturally infected with S. japonicum and in laboratory experiments, mice, dogs, goats, rabbits, cattle, monkeys, guinea pigs, sheep, two species of rats, pigs, horses and buffalo, in descending order of schistosome development rates, have been infected with the parasite (121). Recently, birds have been shown to be a good experimental model for S. japonicum (110). Among the above-mentioned animals, cattle are the most important source of contamination of the environment (13,121). In the Philippines, animal reservoirs were considered responsible for about 25% of the total potential environmental contamination (128). The animal reservoir hosts included dogs, pigs, carabao, cattle, goats and rats (63). In Japan, several species of rodents (89,103), cows (88,179) and dogs (88) were the reservoir hosts before transmission was brought under control. In Sulawesi, Indonesia, at least 13 species of wild and domestic animals, including rats, dogs, cattle, buffalo, civet cats, shrews, wild pigs and deer, have been found to be infected with S. japonicum (19,79,103).

3. PATHOGENESIS

There is general agreement that the eggs deposited by S. japonicum adult female worms are the chief cause of tissue damage, consisting of an inflammatory granulomatous reaction and a pseudotubercle formation followed by fibrosis and the sequelae of the disease syndromes. However, the mechanisms of the pathogenic role of the egg remain controversial. The presence of dead worms, metabolic products or toxins produced by the worms or concurrent malnutrition have not been reported to contribute to the pathological process (194). The pathogenesis of S. japonicum egg granulomas has been studied extensively in experimental animals, though not as thoroughly as that of S. mansoni which has been shown to be largely a manifestation of delayed hypersensitivity or T-lymphocyte mediated immunity (182,189,194,198). In the experimental mouse model, the presence of many plasma cells in areas of periportal inflammation suggests abundant antibody production, while necrotic abscess-like lesions in the granulomas made up of polymorphonuclear cells and Hoepli precipitates suggest antigen-antibody complex-mediated reactions. S. japonicum soluble egg antigens (SEA) elicit immediate footpad swelling in sensitized mice rather than delayed reactions. When animals were previously sensitized with eggs injected subcutaneously, granulomas formed around eggs injected into the lung; no granulomas were observed if sensitization occurred by intraperitoneal injection or by natural infection. Thus, it has been suggested that S. japonicum egg granulomas might be B-lymphocyte or antibody mediated, rather than T-lymphocyte mediated (182,190,198).

This hypothesis, however, has been challenged by the results of recent experiments. Olds & Mahmoud (144) showed that the formation of pulmonary granulomas in mice was dependent upon the integrity of T-lymphocyte mediated immune response although passive transfer studies with lymph-node cells or spleen cells gave negative results. Pulmonary granulomas were composed of lymphocytes, macrophages and eosinophils. Depletion of either eosinophils or lymphocytes by relevant antisera reduced granuloma size significantly and reduced the numbers of corresponding cells. Garb et al. (67) found that not only an immediate footpad response but also a delayed footpad response was produced by an injection of SEA into footpads of infected mice if the mice were heavily infected (with 25 cercariae instead of five) and a high concentration (50 μ g instead of 5 μ g) of SEA was used. Cheever et al. (24,25) recently found that T-lymphocyte-regulated eosinophils, lymphocytes and macrophages, which were abundant in the heterozygous littermate control, were scant in the liver granulomas of infected nude mice, whereas in these same infected mice neutrophils were abundant and the granulomas were focally more destructive in the controls. In B-lymphocyte depleted mice, in which there are no circulatory antibodies to eggs and no antibodies in the granulomas themselves, however,

normal circumoval granulomas were found in the liver and the subsequent hepatic fibrosis was similar to that in mice with B-lymphocyte depletion. These results indicate that the formation of S. japonicum egg granulomas is regulated by T-lymphocytes which determine the size and the character of the egg granulomas as in S. mansoni infections. Furthermore antibody or immune complex is not necessary in the formation of granulomas or hepatic fibrosis (22,24). On the other hand, minimal egg granuloma formation in S. japonicum infection does not require antibody or T-lymphocytes (22).

In the mouse models, the size of egg granulomas reaches a maximum and then decreases considerably 6-10 weeks after infection (120,145,197,199). The phenomenon may be due to a decline in granulomatous hypersensitivity (199). Immune modulation of hepatic and pulmonary granulomas can be transferred by serum, but not by spleen and lymph node cells, from chronically infected animals. High portal pressure caused by the infection is also lowered after serum transfer. The serum modulatory factor identified as an immunoglobulin is localized in the IgG₁ fraction (145). Garcia et al. (68) found that sera from humans with chronic S. japonicum infection can inhibit embryonation of the eggs in mice and this may be a cause of modulation (69).

In summarizing the recent literature Cheever (22) concluded: "T-cells are of major importance for the formation of large granulomas around the eggs of both S. mansoni and S. japonicum, but modulation of the size of granulomas is primarily cell mediated for S. mansoni and perhaps mainly antibody mediated for S. japonicum." On the other hand, in S. japonicum infected mice, Olds & Stavitsky (146) demonstrated that cellular and humoral regulations were both involved in the modulation of egg granulomas. Cellular mechanisms were maximal already at 10 weeks while serum-mediated modulation predominated during the chronic stage of the infection at 20 and 30 weeks. Moreover, a few experiments have shown that granulomatous inflammation and its sequela, portal hypertension, are inhibited by T-lymphocytes from 10 week-infected mice and by sera from 20 to 30 week-infected mice (146,171).

Cell composition of S. japonicum granulomas in mice has been described by several investigators (25,144,199); they are composed mainly of mononuclear cells, macrophages and eosinophils. The relative percentages of different cells change with the period of the infection and the immunopathological status of the host (25,144).

Although progress had been made in the understanding of pathogenesis of S. japonicum, divergences of opinion between different investigators remain and must await further clarification to be resolved. Furthermore, there are serious gaps in our knowledge concerning the relationship between immunopathogenesis of S. japonicum infection in animal models and pathogenesis of acute and chronic human disease (182). Studies on human pathology are infrequent and a better understanding of the pathogenesis of S. japonicum infection in man would promote morbidity control.

4. PATHOLOGY

Present knowledge of the histological and anatomical pathology of human schistosomiasis due to S. japonicum is limited as only a few autopsy studies have been made. Currently autopsies are rarely performed in S. japonicum endemic countries and schistosomiasis is progressively decreasing as a cause of death.

4.1 Worm and egg distribution in host body

Adult worms are found almost exclusively in the portal venous system in different hosts including man (22). In experimentally infected rabbits, the worms are sometimes found in the lungs (30) and occasionally in other ectopic sites, such as testis (30) and kidney (222). In mice infected with a single worm pair, the worms migrated daily within the portal system; they returned to a few localized sites in the intestine to lay eggs thereby producing large focal lesions. In the intestine, 47% to 89% of eggs were

concentrated in focal lesions while segments adjacent to the intestine appeared to be basically normal. Large bilharziomas in the intestine of the infected rabbits also suggested that some worm pairs aggregated near a lesion (30).

Egg distribution in animal hosts has been reviewed (22). The relative distribution of S. japonicum eggs in the liver, small intestine and colon of the infected animals varied with both the host species and the parasite strain. The percentage of the egg load in the liver varied from 11-22% in Aotus monkeys infected with a Japanese strain of S. japonicum to 45-75% in rabbits infected with a Taiwan strain of S. japonicum. In mice, eggs were predominantly distributed in the small intestine and to a lesser extent in the colon in infections with either the Japanese or the Philippine strain (26) (Table 1). However, in the monkey and the rabbit, egg distribution in the intestine differed noticeably. In monkeys infected with the Philippine strain, 41% of the eggs were in the small intestine and 18% in the colon, whereas in monkeys infected with the Japanese strain, the relative egg distribution was 3% in the small intestine and 59% in the colon. On the other hand, in rabbits, schistosome eggs of the Philippine strain were deposited overwhelmingly in the colon while an average of 60% of the eggs of the Japanese strain were found in the small intestine and 30% in the colon (27). Between 1973 and 1979, reports of experimental infections with the Japanese strain indicated that the distribution of the lesions and the eggs in the small and large intestine changed markedly (32). In infected birds, higher egg deposition was seen in the ileum (110). In quantitative tissue schistosome egg counts made in 15 autopsies in China (138), the mean total egg count was 101.2 million in the liver, 5.2 million in the rectum and 7.8 million in the colon. Egg concentration was highest in the liver and rectum, then, in descending order, in the sigmoid colon, descending colon, transverse colon and ascending colon, while the small intestine was only lightly affected. These results were confirmed by several investigators (54,120,138).

An adult female worm usually deposits from 1000 to 3500 eggs per day and the eggs can live for about 22 days in the host tissue (120). The frequency of severe clinical disease in S. japonicum infection has generally been considered to be higher than in other forms of schistosomiasis. The quantitative difference in fecundity of the adult female worm has been cited as the cause (151). The mean size of hepatic granulomas induced by S. japonicum was significantly smaller than that induced by S. mansoni infection (56). The cytotoxicity and antigenicity of S. japonicum eggs produce a more severe pathology than that produced by other forms of schistosomiasis at similar quantitative levels. The number of eggs per worm pair deposited in tissues of rabbit hosts increased with time (29). The passage of eggs in the faeces per worm pair per day differed greatly among different animal hosts and even within the same host. This also varied significantly between strains of S. japonicum (29), and even within a same strain between different batches of infecting cercariae (32). There was less correlation between the number of eggs passed in the faeces and the number of worm pairs recovered in the animal body, although in rabbits infected with a Japanese strain, and not a Philippine strain, a direct correlation was found between the number of worm pairs and the number of eggs per day in faeces (29). The total number of eggs deposited in the host tissue depends on the number of worm pairs present. A large proportion of the eggs are retained in the host tissue. If the eggs have not completely penetrated the intestine and not been evacuated with faeces, they tend to calcify in the host tissue. Calcified eggs are not efficiently eliminated by the host and may accumulate in enormous number. The pathogenetic significance of the calcified eggs has not been defined. However, the cellular reaction surrounding the calcified eggs is usually slight (22,212).

4.2 Factors influencing pathology

The occurrence and the severity of pathological changes due to S. japonicum infection in man may be altered or influenced by several different factors acting independently or synergistically.

4.2.1 Intensity of infection

In experimentally infected mice, the size of hepatic granulomas decreased with increasing intensity of S. japonicum infection (23). Several reports suggested that a positive correlation existed between intensity of S. japonicum infection (as measured by stool egg count) and severity of the disease (51,104,107,200,211). In general, such observations apply to groups rather than to individuals (48). One community-based survey found no correlation between intensity of infection and clinical morbidity (148).

4.2.2 Strain of S. japonicum

At least four geographical strains, from China, the Philippines, Japan and Indonesia may infect man (45). By using schistosome cercariae of different geographical strains to infect a same animal species of a same origin, considerable differences were observed in worm recovery, behaviour of worms, patterns of egg distribution, passage of eggs in the faeces and hepatic and intestinal lesions as well as morbidity (22,27,29,30,31,135).

Little is known of the importance of geographical strains in the development of human disease. No comparative studies have been made in man. However, the literature indicates that there might be some differences in clinical and pathological manifestations that may be due to the pathogenicity of the different strains. In particular, the Chinese strain seems to cause the most severe disease. For example, in China, hepatic disease is quite severe and hepatic coma is the second most common terminal event of the disease (116,120,138), while, in the Philippines, the main cause of death is usually massive upper gastrointestinal bleeding (14,128). Moreover, the schistosomiasis mortality rate in China was relatively high before, and in the early phase of, the national control programme in some highly endemic villages. For example, in Jiashan County, Zhejiang Province, more than 17 000 fatalities related to the infection were recorded during a 10-year period (118). "No man's village", or "village without villagers", and "big belly village" with a high frequency of persons suffering from hepatosplenomegaly and/or ascites could be found in many endemic counties in several provinces of China (121). Finally, a distinct disease syndrome, dwarfism, associated with schistosomiasis was frequently observed in the early 1950s in endemic areas in China. In three villages in Qingpu County, Shanghai Municipality, where the prevalence was 98%, dwarfism due to schistosomiasis was seen in 4% of the population (34). Recent observations on dwarfism have not been reported from other S. japonicum endemic countries in Asia.

In general, however, the comparative rates of morbidity in China have been observed to differ from province to province, prefecture to prefecture and even county to county.

4.2.3 Host genetic factors

Genetic factors have been reported to influence the development of severe disease. In a study similar to that reported for S. mansoni infection (150), Wang et al. (184) examined blood-group distribution among 1601 persons with late-stage schistosomiasis and 39 626 healthy controls. Those with late-stage schistosomiasis had a statistically significant higher frequency of blood group A (36.2% against 27.5% in the control group) and a lower frequency of blood group B (26.3% against 32.3%) and blood group O (26.0% against 30.5%). In another survey of 24 human leukocyte antigens (HLA) among 30 patients in the early stage and 30 patients in the late stage of the chronic form of schistosomiasis, compared with healthy individuals, HLA-A1 and HLA-B13 were shown to be closely associated with the late stage of the disease (185). In other studies by Cai et al. (17), HLA-A1 was again shown to have a significant relationship with the disease (17). Ohta et al. (141), who examined HLA haplotypes in persons with hepatic schistosomiasis, with schistosome infection without hepatic disease or with liver cirrhosis without schistosome infection, found that HLA-Bw44-DEN haplotype was specific for patients with hepatic schistosomiasis. In a recent study on the relationship between

immunogenetic factors and clinical forms of schistosomiasis, HLA-B16 was found in nine out of 34 patients with cerebral schistosomiasis (26.5%), while none out of 15 patients with hepatosplenic schistosomiasis had this HLA specificity. The difference in frequency of this HLA haplotype between the two groups was significant ($P = 0.025$) (140). However, no apparent relationship between immunoglobulin allotypes and S. japonicum infection could be demonstrated in a local population in the Philippines (227). Immune response to schistosomal adult worm antigen was investigated in persons infected with S. japonicum by measuring antigen-specific proliferative response of the peripheral T-lymphocytes in vitro. A strong association between the HLA-Aw24-Bw52-Dw12 haplotype and the group with a low responsiveness was demonstrated (165).

4.2.4 Immune status of the host

Although infection with S. japonicum occurs irrespective of race, sex and age, infected individuals show some degree of protective immunity to superinfection. This is considered to be only incomplete or partial immunity (47,119,135). It is generally accepted that people from nonendemic areas develop a particularly serious form of acute disease. In China, persons with chronic schistosomiasis in endemic areas have not often been observed to develop the acute syndrome, i.e. Katayama fever, when they were re-exposed (138).

4.3 Disease in different organs

4.3.1 Stomach

Gastric schistosomiasis identified by histopathological examination of the gastric tissue from surgical or biopsy specimens has frequently been reported in Chinese literature. To date, at least 590 clinical cases have been reported (43,62,154,183,186,188,215,237,240). It is believed that subclinical cases are frequent but remain undiagnosed owing to lack of symptoms and insensitive diagnostic procedures. Among the 590 reported cases, 318 (53.9%) also had gastric cancer. Although the data from hospital patients are markedly biased towards the severe form of gastric schistosomiasis, gastric involvement in S. japonicum infection is probably not uncommon. It has been suggested that the pyloric and gastric coronary veins which drain the stomach venous blood are ramifications of the portal venous system and, in the presence of portal hypertension, the high venous pressure forces the eggs to flow backwards towards the venules and to lodge themselves under the gastric mucosa with the ensuing granulomatous reaction (62,237).

The clinical presentation of gastric schistosomiasis includes chronic gastritis (43,186,237,240), chronic ulcer (43,183,186,237,240), pyloritis (186), pyloric obstruction (186,215,237), gastric perforation (186), gastric bleeding (43,186,215), polyps (240) and gastric cancer (43,62,154,183,186,188,215,237,240).

In Japan, Amano (6) presented 91 cases of gastric schistosomiasis diagnosed at surgery, of which 53 (58.2%) were complicated with gastric cancer. The eggs were found mainly in the mucosa of the stomach.

4.3.2 Intestine

In S. japonicum-infected animals, intestinal lesions tend to be focal and isolated, leaving macroscopically normal bowel elsewhere (22,26,30). Sandy patches were seen in areas with heavy egg deposition and calcified eggs were observed radiologically (30). In man, diffuse involvement of the large intestine was observed in a large series of surgical specimens, the rectum and sigmoid colon being the most affected (37). Eggs were found in increasing numbers from the small bowel to the rectosigmoid region (128). This phenomenon in China (120) may be due to the predominant localization of adult worms of the Chinese S. japonicum strain in the inferior mesenteric and superior haemorrhoidal veins rather than in the superior mesenteric vein. However, other investigators have considered the habitat of S. japonicum adult worms to be situated higher up in the gastrointestinal tract than that of S. mansoni (3,10,47).

Egg granulomas were found in the duodenal bulb causing clinical manifestations in 11 patients who underwent surgical treatment for persistent upper abdominal pain. Ulcers of the duodenal bulb were found in five patients and one of these cases was complicated with duodenal perforation and serious bacterial infection (186). The eggs were deposited mostly in submucosa or at the bottom of mucosa (6,186).

In one report by Chen et al. (37), 229 cases of granulomatous disease in the large intestine due to S. japonicum infection were reported without parallel control observations. In 186 of the cases (81.2%), most of the lesions were found in the rectum and sigmoid colon. Other lesions included: caecum, 11 cases; descending colon, 10; transverse colon, 9; splenic flexure of the colon, 7; hepatic flexure of the colon, 4; and ascending colon, 2. Multiple lesions with segmental distribution were found in 27 cases. The pathological features of schistosomal disease in the large intestine were mainly mucosal hyperplasia, pseudopolyposis, ulceration, thickening and enduration of the intestinal wall, and bowel stenosis and obstruction, the last two being rare manifestations. The mesentery and retroperitoneum were frequently adherent to the intestine presenting as a mass in the abdomen. The data from this and other studies on the relationship between intestinal schistosomiasis due to S. japonicum and intestinal cancer are reviewed in section 6.2.

4.3.3 Liver and spleen

During the past decade there have been few papers which provide information on human pathology due to S. japonicum infection. Three autopsy series of 81 cases of late schistosomiasis were summarized by Chinese investigators (138). In two of these three autopsy series the average weights of the liver were 893 g and 1044 g respectively; no data were reported for the third series. The surface of the liver was generally irregular with nodular swelling, two to eight cm in width, and with shallow ridges and fibrosis giving it a rugged appearance. Shrunken and hard livers were occasionally seen. On section the liver presented wide bands of fibrous tissue surrounding the larger portal canals. Portal fibrosis resembling Symmers' clay pipestem fibrosis was seen in almost all cases. Microscopically, extensive fibrosis and neovascularization were seen in portal areas accompanied by chronic pseudotubercles with chronic inflammation and slight cellular infiltration surrounding the eggs. The portal tracts were broad; however, the hepatic lobules were basically preserved although fatty degeneration and cloudy swelling of the liver cell, focal hepatic cell necrosis with cell infiltration and atrophy of the liver cells were common. Usually no significant changes could be seen in the larger hepatic arteries and bile ducts. Both endophlebitis, with or without obstruction with focal endothelial proliferation, and fibrosis of the portal veins were observed in some cases. The total tissue egg counts after liver digestion ranged from 2.1 million eggs to 881.5 million eggs in 10 autopsies (138).

Compared to the very few postmortem studies of liver pathology, many spleen specimens have been examined from splenectomies performed in the 1960s and 1970s in China. At that time surgery was performed on tens of thousands of persons with schistosomiasis and large spleens and/or pancytopenia due to hypersplenism (138). The average spleen weight was 1220 g in 64 cases of late schistosomiasis at autopsy while it averaged 837 g in 32 cases of portal cirrhosis (not due to schistosomiasis), and 545 g in 14 cases of postnecrotic cirrhosis (138). It was suggested that the spleens were larger in late stage schistosomiasis than in the latter two types of liver cirrhosis because of the significantly higher portal pressure (120).

In hepatosplenic schistosomiasis the splenic capsule was thickened and usually adhered to the surrounding tissues. Passive congestion, as well as hyperplasia of the reticulo-endothelial system, lymph follicle atrophy and fibrotic proliferation, were observed. Schistosome pigment deposits were sometimes seen, but schistosome eggs were rarely found in the spleen (120).

4.3.4 Kidney

S. japonicum eggs have been rarely observed in the kidneys (120). Experimental infection with S. japonicum in both mice and rabbits has suggested that immune complex deposited in the kidney may cause glomerulonephritis (159,220) and, in rabbits, may also induce renal amyloidosis (30,159). Diffuse renal lesions were observed in two out of 10 rabbits by Jones et al. (97) 32-39 weeks after infection with S. japonicum. The animal with the highest concentration of serum immune complex had the most severe nephrotic changes. Eight months after experimental infection in rabbits, renal biopsies showed focal, diffuse intracapillary, and crescentic glomerulonephritis with mesangial and subendothelial immune complex deposition as well as amyloid deposits. IgG and IgM deposition was shown by immunofluorescence in the mesangial matrix and peripheral capillaries. Subendothelial and mesangial immune complex deposition in the glomeruli was demonstrated by electron microscopy (159). Similar pathological changes and immune complex deposition were seen in experimentally infected mice but S. japonicum antigens were not identified by indirect immunofluorescence (220). Glomerulonephritis has been frequently reported in human hepatosplenic disease due to S. mansoni infection (8), and its antigen was detected in renal glomeruli (86); however, nephropathy associated with advanced liver disease of S. japonicum infection is rare (205).

4.3.5 Lung

Inflammatory reactions associated with schistosomulum penetration were either mild or absent in the lung during primary infections in experimental animals. However, significant inflammatory reactions around schistosomula were observed after subsequent repeated infections (120). In man, outside of the portal system, S. japonicum eggs are most frequently found in the lung (120). It has been suggested that schistosome eggs reach the lungs by passing through the collateral circulation of portosystemic anastomosis, and the lungs usually become involved after the development of advanced hepatic fibrosis and portal hypertension (213). However, in the Chinese scientific literature, pulmonary roentgenological signs were observed in as many as 77% of acute cases of schistosomiasis. In the late stage of chronic schistosomiasis a different pulmonary roentgenological pattern was present in only 9% of cases (120,138). At autopsy, diffuse pulmonary involvement in advanced chronic schistosomiasis was common, i.e., in 18 (82%) of 22 cases (87,235).

The main pulmonary lesions in S. japonicum infection are similar to those in S. mansoni infection: pulmonary obliterative arteriolitis which may be widespread. The subsequent increase of pulmonary arterial pressure in turn increases the load of the right ventricle of the heart and causes right heart failure. However, clinically, cor pulmonale due to S. japonicum infection does not appear to occur as frequently as that seen in S. mansoni infection (101,162), even in hepatosplenic disease (204).

Inokuchi (92,93) studied the pulmonary lesions caused by S. japonicum eggs in both animal experiments and at autopsy. Pulmonary fibrosis could not be induced by experimental infection in either rabbits or rats, and only non-specific thickening of the alveolar walls was reported (93). Among 183 autopsy cases with S. japonicum infection in Japan, schistosome eggs were found in the lung in 56 cases while pulmonary fibrosis was found in 15. The frequency of eggs in the lung increased in parallel with the severity of hepatic fibrosis. However, no direct relationship was found between the number of eggs in the lung and pulmonary fibrosis (92). Furthermore, the aetiology of the pulmonary fibrosis was probably due to causes other than schistosomiasis. The author concluded that pulmonary fibrosis due to S. japonicum infection alone was rare.

4.3.6 Central nervous system

S. japonicum commonly affects the brain whereas S. mansoni and S. haematobium usually affect the spinal cord (167). It is generally accepted that intracranial egg deposition occurs through a vascular route as shown by histopathological studies (167).

However, the actual pathway to the brain remains controversial. Eggs are rarely found in the brain of experimentally infected animals (22,28,30) and adult S. japonicum have never been recovered from the brains of either experimental animals or humans. Hepatosplenic schistosomiasis was present in most of the few reported cases of S. mansoni cerebral lesions (167), whereas this was usually not observed in S. japonicum infections (210,214). At the early stage of cerebral involvement, S. japonicum eggs were observed in the leptomeninges and cerebral cortex. Later, egg granulomas were randomly distributed causing localized lesions of the brain (120). Histologically, the granuloma consists of three layers: a necrotic centre containing one or more eggs, a middle layer with epithelioid cells, giant cells, eggs and lymphocytes, and an outer layer with an aggregation of lymphocytes mixed with plasma cells, eosinophils, fibroblasts and giant cells (81). Calcification of the lesions was also reported (126).

4.3.7 Others

Apart from the portal system, lungs and brain, egg granulomatous lesions have been found in the skin (109), breast (236), pectoralis major muscle (95), thyroid, pericardium, kidney, adrenal cortex, reproductive organs of both sexes (120) and ureter (229).

S. japonicum eggs are rarely seen in endocrine glands. However, the infection itself (not egg deposition) can cause schistosomiasis dwarfism (34). In these patients, body growth and development are retarded and significant pathological changes are apparent in the skeleton, endocrine glands as well as reproductive organs. In autopsy studies, degeneration and atrophy of the pituitary gland, sexual glands, adrenal cortex and thyroid were observed. Moreover, the number of eosinophilic cells of the anterior pituitary was reduced (34).

5. CLINICAL PRESENTATION

5.1 S. japonicum infection

5.1.1 Assessment of the infection

The diagnostic tests for S. japonicum infection are not as simple as those for S. haematobium infection (170,213). For parasitological evidence of infection, direct observation both of S. japonicum eggs in the faeces and of miracidia from hatched eggs is ideal but the sensitivity of these current techniques is low in lightly infected populations, especially in areas where low prevalences after control have been achieved. In such situations repeated examinations are necessary (105,108,120,170,206,224,225). Serological tests, although more sensitive than stool examination, are less specific; in particular, they do not differentiate between past and current infection and may remain positive for up to three or more years after cure (120,130,131,138). Identification of active infection by measuring circulating S. japonicum antigen shows promise. However, such tests are still under experimentation (85,156,208) and the application of this technique in humans has not been satisfactory (156).

In the Philippines and Indonesia the infection is presently being assessed almost exclusively by parasitological techniques: stool examination by merthiolate-iodine-formaldehyde concentration, and more particularly the Kato thick smear technique (2,15,76,108,129). The quantitative Kato technique provides reproducible estimates of prevalence and intensity of infection for epidemiological assessment (130).

In China, the miracidium hatching test after concentration of the eggs through a nylon tissue bag has been widely used (228, see Annex). It is simple, and its high sensitivity has been recognized (123), but it has not been standardized for quantitative measurements (129). It is generally accepted that three consecutive negative hatching tests rule out the presence of infection (123).

Microscopical examination of rectal biopsy specimens is a highly sensitive clinical diagnostic technique, but this invasive procedure is neither simple nor convenient for population-based surveys and viable eggs in the tissue are rare. It is not feasible to differentiate the recently dead eggs (an indication of treatment) from those that have been dead for a long time (treatment is not indicated) and this may lead to unnecessary repeated treatment (123).

Various immunological tests for the demonstration of antibodies in human sera have been evaluated. Different antigens and test systems have been used, such as the circumoval precipitin test (COPT), the enzyme-linked immunosorbent assay (ELISA), the indirect haemagglutination (IHA) test, and the indirect fluorescent antibody (IFA) test (15,120,131,132). The sensitivity of these tests is usually higher than that of any current stool-examination technique but the specificity is lower (108,120,130,206, 224,225). Thus, serological results from population studies must be interpreted with caution. No current serological test can distinguish between past and active infection. While treatment should generally be given only to persons actually excreting S. japonicum eggs, treatment of persons who have positive serological tests may be considered if such individuals are symptomatic and have a known history of exposure (206).

5.1.2 Relationship of prevalence and intensity of infection to morbidity

During recent years, cross-sectional and community-based studies on the morbidity of S. japonicum infection have provided new information on the relationship between the prevalence and intensity of infection as estimated by stool egg counts and the occurrence of clinical findings (51,107,148,200,209). Ideally repeated stool examinations would be done in population studies, but are rarely feasible in the field. Thus most epidemiological studies classify infection on the basis of the examination of one or two samples from a single stool specimen.

As with other schistosome infections, community surveys show that males usually have higher prevalence rates and intensity of infection than females (51,200,211). However, the peak prevalence in S. japonicum infection in a community is not as distinct as that in S. haematobium infection, in which the 10-14 year age group usually has the highest rate (213). Peak prevalence is also somewhat different from S. mansoni infection, in which peak prevalence and the highest intensity of infection are usually seen in the 10-19 year age group (170). Peak prevalences of S. japonicum infection have been variously reported in the 15-19 (2,51,209), 20-24 (148), 25-29 (138), 30-39 (107) and 50+ (76,160) year age groups by different investigators. Interestingly, in one field study the highest prevalences were found in the 10-14 year age group in village A while in village B in the same county the rate was highest in the 50-59 year age group (200). Usually, in the general population, infection rates increase significantly in the 5-9 and 10-14 year age groups over the preceding age group and then in a slight upward, though fluctuating, trend reach a peak at which they remain fairly steady or show a gradual fall. Sharp differences between age groups usually do not occur as they do in S. haematobium infections (170).

Intensity of infection may (209) or may not (51,200) parallel the prevalence rates. Peak prevalence and peak intensity of S. japonicum infection differ from those of S. haematobium and S. mansoni infections and this may be due to, among other causes: (a) differences in frequency and pattern of water contact; (b) high frequency of treatment in the S. japonicum area studied (200); (c) longer life span of S. japonicum (122,128,138); (d) differences in acquired immunity between these types of schistosomiasis.

In community studies, a major proportion of the population is usually uninfected and most of the infected persons have light infections (1-100 eggs/g faeces - epg), a few have moderate infections (101-400 epg), while heavy infections (over 400 epg) are rare (51,148,200). It has been shown that a small proportion of the population (4.1% to 6.6%) excretes about half of the total eggs in stools of the whole infected population (107,209).

Most persons with S. japonicum infections are asymptomatic (51,107). One report from China showed that a village with a higher prevalence had a higher mean faecal egg count (200), while another report from the Philippines showed no relationship between prevalence and the mean faecal egg count (148). In several studies, the frequency and severity of clinical findings were positively correlated with the intensity of infection, especially when heavily infected persons were compared to others in the community (51,107,148,200,209,212).

The relationship between S. japonicum infection and the occurrence of morbidity as assessed in clinical findings is shown in Table 2. Diarrhoea and abdominal pain were correlated with infection or high faecal egg counts in some studies (76,107,147,148,211) but there was no correlation in others (51,200). Weakness was also reported to be correlated with S. japonicum infection (76,147,200). Most of the studies showed the relationship between the infection, especially heavy infection, and hepatomegaly. In a report from Lindu valley, Indonesia (104), where the intensity of infection was high (mean of 463 epg faeces), high percentages of hepatomegaly (31%) and splenomegaly (61%) were recorded (no data on malaria rates were cited). In a survey of two barangays (villages) in Irosin, Sorsogon, the Philippines, with a prevalence rate of 42%, a very high frequency of palpable liver (97%, 127/131) and a moderate frequency of splenomegaly (11%) were found by Rubio (160).

5.2 Acute phase

Penetration of the skin by S. japonicum cercariae may be associated with local pruritus, erythema and papules. Acute disease or Katayama fever is usually observed either in persons living in the endemic area at the time of their first exposure or in uninfected persons who reside elsewhere and enter the endemic area for the first time (120,128,138,139,151,192). However, reports on hospitalized patients now suggest that the acute syndrome is not limited to these two groups, but may also be seen in two other groups: (a) persons with an active chronic infection or (b) persons having a recent history of infection with documented treatment and cure. It has been suggested that the acute syndrome in these two latter groups is due to a massive exposure to S. japonicum cercariae within a short period of time (40,138).

The frequency of acute infections in China is at present much less than it was in the 1950s and 1960s. Acute infections tend to occur during the rainy season particularly in the flooded areas where Oncomelania snail populations are dense and the prevention and control activities limited. For example, in Hubei Province, China, where the extensive marshland and lake areas are highly endemic, 2984 persons in 24 counties were reported to have acquired acute infections in 1983; 80% were males and 56% were students in primary or secondary schools (61). In another study in Hubei Province, of 95 acute infections that occurred during three months in 1982, among 1034 persons exposed to infection from a single production brigade, the distribution was a negative binomial according to age and household size (113).

The incubation period or the interval between exposure to infection and the onset of fever is now well documented. Among 105 persons without prior history of S. japonicum infection and with only a one-day exposure to infested water, the mean incubation period was 41.5 days, ranging from 14 to 84 days (138).

Fever is the main symptom of the acute syndrome. Most of these patients (70%) present with intermittent or remittent fever peaking in the late evening. The temperature returns to normal or below 38°C in the early morning. Rigor, sweating, headache and general muscular pain are usually associated with the fever. Gastrointestinal disturbances were common, consisting of loss of appetite, nausea, abdominal pain and distension, and diarrhoea with mucus and bloody stools. On physical examination, the liver is usually enlarged and tender. A slightly enlarged spleen can be palpated in about one-third of the patients. Lymphadenopathy and arthralgia are rarely seen (40,138) and do not seem to be characteristic features of acute S. japonicum infection. However, some investigators (125,190,192) state that these clinical signs are observed in both acute S. mansoni and S. japonicum infections.

Clinical pulmonary schistosomiasis is frequently seen in the acute phase of the infection. Coughing is a predominant symptom associated with fever and other acute symptoms. On auscultation, dry or moist rales can be heard. The appearance of the chest upon radiological examination has been well documented in the earlier Chinese literature. There are mainly diffuse, mottled opacities or military shadows, poorly or well defined according to the stage of the acute infection. Hazy shadows also occur with symmetrical distribution in the mid- and lower lung field. The pulmonary hilus is usually enlarged and vascular markings are increased (40,120). Abnormal lung roentgenograms and pulmonary symptoms have been variously reported to occur in 13% (11/82) of cases by Zhou et al. (in reference 138), 40% (16/40) by Chen et al. (40), 65% (17/26) by Chen et al. (in reference 138) and were as high as 77% according to Mao et al. (120). Within 3-6 months after chemotherapy, the abnormal radiological signs disappeared while the clinical respiratory symptoms usually regressed within 1-4 weeks (40,120). These symptoms and signs in the lung are considered to be related to an inflammatory reaction induced by newly deposited eggs. Cor pulmonale has not been observed in the acute phase of the infection.

Symptoms of meningoencephalitis with or without epilepsy may appear in the acute phase (110,138). Some investigators believe that these symptoms are caused by biochemical or immunological effects of the eggs with or without the presence of cerebral egg deposition (81,214).

Acute S. japonicum infection causes severe morbidity, in contrast to acute S. haematobium and S. mansoni infections which are usually self-limited (135,152,173). If untreated, Katayama fever may cause death, but generally it is also self-limited and progresses to the chronic phase. In China praziquantel has been highly effective for treatment of acute S. japonicum infection. Before praziquantel was available in China, the mortality rates among patients in hospital with the severe form of acute infection ranged from 2.2% (3/138), 2.8% (18/629) to 20.7% (18/87) in different reports (138).

5.3 Chronic phase

In general, more than half of the chronic cases of schistosomiasis are asymptomatic although stool examinations may reveal S. japonicum eggs. Severity of the disease may be related to intensity and duration of the infection, location of the egg deposition, immune status of the host, and concomitant diseases.

The general symptoms reported in infected persons, especially persons with heavy infections, are: weakness, fatigue, abdominal pain, irregular bowel movements and blood in stools. The infected individuals usually have normal appetites and their working capacity is not, or only slightly, hindered (120). In one community-based study in Leyte, the Philippines, Domingo et al. (51) indicated that, although the study was conducted in an S. japonicum endemic area with moderate prevalence (32%) and intensity of infection, the associated morbidity was low. Moreover, the pathological effects of the infection did not seem to be more significant than those observed by the authors for S. mansoni infection in a similar community study in Kenya.

Reliable mortality data for schistosomiasis with longitudinal observations in large populations are not available. In the Philippines (14), 154 randomly selected schistosomiasis cases were followed up for 12 years and the risk of death related to schistosomiasis was determined. Among 23 persons who died from various causes during the observation period, eight had signs and symptoms pathognomonic of schistosomiasis (including melaena, haematemesis and epilepsy) that were considered the main causes of death. Among the survivors, 54% of the initially symptomatic persons became asymptomatic during the 12 years without treatment. In a hospital series in China, the terminal events of 290 cases of late-stage schistosomiasis were mainly upper gastrointestinal bleeding (54%) and hepatic coma (26%) (116). Operative and post-operative complications related to splenectomy (11%) and other complications related to schistosomiasis were also reported causes of death.

5.3.1 Gastric schistosomiasis

Gastric schistosomiasis, uncomplicated by gastric cancer, usually has the appearance of gastric ulcer or chronic gastritis (5,237). However, upper abdominal pain is not consistent, is unrelated to meals, and responds poorly to symptomatic treatment. Gastric bleeding and pyloric obstruction are the common sequelae (183,186,237,240). Gastric schistosomiasis is not usually correctly diagnosed, either clinically or radiologically, before surgery or biopsy through gastroscopy (186,237). Gastric schistosomiasis with gastric cancer is described in section 6.1.

5.3.2 Intestinal schistosomiasis

Significant disease of the small intestine due to S. japonicum infection has rarely been seen either clinically or pathologically (120) whereas disease involving the large bowel is frequent (37,120,138). However, eight cases of ulcers of the duodenal bulb showing S. japonicum eggs in the surgical specimens and another three cases with egg granulomas but without ulceration in the duodenal bulb have been reported (186). In Japan, 31 cases of schistosomiasis with duodenal ulcers were reported by Amano (5) among 1458 cases of various gastrointestinal diseases requiring surgical intervention.

Chronic diarrhoea is a common symptom of colonic schistosomiasis. In a report of 433 patients with chronic diarrhoea, schistosomiasis was second only to amoebiasis as the most commonly associated infectious agent (169).

In a community-based survey conducted by Cheng et al. (in reference 138) in three former heavily endemic communes in Kunshan County, Jiangsu Province, China, 58 827 persons were studied and 555 (0.94%) of them were diagnosed as having colonic disease due to schistosomiasis. Diagnosis was made on the basis of: (a) a history of S. japonicum infection or the presence of eggs in stool at the time of survey; (b) symptoms including left lower abdominal pain, irregular bowel movements with diarrhoea or constipation, or both, and sometimes with mucus or blood in stool; (c) palpable abdominal mass in the left iliac fossa after defecation; (d) sigmoidoscopy showing rough, thick or atrophied mucous membrane, or with polypoid hyperplasia or ulceration and schistosome eggs on biopsy; and (e) barium studies with X-ray examination revealing a picture of chronic ulcerative colitis or stricture or filling defect of the colon. The male:female ratio of the colonic disease was 1:2.8; in another report, it was 1:4.0 (138). It was suggested that this disproportion might be due to the relatively lower probability of women being treated because of their heavy household duties, pregnancy and breast-feeding, although unspecified endocrine disturbances in women were also cited.

Data from 229 hospital patients with granulomatous disease of the large intestine due to schistosomiasis were reported but without information on a comparable control group of patients (37). Diffuse involvement and multiple lesions of the large intestine were seen in 186 (i.e., 81.2%) of the patients although the disease was mainly localized in the rectum and sigmoid colon. A history of colic of up to 10 years' duration was common, although 10 patients had no symptoms before bowel stricture or obstruction. The main complaints of the patients were diarrhoea (93%) and lower abdominal pain (90%). In quite a number of patients, a history of alternate diarrhoea and constipation with thin cord-like stools was reported. Usually the patients were able to work until the disease became advanced or complications were superimposed. On examination, palpable tumefactions in the left lower abdomen were recorded in 54 patients, splenomegaly in eight and retardation of physical development in five young persons. Other complications included intestinal fistulae or perforation, perianal fistulae, intussusception and perforation or intestinal haemorrhage. From radiological examination, the authors classified the colorectal disease into three types: (a) ulcerative colitis, (b) localized narrowing, and (c) polypoid and extraneous (obstructive) type. While 124 patients were subjected to various surgical procedures, 105 patients with less severe disease were treated with antischistosomal drugs. Of the latter, 50 patients were followed up for 2-10 years with a satisfactory outcome in most cases.

5.3.3 Hepatosplenomegaly

The left lobe of the liver is usually disproportionately enlarged in S. japonicum (and S. mansoni) infection. On palpation, the liver is smooth, firm and without tenderness. The hardness of the liver increases as the disease advances. The surface in severe cases may be nodular or irregular, but a shrunken liver is rarely seen either at surgery or at autopsy (120,123,138). The appetite remains normal, even in advanced disease; decrease in food intake is usually not significant. Jaundice, spider naevi, palmar erythema, gynaecomastia, altered hair distribution, neuropsychiatric manifestations, bleeding diathesis, and signs of liver failure are uncommon (49,123,138).

Splenomegaly occurs frequently in S. japonicum infection, especially in the late stage (120,139) or in heavy infections (104). The enlarged spleen may be palpated below the level of the umbilicus or across the abdominal midline, or may fill most of the abdominal cavity (49). During the period 1954-1977, splenectomy was done in 5151 patients with splenomegaly due to schistosomiasis in Qingpu County, Shanghai Municipality, where the total population of the County is about 400 000. Most patients had Hackett size spleens equal to or greater than 3 and/or with hypersplenism (138).

Advanced hepatosplenic disease is usually associated with abdominal collateral vein dilatation and oesophagogastric varices. Haematemesis, melaena and ascites are frequent. Moreover, loss of libido in adults, impotence in men, and infertility and amenorrhoea in women are not uncommon (120).

5.3.4 Ascites

Ascites, associated with the late stage of schistosomiasis, has a more protracted natural evolution than liver cirrhosis and may persist for as long as 10 to 20 years with a variable clinical course (143). The appearance or relapse of ascites in advanced schistosomiasis may be triggered by: haematemesis, other superimposed infections, malnutrition, or hepatotoxic-drug administration (120). As with ascites in other hepatic diseases, portal hypertension and hypoalbuminaemia are the main factors causing its formation. Portal hypertension is present in most of the patients with advanced schistosomiasis. However, even in patients with hypoalbuminaemia, ascites is not often seen. Secondary aldosteronism and reduction of renal plasma flow resulting in subsequent disturbance in renal function and haemodynamics, may also play important roles (216,221). Eggs have rarely been observed in ascitic fluid (143).

5.3.5 Upper gastrointestinal haemorrhage

Blood loss due to bleeding of oesophagogastric varices is the major cause of death in S. japonicum infection (49,116,117,147). Rupture of the varices usually occurs in the lower third of the oesophagus and the fundus of the stomach. Of 131 patients with late-stage schistosomiasis who died from oesophageal bleeding, the number of bleeding episodes was recorded in 113 of whom 68 (60.2%) died after the first attack; of 107 patients followed up for one year or more 70 (65.4%) died within one year (116). In the same series, of 122 cases with oesophageal bleeding whose causes of death could be traced, 81 (66%) died from blood loss, and 32 (26%) developed hepatic coma shortly after a bleeding episode.

It has been reported that, after splenectomy with or without porto-systemic anastomosis, the frequency of episodes of oesophagogastric bleeding decreases significantly owing to the decrease of portal pressure (116,120,138). In China, apart from medical treatment with antischistosomal drugs, the surgical approach has been the main treatment for portal hypertension and its sequela of upper gastrointestinal bleeding.

5.3.6 Growth retardation

Schistosomiasis dwarfism was quite common in endemic areas in China in the 1950s. It was one of the four special types of late schistosomiasis, the others being huge

splenomegaly, ascites, and colonic tumoroid proliferation (123). Today, schistosomiasis dwarfism is rare.

Individuals afflicted with schistosomiasis dwarfism had acquired a usually repeated or heavy infection during childhood. Their physical growth and sexual development are retarded. Apart from other symptoms of schistosomiasis, features of this condition are a lack of growth acceleration during puberty, a short and slight stature with an older facies, a lack of secondary sexual characteristics and underdeveloped sexual organs. The patients are mentally alert and their clinical state is usually attributed to pituitary dwarfism. After early antischistosomal and supplementary treatment, such as splenectomy, gonadotherapy and zinc sulfate administration, satisfactory results can be expected (34,123).

5.4 Cerebral schistosomiasis

S. japonicum infection mainly affects the brain, while spinal cord involvement is rare. No population-based survey is available for the assessment of the prevalence of cerebral involvement due to S. japonicum. In Palo District, Leyte, the Philippines, an area highly endemic for schistosomiasis, Hayashi (81) reported that 285 patients, or 1.1% of the inhabitants, had epilepsy while the prevalence was about 0.3 to 0.5% in non-endemic areas. The difference was considered to be due to S. japonicum infection. Among adult hospital patients in China, the prevalence of cerebral schistosomiasis among schistosomiasis patients ranged from 1.7 to 4.3% (120,214).

Clinical manifestations of cerebral schistosomiasis differ greatly between those seen in the acute phase and those in the chronic phase of the infection. In the former, the usual presentation is meningoencephalitis without localized findings but with fever, headache, vomiting, dysphasia, hemiparesis, blurred vision and disturbance of consciousness (100,120,214). In one case reported by Kirchoff et al. (100) non-specific treatment with dexamethasone resulted in the disappearance of the cerebral symptoms and the resolution of abnormalities detected by CT scan. In this case, antischistosomal treatment should nevertheless have been included initially (101,203). Epileptic seizures are the main clinical manifestation of cerebral schistosomiasis in the chronic phase of S. japonicum disease. Neurological findings mimicking cerebral tumour and stroke have been reported in a few cases (214). Cerebral schistosomiasis with a huge calcified mass occupying the entire right occipital region, which was identified by X-ray examination, by CT scan and subsequently by biopsy upon operation, was reported by Morimoto et al. (126). Epileptic seizures, Jacksonian convulsions and grand mal seizures were frequent, while psychomotor and autonomic seizures were rarely observed (81,120,138,214).

Electroencephalograms (EEGs) recorded in 75 persons with cerebral schistosomiasis by Hayashi (81) in Leyte were judged to be normal in 24 (32%), borderline in 13 (17%) and abnormal in 38 (51%). The abnormal and borderline EEGs were characterized by random and paroxysmal slow waves with asymmetry.

5.5 Pulmonary schistosomiasis

Among 17 hospital patients with chronic S. japonicum infection in Manila, the Philippines, restrictive ventilatory defects were shown in five patients and a combined restrictive-obstructive ventilatory defect in one asymptomatic patient, based on chest X-ray examination, blood gas analysis and pulmonary radionuclide scan (161).

It has been suggested that cor pulmonale is a complication of hepatic schistosomiasis with portal hypertension and collateral circulation. However, in a prospective study of 65 consecutive hospital patients with schistosomiasis including 43 patients with hepatosplenic disease, Watt et al. (204) found that only one of these 43 patients had pulmonary hypertension, while none of the remaining 22 patients without hepatosplenic disease had cardiopulmonary involvement. The relatively uncommon occurrence of cardiopulmonary disease in severe schistosomiasis due to S. japonica

in comparison with that in S. mansoni infection may be due to a reduced inflammatory response in the lung to S. japonicum eggs (198). The eggs may cause smaller lung granulomas and are eliminated more quickly from the lungs than those of S. mansoni (204).

During a 3-year period in a Chinese hospital specialized in schistosomiasis treatment only 10 cases of chronic cor pulmonale were observed, all in patients with hepatosplenic schistosomiasis. During this same period, 723 cases of hepatosplenic schistosomiasis were treated. The rate of cardiac complications among patients with hepatosplenic schistosomiasis was 1.4% while no such complications were observed in the earlier stages of chronic schistosomiasis. The clinical manifestations were progressive dyspnoea on exertion, cough, weakness, a pulmonic systolic murmur and accentuation and splitting of the second heart sounds in the pulmonic valve area on auscultation. Roentgenograms showed enlargement of the pulmonary artery and right ventricular hypertrophy. The electrocardiograms (EEGs) indicated right axis deviation, right ventricular hypertrophy and strain. Cardiac catheterization confirmed the presence of significant pulmonary hypertension (235). The authors suggested that early diagnosis and treatment may arrest or slow down the progression of the cardiovascular pathology. Olveda & Icatlo (147) mentioned that, in the past, cor pulmonale in children caused by pulmonary schistosomiasis was not infrequent in the Philippines, but in recent years, the number of such cases has declined noticeably.

5.6 Renal involvement

Animal experiments have suggested that, as in S. mansoni infection (152), immune complex nephropathy in hepatic disease of S. japonicum infection can be induced and immune complex deposited in glomeruli (159,220); however, no such disease has been documented by biopsy or necropsy in man (205). In a community study of 244 infected persons in a rural area in the Philippines, no relationship could be found between S. japonicum infection and proteinuria (205). In 100 hospital patients, 64 had portal hypertension, but renal function abnormality was not significantly more common than in an age- and sex-matched control group (205). A renal biopsy specimen from a schistosomiasis patient with nephrotic syndrome showed neither S. japonicum antigen nor S. japonicum antibody. Two months after praziquantel treatment, the renal disease did not change as determined from renal function tests and a renal biopsy specimen examined by electron microscopy and the fluorescent technique. It was suggested that glomerulonephritis is rare in schistosomiasis due to S. japonicum, including the hepatosplenic form of the disease (205).

5.7 Laboratory findings

5.7.1 Haematology

In acute infection, there is an increase in concentrations of blood leukocytes and eosinophils. The peripheral leukocyte count is usually within 10 000-30 000 per mm³, but may be as high as 50 000 per mm³. Eosinophils are generally between 15 and 50% of the total count, but are occasionally higher than 90%. Anaemia and an increased erythrocyte sedimentation rate were reported to be common (40,120). In experimental acute infections in rabbits, anaemia was related to a failure of the bone-marrow response rather than to an autoimmune haemolytic process (158). However, another study suggested that soluble extracts from S. japonicum eggs have haemolytic activity on erythrocytes (11).

In hepatosplenic disease, anaemia is either hypochromic normocytic or hypochromic macrocytic. Leukopenia and mild thrombopenia were also common, especially in patients with a huge spleen (120). In patients with clinically significant pancytopenia, splenectomy corrected this condition (120,138).

5.7.2 Liver function

Most investigators feel that liver function usually remains within normal limits in S. japonicum infection, because liver cell damage is not significant and sinusoidal perfusion is unimpaired (49,117,128,135,191,192,195). However, in the Chinese literature liver function impairment has been reported to occur although the degree of altered liver function is not as severe as in other forms of liver cirrhosis (120,138).

A decrease of serum albumin and an increase of globulin concentrations were very common, while reversal of the serum albumin/globulin ratio, i.e., less than 1, was seen in 55-62% of cases with hepatic disease. On electrophoresis, the gamma-globulin fraction was usually elevated. Zinc sulfate turbidity, thymol turbidity and cephalin-cholesterol flocculation tests were usually abnormal. Prolonged prothrombin time and retention of bromsulphalein may be observed in severe cases, especially in those with ascites (120,128). Choline esterase activity was always low (120). Gamma-glutamyl transpeptidase activity was abnormally elevated in 93% of the patients (138). The serum monoamine oxidase level was usually normal whereas it was high in posthepatic cirrhosis (138). Generally, the levels of serum glutamic oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and serum bilirubin were either within normal limits or slightly elevated (120). However, in hepatic coma, the levels of SGOT, SGPT and serum bilirubin were usually high and a higher level of arterial blood ammonia was common (138). Serum β_2 -microglobulin levels in hepatic schistosomiasis were elevated in 48% (15/31) of patients in a hospital series whereas these levels were abnormal in 57% (12/21) of patients with liver cirrhosis. However, the average level was significantly higher in the latter ($4192 \pm 2904 \mu\text{g/l}$) than in the former series ($3125 \pm 1293 \mu\text{g/l}$), while the average level of 40 normal persons was $1487 \pm 372 \mu\text{g/l}$ (94).

5.7.3 Renal function

It is generally accepted that in liver disease, any renal dysfunction is secondary to haemodynamic disturbances of the liver. Hepatic schistosomiasis without ascites is usually associated with normal renal function. Impairment of renal function may be observed in severe cases of ascites especially in those with prolonged or refractory ascites (216,221). The abnormal renal function is manifested by proteinuria, decrease of urine volume as well as of urinary sodium and potassium output, lower clearance rates of para-aminohippuric acid and of endogenous creatinine, low excretion rate of phenolsulphophthalein (221), and radiological abnormalities of the kidney (216).

5.7.4 Endocrine function

Endocrine function of the anterior pituitary, thyroid, gonad, pancreas and adrenal cortex may be altered in hepatosplenic schistosomiasis. Twenty-four hour urine excretion of the follicle-stimulating hormone (FSH) was usually lower than normal (120) and the luteinizing hormone-releasing hormone stimulation test showed weak or no response in nine out of 10 cases (207). Out of 29 cases, 11 showed an elevated level of the thyroid-stimulating hormone (TSH), while the other 18 cases were normal. The mean T3 (triiodothyronine) values were low but T4 (thyroxine) levels and ^{125}I -T3 plasma combination ratio were basically normal (207). Of 10 patients examined, the plasma E2 (oestradiol) level was high in five (three males and two menopausal females) and the E3 (oestriol) level was high in only one male (207). Glucose tolerance tests in 24 patients showed a high peak in 12; the blood glucose curve was similar to that of diabetes in eight and normal in four. Among 13 patients subjected to insulin determination, 11 showed a delayed type reaction and two showed a low reaction (187). This suggested a possible relationship between the abnormal glucose metabolism and the pathological changes of the liver and pancreas. Twenty-four hour urine 17-ketosteroid levels were significantly decreased and only 24% of the patients showed a normal reaction to the adrenocorticotrophic hormone (ACTH) test (120).

5.7.5 Immunological function

Cell-mediated immune functions have been observed on the basis of the streptokinase-streptodornase (SK-SD) skin test, the rosette formation test, and lymphocyte transformation. Fan et al. (58) reported that, out of 130 patients with hepatosplenic schistosomiasis, 100 (77%) showed negative reactions by SK-SD skin test, while only 4% of the normal controls were SK-SD negative. The average rosette formation rate in 144 cases of hepatosplenic schistosomiasis was $51 \pm 14\%$ which was significantly lower than the $66 \pm 8\%$ in 100 normal subjects. Lymphocyte transformation rates in 56 patients in the acute phase, 50 patients in the early stage of the chronic phase, 41 patients in the late stage of the chronic phase (hepatosplenic disease) and 30 normal subjects were $29 \pm 1.6\%$, $48 \pm 1.8\%$, $33 \pm 1.3\%$ and $61 \pm 1.7\%$ respectively (41). The lymphocyte transformation rate stimulated by phytohaemagglutinin (PHA) was markedly depressed in patients with schistosomiasis, especially those in the acute phase and those with hepatosplenic disease (41,106). While stimulated by S. japonicum SEA, the lymphocyte transformation rate in acute schistosomiasis was significantly higher than that in chronic schistosomiasis with or without hepatic disease, as well as normal controls (64).

IgM and IgG levels were markedly elevated in S. japonicum infected persons, especially IgM levels in acute infection and IgG levels in hepatosplenic disease, while IgA levels were significantly elevated in acute and hepatosplenic disease but not in the early stage of the chronic phase (41,59). In infected mice, respectively, 18-fold, five-fold and three-fold increases in the levels of IgG₁, IgM and IgA was demonstrated by radial immunodiffusion by Little et al. (111). Fu et al. (64) reported that circulating immune complexes (CIC) of S. japonicum could be identified in 40 out of 63 (63%) persons with acute infection, and in only 15% of chronic infections (64). However, in monkeys infected with S. japonicum, no CIC could be detected within seven months of infection, whereas in monkeys infected with S. mansoni, high levels of CIC were found (12). Serum C3 and C4 levels in hepatosplenic schistosomiasis were low (58,60), and the rheumatoid factor (19%) and anti-nuclear antibody (36%) were also detected (58). Tu et al. (180) found that serum levels of C3 and C4 were low in hepatosplenic disease while CIC levels were elevated and negatively correlated with C4 levels.

5.8 Complications

5.8.1 Viral hepatitis

Viral hepatitis is prevalent in S. japonicum endemic areas. It is therefore expected that individuals with schistosomiasis may also acquire viral hepatitis. Some, but not all, studies in S. mansoni endemic areas have shown significantly higher frequencies of serological markers of infection with hepatitis B virus (HBV) in schistosomiasis patients as compared to normal controls (4,57). A higher prevalence of HBV antigenaemia was especially seen in patients with hepatosplenic schistosomiasis due to S. mansoni and it was suggested that HBV infection played a role in the development of more severe forms of liver disease among such patients (4).

Cai et al. (18), using five serum markers of HBV infection including HBsAg, anti-HBs, anti-HBc, HBeAg and anti-HBe, examined three groups of individuals, i.e., 231 persons with hepatic schistosomiasis, 232 persons with the early chronic phase of schistosomiasis and 557 persons from the general population. The HBV infection rates (as assessed by positivity of any of the five HBV markers) in these three groups were 55%, 15% and 8%, respectively. Persons with schistosomiasis had higher HBV positive rates than the general population and hepatosplenic patients had significantly higher HBV positive rates than either the group with early chronic schistosomiasis or the general population group. Among patients with hepatosplenic schistosomiasis, liver function tests were more abnormal in patients with HBV infection than in those without. The reason why persons with hepatosplenic disease have a higher HBV infection rate is not clear, but it is suggested that reduced cellular immunity may play a contributing role.

In a community study of both infections in Leyte, the Philippines, Domingo et al. (50) could find no significant differences in HBV exposure (either HBsAg or anti-HBs or anti-HBc was positive) and HBsAg positive rates among those without schistosomiasis, those with the infection and those with hepatosplenic schistosomiasis.

Jin & Li (96) followed up 102 patients with hepatosplenic schistosomiasis three years after treatment with praziquantel and compared the patients who were HBsAg-positive with those who were HBsAg negative. It was found that the prognosis for these two groups was different. In the HBsAg-positive group, 13 out of 43 (30%) patients died, while, in the HBsAg negative group, only 4 out of 59 patients (7%) died during the same period. The causes of death in these 17 patients were hepatic coma in 7 patients, haematemesis in 4, haematemesis with hepatic coma in 3, primary peritonitis in 1, liver cancer in 1 and pulmonary infection in 1.

Gui et al. (72) reported that false positive reactions for HBsAg by the reciprocal haemagglutination (RPHA) method were as high as 74% (40 out of 54) in acute schistosomiasis. High titres of heterophile antibody (≥ 100) were common in the acute disease and the fact that antibody can be agglutinated with sheep red cells and absorbed by SEA of S. japonicum may explain this finding. In these same cases no HBsAg was detected by radioimmunoassay (RIA) and ELISA. After antischistosomal treatment, the false positive reaction for HBsAg by the RPHA method became negative. In chronic schistosomiasis, heterophile antibody may also be detected but at a low titre level. It was concluded from this study that to avoid false positive results in the detection of HBV infection in schistosomiasis, the RPHA method, though easy, quick and sensitive, should not be used.

5.8.2 Hepatic coma

In hepatosplenic schistosomiasis, liver parenchymal damage is not severe (104,193) and the incidence of hepatic coma is low. However, hepatic coma is frequently observed in hospital patients with hepatic schistosomiasis in China (116,128,138,212), especially in those with ascites. In two series reported by Fu et al. (in reference 138) and the Yiyang Prefectural Institute of Schistosomiasis (in reference 138), the respective prevalences of hepatic coma among hospital patients with hepatosplenic schistosomiasis were 5.1% (106/2065) and 3.4% (116/3432). Hepatic coma was induced by bleeding, superimposed infection, post operative state, high protein diet or blood electrolyte disturbance after repeated diuretic therapy. Prognosis was comparatively better in these patients than in those with hepatic coma without a history of the above concurrent conditions (138). Patients with hepatic coma usually had abnormal hepatic function and their arterial blood ammonia levels were often high (138). The mortality rate was very high: 71.7% (76/106) and 55.2% (64/116) during the period of hospital observations in the two series of patients (138).

5.9 Ultrasound and CT scanning

Recently, there has been a number of reports on ultrasound and CT image findings in S. japonicum-infected patients (10,78,133). Neither the spectrum of the ultrasound pattern nor the differential diagnosis compared to liver disease of other aetiologies have yet been fully described. Murakami (133) reported that typical hepatic ultrasonograms in chronic S. japonicum infections showed irregularity of liver surface, distortion of hepatic veins and septum formation with echo-dense areas 2-3 mm in width. The least severe type showed a linear echo-dense area and/or high echo spots. There was also an intermediate form between these two types. Individuals with a large number of calcified eggs revealed a typical ultrasonographic pattern while those with less calcification showed no distinct patterns. The author suggested that ultrasonography was a simple and useful method for detecting chronic S. japonicum infection compared with CT.

Hepatic calcification and distortion of the liver surface related to S. japonicum infection can be visualized by CT scanning. CT was more sensitive than radiological techniques for identifying tissue calcification (78). Hamada et al. (78) identified

three cases of chronic schistosomiasis characterized by a geographic or band-like lesion of increased attenuation localized at the outer zone of the liver. Araki et al. (10) described capsular calcification and septal calcification in chronic S. japonicum infection in 17 Japanese patients. Irregular hepatic contour and a notch of the hepatic contour were seen at the junction of the capsule presenting pseudolobation. A geographic or band-like calcification, the so-called "turtleback-like calcification" of the liver image, appeared to be a pathognomonic CT feature of hepatic schistosomiasis.

6. RELATIONSHIP BETWEEN SCHISTOSOMA JAPONICUM INFECTION AND CANCER

6.1 Gastric cancer

Several clinical investigators have suggested a relationship between gastric schistosomiasis and gastric cancer (5,43,62,154,186,188,237,240). Most of the patients with gastric schistosomiasis have chronic gastritis, gastric ulcer and intestinal metaplasia, and it is considered that intestinal epithelial metaplasia is closely correlated with gastric cancer (154,186,237). Atypical hyperplasia of the glandular epithelium of the stomach is often seen in gastric schistosomiasis and this may also play a role (62,154,237). Surgical data from one hospital showed that gastric cancer was found in 15 out of 20 specimens (75%) taken from patients with gastric schistosomiasis, while in 1046 specimens taken from patients without schistosomiasis the incidence of gastric cancer was significantly lower at 47% (493/1046) (62). In another hospital series, schistosome eggs were found in 12 out of 368 (3.3%) specimens from gastric cancer patients, while only 14 out of 973 (1.4%) non-malignant specimens, mostly from patients with gastro-duodenal ulcers, showed eggs (186). In Japan, the faecal egg-positive rate was higher among individuals with gastric cancer (15%, 55/362) than those without (7%, 46/630) (5).

In contrast, a retrospective epidemiological study of death due to cancers of the digestive system in seven counties in Jiangsu Province, China (75), showed that, although there was a positive correlation between colorectal cancer and schistosomiasis, a negative correlation was observed between relative risk of schistosome infection and gastric cancer. In other words, the higher the schistosomiasis prevalence, the lower the relative risk of gastric cancer in the communities (Table 3). Another epidemiological survey in 24 provinces of China also showed no significant correlation between schistosomiasis and gastric cancer (112).

6.2 Colorectal cancer

Several studies have been published (1,7,36,42,44,70,80,166,217,231,233) on colorectal cancer associated with S. japonicum infections. The question whether or not schistosome infection plays a predisposing role in the causation of this cancer is controversial.

Cheever (20,21) pointed out that in animal experiments, schistosomal lesions of the large intestine were not associated with tumours. Furthermore, in humans, there was no evidence that colorectal cancer was more frequent in infected persons than in the general population. However, a causal correlation has been suggested by some Chinese and Japanese investigators. Liu et al. (112), in analysing the mortality data of colorectal cancer and S. japonicum infection from 24 provinces in China covering a population of 850 million, showed a parallel correlation between mortality rates due to colorectal cancer and to schistosomiasis in endemic areas, especially in areas with high prevalence rates. They concluded that schistosomiasis was one of the factors causing colorectal cancer in the endemic areas. Xu & Su (217) reported that the prevalence of S. japonicum infection was positively correlated with colorectal cancer mortality in five counties in Jiangsu and Zhejiang Provinces, China. However, in a case-control study, the authors found that the relative risk was significantly higher only for rectal cancer, but not for colon cancer, when associated with schistosomiasis. In a retrospective review of mortality due to all malignancies in seven endemic counties, Guo et al. (75) reported that the prevalence rate of schistosomiasis and the mortality rate due to colorectal cancer increased in parallel. No such correlation could be found between prevalence of

schistosomiasis and mortality due to liver and oesophageal cancers. In a further case-control study, Guo et al. (74) showed that persons with schistosomiasis had a significantly higher mortality rate due to colorectal cancer than those without.

A nationwide retrospective survey of cancer in China between 1973 and 1975 indicated that cancer of the large intestine was mainly observed in the provinces of Zhejiang, Jiangsu and Fujian and in the Shanghai Municipality; this distribution coincided with a high prevalence of schistosomiasis (232). However, no information was provided on whether or not diagnosis of colorectal cancer was confirmed histopathologically. In a highly endemic area for schistosomiasis, Jiashan County, the prevalence rate of cancer of the large intestine was 44.2 per 100 000, the highest in China (35). In Japan, high mortality due to cancer of the large intestine was seen in Yamanashi and Kurume Prefectures which were also highly endemic for schistosomiasis (5).

In a limited study of 68 cases of colorectal cancer in Leyte, the Philippines, those infected with S. japonicum were compared to a group of uninfected persons (1). No differences in age, sex, location of lesions or histological type of the tumour could be demonstrated.

In China, two epidemiological surveys (218,231) found no relationship between schistosomiasis and cancer of the large intestine. Both studies were carried out in Haining County, Zhejiang Province, in 1977-1978. The first prospective study included case history, physical examination, occult blood test, rectal finger examination, exfoliative cytological examination and rectoscopy. Among the 198 950 persons over 30 years of age who were screened, 75 cases of colorectal malignant tumours were found or a rate of 37.7 per 100 000 persons (231). When comparing the number of cases with cancerous changes in the intestine in three schistosomiasis prevalence areas, no correlation was observed among the rates of malignancy according to high, moderate and low prevalence of schistosomiasis (218).

Two more recent studies which included data from Haining County, Zhejiang Province, where the above-mentioned surveys were carried out, came to a different conclusion. Liu et al. (112) reviewed mortality data from 24 provinces and found that the highest mortality due to colorectal cancer was in the four provinces which also had the highest prevalence of schistosomiasis and the highest mortality due to schistosomiasis. In a retrospective review, Xu & Su (217) found that mortality from colorectal cancer was highly correlated with the prevalence of schistosomiasis in four counties of Jiangsu Province. The authors also presented data obtained from the Haining County Cancer Registry of Zhejiang Province for 24 communes showing that the incidence of colorectal cancer was significantly correlated with the prevalence of schistosomiasis. Furthermore, in a case-control study in which 252 cases of colorectal cancer out of the 415 known cases of colorectal cancer in Kunshan County, Jiangsu Province, were compared to two matched control groups, a strong association (odds ratio 8.3) between rectal cancer and a history of schistosomiasis was observed, but no association was found between colon cancer and a history of schistosomiasis.

Several reports have compared the mean ages at the time of diagnosis of colorectal cancer with and without schistosomiasis (Table 4). Patients with cancer associated with schistosome infection were, on average, several years younger than those with colorectal cancer alone during the same period (1,44,233). In Japan, malignant colorectal tumours in endemic areas were found in younger age groups compared with those in non-endemic areas (7). The cause of the earlier onset of malignancy has been attributed to S. japonicum infection which is thus considered to be a potential co-carcinogen. However, a report from China showed no significant age difference (42).

More than half of colorectal cancers associated with schistosomiasis were located in the rectum (42,233) or rectosigmoid area (1,36). This distribution is consistent with the predilection of sites by schistosomes for egg deposit (37,120).

Schistosome infection may have a negative effect on prognosis of colorectal cancer. In a report by the National Cooperative Group on Pathology and Prognosis of Colorectal Cancer (136), the five year survival rate was 45.6% (196/430) in cases complicated with schistosomiasis, which is significantly lower than the rate of 50.9% (1383/2717) in cases without schistosomiasis.

Data on schistosomiasis associated with malignant tumours are impressive but explanations of the association remain speculative (70). Generally, patients with chronic inflammatory disease of the intestine have an increased risk of developing colorectal cancer, and an increased risk of colorectal cancer in ulcerative colitis has been well established (52,210). The presence of epithelial dysplasia is probably the important predisposing cancer-related factor. Among patients with schistosomal colitis but without cancer, over half had mild to severe grades of colonic epithelial dysplasia resembling the changes observed in long-standing chronic ulcerative colitis and a severe degree of dysplasia could be considered as cancer-in situ (35). In schistosomiasis associated colorectal cancer, a 10-year or more history of symptomatic colitis or of schistosomiasis has usually been reported (36,44). The long latent interval between the onset of infection and the development of cancer suggests that schistosome infection contributes to cellular changes that lead to premalignant transformation of intestinal epithelial cells (36). In a previously highly endemic county where transmission had been interrupted for several years, the mortality rate due to colorectal cancer did not decrease (74).

Epithelial proliferation and polyp formation are associated with the malignant transition, and continuous epithelial proliferation adjacent to a chronic schistosomal ulcer seems to be precancerous (36). Schistosomiasis is associated with a depressed immune state, especially of the T-lymphocyte-mediated immune function, and it has been suggested that such a state favours cancerous changes (136,241).

6.3 Liver cancer

The aetiological relationship of hepatic schistosomiasis with primary liver cell cancer has long been debated (16,53,66,102,127,134,142). In recent years, Inaba et al. (91) analysed the mortality rate from liver cancer in endemic areas and compared these data with the national statistics for cancer. They observed significantly higher mortality rates due to liver cancer among both sexes in the S. japonicum endemic areas. In a later case-control study of 62 cases of liver cancer and their matched controls, schistosome infection and the presence of HBsAg were both important risk factors in the aetiology of liver cancer (90). Another case-control study of 166 persons who died in 1982-1983 from liver cancer and their matched controls, i.e. 166 persons who died from nondigestive tract cancer and 166 healthy persons, was done in a previously heavily endemic area for S. japonicum in China. There was a significant difference in history of S. japonicum infection between the two groups. After excluding smoking habits and family histories of liver cancer, a significantly higher frequency of history of S. japonicum infection in cases with liver cancer compared with the control groups was reported (73).

In contrast, most studies have shown no relationship between liver cancer and schistosomiasis. In S. mansoni endemic areas, hepatomas were equally frequent in uninfected and schistosome infected persons in autopsy series from Brazil, Puerto Rico, Egypt and Mozambique (20,53). In a retrospective histopathological study of 25 cases of primary liver cancer in the Philippines between 1970 and 1984, only one had S. japonicum eggs but no control data were given (1). In China, two large retrospective epidemiological surveys, one national and the other in seven counties heavily endemic for schistosomiasis, showed no correlation between S. japonicum infection and primary liver cancer (75,112). In Japan, no positive correlation between primary liver cancer and schistosome infection was found by Kamo & Ebato (99) among a series of 16 cases of liver cirrhosis, 11 cases of primary cancer of the liver, and 27 sex- and age-matched hospital patients without liver disease. Liver cell cancer and serum HBsAg were more frequent at autopsy in those with schistosomiasis than in those without. Most of those with

schistosomiasis and liver cancer exhibited posthepatic cirrhosis including macronodular or mixed macro- and micro-nodular cirrhosis, superimposed on schistosomal fibrosis (35,134). HBV is a well known hepatic carcinogen and the apparent increased frequency of liver cancer in patients with schistosomiasis is better explained by the high frequency of HBV infection and its sequela, cirrhosis, rather than by schistosomiasis (46,55,66,134). Most epidemiological or clinical evidence indicates that hepatic schistosomiasis is not a predisposing factor towards development of liver cancer (99,134,142).

On the other hand, experimental S. japonicum infection increased the susceptibility of liver tissue to a carcinogen (16). Miyasato (124), by comparing two groups of experimental mice, the one treated with the carcinogen N-2-fluorenylacetamide (2-FAA) and the other with 2-FAA plus schistosomiasis and observed for 40 weeks, found liver cancers in 24 of the 77 mice (31%) in the 2-FAA plus schistosomiasis group while cancers were seen in 6 of the 86 mice (7%) ($P < 0.005$) in the 2-FAA treated group. Furthermore, the liver cancer had an earlier onset and advanced nature in the 2-FAA plus schistosomiasis group compared with the 2-FAA group. Thus schistosomiasis may act as a co-carcinogen in some situations (124,128).

7. EFFECT OF TREATMENT ON DISEASE

Before praziquantel became available most antischistosomal drugs for S. japonicum infection had a high ratio of toxicity compared with their therapeutic efficacy. A number of antischistosomal drugs effective against S. haematobium or S. mansoni infection are either not effective (hycanthone, metrifonate, oxamniquine, etc.) or less effective (niridazole, antimonials) against S. japonicum infection. Since the late 1970s, when praziquantel was found effective against S. japonicum, the situation has changed dramatically. Praziquantel now plays an important role in schistosomiasis control programmes. Although S. japonicum had been eradicated from focal endemic areas in Japan (179) and some endemic counties in China (33,118) where the standard of living has been dramatically improved, it is at present not feasible to eradicate the disease in all endemic areas of the world. Chemotherapy is generally recognized to be the most important, the most rapid and the cheapest method to reduce morbidity due to S. japonicum (98,172,196,211).

7.1 Egg excretion

The efficacy of praziquantel against S. japonicum was first reported by Santos et al. (163) in 1979. Treatment with a total of 60 mg/kg in three divided doses at four-hour intervals yielded a stool egg-negative rate of 80% (60/75) and an egg reduction rate of 96% at six-month follow-up. Since this first report in 1979, many reports and review papers have consistently shown promising therapeutic effects and mild side effects (9,38,39,40,47,65,71,77,114,115,138,139,149,160,164,177,223,226,234,239). The total doses used were mainly 40, 50, 60 or 70 mg/kg administered in divided doses in one or two days. However, single-dose treatment with 40 or 50 mg/kg was also used. In acute schistosomiasis with heavy infection, a total of 120 mg/kg in four to six days was used in China (38,40,137). Parasitological cure as confirmed by repeated hatching tests (3-6 tests) at six to 12 months after treatment was higher than 97% in China in areas where the transmission was basically interrupted and when a total dose of 60 mg/kg was used (38,65,114,137,234,238). When this dosage was given to dogs and rabbits experimentally infected with S. japonicum (38,115,137,168), complete parasitological cure was achieved. However, when 60 mg/kg of praziquantel were given in divided doses on the same day in the Philippines, the cure rate as assessed by the Kato-Katz stool examination method was 80%. This cure rate is lower than that observed in China where sensitive miracidial hatching tests were used for assessment of cure (139,160,163,164). Reinfection after treatment (and possibly strain differences) may also contribute to this difference in results. WHO currently recommends a dosage of 60 mg/kg in two divided doses given at a four-hour interval on the same day (212).

In addition to praziquantel, amoscanate (nithiocyamine) was widely used for the treatment of *S. japonicum* infection in the late 1970s and early 1980s in China. The drug has the advantages of a satisfactory efficacy and a very low cost. However, untoward side effects, especially liver damage and cardiac arrhythmias, hinder its large-scale use (38,114). Phenithionate, an analogue of amoscanate, used in China, has been shown to have an acceptable therapeutic effect and milder side effects compared with amoscanate (38,114,157). In one trial, 88 (97.8%) out of 90 persons were negative by stool miracidial hatching tests at six-month follow-up (157). However, jaundice due to the drug was observed in 9 (1%) out of 888 persons (38,157).

Toxicity and adverse side effects from praziquantel, both in animals and humans, have been studied thoroughly and the drug is considered to be safe for use in the general population (9,38,39,47,65,71,137,138,139,160,164,168). Transient serious side effects have been reported in a very few individuals, including bloody diarrhoea (202), cardiac arrhythmia (39,219), syncope (137), epileptic seizures, serious skin rashes (39,65), etc. No deaths due to the drug have been reported in more than one million persons treated in China (38).

7.2 Decrease in morbidity

7.2.1 Symptomatic improvement

Clinical improvement of acute disease is dramatic after treatment. Generally, three to five days after the beginning of praziquantel therapy, without antipyretics or corticosteroids, subsidence of fever is noted in association with marked general improvement. Temperature returns to normal within an average of 9.5 days after the start of treatment (38,40).

Heavily infected or symptomatic patients in the chronic phase show a noticeably favourable response after treatment; symptoms disappear, body weight increases and working capacity improves (38,138).

7.2.2 Hepatomegaly and splenomegaly

After praziquantel treatment, regression of liver and spleen size has been reported in Indonesia (77), the Philippines (160) and China (234,239). Spleen size regression was shown to be less significant than that of liver size at short-term follow-ups (77,160). A four-year follow-up was done on 287 patients out of an original cohort of 502 in Jiaxing County, Zhejiang Province, where transmission was practically interrupted. Before treatment, 110 of the 287 patients who were subsequently followed had a palpable liver below the right costal margin, 193 more than 2 cm below the xyphoid and 96 had splenomegaly. Physical examination carried out four years later revealed hepatomegaly below the right costal margin in 35 persons, i.e. a 68% decrease, and at more than 2 cm below the xyphoid in 78 persons, i.e. a 60% decrease, and splenomegaly in 19 persons, i.e. a 80% decrease (239). Among an original cohort of 224 persons, in whom the rate of hepatomegaly before treatment was 42% (93/224) below the right costal margin and 70% (156/224) below the xyphoid, a decrease to 14% (30/224) and 22% (49/224) respectively, was observed at seven years after treatment. The splenomegaly rate fell from 33% (73/224) before treatment to 8% (18/224) at seven years after treatment (238). In Leyte at four years after praziquantel treatment, 78 patients also showed remarkable improvement (55%) of hepatosplenomegaly (82).

7.2.3 Cerebral schistosomiasis

The prognosis for cerebral schistosomiasis after antischistosomal drug treatment is guarded. Among 99 persons with symptoms of epileptic seizures who were treated with trivalent antimonials and followed up for 4-19 years, 50 (51%) had ceased to have seizures and 22 (22%) continued to have seizures but at a decreased frequency. However, during the follow-up period five patients died of accidents related to the seizures (138). In a six-year follow-up of 70 cases, Hayashi et al. (83) reported that

only 17% had no seizures after treatment with stibophen and niridazole, while 75% of the patients treated with praziquantel had no seizures during the last four years. Praziquantel seemed to be more effective than the other drugs in reducing the occurrence of seizures. A seven-year follow-up of 60 cases in Leyte (84) revealed that in 45 persons (75%) the seizures disappeared and that abnormal EEGs were seen in 23% of the cases upon follow-up in contrast to 43% before treatment with antischistosomal and anticonvulsant drugs.

Cerebral schistosomiasis has been successfully treated with praziquantel (201). Among nine patients with epileptic seizures due to schistosomiasis and treated with praziquantel, eight were cured and one showed improvement. The effectiveness of treatment was confirmed at a six-month follow-up with clinical history, clinical examination, EEG and CT scans; the latter showing dissipation of cerebral oedema and complete or near-complete resolution of mass lesions.

7.2.4 Epidemiological impact

The effect of mass chemotherapy with praziquantel on incidence in 1800 school children at Dagami, Leyte, was reported by Tanaka et al. (176,177). One year after mass chemotherapy incidence was markedly reduced and remained low for the next four years during which yearly stool examinations and treatment of those infected were carried out. In the same district, a small-scale environmental modification programme did not contribute to the decrease of the incidence (175,178).

In some follow-up studies, serological tests were performed periodically. A statistically significant reduction of prevalence by 15-17% according to the ELISA was detected in the second and third year of a control programme using selective population chemotherapy in Leyte (226). Fu et al. (65) reported that, while nearly 100% of the infected subjects in Shanghai had become egg negative by stool examination in the follow-up period, COPT negative rates were 30% and 52% at 9-12 and 30 months after treatment, respectively. Antibody persisted longer than excretion of eggs in stool. Negative conversion rates of 84% (135/160) with ELISA and 89% (39/44) with COPT were reported by Zhou et al. (239) after a four year follow-up. After seven years, negative conversion rates of 92% (99/108) with ELISA and 85% (46/54) with COPT were reported (238).

8. CONCLUSIONS

S. japonicum infection is generally considered to be more severe than S. mansoni infection since S. japonicum female worms have a much higher egg output and the eggs are laid in large aggregates that induce intensive tissue reaction. The pathogenesis of S. japonicum infection is somewhat different from that of S. mansoni infection probably because modulation of the egg granuloma in the former is antibody mediated. The clinical manifestations are varied, but the liver and lower intestinal tract are the most severely affected organs. Acute schistosomiasis is more frequently seen in S. japonicum infection than in other forms of schistosomiasis. Pulmonary schistosomiasis is usually seen in the acute phase which induces discomfort to the patient but no serious sequelae. Compared with schistosomiasis due to S. mansoni, cor pulmonale is far less frequent in hepatic S. japonicum infections and glomerulonephritis is rare. The major cause of death is blood loss due to upper gastrointestinal bleeding from oesophagogastric varices, the sequela of portal hypertension. However, hepatic coma secondary to the bleeding and to impaired liver function is not uncommon, although concomitant HBV infection may be a complicating factor. In human infection, apart from liver involvement, the tissue density of S. japonicum eggs increases from the small bowel towards the rectum. The rectum and the sigmoid colon usually have heavy egg burdens and show severe morbidity. The hypothesis that colorectal cancer in endemic areas is most probably related to schistosomiasis is supported by epidemiological and clinico-pathological data while the relationship of the infection to gastric cancer is doubtful and there is no conclusive evidence for an association between the infection and liver cancer. Intensity of the infection is a major factor in the development of disease. Intensive control programmes

using praziquantel have reduced both the disease rates and the intensity of infection in most endemic communities. Control programmes still confront difficulties regarding elimination of Oncomelania hupensis snail habitats, provision of safe water supply and sanitation, and interruption of the transmission. Moreover, they must rely on relatively insensitive diagnostic techniques for the assessment of infection and morbidity. While repeated chemotherapy is playing a major role in the control of morbidity, a better understanding of the disease and improved control measures, including better diagnosis, are necessary.

RESUME

PROGRES DE L'EVALUATION DE LA MORBIDITE DUE AUX INFESTATIONS A SCHISTOSOMA JAPONICUM : PANORAMA DE LA LITTERATURE RECENTE

On considère en général que les infestations à Schistosoma japonicum sont plus graves que celles à S. mansoni, car la femelle de S. japonicum pond beaucoup plus d'oeufs qu'elle dépose en gros amas et qui induisent une forte réaction tissulaire. La pathogénie de l'infestation à S. japonicum est quelque peu différente de celle de l'infestation à S. mansoni, probablement parce que les phénomènes modulant des granulomes chez la première sont médiés par anticorps. Les manifestations cliniques sont variables, mais les organes les plus gravement atteints sont le foie et les voies digestives basses. La schistosomiase aiguë s'observe plus souvent dans les infestations à S. japonicum que dans les autres formes de schistosomiase. La schistosomiase pulmonaire s'observe en général au cours de la phase aiguë, qui est très inconfortable pour le malade, mais ne laisse pas de séquelles graves. Le coeur pulmonaire est beaucoup moins fréquent dans les atteintes hépatiques dues à S. japonicum que dans la schistosomiase à S. mansoni, et la glomérulonéphrite est rare. La principale cause de décès est l'hémorragie digestive par rupture de varices oesophagiennes, séquelles de l'hypertension portale. Toutefois, il n'est pas rare de rencontrer un coma hépatique faisant suite à ce type d'hémorragie et à une altération de la fonction hépatique, et une hépatite B concomitante peut constituer un facteur de complication. Chez l'homme, en dehors de l'atteinte hépatique, la densité tissulaire des oeufs de S. japonicum va en augmentant de l'intestin grêle au rectum. Le rectum et le sigmoïde présentent en général une forte charge ovulaire, entraînant des manifestations graves. L'hypothèse selon laquelle les cancers rectocoliques soient très probablement liés à la schistosomiase dans les régions d'endémie s'appuie sur des données épidémiologiques et anatomocliniques, alors qu'il est peu probable qu'il y ait une relation entre cette infestation et le cancer de l'estomac et que rien ne permet d'affirmer qu'elle soit associée au cancer du foie. L'intensité de l'infestation est un facteur important de l'évolution de la maladie. Les programmes de lutte intensive avec le praziquantel ont réduit à la fois la morbidité et l'intensité de l'infestation dans la plupart des communautés d'endémie. Ils se heurtent toujours à des difficultés en ce qui concerne l'élimination des habitats d'Oncomelania hupensis, l'approvisionnement en eau et l'assainissement, et l'interruption de la transmission. En outre, ils doivent se fier à des techniques de diagnostic relativement peu sensibles pour l'évaluation de l'infestation et de la morbidité. Alors que la chimiothérapie répétée joue un grand rôle dans la réduction de la morbidité, il faudrait acquérir une meilleure connaissance de la maladie et améliorer les mesures de lutte, notamment au niveau du diagnostic.

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TABLE 1. SEGMENT OF INTESTINE AFFECTED BY S. JAPONICUM INFECTION IN DESCENDING ORDER ACCORDING TO EGG DENSITY, OR EGG NUMBER, OR SEVERITY OF PATHOLOGY

Host	Results	Reference
Mouse (26)	Small intestine, colon (Japanese and Philippine strains)	Cheever & Duvall
Monkey	1. Small intestine with 41% of egg load, colon with 18% of egg load (Philippine strain) 2. Colon with 59% of egg load, small intestine with 3% of egg load (Japanese strain)	Cheever et al. (27)
Rabbit	1. Colon, small intestine (Philippine strain) 2. Small intestine, colon (Japanese strain)	Cheever et al. (29)
Jird	Ileum, upper colon, jejunum	Liang et al. (110)
Human	Rectum, sigmoid colon, descending colon, small intestine	Mao et al. (120)
Human	Rectum, sigmoid colon, descending colon, transverse and ascending colon, small intestine	Sichuan Institute of Parasitic Diseases (in reference 138)

TABLE 2. RELATIONSHIP BETWEEN S. JAPONICUM INFECTION AND OCCURRENCE OF MORBIDITY IN POPULATION STUDIES

Country	No. examined	Age group (years)	Prevalence (%)	Correlation between infection or faecal egg count and:					Reference
				Weakness	Abdominal pain	Diarrhoea	Hepatomegaly	Splenomegaly	
China									
Village A	778	2-65	26	No	No	No	(Heavily infected: No (yes	No	Warren et al. (200)
Village B	1 532	2-65	14	Yes	No	No	(Others: no	No	
Indonesia	233	All	65	Yes	Yes	Yes	Yes	No	Hadidjaja (76)
Philippines	851	All	40	-	Yes	Yes	Males: yes Females: no	Males: yes Females: no	Lewert et al. (107)
Philippines	1 010	All	32	No	No	No	Yes	No	Domingo et al. (51)
Philippines	755	All	43	-	-	Yes	Yes	Yes	WHO Workshop (209)
Philippines									
Village A	289	All	26	No	Yes	Yes	No	No	Olveda et al. (148)
Village B	824		39				Yes	No	
Village C	1 113		44	Yes	Yes	Yes	Yes	Yes	

TABLE 3. RELATIVE RISK OF CARCINOMA OF THE LARGE INTESTINE AND STOMACH IN RELATION TO S. JAPONICUM INFECTION^a

Degree of endemicity	Prevalence	Cancer of large intestine ^b		Cancer of stomach ^b	
		RR	95% CL	RR	95% CL
Non-endemic	0	1.00		1.00	
Very low	<1.0%	1.11	0.83-1.48	1.00	0.91-1.09
Low	1-9.9%	1.94	1.56-2.40	0.96	0.89-1.03
Moderate	10-29.9%	2.04	1.65-2.53	0.92	0.85-0.99
Heavy	30-49.9%	3.17	2.57-3.90	0.84	0.77-0.91
Hyperendemic	>50%	4.18	3.34-5.24	0.79	0.71-0.88

^a Based on Guo et al. (75).

^b RR = relative risk (relative risk is expressed as a multiple of the risk assessed in non-endemic areas).

CL = confidence limit.

TABLE 4. COMPARISON OF MEAN AGE AT TIME OF DIAGNOSIS BETWEEN PATIENTS WITH COLORECTAL CANCER AND WITH OR WITHOUT S. JAPONICUM INFECTIONS

Colorectal cancer with schistosome infection		Colorectal cancer without schistosome infection		Reference
Number of cases	Mean age (range) (in years)	Number of cases	Mean age (range) (in years)	
22	51 (20-78)	46	59 (22-87)	Abanilla (1)
69	49.3 (25-80)	102	50.5 (18-78)	Chen (42)
289	40.3	165	46.8	Chuang et al. (44)
279	44.7 (20-69)	653	49.1 (16-69)	Zhao & Wong (233)

ANNEX

AN EGG CONCENTRATION METHOD USING A NYLON TISSUE BAG
FOR SURVEY OF S. JAPONICUM INFECTION

(from Yu et al., 228)

The faeces (about 20-30 g) are first emulsified in water. They are then filtered through a copper gauze (60 meshes per inch) into a nylon-tissue bag (260 meshes per inch) with a small bottom hole held shut by a clip. The residue in the bag is further washed by water until it becomes clear. Anything smaller than the mesh of the copper gauze and bigger than that of the nylon tissue will remain at the bottom of the bag. The clip is removed and the sediment at the bottom of the bag is released for the miracidial hatching test or for direct microscopical examination.

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