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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 circumoval 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 maintenace 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 I

Patterns of egg laying by *Schistosoma mansoni, S. japonicum* and *S. haematobium*

	S. mansoni	*S. japonicum*	*S. haematobium*
Oviposition	Single eggs	Clusters	Clusters
Eggs per worm pair per day	800	3000	800?
Nesting	Rare	Common	Common

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

Distribution of schistosome eggs in the tissues

	Percent distribution		
	S. mansoni	*S. japonicum*	*S. haematobium*
Human[1]			
Liver	16	high	5
Small Intestine	19	low	3
Colon	36	high	16
Urogenital System	20*	nil	61
Mouse[2]			
Liver	77	42	31
Small Intestine	20	49	5
Colon	2	9	62
Urogenital System	nil	nil	ND**

* 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 (Tsutsume & 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*

Host	Symmers' fibrosis		Cirrhosis		Hepatoma	
	S. mansoni	*S. japonicum*	*S. mansoni*	*S. japonicum*	*S. mansoni*	*S. japonicum*
Human	+	+	0	?	0	+
Chimpanzee	+	+	0	0	0	0
Monkey**	0	0	0	0	0	0
Rabbit	0	+	0	+	0	0
Mouse	0***	0	0	0	+	+

* 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 (Domingo 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

	S. mansoni	*S. japonicum*	*S. haematobium*
Eggs in small intestine	± (*)	±	±
Eggs in colon	+++	+++	++
Inflammatory polyps colon	++ (Egypt)	++	±
Adenomatous polyps colon	0	+	0
Colon carcinoma	0	+	0

(*) 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 circumoval 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.

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REFERENCES

ANDRADE, Z. A., 1965. Hepatic schistosomiasis. Morphological aspects. *Progress In Liver Diseases. 2:* 228-242. H. Popper and F. Schaffner, Eds. Grune & Stratton, N. Y.

ANDRADE, Z. A., 1968. Can schistosomiasis cause hepatic cirrhosis. *Gaz. Med. Bahia 68:* 34-41.

ANDRADE, S. A. & ANDRADE, S. G., 1970. Pathogenesis of schistosomal pulmonary arteritis. *Am. J. Trop. Med. Hyg. 19:* 305-310.

BOGLIOLO, L. 1957. The anatomic picture of the liver in hepato-splenic schistosomiasis mansoni. *Ann. Trop. Med. Parasitol. 51:* 1-14.

BOROS, D. L. & WARREN, K. S., 1970. Delayed hypersensitivity-type granuloma formation and dermal reaction induced and elicited by a soluble factor isolated from *Schistosoma mansoni* eggs. *J. Exp. Med. 132:* 488-507.

BUCHANAN, R. D.; FINE, D. P. & COLLEY, D. G., 1973. *Schistosoma mansoni* infection in mice depleted of thymus-dependent lymphocytes II. Pathology and altered pathogenesis. *Am. J. Path. 71:* 207-214.

BYRAM, J. E.; DOENHOFF, M. J.; MUSSALLAM, R.; BRINK, L. H. & VON LICHTENBERG, F., 1979. *Schistosoma mansoni* infections in T-cell deprived mice, and the ameliorating effect of administering homologous chronic infection serum. II. Pathology. *Am. J. Trop. Med. Hyg. 28:* 274-285.

CERRI, G. G.; ALVES, V. A. F. & MAGALHÃES, A., 1984. Hepatosplenic schistosomiasis mansoni: ultrasound manifestations. *Radiology 153:* 770-80.

CHEEVER, A. W., 1968. A quantitative post mortem study of schistosomiasis mansoni in man. *Am. J. Trop. Med. Hyg. 17:* 38-64.

CHEEVER, A. W., 1969. Quantitative comparison of the intensity of *Schistosoma mansoni* infections in man and experimental animals. *Trans. R. Soc. Trop. Med. Hyg. 63:* 781-795.

CHEEVER, A. W., 1985a. *Schistosoma japonicum:* the pathology of experimental infection. A review. *Exp. Parasitol. 59:* 1-11.

CHEEVER, A. W., 1985b. *Schistosoma haematobium:* the pathology of experimental infection. A review. *Exp. Parasitol. 59:* 131-138.

CHEEVER, A. W. & ANDRADE, Z. A., 1967. Pathological lesions associated with *Schistosoma mansoni* infection in man. *Trans. R. Soc. Trop. Med. Hyg. 61:* 626-639.

CHEEVER, A. W. & ANDERSON, L. A., 1971. Rate of destruction of *Schistosoma mansoni* eggs in the tissues of mice. *Am. J. Trop. Med. Hyg. 20:* 62-68.

CHEEVER, A. W. & POWERS, K. G., 1971. Rate of destruction of *Schistosoma mansoni* eggs and adult worms in the tissues of rhesus monkeys. *Am. J. Trop. Med. Hyg. 20:* 69-76.

CHEEVER, A. W.; KUNTZ, R. E.; MYERS, B. J.; MOORE, J. A. & HUANG, T. C., 1974. Schistosomiasis haematobia in African, hamadryas and gelada baboons. *Am. J. Trop. Med. Hyg. 23:* 429-448.

CHEEVER, A. W.; KAMEL, I. A.; ELWI, A. M.; MOSIMANN, H. E. & DANNER, R., 1977. *Schistosoma mansoni* and *S. haematobium* infections in Egypt. II. Quantitative parasitological findings at necropsy. *Am. J. Trop. Med. Hyg. 26:* 702-716.

CHEEVER, A. W.; KAMEL, I. A.; ELWI, A. M.; MOSIMANN, J. E.; DANNER, R. & SIPPEL, J. E., 1978. *Schistosoma mansoni* and *S. haematobium* infections in Egypt. III. Extrahepatic pathology. *Am. J. Trop. Med. Hyg. 27:* 55-75.

CHEEVER, A. W.; DUVALL, R. H.; MINKER, R. G. & NASH, T. E., 1980. Hepatic fibrosis in rabbits infected with Japanese and Philippine strains of *Schistosoma japonicum. Am. J. Trop. Med. Hyg. 29:* 1327-1339.

CHEEVER, A. W. & DUVALL, R. H., 1982. *Schistosoma japonicum:* migration of adult worm pairs within the mesenteric veins of mice. *Trans. Roy. Soc. Trop. Med. Hyg. 76:* 641-645.

CHEEVER, A. W.; BYRAM, J. E.; HIENY, S.; VON LICHTENBERG, F.; LUNDE, M. L. & SHER, A., 1985a. Immunopathology of *Schistosoma japonicum* and *S. mansoni* infections in B cell depleted mice. *Para. Immunol. 7:* 399-413.

CHEEVER, A. W.; BYRAM, J. E. & VON LICHTENBERG, F., 1985b. Immunopathology of *Schistosoma japonicum* infection in athymic mice. *Para. Immunol. 7:* 387-98.

CHEEVER, A. W.; DUVALL, R. H.; HALLACK, T. A. Jr.; MINKER, R. G.; MALLEY, J. D. & MALLEY, K. G., 1987. Variation of hepatic fibrosis and granuloma size among mouse strains infected with *Schistosoma mansoni. Am. J. Trop. Med. Hyg. 37:* 85-97.

CHEN MING-CHAI; CHUANG CHI-YUAN; CHAN PEI-YU & HU JEN-CHUN, 198[illegible]. Evolution of colorectal cancer in schistosomiasis: transitional mucosal changes adjacent to large intestinal carcinoma in colectomy specimens. *Cancer 46:* 1661-75.

DIMMETTE, R. M.; ELWI, A. M. & SPROAT, H. F., 1956. Relationship of schistosomiasis to polyposis and adenocarcinoma of large intestine. *Am. J. Clin. Path. 26:* 266-276.

DOMINGO, E. O.; WARREN, K. S. & STENGER, R. J., 1967. Increased incidence of hepatoma in mice with chronic schistosomiasis mansoni treated with a carcinogen. *Am. J. Path. 51:* 307-321.

DUNNE, D. W.; LUCAS, S.; BICKLE, Q.; PEARSON, S.; MADGWICK, L.; BAIN, J. & DOENHOFF, M. J., 1981. Identification and partial purification of an antigen (w^1) from *Schistosoma mansoni* eggs which is putatively hepatotoxic in T-cell deprived mice. *Trans. Roy. Soc. Trop. Med. Hyg. 75:* 54-71.

DUNNE, D. W.; HASSOUNAH, O.; MUSALLAM, R.; LUCAS, S.; PEPYS, M. F.; BALTZ, M. & DOENHOFF, M., 1983. Mechanisms of *Schistosoma mansoni* egg excretion: parasitological observations with immune serum. *Para. Immunol. 5:* 1-12.

HALAWANI, A. A.; FARAG, H. & AWADALLA, H. N., 1977. Studies on experimental mixed infection *Schistosoma haematobium* and *Schistosoma mansoni* in the albino mouse. *Tropenmed. Parasit. 28:* 478-480.

HO, Y. -H., 1963. On the host specificity of *Schistosoma japonicum. Chin. Med. J. 82:* 403-414.

INABA, Y.; MARUCHI, N.; MATSUDA, M.; YOSHIHARA, N. & YAMAMOTO, S-I., 1984. A case-control study on liver cancer with a special emphasis on the possible aetiological role of schistosomiasis. *Int. J. Epidemiol. 13:* 408-412.

KOJIRO, M.; KAKIZOE, S.; YANO, H.; TSUMAGARI, J.; KENMOCHI, K. & NAKASHIMA, T., 1986. Hepatocellular carcinoma and schistosomiasis japonica. A clinicopathologic study of 59 autopsy cases of hepatocellular carcinoma associated with chronic schistosomiasis japonica. *Acta Path. Jap. 36:* 525-532.

KASSIS, A. I.; WARREN, K. S. & MAHMOUD, A. A. F., 1978. The *Schistosoma haematobium* egg granuloma. *Cell. Immunol. 38:* 310-318.

MALONEY, N. A.; HINDCHCLIFFE, P. & WEBBE, G., 1987. Loss os resistance to reinfection with *Schistosoma japonicum* after treatment with prazinquantel. *Trans. Roy. Soc. Trop. Med. Hyg. 81:* 247-254.

MATHEW, R. C. & BOROS, D. L., 1986. Regulation of granulomatous inflammation in murine schistosomiasis. III. Recruitment of antigen-specific I-J + T suppressor cells of the granulomatous response by an I-J+ soluble suppressor factor. *J. Immunol. 136:* 1093-1099.

MIYASATO, M., 1984. Experimental study of the influence of *Schistosoma japonicum* infection on carcinogenesis of mice liver treated with N-2-fluorenylacetamide (2-FAA). *Jap. J. Parasit. 33:* 41-48.

OLDS, G. R. & STAVITSKY, A. B., 1986. Mechanisms of in vivo modulation of granulomatous inflammation in murine schistosomiasis japonicum. *Infect. Immun., 52:* 513-518.

OSTREA, E. M. & MARCELO, F. B., 1965. Relationship between pulmonary schistosomiasis japonicum and cor pulmonale. A pathologic study. *Acta Medica Philippina 2 (Ser. 2):* 68-77.

SANTANA FILHO, S., 1964. Carcinoma Primário do Fígado. Thesis, Univ. Bahia.

SULIT, Y. S. M.; DOMINGO, E. O.; DALMACIO-CRUZ, A. E.; DE PERALTA, D. S. & IMPERIAL, E. S., 1964. Parasitic cirrhosis among Filipinos. *J. Philipp. Med. Ass. 40:* 1021-1038.

TSUTSUMI, H. & NAKASHIMA, T., 1972. Pathology of liver cirrhosis due to *Schistosoma japonicum.* Pages 133-146 in Yokogawa, ed., *Research in Filariasis and Schistosomiasis.* University Park Press, Baltimore, MD.

TSUTSUMI, H. & HASUDA, A., 1964. Studies on liver fibrosis (cirrhosis) due to schistosomiasis japonica. III: The state of intervention of ova in the digestive tract. *Kurume Med. J. 11:* 80-87.

VON LICHTENBERG, F.; SADUN, E. H.; CHEEVER, A. W.; ERICKSON, D. G.; JOHNSON, A. J. & BOYCE, H. W., 1971. Experimental infection with *Schistosoma japonicum* in chimpanzees. Parasitologic, clinical, serologic and pathological observations. *Am. J. Trop. Med. Hyg. 20:* 850-893.

WARREN, K. S., 1966. The pathogenesis of "clay-pipe stem cirrhosis" in mice with chronic schistosomiasis mansoni, with a note on the longevity of the schistosomes. *Am. J. Pathol. 49:* 477-489.