PATHOPHYSIOLOGY AND PATHOGENESIS OF HEPATOSPLENIC SCHISTOSOMIASIS MANSONI*

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THE elucidation of the pathophysiology and pathogenesis of a disease has rarely been achieved by study of the human patient alone; the development of an animal model almost invariably has been a prerequisite to understanding. The present discussion is based primarily on the author's observations of clinical schistosomiasis in Brazil and experimental schistosomiasis in this country. The work of many earlier investigators provided the foundation for these studies;[1] and conversations and collaborations with contemporaries, especially William DeWitt, Franz von Lichtenberg, Allen Cheever, and Zilton Andrade, stimulated the ideas and experiments presented below.

HUMAN HEPATOSPLENIC SCHISTOSOMIASIS MANSONI

The study of a disease properly begins with the patient, in this case a human being infected with the helminth *Schistosoma mansoni*. In terms of morbidity and mortality the major clinical manifestation of severe infection with this parasite is the development of liver disease. Although there is ample evidence that this affliction of the liver is a relatively unusual type of disease clinically, pathophysiologically, and pathogenetically, the usual textbook description of hepatosplenic schistosomiasis is virtually identical with that of severe cirrhosis of the liver: "Increasing fibrosis in the liver causes it to shrink. The portal hypertension due to cirrhosis causes the spleen to enlarge, and ascites develops. There is increasing hepatic insufficiency and cholemia, which may terminate the condition in a few years. . . ."[2] A Brazilian patient typical of this description is shown in Figure 1. He was emaciated, had ascites,
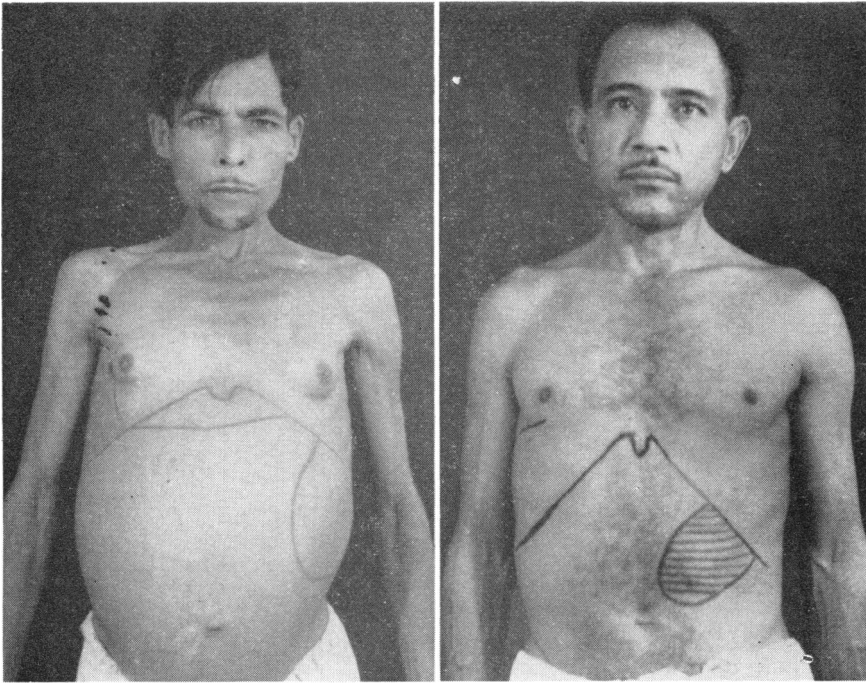
Fig. 1. Brazilian patient infected with *Schistosoma mansoni* presenting a clinical picture
resembling cirrhosis of the liver.
Fig. 2. Brazilian patient infected with *Schistosoma mansoni* presenting a clinical picture
resembling portal vein thrombosis but with a patent portal vein on splenoportography.

gynecomastia, and other stigmata of chronic liver disease, and his liver
function tests were markedly abnormal. Although this patient was in-
fected with *S. mansoni*, there was no definitive evidence that the type of
liver disease from which he was suffering was due wholly or even largely
to infection with that parasite. The tendency to ascribe all forms of
hepatic cirrhosis in endemic areas to schistosomiasis has been noted by
Hashem.[3]

A type of clinical liver disease different from that described above is
exemplified by another Brazilian patient (Figure 2), who also was
infected with *S. mansoni*. In contrast to the patient in Figure 1, he
appeared to be in good general physical condition and did not have
ascites, edema, or any of the other stigmata of chronic liver disease. Such
patients are usually functioning members of society and come to medical
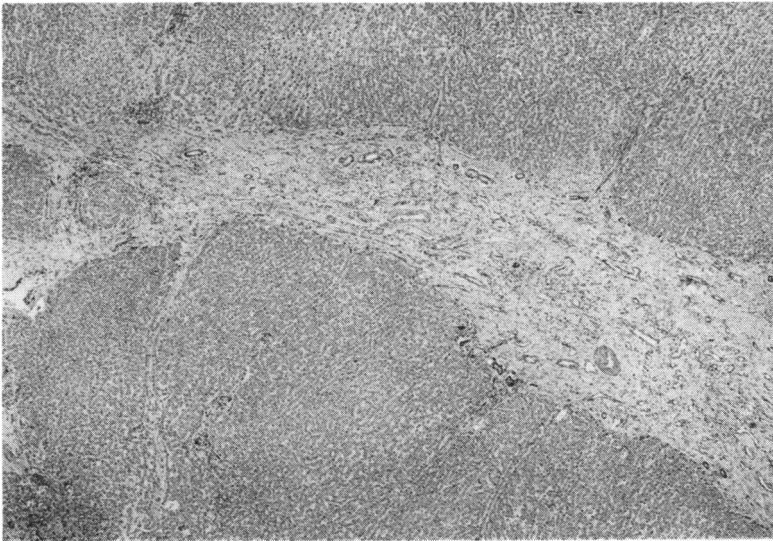attention either through the outpatient department with a complaint of

Fig. 3. Clay pipestem fibrosis in a Brazilian patient with schistosomiasis mansoni. Hematoxylin and eosin stain, ×36. Reproduced by permission from Warren, K. S., The pathogenesis of "clay-pipe stem cirrhosis" in mice with chronic schistosomiasis mansoni.[29]

a dragging feeling in the upper left quadrant of the abdomen (due to marked splenomegaly) or through the emergency ward with massive hematemesis. Examination reveals marked hepatosplenomegaly and the presence of massive esophageal varices. Liver function tests may be almost completely within normal limits or only slightly abnormal.[4, 5] On a clinical level these patients resemble those with extrahepatic portal vein thrombosis,[6] but on splenoportography, their portal veins are usually patent.[4, 7] Pathophysiological studies based on wedged hepatic vein and intrasplenic measurements of pressure have revealed an intrahepatic presinusoidal block to liver blood flow.[8, 9] In spite of this obstructive lesion total liver blood flow in a group of Brazilian patients remained unimpaired, indicating a compensatory increase in arterial blood flow.[9] This pathophysiological state, apparently occurring in relatively large numbers of patients with schistosomiasis, is virtually unique in that it has been reported only in the rare congenital hepatic fibrosis and occasionally in patients with myeloproliferative disorders and sarcoidosis.[10]

The classical pathological picture of the hepatic lesion of schistosomiasis was first described in 1904 by Symmers as "clay-pipe stem cirrhosis."[11] Hashem later suggested that the word "cirrhosis" with its im-

plications of hepatic parenchymal involvement should be replaced by "fibrosis,"[12] and Bogliolo in Brazil[13] has confirmed this lesion as pathognomonic (Figure 3). When Symmers described the disease he suggested that its cause was the schistosome eggs,[11] a large proportion of which lodge in the liver and incite a granulomatous reaction in the portal areas. Although this opinion has been supported by many investigators, including von Lichtenberg in his study of hepatic vascular lesions,[14] others have suggested that toxins produced by the worms,[15] dead worms,[16] or malnutrition[17] may be the primary pathogenic factor in the development of pipestem fibrosis. Hashem has stated, however, that the very uniqueness of the fibrotic lesion, which has nothing in common with the cirrhosis of supposed nutritional etiology, points to a schistosomal origin.[3] Andrade, calling attention to the portal inflammation frequently observed in both chronic mild and advanced schistosomiasis, has recently suggested that it is unlikely to be the result of a confluence of numerous tiny egg-induced granulomas, but that it may be due to hypersensitivity reaction of a delayed type to schistosomal antigens.[18]

In a disease that develops over decades in areas where each person is afflicted with multiple diseases, parasitic and other, it is obviously difficult to go any further in determining the etiology of hepatosplenic schistosomiasis in the human patient. In order to elucidate this problem we must turn, therefore, to models of this disease in the experimental animal.

EXPERIMENTAL HEPATOSPLENIC SCHISTOSOMIASIS MANSONI

An animal model of an infectious disease implies not only the presence of a parasitic organism in the animal but the occurrence of a syndrome similar to that seen in man. Thus, as in the case of the human disease, it is necessary to begin with the clinical picture. In the late 1950's Warren and DeWitt[19] observed that mice infected with *Schistosoma mansoni* developed hepatomegaly, splenomegaly, portal hypertension, and periesophageal varices (Figure 4), findings that have since been confirmed by Cheever[20] and Cameron and Bhattacharyya.[21] In animals with this syndrome, termed murine hepatosplenic schistosomiasis mansoni, hepatic function as measured by serum albumin concentration, icteric index, prothrombin time, and cephalin cholesterol flocculation was relatively normal.[22] Bromsulphalein retention was only moderately abnormal in heavily infected animals.[22] Sadun and Williams[23]
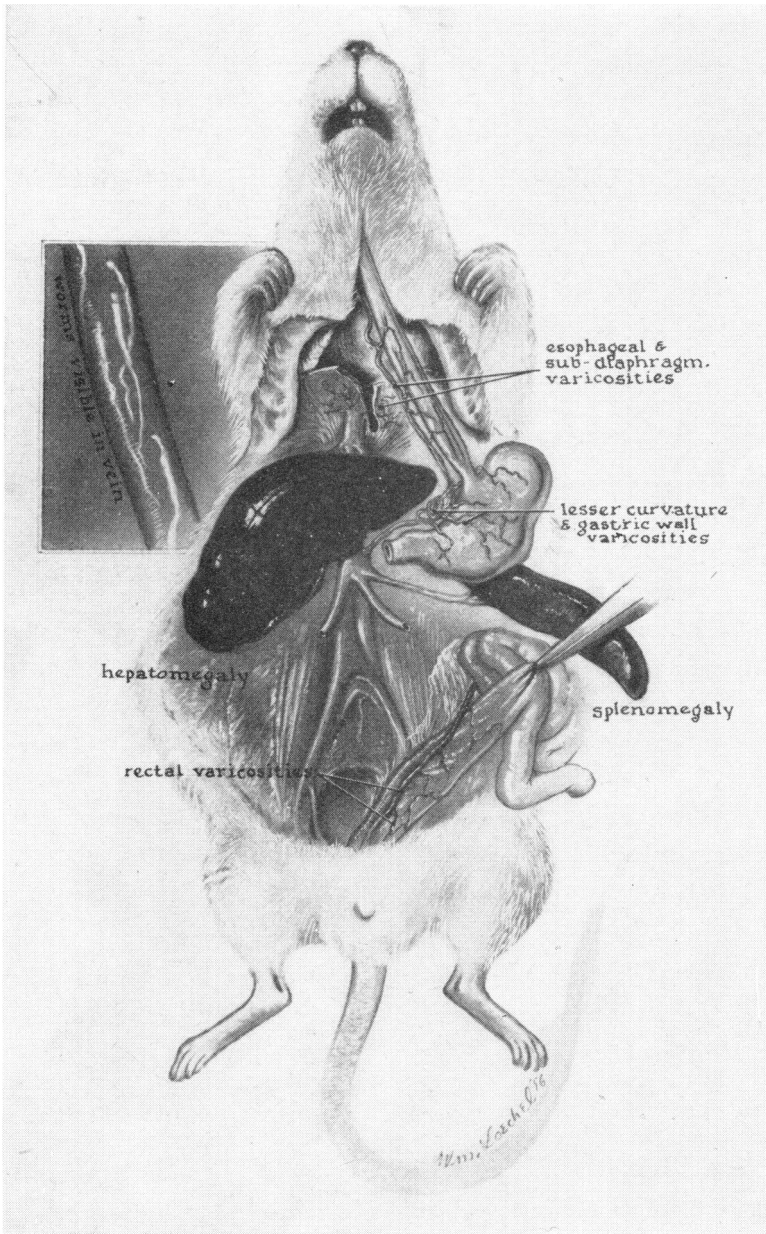
Fig. 4. Mouse with hepatosplenic schistosomiasis mansoni.

have recently found normal serum bilirubin and alkaline phosphatase concentrations and only slightly elevated levels of serum enzyme in mice with hepatosplenic disease.

Pathophysiological studies of schistosomiasis in the murine model were initiated with the demonstration of an increase in portal venous pressure to levels two or three times normal.[19, 22] The presence of extensive portal systemic collateral circulation was subsequently revealed both by x-ray portography[19] and by the injection of a yellow latex medium into the portal mesenteric venous system.[22] In spite of these changes, hepatic blood flow, which was estimated from the rate of clearance of radioactive colloidal gold from the blood, was found to be normal in both early and late infections.[20, 24] A possible explanation for these pathophysiological changes may be found in Cheever's study of hepatic vascular lesions in murine schistosomiasis mansoni,[25] which described the obliteration of small branches of the portal vein and the narrowing and distortion of larger branches by adjacent granulomas. The obstruction was anatomically presinusoidal and it seemed to Cheever to be adequate cause for portal hypertension.[25]

There was a major deficiency in the original animal model described above in that the lesion of the liver, which consisted of large discrete granulomas scattered among the portal areas, did not resemble that seen in humans with hepatosplenic schistosomiasis mansoni.[22] This was because, at the time of the first demonstration of the animal model, mice were usually exposed to such large numbers of cercariae that they developed overwhelming infections that were fatal before large amounts of fibrous tissue formed. A study of graded degrees of infection was therefore undertaken. This demonstrated that mice infected with as few as one pair of worms might develop significant hepatosplenic disease and might live indefinitely.[26] When the experiment was terminated at 25 weeks, a mild degree of portal fibrosis was observed in many of the mice.[27] More severe fibrosis of portal areas was later described by Cheever in C_3H mice infected with S. mansoni for 24 weeks.[28] In view of these observations a group of mice was exposed to low numbers of cercariae and followed for one year. Bands of fibrous tissue were seen in the livers of the animals sacrificed at 24 weeks; by 32 weeks and beyond they were of such an extent in some of the mice as to resemble clay pipestem fibrosis[29] (Figure 5).

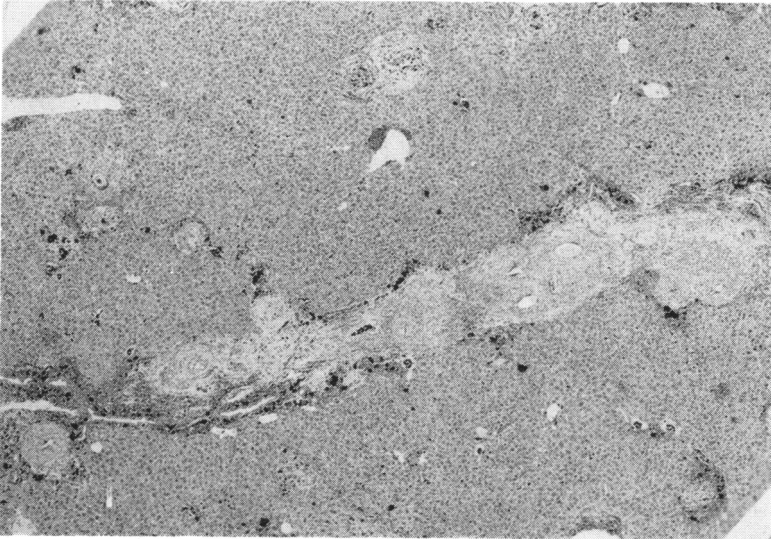As examination of the ultrastructure of the hepatic parenchymal

Fig. 5. Hepatic fibrosis in a mouse with schistosomiasis mansoni of 32 weeks' duration. Hematoxylin and eosin stain, ×36. Reproduced by permission from Warren, K. S., The pathogenesis of "clay-pipe stem cirrhosis" in mice with chronic schistosomiasis mansoni.[29]

cell may provide a sensitive index of injury, portions of the fibrotic liver in chronic murine hepatosplenic schistosomiasis mansoni were observed under the electron microscope.[30] Even parenchymal cells adjacent to granulomas or portal areas displayed no alterations in glycogen distribution or changes in the endoplasmic reticulum or mitochondria.

The availability of an animal model of clinical hepatosplenic schistosomiasis provided an opportunity to study the way in which the parasite caused the disease. Although various methods of separating out the parasite factors theoretically responsible for the disease (toxins, dead worms, eggs) had been established, each of them was found to be associated with some pathological changes in the liver.[1] Using hepatosplenic schistosomiasis as an index, these changes could be considered of major significance only if the mice developed overt disease. In one experimental study, three groups of animals, in each of which one of the factors mentioned above was isolated, were examined not only for gross and microscopic changes in the liver but also for the occurrence of clinical disease.[31] The presence of a toxin produced by the worms was rendered unlikely as the causative factor by the failure of overt disease to develop

in mice that had heavy male or female unisexual infections. The dead worm hypothesis did not appear to apply to the murine model, as treatment that killed the mature worms just prior to the onset of egg production did not result in the occurrence of hepatosplenic disease. The untreated counterparts of the mice, in which there was the usual output of eggs by the worms, all developed hepatosplenomegaly and portal hypertension. Malnutrition due to a diet deficient in protein and lipotropic substances did not exacerbate this syndrome.

Confirmation of the results of the above study has accumulated during the few years since its publication. Although it had been shown that a toxin capable of producing hepatosplenic schistosomiasis was not present in unisexual infections, it had been suggested that such a substance might occur in bisexual infections. By irradiating cercariae Erickson produced bisexual infections in which there was a marked diminution of egg output.[32] These animals did not develop overt clinical disease. In parabiotic mice only one of which was infected with *S. mansoni*, Raslavicius[33] observed only minor signs of lymphoreticular activation unaccompanied by significant liver disease in the uninfected parabiont. The electron microscope studies described above also tended to rule out the presence of a toxic factor involving the liver parenchyma.[30]

The "dead worm hypothesis" was further disproved by two subsequent studies: in one, mice with established hepatosplenic disease reverted to normal after treatment;[34] in the other the rodents were cured of three successive infections.[35] In the latter experiment an average of more than 100 dead worms entered the livers of these animals (equivalent on a weight basis to several hundred thousand worms in a human liver) without inducing overt disease of the liver.

As hepatosplenic schistosomiasis occurs in well-nourished animals in which there is little if any impairment in the absorption of fat and protein,[36] malnutrition does not seem to be necessary for its development. A poor diet may, in fact, even protect the animals, as it has been shown to limit the production of eggs by the worms.[37]

The eggs produced by the schistosomes thus were the only factor that led to overt hepatosplenic disease in mice. In addition, they appeared to be responsible for the occurrence of lesions resembling clay pipestem fibrosis in mice with chronic schistosomiasis.[29] In the earliest stages of the disease (eight weeks) when the individual granulomas around the schistosome eggs were at their maximal size they appeared to be scat-

tered singly and at random among the portal areas. By 16 weeks, when there was a marked diminution in the mean size of the granulomas, the lesions began to occur in strands a single granuloma thick. Later on more granulomas were observed on the periphery of the strands, the eggs appeared to be resorbed in many areas, and the residual collagen fibers changed from a concentric to a parallel orientation, thus developing an appearance similar to that of clay pipestem fibrosis. Recently changes resembling early clay pipestem fibrosis in man were observed in a chimpanzee with a heavy *S. mansoni* infection of seven months' duration.[38]

The granulomatous reaction of the host to the schistosome eggs, which appears to be responsible for the development of clay pipestem fibrosis, thus appears to participate in and perhaps play a crucial role in the development of overt hepatosplenic disease. The granuloma that surrounds the individual schistosome egg trapped in the host tissues is a circumscribed lesion consisting of eosinophils, macrophages, lymphocytes, epithelioid cells, and giant cells. In its acute form it is a large lesion, at times approaching 100 times the volume of the schistosome egg alone. Later, when the inflammatory cells are gone, a residue of fibrous tissue is left behind. The etiology of this reaction remained unknown until recent experiments that used a method described in the classical studies of von Lichtenberg[39] revealed that animals previously exposed to schistosome eggs developed a sensitization reaction (accelerated formation of augmented granuloma) that was specific and that could be transferred by the white cells of the host but not by serum. These results suggested that the granuloma was an immunological reaction of the delayed hypersensitivity type.[40]

The granulomatous process can be considered as a dynamic series of reactions: 1) the evolution and devolution of the individual lesion; 2) the change in the mean size of the granuloma due to the gradual accumulation of lesions in different stages of development; 3) the alteration in granulomatous response during the course of the disease; and 4) the development of residual fibrous tissue with changing rates of resorption. The development of the individual granuloma around schistosome eggs isolated from the livers of infected mice and injected via a vein of the tail into the lungs of uninfected mice was described by von Lichtenberg.[39] The lesions reached their maximum size by 16 days and gradually receded thereafter until they were almost gone by 128
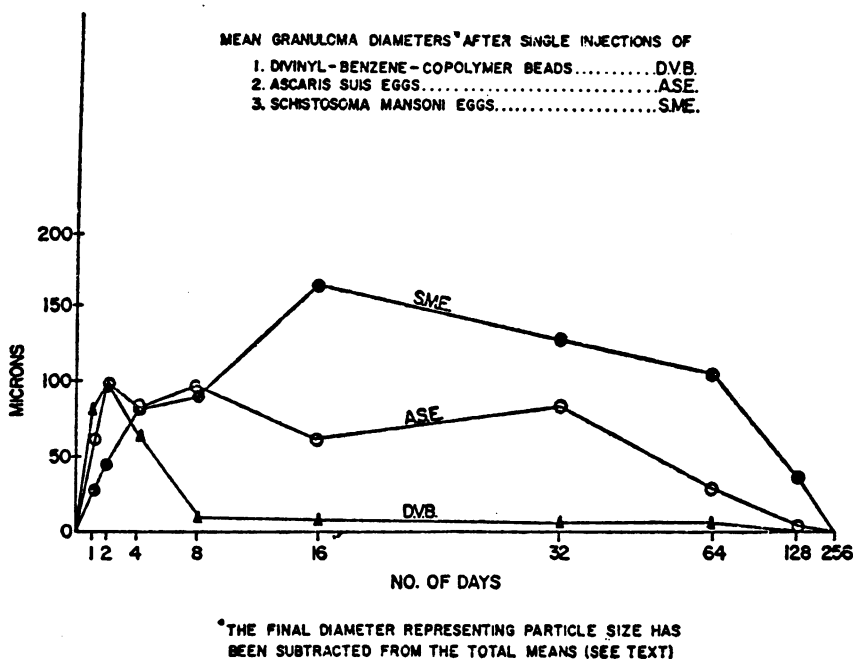
Fig. 6. Course of granuloma formation around *Schistosoma mansoni* eggs isolated from infected animals and injected intravenously into the lungs of mice. Reproduced by permission from Lichtenberg, F. v., Host response to eggs of *S. mansoni*. I. Granuloma formation in the unsensitized laboratory mouse.[39]

days (Figure 6). To complicate matters, however, granulomas in the livers of infected animals may be found in all stages of development. As described in another study,[29] the mean size of the granuloma reached its peak in the acute stage of the disease, when all of the granulomas were newly formed. As the proportion of older receding lesions gradually increased, the mean size of the granuloma decreased sharply[29] (Figure 7). This change in size was so marked that the question arose of whether other factors might be involved. As an answer to this question a marked diminution was observed in the granulomatous response to eggs newly trapped in the tissues in the later stages of stronic murine schistosomiasis.[27] While this alteration in the response of the host was confirmed by Cheever, he found it to be of a much lesser degree than had previously been suggested.[20] As both of the above studies differentiated new egg lesions from older ones in the livers of infected animals on purely histological grounds, they must be consid-
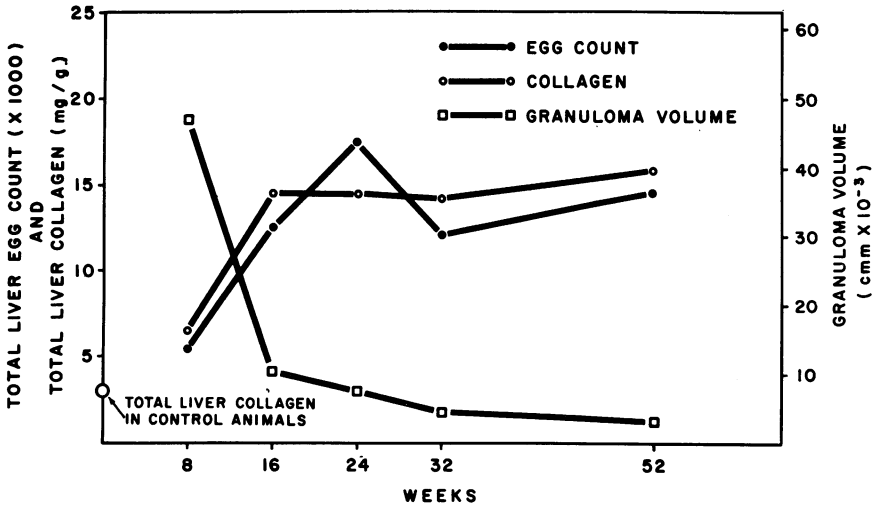
Fig. 7. Mean volume of ganulomas around schistosome eggs in the livers of mice at various time periods from 8 to 52 weeks after infection with *Schistosoma mansoni*. Reproduced by permission from Warren, K. S., The pathogenesis of "clay-pipe stem cirrhosis" in mice with chronic schistosomiasis mansoni.[29]

ered relatively inexact.[20, 27] Recently eggs isolated from the livers of groups of animals infected for eight weeks were injected into the lungs of other mice at different stages from two to 32 weeks after the inception of mild infections with *S. mansoni*. Granuloma formation around the eggs in the lungs was markedly diminished in mice infected for 16 weeks or longer.[41] In relation to the large amounts of fibrous tissue found in the livers of chronically infected animals[28, 29] experiments now in progress suggest that the hepatic collagen in the later stages of infection turns over far more slowly than that in the earlier stages.[42] In addition, the accumulated fibrous tissue may have an effect on the formation of new granulomas and on the rate of resorption of eggs.

Much evidence has been presented pointing toward the essential role of the parasite egg in the development of hepatosplenic disease, but the evidence relating the role of the host's granulomatous reaction to the occurrence of overt disease must also be considered. One series of experiments was performed in which exposure of four groups of animals to different numbers of cercariae resulted in different degrees of infection, from massive to mild. Mice with the heavier infections harbored relatively large numbers of eggs in their livers when the mean

size of the granuloma was at its peak. These animals had severe portal hypertension and 40 to 50 per cent of them had large esophageal varices. Although mice with the light infections eventually had a higher concentration of eggs in their livers, this occurred at a time when the mean size of the granuloma was much less. Thus only moderate portal hypertension and occasional esophageal varices were observed.[26] Cheever also noted that at stages when the mean size of the granuloma was smaller (early massive infections or late light infections), portal hypertension was slight and portal systemic collaterals were rare.[20] In a comparative study in mice, gerbils, multimammate rats, and hamsters he found that portal hypertension was functionally and morphologically most severe in mice, the animals that had by far the most extensive granulomatous reactions.[20]

Suppression of the formation of granulomas around schistosome eggs might provide definitive proof of the role of the host in the development of hepatosplenic disease. The recent demonstration that the granuloma represents a form of delayed hypersensitivity[40] has suggested the use of several methods previously devised to inhibit this type of immunological reaction. These methods, which include immunosuppressive drugs,[43] neonatal thymectcmy,[44] and heterologous antilymphocyte serum,[45] have all resulted in suppression of granuloma formation around schistosome eggs injected into the tissues of previously unsensitized mice. Partial suppression was found in sensitized animals, but significant degrees of suppression have not as yet been observed in infected animals.

In conclusion: the development of an experimental model of hepatosplenic schistosomiasis has led to the demonstration that the schistosome egg is the parasite factor essential for the occurrence of overt disease. Further, it has been suggested that the granulomatous response of the host to the parasite plays a crucial role in the disease process and that if formation of granulomas could be suppressed by pharmacologic or immunologic means, overt disease might not develop in spite of heavy and uncontrolled infection by the parasite.

SUMMARY

The clinical state, pathophysiology, pathology, and pathogenesis of human and experimental hepatosplenic schistosomiasis mansoni are discussed. It is suggested that schistosomiasis leads to the development of

an almost unique form of liver disease manifested by the signs and symptoms associated with portal hypertension unaccompanied by the stigmata of chronic hepatic parenchymal disease and marked derangement of liver function tests. Pathophysiologically there is a presinusoidal block to liver blood flow and although historically the etiology of the classical pathologic lesion "clay pipestem cirrhosis" was ascribed to the schistosome egg, there have been conflicting opinions on this point.

In order to elucidate the pathogenesis of the disease, an experimental murine model of hepatosplenic schistosomiasis mansoni was developed which also had the characteristics of portal hypertension and relatively intact liver function. Pathophysiologically, including unimpaired total liver blood flow, it also resembled the human disease. In addition, a clay pipestem type of lesion was described in the chronic stages. The etiology of both the clinical state and the pathologic lesion have been ascribed to the egg of the parasite. The granulomatous reaction of the host to the schistosome egg (an immunological reaction of the delayed hypersensitivity type), which involves far greater amounts of tissue than the egg alone, appears to play a crucial role in the development of hepatosplenic disease. The dynamics of the formation of granulomas have been discussed in relation to their role in the occurrence of the clinical disease. Attempts to suppress granuloma formation in order to establish its pathogenic function in a definitive manner have met with partial success.

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