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" HAEMORRHAGIC TENDENCY IN BILHARZIAL HEPATIC FIBROSIS"

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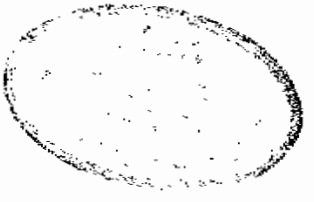

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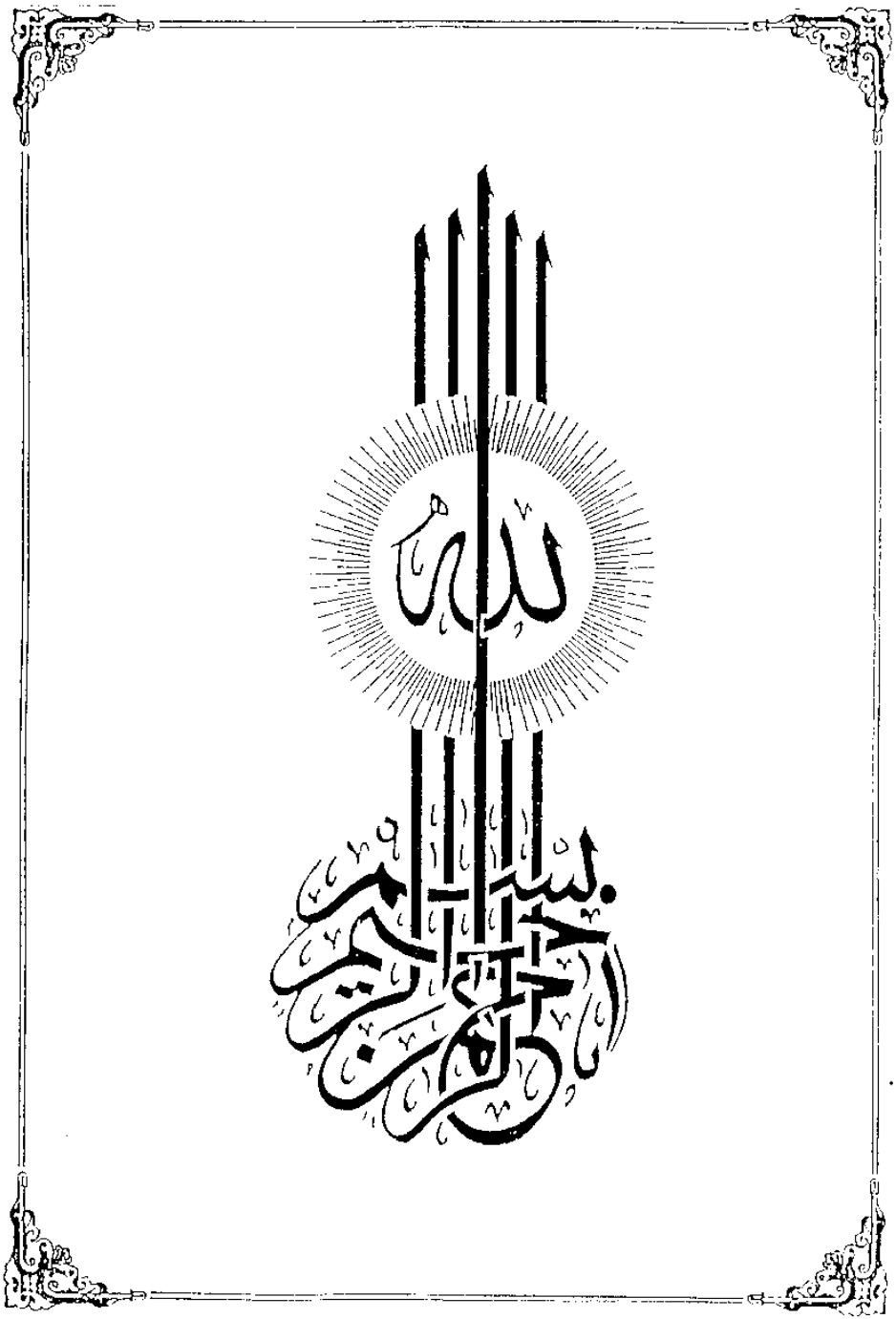

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CHAPTER I

Schistosomiasis is considered the first among the health problems in Egypt, affecting the majority of the population, both sexes and all ages are affected by this disease that may end terminally in early death.

The ancient Egyptians had fair knowledge of urinary tract anatomy and bilharzial eggs has been found in 3000 years old mumies.

Kamel (1962) came to the conclusion in his article about the historical account of bliharziasis that ancient Egyptians identified the bilharzia eggs, but they were unable to treat the disease.

Informations about schistosomiasis were detected in different medical papyri discovered at different periods. Intrestingly enough the discovery of these papyri came just in the same period in which Thoedor Bilharz discovered the warm. El-Halawani (1962) considered T.Bilharz the landmark in history of Egyptian medicine in particular and tropical medicine in special.

BILHARZIAL HEPATIC FIBROSIS

This clinicopathological entity waited long before identifying the true etiological nature even after the discovery of human schistosomes and their products as the main causal pathogen. Many other factors are still blamed.

It has been found by Erfan et al 1957 that not every case presenting with hepatosplenomegaly in Egypt is bilharzial; and even bilharzial cases may be partialy so because other etiological factors, nutritional, viral infection and others my be blamed, (Mousa 1976, DEWITTE 1959, Hashem 1962). The disease is common in lower Egypt especially the north parts of Nile delta where both species of schistosoma exists while it is rare in upper Egypt where only haematobium exists, but now incidence is increasing after the high dam,(A.Mousa 1976). In heavily infested areas with mansoni 50% of the people show hepatosplenic involvement while in pure haematobium infection liver is involved in 15% (Sadek 1976). The liver acts as nursury for human schistosoms before maturity and on certain occasions after maturity according to the severity of infection and acquired resistance of the host. The disease starts

when ova or embolisedwarms are impacted in the intra-hepatic tributaries of the portal vein.

The coarse of the disease is slow and progressive and the disease may be arrested and becomes latent with early treatment to lead to more or less normal active life. If the case is neglected and exposed to reinfection the disease will follow its coarse until there is well established hepatic fibrosis with subsequent portal hypertention.

History of the disease:

Cirrhosis of the liver with ascites has been described by Erisistratus in Alexandria 300 b.c. to be followed by several authers in Europe and middle east counteries. Fugu in 1847 described a syndrome of hepatosplenic enlargement with ova in the liver and spleen and intestine. Also it was described by japanese physicion and termed Takayama disease, (Mousa, 1976) In 1885 Kartulis in Alexandria described a similar syndrome among bilharzial cases. The earliest description of the disease was given in Egypt by Symmers 1904, who described the hepatic lesion in relation to laterally spined eggs as clay stem cirrhosis. Day and Ferguson considered in 1909 that the splenic enlarge-

ment in hepatic cirrhosis in Egypt is the result of infective agent probably protozoal and perhaps leishmanial in origin. Day and Richard 1924 considered the splenomegaly as form of Banti's disease and adviced splenectomy for it. After the life cycle of schistosomes was discovered in Egypt by Leiper 1915, the way was opened to animal experimentation with this parasite. Fairly in 1920 in Egypt began his investigation on monkeys to establish the pathological lesions of early clinical picture when he noticed a febrile illness among the australions in Egypt, he found that the tissue changes are out of proportion to the deposited ova, so the cirrhotic changes could be related to some toxic material liberated. El-Kadi in 1923 suggested bilharzial infection as cause of the triad, intestinal bilharziasis. hepatic and splenic enalrgement especially when it responds to treatment. Day 1933 reported the association of hepatosplenic enlargemnet with intestinal bilharziasis and found ova in wedges removed from the liver during operation. He reported the improvement with anti bilharzial treatment.

Day put the etiology of diffuse bilharzial fibrosis as oval while that of Symmer's due to death of the warms in the large portal tracts. Lee 1928 suggested

that the ova is the most important factor becuase unisexually infected hamesters had never developed liver cirrhosis 3 months after infection. Ibrahim 1928 accused Day's theory of bilharzial nature of endemic hepatosplenomegaly because of the occurance of the disease in early childhood and rarity after 30 years and also reported the endemic syndrome occured in localities free form bilharzia and he could not cure his cases with tarter emetic.

Although ova was demonstrated in the liver showing multinodlular cirrhosis, but the combination of the so called Egyptian splenomegaly with other types of cirrhosis of the liver made the etiologic relationship difficult to settle. Madden 1954 concluded that Day's views regarding the bilharzial nature of the syndorme had not been entirely accepted. Souror 1930 described the histopathology of the disease as interstitial fibrosis around small and large ducts and so different from other forms of cirrhosis. Girgis 1934 postulated a toxic cause for the pathology, the toxin released from the male warm either living or dead.

In 1931 Brompt and Chevalier found that the mice are the laboratory animal of choice for experimental schistosomiasis.

Incidence:

Bilharzial hepatic fibrosis occur in 100% in combined urinary and intestianl schistosomiasis and in 60% of the urinary cases of children (El-Gholmy et al 1955) The disease is commoner in lower Egypt especially the northern parts of the Nile Delta, where both species of schistosoma exist, while it is rare in upper Egypt where haematobium exists. In areas heavily infested with mansoniasis, 50% of people show hepatosplenic involvement while in pure urinary Bilharziasis, the liver is involved in about 15% of cases. (Mousa 1976).

PATHOGENESIS

Many theories were put because the pathogenesis is controversial, early studies were based on autopsy finding but now needle biopsy enabled to investigate the earlier stages of the disease. Also animal experimentation helped much in the study and evolution of the disease. The consensus of opinion now is that the lesions in the liver is induced by toxins of ova and dead warms exciting specefic response, The discrepancy between the reactions and the number of ova and worms encountered in such lesions raised great discussions.

The immunocytochemical techniques after their application to liver biopsy material has given some clarification to the pathogenesis.

Koppish 1941, stressed that the damage in man is mostly caused by ova sufficiently deposited over years in the portal tracts. Hashem 1947 in his experiments, injection of living ova resulted in pathological lesions similar to the human disease, but after injection of warm extracts intraperitonealy or in the portal vein, no damage occured. He concluded that the final picture was the result of fibrosis enchroaching on the vascular supply of liver parenchyma causing some distortion of the normal architecture and he provided the term fine and coarse fibrosis instead of diffuse and clay pipe stem cirrhosis. Meleny 1953 concluded that most of the pathology is produced by fertilized ova and dead warms forming the localised lesions, if numerous enough lead to extensive scarring. The early periportal cellular infilteration was interpreted as allergic phenomena resulting from the presence of schistosomes in porto-mesenteric veins, it decreased as the infection continue and did not appear to contribute significantly to ultimate cirrhosis of the liver. Dewitte and Warren 1959 said that if toxic theory is true the liver cells will

be attacked diffusely and will be associated with severe derangement of liver function but Hamilton 1938 said that the thrombophlebitis and periphlebitis owing to death of adult warms and ova are common dominators of the disease and also added that antibilharzial therapy has important influence on production of liver fibrosis. Filho 1960 also found that there was diffuse intimal reaction in the vessels free of ova and worms in addition to the focal intimal reaction in blood vessels containing necrotized warms. This was common during reinfections suggesting a toxiallergic reaction to circulation of schistosomulae during development of immunity. Andrade 1969 by immunocytochemical methods was able to demonstrate antigen antibody in liver of mice infected with schistosoma mansoni and so provide support for the immunological nature of such self perpetuating hepatic involvement. Hashem et al 1962 was able experimentaly to produce schistosomiasis in animals on normal diet. He also studied the effects of various deficient diets on the evolution of the disease in animals, he concluded that dietary deficiency may make the liver more vulnerable to schistosomal infection in the earliest stages. In late stages deficiency of diet create unfavourable medium for proper

development and reproduction of warms during the infection. Abdin 1963 put an autoimmune theory as the only satisfactory explanation for marked and diffuse protal thickening where ova are few or absent. Warren 1961 found that sensitization could be transfered between histocompatible mice with lymph node or splenic cells but not with sera. These results strongly suggested that the egg granulomata is essentially a mediated type of immunological response as a manifestation of delayed hypersensitivity, this may be supressed and regulated by blocking antibodies and may function to prevent the occurence of circulating antibody complex. Menezes 1967 said that the warms not only obstruct the vascular lumen but cause destruction of their walls inducing inflamatory reaction with proliferation of the subintimal connective tissue. Deposition of ova in the newly opened capilaries is caused by increased fibrosis. Boros and Warren 1971 could isolate from the eggs the antigen responsible for the host reaction. In an attempt to isolate the specific molecule which inhibit the chain of events leading to hepatosplenic schistosomiasis. After the eggs is laid by the warm, the egg embryonates, after few days begins to secrete soluble substances which pass through the pores of the egg shell, they

contain enzymes which facilitate the passage of the egg through the tissues, these secretions sensitize the host resulting in development of thymolymphocytic memory cells, following sensitization the further antigenic secretions stimulate the memory cells to release their lymphokins which can affect the migration of microphages and eosinophils. Thus the lymphocytes and macrophages and eosinophil gather about the egg nidus in tissues resulting in formation of granuloma. Continued secretion of the antigen result in chronic inflammation characterised by epitheliod cells, giant cells and fibroblasts. A large area of tissue is destroyed by inflammatory reaction propably due to release of lymphotoxins and lysosomal enzymes. Healing is accompanied by fibrous scar.

Pathological Features of Hepatic Schistosomiasis:

The liver is shrunken in size but may not be reduced in weight, surface shows slight irregularities in the form of shallow depressed areas separating moderately raised areas, otherwise the surface is smooth, the capsule is slightly thickned in diffuse manner. Sometimes with adhesions to the under surface