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ORIGINAL ARTICLE

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Chronic hepatitis in experimental schistosomiasis

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Abstract Histological features of chronic active and chronic persistent hepatitis were observed in mice, rabbits and non-human primates infected with either *Schistosoma mansoni* and *Schistosoma japonicum*. In early infection hepatitis appeared as a reactive change due to liver damage caused by the deposition of schistosome eggs, but portal and septal cellular infiltrations tended to remain long after parasite aggression had diminished or disappeared, either spontaneously with time or after chemotherapy. In rabbits, and to a lesser degree in monkeys, a picture of chronic active hepatitis was present, with evolution to cirrhosis in the former. The experimental findings indicate that schistosomiasis has the potential to induce chronic hepatitis and suggest that the current assumption that chronic hepatitis seen in humans with schistosomiasis is always due to concomitant viral infection should be reviewed.

Key words Experimental schistosomiasis · Schistosomal hepatitis · Chronic hepatitis · Hepatic schistosomiasis

Introduction

Histopathological features of chronic persistent and chronic active hepatitis were described long ago as an important manifestation of schistosomiasis, both in man [1] and in experimental animals [2, 20]. Chronic active hepatitis, assumed to be aetiologically related to schistosomiasis, correlated well with pipestem fibrosis [4] and with decompensated hepatosplenic disease [3].

When serological and tissue markers for hepatitis B virus (HBV) became available, it was demonstrated that: concomitant HBV infection was much more common in patients with hepatosplenic schistosomiasis than in the general populations (blood donors) [21]; HBV infection was more frequent in hepatosplenic than in hepatointestinal schistosomiasis [12, 17, 21]; HBV viraemia tended to persist for prolonged periods in hepatosplenic patients [16] and HBV infection in hepatosplenic schistosomiasis was usually associated with chronic active hepatitis and decompensated hepatosplenic disease [21]. Co-infection with HCV was also identified in patients with chronic schistosomiasis [25]. These studies helped to establish the present-day consensus that whenever chronic hepatitis is found in a patient with schistosomiasis it results from an associated infection with a hepatotropic virus. However, the relationship of schistosomiasis itself with chronic hepatitis has been little explored. To evaluate the potential of schistosomiasis to cause chronic hepatitis we examined the livers of several animal species infected with *Schistosoma (S.) mansoni* or *S. japonicum*, before and after curative treatment, to inquire whether chronic hepatitis, at least under experimental conditions, could be considered to be a component of the histopathological picture of schistosomiasis.

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Materials and methods

Routine histological sections were taken from the files of the Laboratory of Parasitic Diseases, National Institutes of Health (NIH), and microscopically examined. These were 5 μm thick sections of formalin fixed and paraffin embedded livers, stained with haematoxylin and eosin, Masson trichrome and picrosirius-red, from mice, rabbits and non-human primates infected with either *S. mansoni* or *S. japonicum*.

BALB/c mice were exposed to ten *S. mansoni* cercariae subcutaneously, treated with stibophen 14.5 weeks later and 54 of these were examined periodically over the next 41 weeks [11]. Groups of nine and 15 untreated mice were also examined at 14.5 and 22.5 weeks. Treated and untreated mice not exposed to *S. mansoni* were also examined, a total of 23 being studied.

All other animals were exposed percutaneously to Puerto Rican strains of *S. mansoni* or to Philippine or Japanese strains of *S. japonicum*. *S. mansoni*-infected animals included five chimpanzees, five capuchin monkeys and 16 African green monkeys. *S. japonicum*-infected animals were 21 capuchin monkeys, nine chimpanzees and 34 rabbits. Rabbits were treated with 25 mg/kg amoscanate by mouth 20 (experiment 1) or 11 (experiment 2)

Table 1 Parasitologic information on animals examined histologically (*ND* not done, *S. schistosoma*)

Host	Parasite species	Number	Weeks	Worm pairs	Eggs/g liver	Reference
BALB/c mouse	*S. mansoni*	9	14.5	1.2	5700	Cheever et al. 1992 [11]
BALB/c mouse	*S. mansoni*	10	19.5	0 Rx[a]	6100	Cheever et al. 1992 [11]
BALB/c mouse	*S. mansoni*	8	22.5	0 Rx	7500	Cheever et al. 1992 [11]
BALB/c mouse	*S. mansoni*	9	29.5	0 Rx	3700	Cheever et al. 1992 [11]
BALB/c mouse	*S. mansoni*	9	43.5	0 Rx	4000	Cheever et al. 1992 [11]
BALB/c mouse	*S. mansoni*	18	55.5	0 Rx	3800	Cheever et al. 1992 [11]
BALB/c mouse	*S. mansoni*	15	22	1.3	17400	Cheever et al. 1992 [11]
Capuchin monkey[b]	*S. mansoni*	5	30	51	2242	Barral-Netto et al. 1983 [6]
Capuchin monkey[b]	*S. japonicum*	16	30	5	3419	Barrel-Netto et al.1983 [6]
Capuchin monkey	*S. japonicum*	5	13–30	15–118	700–8000	Cheever et al. 1974 [9]
African green monkey	*S. mansoni*	5	13	126	600	Cheever and Duvall 1974 [8]
African green monkey	*S. mansoni*	6	134	134	1800	Cheever and Duvall 1974 [8]
African green monkey (repeated infection)	*S. mansoni*	5	134	581	3600	Cheever and Duvall 1974 [8]
Rabbit experiment 1	*S. japonicum*	6	20–26	ND	26950	Dunn et al. [14]
Rabbit experiment 1	*S. japonicum*	6	36–40	0 Rx	21160	Dunn et al. [14]
Rabbit experiment 1	*S. japonicum*	6	46–60	0 Rx	10430	Dunn et al. [14]
Rabbit experiment 2	*S. japonicum*	7	11	ND	17830	Cheever et al., unpublished
Rabbit experiment 2	*S. japonicum*	5	17	0 Rx	ND	Cheever et al., unpublished
Rabbit experiment 2	*S. japonicum*	4	47	0 Rx	6170	Cheever et al., unpublished
Chimpanzee	*S. japonicum*	9	9–82	12–352	900–5100	Sadun et al. 1970 [22]
Chimpanzee	*S. mansoni*	5	104–156	212–748	139–1103	Lichtenberg et al. 1971 [20]

[a] Rx indicates mice treated at 14.5 weeks of infection. Rabbits were treated 20 (experiment 1) or 11 weeks (experiment 2) after infection
[b] These monkeys were born at the National Institutes of Health

weeks after exposure to 100–600 cercariae. In rabbits wedge biopsies of the liver were taken periodically before and after treatment, as indicated in Table 1. Perfusion of the portal vascular system was performed to recover adult warms. Details of these experiments are given in the references cited in Table 1.

Most of the capuchin monkeys studied were born at the NIH (Table 1). The remaining non-human primates studied were obtained from commercial sources. The principles of laboratory animal care noted in NIH publication number 85-23, revised 1985 (or previous versions, as many of the experiments were completed before 1985) were followed in all experiments.

The material was examined mainly to detect morphologic signs of chronic hepatitis, as classically defined [18]. We have applied the terms "chronic persistent hepatitis" and "chronic active hepatitis" because of the morphological similarity of these changes to those used for human hepatitis. No aetiologic or pathogenetic simularities should be assumed. Briefly, chronic hepatitis consists of focal and/or diffuse infiltration of mononuclear inflammatory cells in portal spaces and sometimes extending along fibrous septa. Three varieties of chronic hepatitis were considered: chronic persistent hepatitis when the inflammation was restricted to the portal and septal fibrous tissues; chronic active hepatitis when the inflammatory cells, and sometimes the extracellular matrix, extended beyond the portal parenchymal borders, isolating viable and/or necrotic (apoptotic) hepatocytes; granuloma-associated hepatitis when portal and lobular inflammatory changes with many eosinophils were associated with active, destructive parasite-induced lesions. These hepatitic changes were separated spatially from the granulomas.

Results

S. mansoni infected mice

Mice were first examined 14.5 weeks after infection, immediately prior to treatment. There was granuloma-associated hepatitis with diffuse cellular infiltration in the enlarged portal spaces reaching the limiting plate of hepatic parenchyma, leaving a few hepatocytes isolated in the middle of the inflammatory cells. Periovular granulomas were present in most but not all inflamed portal spaces. Focal proliferation of bile ducts and periductal capillaries also occurred (Fig. 1). In early infection the predominant cell was the eosinophil, with macrophages, lymphocytes and plasma cells in much smaller numbers. The parenchyma exhibited single liver cell necrosis followed by focal infiltration of eosinophils and mononuclear cells and tiny foci of sinusoidal cell proliferation. Infiltration around hepatic vein branches occurred frequently but without evident alteration of the endothelial lining.

Later, at 22.5 weeks, schistosomal granulomas in untreated mice tended to be concentrated in periportal areas. The non-specific cellular infiltration became more lymphocytic than eosinophilic, focally distributed rather than diffuse, and bile duct proliferation became prominent. Alterations within the hepatic lobules disappeared and the granulomas decreased in size and cellularity.

After treatment schistosomal granulomas gradually disappeared, but changes of chronic persistent hepatitis remained for some weeks. Towards the end of the experimental period portal infiltration became scanty and a few residual lymphocytes and plasma cells being clustered here and there within the fibrotic portal spaces (Fig. 2). The latter often showed accumulation of brown pigment, free or inside macrophages. Total disappearance of portal infiltration was observed rarely and only at the very end of the experimental period. Hyperplastic bile ducts tended to remain so, especially in some large portal spaces.

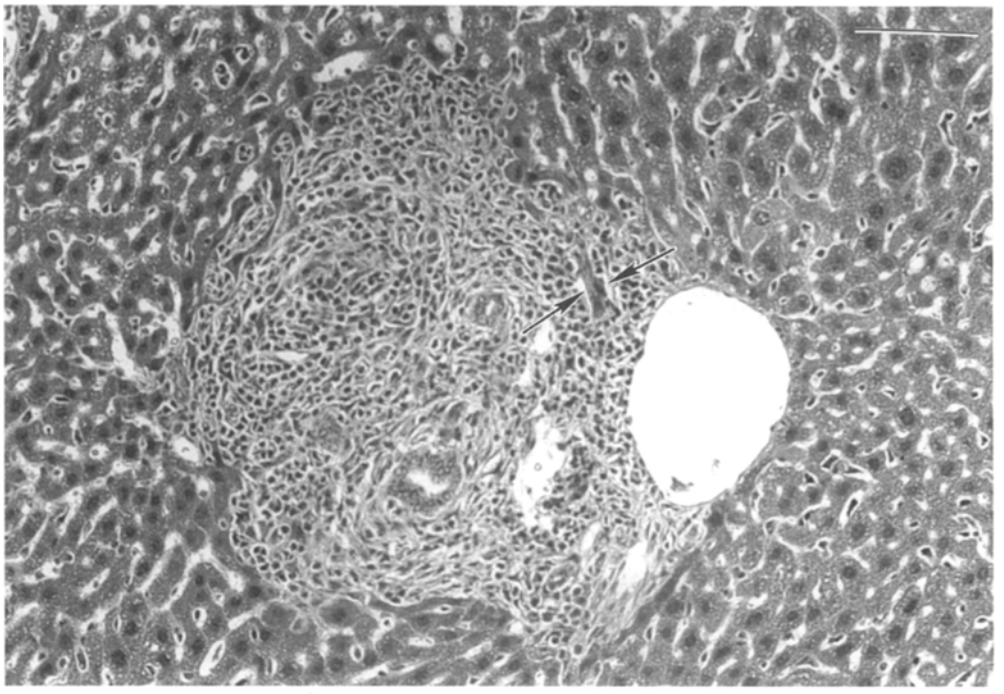

Fig. 1 Portal space of a mouse exhibiting diffuse mononuclear infiltration at 22.5 weeks of infection. There is a remnant of a schistosome egg (*arrows*), but no periovular granuloma. At the periphery of the lesion there is destruction of the parenchymal limiting plate and a few hepatocytes appear dissociated by the inflammatory infiltrate. Haematoxylin and eosin (H & E), ×200. *Bar* 100 μm

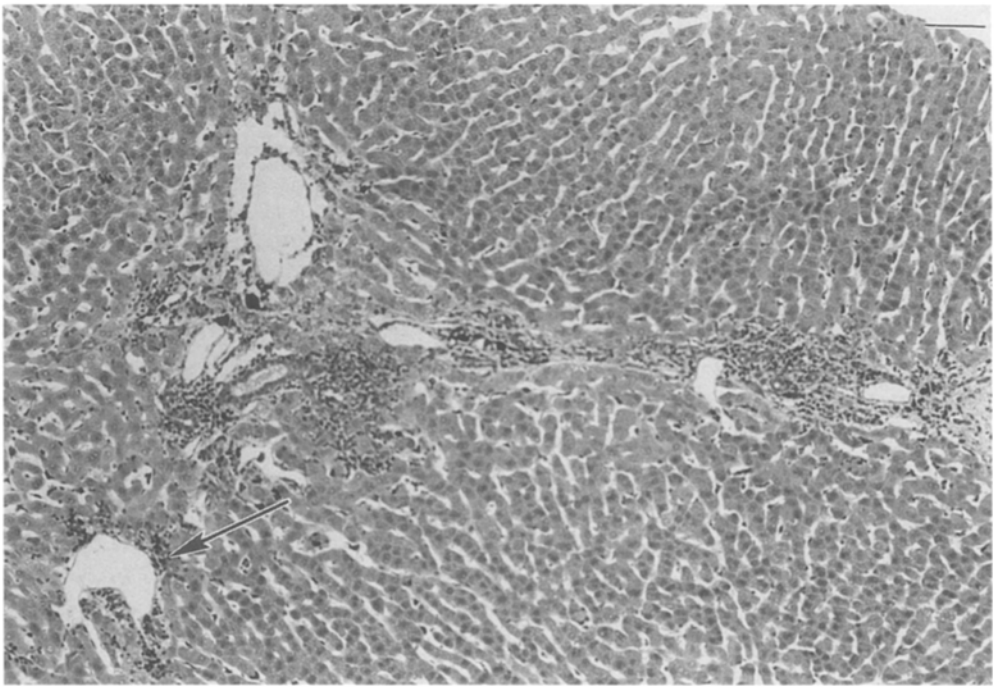

Fig. 2 Small foci of lymphocytic infiltration are seen along a thin strand of septal fibrosis, which is connecting a portal space (right) to central veins on a background of a normal-looking hepatic parenchyma. Some lymphocytes are distributed around a central vein (*arrow*). This mouse was treated at 14.5 weeks of *Schistosoma (S.) mansoni* infection and was sacrificed 8 weeks afterwards. H & E, ×100

Non-infected control animals, treated or not, exhibited liver histology within normal limits.

S. japonicum infected rabbits

Biopsy material obtained prior to treatment (20th week of infection) already showed advanced portal and septal fibrosis with large granulomas formed around isolated or clustered schistosome eggs, sometimes with purulent necrosis or epithelioid and giant cells. Signs of hepatitis (diffuse and focal, portal and septal) were present in the large majority of cases. During the active stage (first biopsy) hepatitic changes were difficult to distinguish from extensions of the granulomatous reactions. However, when parasite-related lesions involuted, either spontaneously or as a result of treatment, hepatitic changes usually became more evident. Dense collections of mononuclear cells were seen in the enlarged portal spaces and along the fibrous septa. Frequently the inflammatory

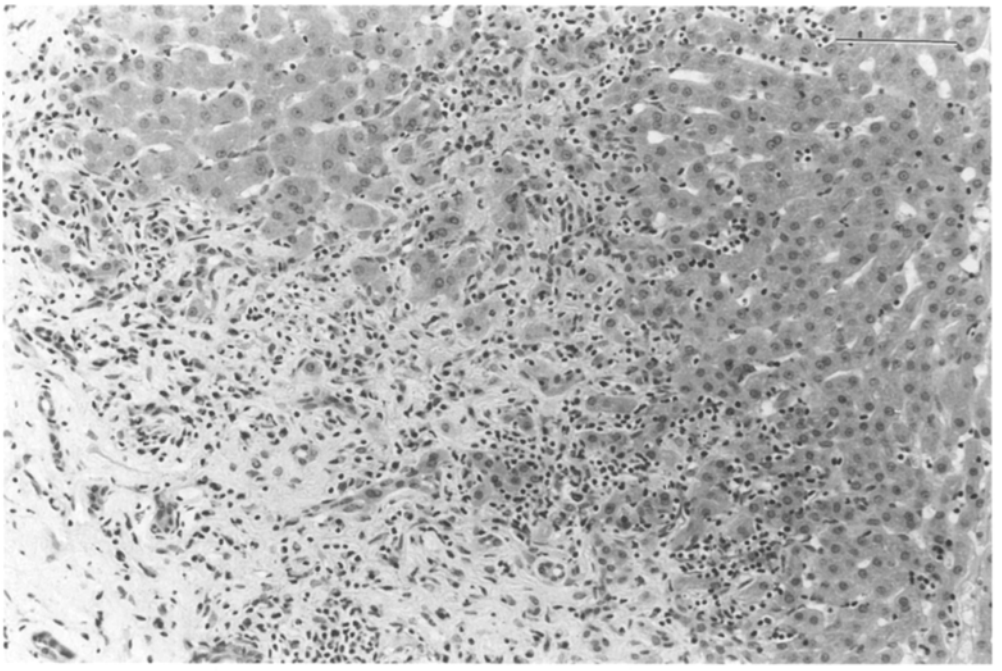

Fig. 3 Changes of chronic active hepatitis are seen in a liver biopsy of an untreated rabbit infected with *S. japonicum* for 26 weeks. At the periphery of the fibrotic and enlarged portal space, away from the periovular granulomas, the mononuclear inflammatory cells and accompanying fibrosis seem to invade the parenchymal border making irregular the portal-parenchymal limits. Masson trichrome, ×200

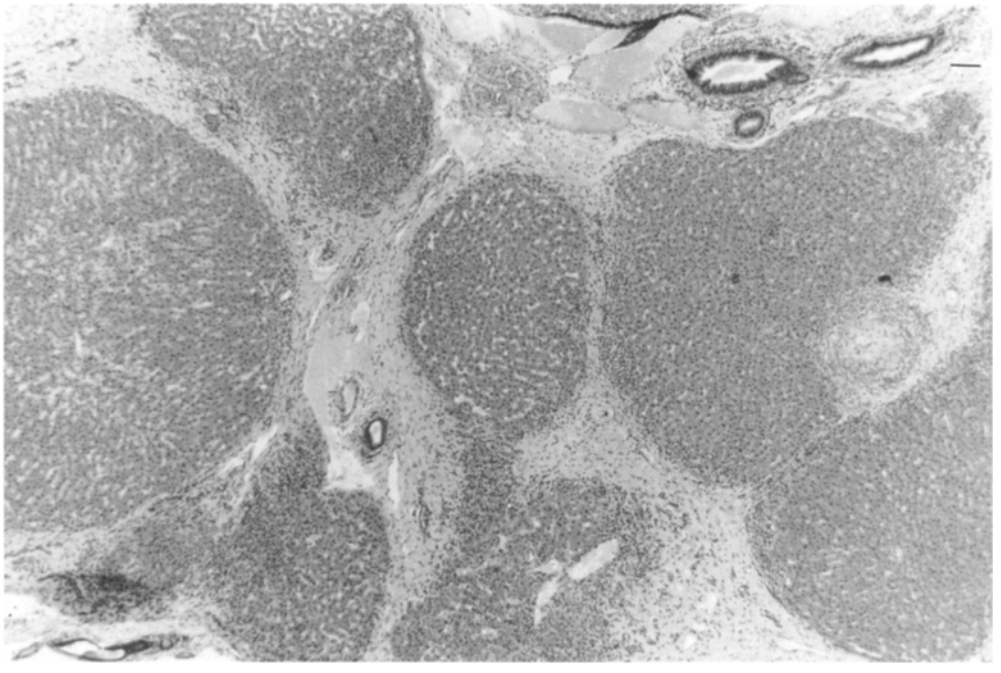

Fig. 4 The same animal from Figure 3 presented a well developed cirrhosis at 36 weeks, 10 weeks following treatment. The hepatic regenerating nodules of different sizes are separated by dense fibrous septa. Chronic active hepatitic changes are present at the periphery of the nodules. Schistosomal lesions have almost completely disappeared. Masson trichrome, ×50

cells infiltrated beyond the parenchymal border in focal areas, dissociating hepatocytes and being associated with slender fork-like extensions of the extracellular matrix (Fig. 3). In 3 of 34 rabbits examined, marked diffuse infiltration and hepatic cord dissociation at the perilobular border were observed. In these cases subsequent material revealed marked changes of chronic active hepatitis and cirrhosis, even when the schistosomal lesions showed considerable involution (Fig. 4). The hepatitic lesions were present in all sections of liver from these rabbits and involved most portal tracts. Hepatitic changes either increased, stabilized or decreased with time while the periovular granulomas were being resorbed. In a few cases all the changes, hepatitis included, progressively disappeared over time, with almost complete normalization of liver histology. No evidence of coccidial infection was seen in histological sections and bile from the gall bladder contained no coccidia. No hepatitis was seen in 12 uninfected rabbits.

S. japonicum infected capuchin monkeys

The presence of lymphocytes, plasma cells, macrophages and few eosinophils was noted in medium-sized and

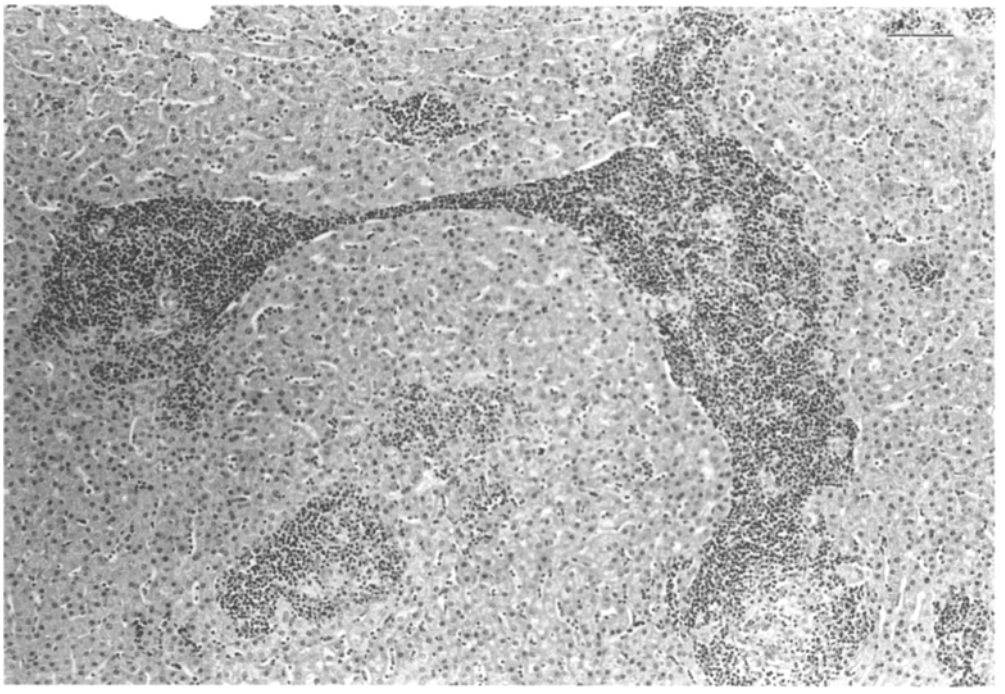

Fig. 5 The section is from the liver of an African green monkey which was heavily infected with *S. mansoni* for 30 months. Dense lymphocytic infiltration is present in portal areas and along fibrous septa. Small periovular granulomas formed mainly by epithelioid cells are seen scattered within the dense lymphocytic infiltration. H & E, ×100

large portal spaces, sometimes in the absence of granulomas or eggs (chronic persistent hepatitis).

Granulomas were often pluriovular, relatively small, rounded, discrete, scattered in distribution and usually involving small portal spaces. Some granulomas contained calcified eggs. The predominant cells in the granulomas were eosinophils. Epithelioid and giant cells were also present.

Later, there were larger, rounded, focal areas of fibrosis, sometimes with tuberculoid granulomas at their centres. Then, portal hepatitis was either residual or absent.

With heavier infections the number of granulomas was greater. The latter appeared concentrated in enlarged portal spaces with moderate fibrosis, but maintained the general pattern of isolated (non-confluent) granulomas. Hepatitis was mild and related to circumoval granulomas. Septal fibrosis was absent.

S. mansoni infected capuchin monkeys

Hepatitis was granuloma-associated and always mild, much less evident than in the *S. japonicum* infected group. Granulomas were usually centred on a single egg, seemed more cellular and less fibrotic than those of *S. japonicum* infection, but were small, round and scattered (isolated). No marked portal fibrosis and no septal fibrosis was seen. Three uninfected capuchin monkeys showed no hepatitis.

S. mansoni infected African green monkeys

In 12-week-old infections periovular granulomas were few and appeared widely separated by portions of normal-looking parenchyma. Granulomas were formed by small collections of eosinophils and lymphocytes around a central area containing egg debris, epithelioid cells and occasional giant cells. The same type of cellular infiltrate was seen in portal spaces, in the absence of eggs (chronic persistent hepatitis). There was no septal fibrosis, or evidence of vascular and fibroblastic proliferation. Portal fibrosis was minimal.

In older (30 months) light infections only a few, small, isolated periovular granulomas were present in the liver. With heavy infections there were more severe egg-induced hepatic lesions. When this occurred, the signs of chronic persistent hepatitis became more evident, sometimes with dense lympho-macrophagic infiltration of portal spaces and formation of septal fibrosis. In some areas the cellular infiltration caused disruption of the parenchyma-stromal limits (Fig. 5). Six uninfected monkeys showed no hepatitis.

S. japonicum infected chimpanzees

Portal cellular infiltrations away from granulomas formed focal collections of lymphocytes in some enlarged portal spaces, sometimes resembling lymphoid follicles. Granulomas were present in medium-sized portal spaces, and showed marked predominance of eosinophils. Pipestem fibrosis without septal fibrosis was seen in one case. With early septum formation cellular infiltrations appeared along the septa, with extensions to the parenchymal periphery in focal areas. No uninfected chimpanzees were examined.

S. mansoni infected chimpanzees

Changes of mild chronic persistent hepatitis were sometimes present. In a case with severe egg-induced lesions,

pipestem fibrosis and early septal fibrosis, hepatitic changes were almost absent.

Discussion

In addition to periovular granulomas, the extensive experimental material examined disclosed that morphological signs of chronic hepatitis are frequently present in experimental schistosomiasis, although with variable patterns and degrees of severity. These variations appeared related to animal species, parasite strain, parasite load, time of infection and even individual host factors. But chronic hepatitis, at first of reactive type and later persistent or active, appeared as a frequent, and sometimes marked, histopathological feature of experimental schistosomiasis.

In the mouse, hepatitis was clearly a response related to egg-induced granulomas during early infection but tended to change its cellular composition from eosinophilic to lymphocytic and to persist for some time after parasite stimuli had decreased, either spontaneously or following cure by chemotherapy. We designated these lesions as chronic persistent hepatitis. This latter picture never changed to an active form, but slowly evolved to residual accumulations of lymphocytes and pigmented macrophages. It has not been determined for how long a portal mononuclear infiltration will remain after its cause has been removed. However persistence of inflammatory cells may be related to the presence of residual schistosome antigens within portal spaces. We emphasize that "chronic persistent hepatitis" and "chronic active hepatitis", as used here, may not have the same connotations as these terms do in diagnostic human pathology.

Hepatitic changes were prominent in rabbits infected with *S. japonicum*, with chronic active hepatitis and progression to cirrhosis being observed in some cases. This latter picture not only resembled advanced schistosomiasis japonica in man [24], but also mimicked the development of cirrhosis in the course of chronic active hepatitis aof other aetiologies [5, 7]. Althouth spontaneous biliary cirrhosis has been described in rabbits [23], no particular involvement of the biliary structures was present in the rabbits infected with *S. japonicum*.

The non-human primates did not exhibit consistent and prominent hepatitic changes. There were great individual variations among them, but when more severe degrees of hepatitis were present a correlation with the number of periovular granulomas and with the development of septal fibrosis was apparent. The mild hepatitic changes in non-human primates, and in chimpanzees in particular, call for particular caution in attempting to relate our findings to schistosomal infections in humans.

The experimental study of schistosomal hepatitis is hampered by the fact that non-specific infiltration of portal spaces is commonly observed in laboratory animals. These changes can be aggravated by schistosomal infection, as shown by Warren et al. [26] in murine hepatitis. The animals used in the present study were relatively pathogen-free and liver sections from control animals always showed normal histology. Also, the behaviour of hepatitic changes following curative chemotherapy permitted the observation that such changes, at least in the rabbits, may develop a self-perpetuating mechanism similar to chronic active hepatitis in humans, and progressively evolve when, on the contrary, direct parasite-induced lesions are involuting. This particular evolution of schistosomal chronic hepatitis was not observed in the other hosts studied, although one green monkey presented an infiltration in the portal areas that was so marked as to simulate a lympho-proliferative disorder (see Fig. 5). However, the infiltrate was polyclonal and exhibited no cellular atypia.

It is not known whether man may develop schistosomal hepatitis and if so to what degree the changes would be comparable with rabbits, or with the other hosts. The frequent association of schistosomiasis with viral hepatitis in humans has been documented by several investigators, and also denied by others [13, 15, 19]. Cases of chronic active hepatitis have been observed in hepatosplenic patients in the absence of viral markers [21]. Evidently, co-infection with non A-non B viruses are difficult to exclude, but follow up to such patients after curative treatment of schistosomiasis may help clarify whether hepatitis is an important component of the parasitic disease itself. Our present findings in experimental animals cannot be directly transferred to humans, but at least they strongly suggest that a role for schistosomiasis in causing chronic hepatitis in man cannot be ruled out, and that this subject deserves further study.

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