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PLASMA RENIN ACTIVITY IN BILHARZIAL HEPATOSPLENOMEGALY

THESIS

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BY

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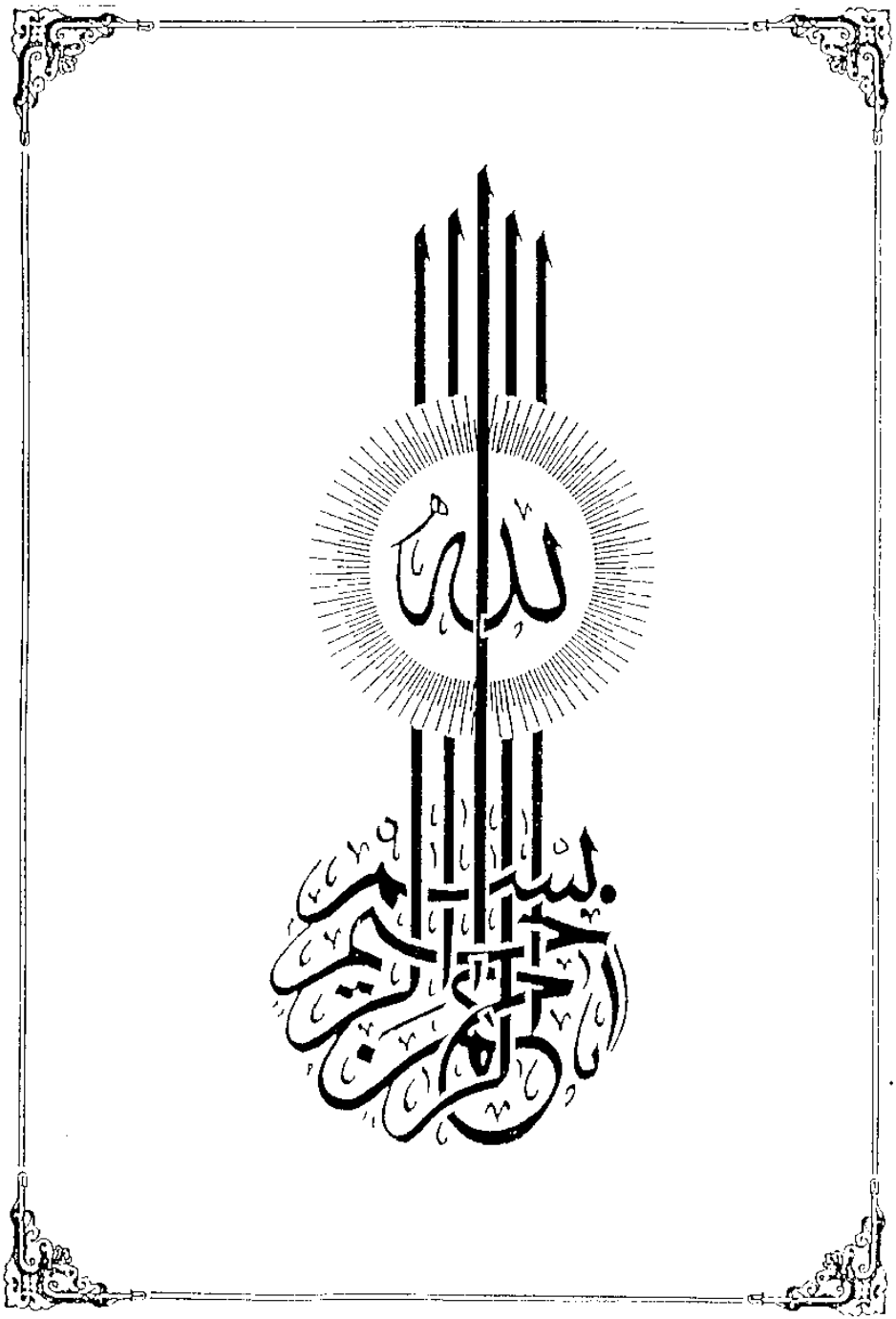

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HEPATOSPLENIC SCHISTOSOMIASIS

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Liver involvement is the most serious problem in patients infected with schistosomiasis. It results from prolonged and repeated embolization by ova which have drifted back from the portal territories (El-Mofty , 1962).

Liver involvement is variable being found in: 37% of cases of intestinal schistosomiasis, 10% of urinary schistosomiasis and in 32% of combined intestinal and urinary affection (Mousa et al., 1967). Fifty per cent of patients with rectal schistosomiasis have granuloma in the liver (Sherlock, 1985).

Kartulis (1885) described liver involvement in schistosomiasis but Symmers , 1904 was the first to note that extensive scarring and thickening of the portal tracts occurred in response to the deposition of schistosoma ova at these sites and he gave it the term (Clay pipe-stem cirrhosis) .

Hashem (1947) suggested the term periportal bilharzial fibrosis to distinguish it from other types of cirrhosis , since the bilharzial lesions do not cause necrosis of liver tissue followed by regenerating nodules .

Other terms given to schistosomal liver affection are: Symmer's fibrosis , bilharzial fibrotic liver, and to emphasize the splenomegaly component of the disease other terms were used: endemic hepatosplenomegaly, Egyptian splenomegaly , Egyptian hepatosplenic bilharziasis, bilharzial splenomegaly and hepatosplenic schistosomiasis (Elwi , 1976) .

These terms describe a chronic disease of the liver charecterized by granulomatous reaction , portal fibrosis , angiomatoid lesions and presinusoidal portal hypertension . The extent and severity of this chronic liver disease correlates with the intensity and duration of egg production by fertile worm pairs and hence with the number of eggs excreted per gram of stool (Dunn and Kamel , 1981) .

Hashem (1947) classified bilharzial liver fibrosis into fine and coarse periportal fibrosis depending on whether the large or small portal tracts are mainly involved . In practice the validity of this classification is very questionable at the present time (Elwi , 1976) .

Moreover Kamel et al. (1978) denied the presence of the fine type and distinguished only 2 types : the coarse and the microscopic form of fibrosis which could be seen in the large or small portal tracts and could be considered as septal fibrosis .

Pathogenesis of Hepatic Schistosomiasis :

The pathogenesis of hepatic schistosomiasis is controversial but the majority of workers accepted that granulomatous lesions and fibrosis produced by deposits of schistosoma ova form the basis of this disease in man. Other factors have been considered in the pathogenesis such as: worm toxins, dead schistosomes, malnutrition, hypersensitivity and autoimmunity .

1. Role of schistosoma ova :

Koppisch (1941) stated that in man probably most of the damage is accomplished by the ova, if they continued to be deposited in sufficient numbers over several years they would ultimately lead to progressive fibrosis of the portal spaces. Following the injection of schistosoma mansoni ova into the portal veins of the dogs, Hashem , 1947 reported that the terminal picture of hepatic schistosomiasis was essentially the result of fibrosis consequent on infiltration by bilharzia ova or occasionally worms in and around fine portal tracts .

Warren and DeWitt (1958) , DeWitt and Warren ,1959 and Cheever , 1965 reported that the cardinal features of the human disease could be reproduced in mice heavily infected

with schistosoma mansoni . It was primarily due to penetration of the portal canals of the liver by a large number of schistosoma ova with subsequent formation of granulomata .

Cameron and Ganguly (1964) followed the infection with schistosoma mansoni in mice. They considered that the most potent factor in reproducing the lesion was the ovum especially the egg shell .

Kamel et al. (1978) stated that Symmer's clay pipestem fibrosis of the liver was clearly related to the presence and intensity of schistosoma mansoni and schistosoma eggs were found concentrated in areas of portal fibrosis .

Recently it was found that hepatic fibrosis has been generally directly proportional to the number of worm pairs recovered and to the number of ova in the liver in experimental animals (Cheever et al., 1983 and Morcos et al., 1985).

2. Role of toxins :

Vilella (1943) considered the proliferative reaction around living ova as an allergic response of the human organism to the material discharged by the embryo and probable toxins secreted by the worms .

Jaffe et al. (1945) found midzonal necrosis of the liver in mice and guinea pigs with schistosoma mansoni unisexual infection and they thought that the toxins of the worms can cause cirrhosis .

Meleney et al. (1952) supported that view suggesting that the presence of both sexes might have a more toxic effect on the liver. Also Warren , 1961 stated that toxins produced by adult worms as well as an allergic reaction to their presence are responsible in the early stages of the disease . More recently, it was found that products secreted by live ova as well as soluble egg antigen (SEA) exerted a dose dependent stimulatory/ cytotoxic effect on cultured human fibroblasts (Boros and Lande , 1983) . Thus some unsequestered secretions could cause a local as well as more distant fibroblast stimulation .

3. Role of dead schistosomes :

Day (1924) considered that Symmer's fibrosis was due to death of worms in the portal tracts and that diffuse fibrosis was due to oviposition .

Sorour (1930) stated that fibrosis was induced by the proliferative endophlebitis evoked by the impacted dead worms . Hamilton et al., 1939 reported that thrombophlebitis

produced by embolic dead worms caused destruction of the portal veins and then eggs carried to such areas were trapped in the narrowed or obstructed venous channels, this would explain the heavy deposition of eggs in the large portal tracts. They also added that anti-bilharzial therapy probably has an important influence on the production of liver fibrosis.

Gillman (1957) suggested that bilharzial lesions were consequent on contracture of intra and perivenous scar tissue evoked by both bilharzial ova and more especially by dead worms . In 1963 , Abdin suggested an anitgen-antibody reaction resulting from death of the worms as being responsible for the lesion .

Later, Menezes (1967) concluded that portal fibrosis is mainly due to the inflammatory reaction induced by the dead worms and to the proliferation of connective tissue . He demonstrated that the body of the parasite disintegrated after 2 weeks of embolization when the large vessel is transformed to a great number of small capillaries . The deposition of ova in the newly opened capillaries only contribute to the increase of fibrosis .

4. Role of malnutrition :

Symmers (1951) suggested that hepatic changes were

to be most likely attributed to the miserable dietary conditions under which those patients lived . On the other hand DeWitt , 1957[a] reported that hepatosplenic schistosomiasis develops in well nourished animals and that malnutrition does not seem to be necessary for its development . Then DeWitt , 1957[b] found also that a poor diet in fact protects the animal as it limits egg production which is the main cause of the disease .

Hashem and Fahmy (1962) setteled the matter for they were able to produce hepatosplenic schistosomiasis in animals kept on normal diet with an ample supply of proteins and vitamins. They also found that dietary deficiency makes the liver more vulnerable to bilharzial infestation in the early stage while in the late stages dietary deficiency creates an unfavourable medium for the growth and reproduction of the worms .

Immunopathogenesis of Schistosomiasis :

In the last years the role of immunological processes in the pathogenesis of schistosomiasis has been emphasized. This has been best shown by the words of Warren , 1972 : " Schistosomiasis is essentially an immunological disease ".

1. Humoral changes :

Raised serum immunoglobulins in various stages of schistosomiasis have been demonstrated in the sera of infected individuals which are due to either schistosomal antigens (Sadun and Gore , 1970) or increased absorption of intestinal bacterial antigens (Ghanem et al., 1975) .

In acute or early infection IgG antibodies were demonstrated against cercariae, adult worms and eggs . In contrast, the major bulk of IgG antibodies in chronic infections was directed against the eggs, and actually these antibodies play a major role in killing schistosomula and destruction of eggs (Capron et al., 1977) .

Significant higher levels of IgG antibodies were detected in chronic hepatosplenic than the early acute cases (Bout et al., 1980) . IgM antibodies rise in early cases (Lunde and Ottesen , 1980) as well as in chronic cases (Cook et al., 1972) . IgA antibodies were found to be significantly higher in early than in chronic bilharzial cases (Kanamura et al., 1979). IgE antibodies have been shown to be raised in both acute and chronic infection (Hiatt et al., 1979) .

2. Autoimmune reactions :

Gerber (1953) demonstrated anti-liver tissue antibodies

in human schistosomiasis , while Kurata and Node, 1962 demonstrated complement fixing antibodies against extracts from normal liver , lung and colon. Mahmoud , 1972 reported some cases with autoimmune haemolytic anaemia and Ghanem , 1962 detected a rheumatoid-like activity in the serum of some patients. Antinuclear, antimitochondrial and anti-IgG antibodies have been demonstrated by several authors (Ghanem , 1961) and (Ekladios , 1971) . In 1981 , El-Gawhary , demonstrated a high incidence of anti-smooth muscle antibody in bilharzial patients .

3. Cell-mediated changes :

The granulomatous reaction to schistosoma ova is an immunological one of delayed hypersensitivity (Warren , 1973). Granulomata are thought to be the result of an immunologic response to antigens released from maturing schistosome eggs lodged in the presinusoidal capillaries of the liver (Warren et al., 1967) and (Colley , 1977) . Other investigators also have shown the association of immunoglobulins and schistosome antigens with the hepatic lesions of the infected hosts (Boros et al., 1975) , (Andrade et al., 1961) and (Von Lichtenberg , 1964) .

The presence of schistosome antigens which elicit that kind of immunological response has been strongly indicated