COMPARISON OF PATHOLOGIC CHANGES IN MAMMALIAN HOSTS INFECTED WITH SCHISTOSOMA MANSONI, S. JAPONICUM AND S. HAEMATOBIUM

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The hepatic, intestinal and cardiopulmonary lesions produced by Schistosoma mansoni, S. haematobium and S. japonicum in man and experimental animals often bear striking similarities but usually have distinctive features as well. These are often related to parasitologic differences. Thus S. japonicum and S. haematobium lay their eggs in clusters which elicit the formation of large composite granulomas. The worms of these two species also tend to be sedentary, remaining in a single location for prolonged periods, thus producing large focal lesions in the intestines or urinary tract. Worm pairs of these two species also are gregarious and many worm pairs are often found in a single lesion. The size of circunmoval granulomas, and the degree of fibrosis, are T cell dependent. The modulation of granuloma size is largely T cell dependent in mice infected with S. mansoni but is mostly regulated by serum factors in S. japonicum infected mice. In spite of these differences in egg laying and immunoregulation both S. mansoni and S. japonicum produce Symmers’ fibrosis in the chimpanzee while S. haematobium does not, despite the presence of numerous eggs in the liver.

It has been my good fortune to have extensive opportunity to examine experimental animals infected with the three principal schistosome species infecting humans and to have participated in studies at autopsy of Schistosoma mansoni and S. haematobium infected persons. This account is based largely on that experience and from the lessons learned from Brazilian and Egyptian clinicians and collaborators. Information regarding S. japonicum infection in humans is extracted from a literature which I find often confusing and at times conflicting in its conclusions.

Parasitologic and pathologic findings vary greatly in different host species (Ho, 1963) and even in strains of a given species (Cheever et al., 1987). The strain of schistosome and its maintenance may also affect the results. I will emphasize generalities but will also accentuate differences in the reactions of various host species.

PARASITOLOGY

Egg laying (Table I) – The eggs of S. mansoni are laid singly while those of S. japonicum and S. haematobium are laid in clusters. Additionally worm pairs of S. japonicum and S. haematobium tend to cluster in groups and to remain in a single location for prolonged periods (Cheever et al., 1978) with resultant large focal lesions (Figs 1 and 2). The histologic reaction to eggs in such lesions may be predominantly diffuse although it generally retains some granulomatous element.

<table>
<thead>
<tr>
<th></th>
<th>S. mansoni</th>
<th>S. japonicum</th>
<th>S. haematobium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oviposition</td>
<td>Single eggs</td>
<td>Clusters</td>
<td>Clusters</td>
</tr>
<tr>
<td>Eggs per worm</td>
<td>800</td>
<td>3000</td>
<td>800</td>
</tr>
<tr>
<td>pair per day</td>
<td>Rare</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Nesting</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Egg distribution (Table II) – S. mansoni and S. japonicum eggs are located predominantly in the intestines and liver and in humans the colon is much more affected than is the small intestine (despite statements to the contrary in most textbook descriptions of S. japonicum infections). In experimental infections egg distribution differs with host species and parasite strain (Cheever, 1969; 1985a, b). S. haematobium eggs are predominantly in the urogenital tract in infected persons, although surprising numbers are also found in the liver and colon (Cheever et al., 1977). In most experimental hosts S. haematobium eggs are found mainly in the intestines and liver (Cheever et al., 1974).
Fig. 1: gross photograph of the bladder of a 10 year old Egyptian male. The prostate is at the bottom of the photograph and the apex of the bladder at the top. A large dark mass is present in the apex of the bladder and a smaller lesion is present around the right ureterovesical junction. *S. haematobium* worm pairs and numerous live eggs were present in the two lesions but not in the remainder of the bladder, indicating that the worms had remained sedentary in the lesions for some time.

Fig. 2: two large focal lesions (bilharziomas) are present in the colon of this rabbit infected for 1 year with *S. japonicum*. The smaller black nodules are fecal pellets. Presumably nearly all the 51 worm pairs recovered were located in these two bilharziomas as no other gross intestinal lesions were seen.
TABLE II

<table>
<thead>
<tr>
<th>Human</th>
<th>Percent distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>S. mansoni 16</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>19</td>
</tr>
<tr>
<td>Colon</td>
<td>36</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>20*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Percent distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>77</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>20</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>nil</td>
</tr>
</tbody>
</table>

* The large percentage of S. mansoni eggs in the urogenital system is probably related to the simultaneous S. haematobium infection.
** Not reported. In my own experiments I have not found significant numbers of S. haematobium eggs in the mouse bladder.

1 S. mansoni and S. haematobium from Egypt (Cheever et al., 1977). S. japonicum from histologic study of Tsutsumi & Hasuda (1964). In Brazil about 38% of S. mansoni eggs were found in the liver, 15% in the small intestine and 35% in the colon. Eggs in the urogenital system were not counted (Cheever, 1968).

2 S. mansoni (Cheever, 1969, 30 week infection).

S. japonicum (Cheever & Duvall, 1982, 26 week infection).

S. haematobium (Halawani et al., 1977, 16 week infection).

Egg destruction — Eggs of S. mansoni have a halflife of only 8 days in rhesus monkeys (Cheever & Powers, 1971) and one to two months in mice (Cheever & Anderson, 1971) while S. japonicum eggs persist in constant numbers in the tissues of mice for at least 20 weeks after treatment (Maloney et al., 1987). S. haematobium eggs persist in the tissues of humans for prolonged periods (Cheever et al., 1977). It is unclear whether S. haematobium and S. japonicum eggs persist in the tissues because they are calcified or whether they calcify in virtue of their prolonged residence in tissues. Calcified eggs generally do not elicit an inflammatory reaction and they would not appear to be pathogenetically important.

CIRCUMOVAL GRANULOMAS

T-cells are necessary for formation of granulomas of normal size around eggs of all three schistosome species (Boros & Warren, 1970; Kassis et al., 1978; Cheever et al., 1985a) and B cell-depleted mice form normal granulomas around S. japonicum and S. mansoni eggs although no antibody was detected in the circulation or in the tissues (Cheever et al., 1985b). T-cells are the predominant force in modulating the size of granulomas in S. mansoni infection in mice (Mathew & Boros, 1986) while serum factors are the principal modulating factor in S. japonicum infected mice (Olds & Stavitsky, 1986). Fibrosis of granulomas is minimal in T-cell depleted mice and nude mice infected with S. mansoni or S. japonicum (Byram et al., 1979; Cheever et al., 1985b) but fibrosis occurs in the absence of antibody (Cheever et al., 1985a).

S. mansoni eggs contain an antigen cytotoxic for liver cells and nude mice show peculiar areas of necrosis around eggs in the liver (Buchanan et al., 1973; Byram et al., 1979). This necrosis is prevented by passive transfer of antibody (Byram et al., 1979) and is also prevented by the formation of normal granulomas in the absence of antibody, e.g. in B cell depleted mice. S. japonicum eggs lack this toxic antigen and the characteristic necrosis is not noted around S. japonicum eggs in nude mice (Cheever et al., 1985b). S. mansoni infected nude mice in our laboratory (including C57BL/6, BALB/c and outbred NCR nudes) die about 8 weeks after S. mansoni infection and the same is true in most other laboratories. S. japonicum infected nude mice, in contrast, survive well even with heavy infections. Passage of S. mansoni eggs in the feces of T-cell depleted mice is dependent on the host immune reaction while nude mice pass normal numbers of S. japonicum eggs (Cheever et al., 1985b). The relation of egg retention or passage to mortality or tissue reaction to the egg is unclear.

HEPATIC, INTESTINAL AND CARDIOPULMONARY LESIONS

Liver (Table III) — Symmers' clay pipestem fibrosis of the liver is the cause of severe disease in S. mansoni infection and this lesion was well described by Bogliolo (1957) and by Andrade (1965). One clearly similar description exists for S. japonicum infected humans (Sulit et al., 1964) but other accounts include cases with cirrhosis (Tsutumé & Nakashima, 1972), a condition clearly not causally associated with human S. mansoni infection (Andrade, 1968). No statistical analysis has been made to support the association of S. japonicum infection with cirrhosis. S. japonicum infection in rabbits produces both Symmers' fibrosis and cirrhosis (Cheever et al., 1980) but in chimpanzees only Symmers' fibrosis results (von Lichtenberg et al., 1971). The ability to diagnose Symmers' fibrosis by ultrasonography (Fig. 4) (Cerri et al., 1984) will undoubtedly contribute greatly to clinical and epidemiological studies.
TABLE III

Hepatic pathology in *S. mansoni* and *S. japonicum* infections

<table>
<thead>
<tr>
<th>Host</th>
<th>Symmers' fibrosis</th>
<th>Cirrhosis</th>
<th>Hepatoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. mansoni</em></td>
<td><em>S. japonicum</em></td>
<td><em>S. mansoni</em></td>
</tr>
<tr>
<td>Human</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Monkey**</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Mouse</td>
<td>0***</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*None of these lesions occur in *S. haematobium* infections.

**Includes rhesus, capuchin (cebus) and African green (grivet, vervet) monkeys.

***Warren (1966) and Andrade (this Symposium) consider that mice do develop Symmers' fibrosis.

Hepatomas are clearly not associated with *S. mansoni* infection in man (Santana Filho, 1964; Cheever & Andrade, 1967) but occurred in 26% of *S. japonicum* infected individuals as compared to 8.5% of uninfected persons at autopsy in Kurume, Japan (Kojiro et al., 1986). The very high prevalence of hepatoma in this study suggests the presence of other factors as well. A case-control study of patients with hepatoma in Japan also showed schistosome infection to be a significant risk factor (Inaba et al., 1984). Hepatomas can be produced in *S. mansoni* or *S. japonicum* infected mice treated with low doses of carcinogens (Domino et al., 1967; Miyasato, 1984).

Intestinal lesions (Table IV) – Colonic polyposis produces severe diarrhea and characteristic lesions (Fig. 3), particularly in Egypt, and is associated principally with *S. mansoni* infections. The polyps are inflammatory, not adenomatous, and are not associated with colonic cancer (Dimette et al., 1956). Similar lesions are virtually unheard of in Brazil although the intensity of colonic involvement is similar (Cheever, 1968; Cheever et al., 1978). *S. japonicum* infection, in contrast, has been associated with adenomatous polyps and with colonic cancers in an excellent pathological study (Chen et al., 1980). Intestinal cancers have not been described in experimental schistosome infections.

Large tumor-like masses or bilharziomas have been described in humans and experimental animals infected with all three schistosome species. Such lesions are frequently located in or around the intestines.

TABLE IV

Colonic pathology in schistosome infected humans

<table>
<thead>
<tr>
<th></th>
<th><em>S. mansoni</em></th>
<th><em>S. japonicum</em></th>
<th><em>S. haematobium</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggs in small intestine</td>
<td>± (*)</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Eggs in colon</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Inflammatory polyps colon</td>
<td>± (Egypt)</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>Adenomatous polyps colon</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Colon carcinoma</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

(*) The proportion of eggs in the small intestine increases in *S. mansoni* infected cases with Symmers’ fibrosis.

Cardiopulmonary schistosomiasis – Schistosomal pulmonary arteritis related to eggs and granulomas has been described in experimental animals and humans infected with all three schistosome species and associated cor pulmonale occurs in humans (Andrade & Andrade, 1970; Ostrea & Marcelo, 1965). In *S. mansoni* and *S. japonicum* infections this entity is seen only in cases with Symmers’ fibrosis while in *S. haematobium* infection eggs may pass from the venous plexus of the urinary tract to the lungs and are not dependent on the collateral circulation produced by hepatosplenic disease, yet schistosomal cor pulmonale is an infrequent complication of *S. haematobium* infection (Cheever et al., 1978).

Effects of intensity of infection – Heavier schistosome infections are associated with increased frequency of severe pathologic changes in *S. mansoni* (Cheever, 1968), *S. haematobium* (Cheever et al., 1978) and *S. japonicum* (Tsutsumi & Nakashima, 1972).
Fig. 3: surgically resected segment of colon from an Egyptian patient with severe schistosomal colonic polyposis. The polyps are inflammatory rather than neoplastic lesions.

Fig. 4: ultrasonogram of the liver of a S. mekongi infected Laotian patient seen at the National Institutes of Health. The ecogenic semicircle at the bottom is diaphragm. The smaller, round white areas in the center of the photograph are Symmers' periportal fibrosis.
infections in man, but this does not deny the possibility of other important pathogenetic factors such as differences in host hypersensitivity or immunity. The intensity of experimental infections also generally correlates with the pathology produced. Intense infections in mice at times elicit modulatory effects related to infection intensity. The total pathology remains greater in the heavily infected mouse but the pathology per worm pair or per egg may be reduced. Thus heavily infected mice with *S. japonicum* have smaller circulau granulomas than do lightly infected mice while no such effect is seen with *S. mansoni* infections. Total hepatic collagen increases as the number of worms pairs increases but collagen per egg decreases with increasing intensity of infection in mice infected with either species.

**Other differences** — Many other distinctive features of infection with the three schistosome species have not been considered, such as cerebral lesions in *S. japonicum* infection.

**CONCLUSIONS**

The diversity of the lesions associated with *S. mansoni*, *S. japonicum* and *S. haematobium* serves as a useful background for our thinking considering the pathology of schistosomiasis. The variability between the pathology produced in man and in experimental hosts should lead us to be cautious in our generalizations from either human or experimental material and at the same time may motivate us to re-examine our assumptions, to better formulate our questions and to be certain that whenever possible we direct our research to human as well as to experimental schistosomiasis.

**ACKNOWLEDGEMENTS**


**REFERENCES**


