Mem. Inst. Oswaldo Cruz, Rio de Janeiro, Vol. *87*, Suppl. IV, 291-296, 1992

INTERRELATIONSHIP BETWEEN SCHISTOSOMIASIS AND CONCOMITANT DISEASES

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The biological literature contains many examples of mutual influences between different species of parasites, especially with respect to concomitant helminth infections. Several situations are known in which the association of infection by Schistosoma mansoni *with other pathogens in the same host results in a type of disease which differs from the simple summation of the individual effects of each infection.*

The present study concerns concomitant infections involving S. mansoni *and enterobacteriaceae;* S. mansoni *and other helminths such as* Ascaris lumbricoides, *Ancylostomids,* Toxocara canis *and species of the genus* Hymenolepis; S. mansoni *and different protozoa such as* Trypanosoma cruzi, T. brucei, Toxoplasma gondii *and* Plasmodium berghei. *The interaction between hepatitis B virus and* S. mansoni, *leading to prolonged viremia and worsening of liver damage, is also discussed. The paper also treats the simultaneous occurrence of schistosomiasis and other aggravating factors such as malnutrition and neoplasias which may alter the host's response to the trematode.*

Key words: *Schistosoma mansoni* – concomitant diseases

Hosts that are common to certain parasite species may be subjected to pressures resulting in infection or multiple aggravating factors which, from a morbidity viewpoint, may result in clinical manifestations not limited to the simple summation of the individual actions of each parasite species or concomitant aggravating factor. This concomitance of aggravating factors strongly needs to be considered and, although this approach tends to be forgotten in clinical routine, it has been used in a series of situations under natural or experimental conditions (Paperna, 1964; Thomas, 1964; Halvörsen, 1976; Düwell, 1967; Chieffi et al., 1980).

Especially in the case of human or animal infection by *Schistosoma mansoni,* when several aggravating factors occur simultaneously in the same host, such as infection by other pathogens, the clinical manifestations observed may differ from the summation of the signs and symptoms that each factor would produce if it were the only one present. In the present study I shall consider concomitant infections by *S. mansoni* and enterobacteria; *S. mansoni* and other helminths such as *Ascaris lumbricoides,* Ancylostomids, *Toxocara canis* and species of the genus *Hymenolepis; S. mansoni* and different protozoa such as *Trypanosoma cruzi, T. brucei, Toxoplasma gondii* and *Plasmodium berghei.* I shall also discuss the interaction between hepatitis B virus and *S. mansoni,* as well as the simultaneous presence of schistosomiasis and malnutrition and of some types of neoplasias.

Schistosomiasis and enterobacterial infection – In 1954, Ferreira reported for the first time in Brazil the occurrence of prolonged bacteremia in patients with the hepatosplenic form of schistosomiasis mansoni. A few years later, Tai et al. (1958) described a similar phenomenon in patients parasitized by *S. japonicum.* Teixeira (1960) and Neves & Martins (1967) later characterized the occurrence of prolonged bacteremia caused by several *Salmonella* species in patients infected by *S. mansoni,* which resulted in prolonged fever and signs and symptons differing from those habitually observed in salmonellosis not associated with schistosomiasis.

This association of schistosomiasis with *Salmonella* infection was first called "prolonged septicemic salmonellosis". Later, when other enterobacterial species were detected in asso-

ciation with a similar clinical picture, the designation was changed to "prolonged septicemic enterobacteriosis" (Teixeira, 1984).

Associations of this nature have been described in patients infected by *S. mansoni* and *S. japonicum* and in animals parasitized by *S. mattheei* (Ottens & Dickerson, 1972). In the case of human infections by *S. haematobium* there is a tendency towards the development of chronic urinary infections caused by enterobacteria (Hathout et al., 1966), and some patients start to act as urinary *Salmonella* carriers without showing a defined clinical picture (Teixeira, 1984).

Enterobacteria isolated from blood cultures of patients with prolonged septicemic enterobacteriosis usually belong to the genera *Salmonella* and *Escherichia,* although the genus Shigella may also be involved in this picture (Teixeira, 1984). In experimental studies on mice, several other genera of enterobacteria have been found to be likely to associate with *S. mansoni* (Ottens & Dickerson, 1972) (Table I).

TABLE I

Enterobacterial genera detected in association with *Schistosoma mansoni* in experimentally infected mice and in naturally infected humans

Mice:	*Salmonella, Escherichia, Arizona, Klebsiella, Enterobacter, Serratia, Providencia.*
Humans:	*Salmonella, Escherichia, Schigella* (?).

Sources: Ottens & Dickerson (1972); Teixeira (1984, modified).

Among the major clinical manifestations reported by Teixeira (1984) in a study of 100 patients with schistosomiasis with prolonged septicemic enterobacteriosis (Table II) were: fever, hepatosplenomegaly, weight loss, diarrhea, abdominal pains, pale mucosae, adenomegaly, shivering, epistaxis, edema of lower limbs, petechiae, dyspnea and profuse sweating.

Experimental studies have shown that the association of enterobacteria with *Schistosoma* in the same host occurs by bacterial localization and multiplication on the surface and within the tegument of the trematode, as well as in the cecal lumen of the helminth, producing a picture of superparasitism (Young et al., 1973; Ottens & Dickerson, 1972). The presence of receptors on the tegument of the helminth facilitates interaction with enterobacteria (Rocha, 1984).

TABLE II

Major clinical manifestations of 100 patients with prolonged septicemic enterobacteriosis

Complaints/Findings	%
Fever	100
Hepatosplenomegaly	100
Weight loss	100
Diarrhea	100
Abdominal pain	100
Adenomegaly	78
Shivering	68
Epistaxis	63
Edema of lower limbs	60
Petechiae	58
Profuse sweating	51
Dyspnea	51
Cephalea	39
Coughing	36
Ascites	24
Arthralgias	17
Jaundice	17
Others	57

Sources: Teixeira (1984, modified).

Under certain circumstances, the association of enterobacteria with *S. mansoni* or other species of the genus *Schistosoma* may result in rapid and explosive multiplication of microorganisms in the helminth's cecum, causing its death. Otten & Dickerson (1972) showed that different species of enterobacteria injected into mice, hamsters or monkeys infected with *S. mansoni* and in mice or hamsters parasitized by *S. matthei* colonize the trematode's gut, massively multiplying and killing the worms by rupture of the cecum followed by penetration into the helminth's parenchyma and muscle layers. Rocha et al. (1980), in turn, found that while infection by *Salmonella typhi* is well tolerated by *S. mansoni* specimens parasitizing mice, infection by *Escherichia coli* may have a lethal effect on the trematodes.

In the case of prolonged septicemic enterobacteriosis of humans parasitized by *S. mansoni* and other species of the genus, association with the trematode may be beneficial to the bacteria, which may be able to survive for long periods by avoiding the defense mecha-

nisms of the host. Either because of the occurrence of immunodepression brought about by the schistosomal infection or because of the protection provided to the bacteria by the worm's tissues (Collins et al., 1972; Teixeira, 1984), interactions are established between trematode and microorganisms which permit the survival of the latter, so that their full elimination from the host is possible only with specific treatment of schistosomiasis in addition to the use of antibiotics (Teixeira, 1984).

Recently, Chieffi et al. (1989) showed that intraperitoneal inoculation of mice with endotoxin produced by an enteropathogenic strain of *E. coli* 60 days after the onset of experimental *S. mansoni* infection produced significantly higher mortality rates than in the presence of each infection separately or even simultaneously but with inoculation of the toxin preceding the schistosomal infection. Intraperitoneal injection of dexamethasone before endotoxin inoculation into mice with schistosomiasis (Chieffi et al., 1990) was also found to have a significant protective effect. This suggests that tumor necrosis factor (TNF) is involved in the increased lethality occurring after administration of *E. coli* endotoxin to mice with schistosomiasis since endotoxin-producing microorganisms induce TNF production and release by macrophages and other cells (Cerami & Beutler, 1986; Beutler & Cerami, 1987), which can be blocked by previous administration of corticosteroids (Chia & Pollack, 1989).

Schistosomiasis and other helminthic infections – The occurrence of schistosomiasis mansoni seems to prevent infection by certain geo-helminths in patients residing in endemic areas. In support of this hypothesis, Chamone et al. (1990) reported a lower frequency of parasitism by Ancylostomids, *A. lumbricoides* and *Trichuris trichiura* among individuals infected by *S. mansoni* when compared to other individuals residing in the same region but not infected by the trematode.

In a study still underway, Chieffi et al. (unpublished results) raised the hypothesis that the interaction between *T. canis* and *S. mansoni* in experimentally infected mice may alter the clinical course of schistosomiasis, possibly resulting in more benign conditions than in the presence of infection by *S. mansoni* alone, since a lesser increase in spleen volume was observed in mice submitted to double infection.

On the other hand, in a study conducted by Andreassen et al. (1990), mice in the phase of overt schistosomal infection, but not during the period preceding overt infection, expelled more rapidly experimental infections by *Hymenolepis diminuta* and *H. microstoma*, perhaps as a consequence of the intense inflammatory response induced by the presence of *S. mansoni* eggs in the animals at the intestinal submucosal and mucosal levels.

Schistosomiasis and protozoan infections – Previous infection by protozoa such as *T. gondii, T. cruzi, T. brucei* and *Plasmodium berghei yoelii* in mice with schistosomiasis tend to reduce the area of granulomatous reaction around the *S. mansoni* eggs retained in the tissues, suggesting a decreased activity of protective mechanisms due to cellular immunodepression (Mahmoud et al., 1977; Abdel-Wahab, 1974; Genaro et al., 1986; Fagbemi, 1987).

In these cases, however, less marked clinical manifestations would still occur than in controls only infected by *S. mansoni*. Mahmoud et al. (1977) detected lower pressor levels in the portal system of mice with schistosomiasis simultaneously infected by *T. gondii*, as well as the absence of esophageal varices.

Different results were obtained by Kloetzel et al. (1973) who detected a significant increase in *T. cruzi* parasitemia in mice with schistosomiasis when infection by *S. mansoni* preceded inoculation with *T. cruzi*. Another study by the same group (Kloetzel et al., 1977) revealed considerable deleterious effects suchs as weight loss, marked splenomegaly and higher lethality in mice simultaneously infected by *T. gondii* and *S. mansoni* when infection by the trematode preceded infection by the protozoan by 59 days, with unremarkable effects being observed when *T. gondii* inoculation was performed previously. These findings suggest that immunosuppression processes that become established during the course of schistosomal infection may decisively change the response of the host to the protozoa.

Schistosomiasis and hepatitis B virus infection (HBV) – Association between schistosomiasis and HBV infection is considered to be an important cause of worsening of liver disease caused by schistosomiasis, especially when the viral infection becomes chronic (Strauss & Lacet, 1986). This association is more frequently encountered in patients with the

hepatosplenic form of schistosomiasis who have already suffered bleeding episodes, suggesting the effect of patient handling in the hospital on HBV transmission (Strauss & Lacet, 1986).

Several studies carried out in Brazil have indicated a more common association of HBV with more severe forms of schistosomiasis mansoni when compared with the intestinal forms of the disease and with the population at large, as indicated by the data summarized in Table III.

TABLE III

Frequency (%) of HBV infection according to the clinical form of schistosomiasis

Schistosomiasis	Guimarães (1973)	Lyra (1976)	Silva (1979)
Intestinal form	1.5	1.5	0.9
Hepatosplenic form	4.4	7.8	22.5
Normal controls	0.6	1.3	–

Source: Strauss & Lacet (1986, modified).

The presence of HBAgs in patients with schistosomiasis is frequently associated with the occurrence of telangiectasias, jaundice and changes in liver enzyme levels (Lyra, 1984). Madwar et al. (1989), in addition to finding that only 19% of 105 patients with schistosomiasis studied in Egypt had no serological marker for HBV infection, noted a higher incidence of symptoms such as nausea and vomiting among HBV-infected patients with schistosomiasis. These findings raise the hypothesis that part of the clinical symptoms commonly attributed to schistosomiasis may be due to hidden HBV infection.

Patients with concurrent schistosomiasis and HBV, in addition to having a more serious course, may represent an important reservoir of the virus for the community in which they live. Hammad et al. (1990) reported the presence of HBAgs in 58% of children with hepatic fibrosis of schistosomal origin, as opposed to only 2% of children without schistosomiasis.

The presence of schistosomal infection may possibly alter the response of the host to HBV. Patients with schistosomiasis, and with the hepatosplenic form in particular, tend to respond in a less significant manner to vaccination against hepatitis B (Bassili et al., 1987; Ghaffar et al., 1990).

New perspectives for the proper understanding of the interrelationships between schistosomiasis and HBV infection have been recently opened by the study of Anderson et al. (1991) which indicates the possibility of obtaining a viable experimental model for the simultaneous study of the two diseases in the eastern woodchuck (Marmota monax).

Schistosomiasis and malnutrition – Malnutrition, a common occurrence in Brazilian regions endemic for schistosomiasis, plays an important role among the adverse conditions which may modify the course of schistosomiasis when associated with the infection.

Coutinho (1976), in a study in the hinterland of the State of Pernambuco, detected a higher frequency and intensity of signs of malnutrition in individuals infected by *S. mansoni*. At the same time, complications attributable to the trematode were more intense in malnourished patients.

In experimental studies, several investigators have shown increased lethality in mice with schistosomiasis submitted to low-protein diets (Akpom & Warren, 1975; Magalhães et al., 1986; Kanarek et al., 1988) both in severe and less severe situations in which protein ingestion, although insufficient, was not much below levels considered normal.

Apkom (1981), in turn, reported an alteration in granuloma formation around *S. mansoni* eggs in mice submitted to low-protein diets.

On the other hand, host malnutrition may also cause morphological and biological changes in *S. mansoni* specimens. De Witt (1957) detected atrophied and immature *S. mansoni* specimens in mice submitted to severe malnutrition. Magalhães et al. (1986) did not detected any physiological changes in *S. mansoni* specimens obtained from malnourished mice, but did find worms of smaller size. Kanarek et al. (1988) did not detect any significant alterations in the appearance of worms recovered from moderately malnourished mice.

Schistosomiasis and neoplasias – Interrelationships between schistosomiasis and the occurrence of neoplasias such as colon polyps in schistosomiasis mansoni and carcinoma of the bladder in hematobial schistosomiasis have long been known (El-Balkainy & Chu, 1981). However, other forms of association between

neoplasias and schistosomiasis have been reported in the literature.

Paes & Marigo (1981) reported the relatively frequent detection of primitive giant follicular lymphoma of the spleen in patients with schistosomiasis and proposed that this finding may be related to the occurrence of stimulation of lymphoid tissue brought about by the immunological alteratins inherent in schistosomiasis.

Mott (1978) raised the hypothesis of the existence of a relationship between hepatocellular carcinoma and schistosomiasis mansoni because of the high frequency of this type of cancer in certain areas where the parasitosis is endemic. However, Pereira & Gonçalves (1984) did not detect a significant difference in the frequency of schistosomiasis between patients with hepatocellular carcinoma and the general population in the State of Espírito Santo.

In an experimental study in which sarcoma 180 cells were injected into mice with schistosomiasis, Pereira et al. (1986) noted that these animals were more resistant to the tumor than controls not infected with *S. mansoni*. The authors attributed this phenomenon to a possible increase in TNF production and release by macrophages activated by the schistosomal infection, a fact also demonstrated in human patients (Zwingenberger et al., 1990).

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