TOTAL AND SPECIFIC IMMUNOGLOBULIN E IN SCHISTOSOMIASIS

Thesis

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of Master Degree of Clinical Pathology

By

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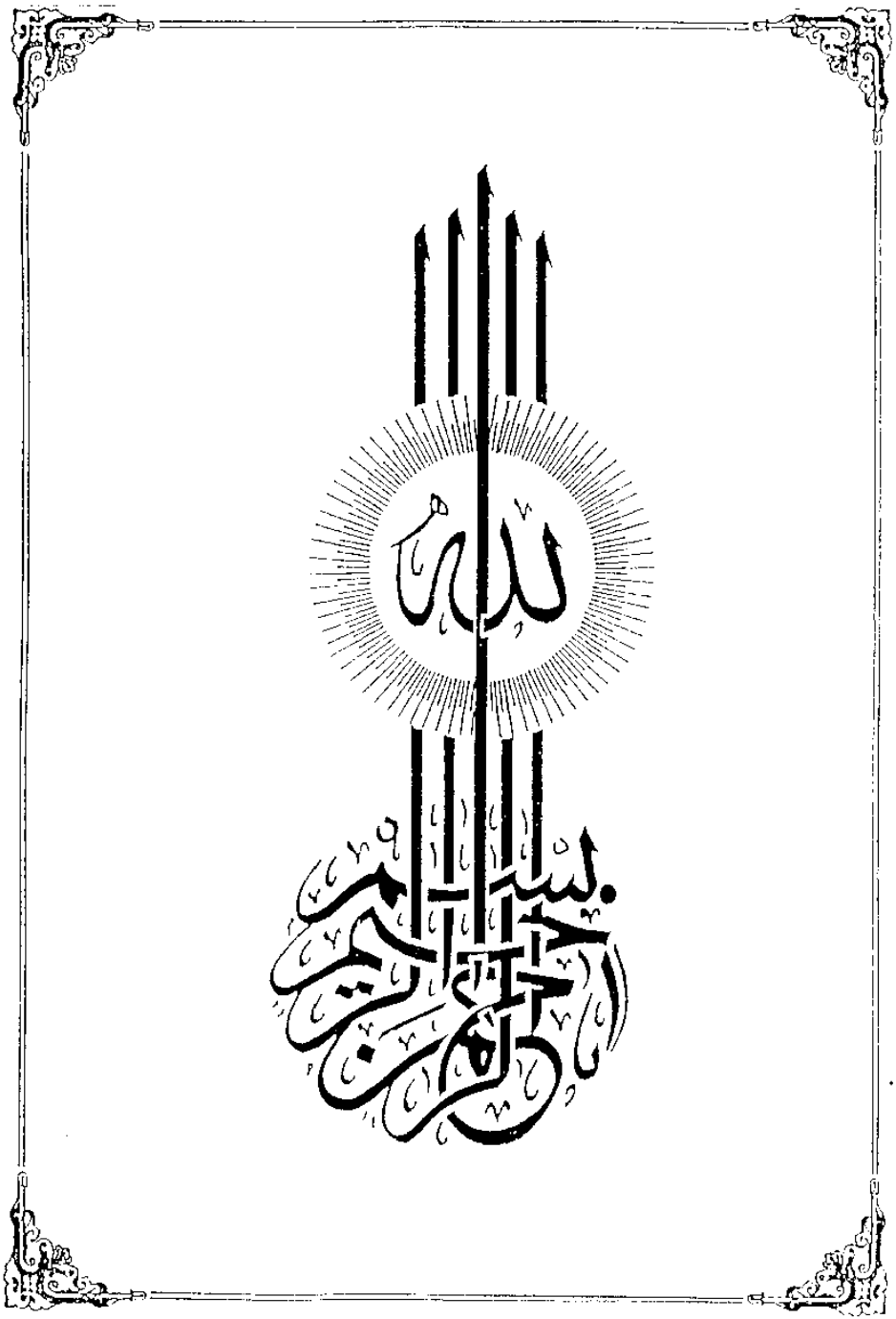
Dedicated To My Mother



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INTRODUCTION AND AIM OF WORK

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Production of antibodies of the IgE class is a distinctive feature of the host response to invasive helminth parasites. The functional importance of these reaginic antibodies is still incompletely understood.

Increased serum IgE levels have been demonstrated in Schistosomiasis, but characterization of the IgE antibody response is still incomplete.

In human Schistosomiasis, circulating immune complexes have also been documented. Whereas IgG and IgM antibodies were frequently demonstrated in these complexes, IgE was only encountered in few cases. IgE containing circulating immune complexes have become of interest since there is evidence that they may activate macrophage-mediated defense mechanisms, against invading schistosomulae in experimental Schistosomiasis.

The aim of this study is to assess the level of total serum IgE and parasite specific IgE in Egyptian bilharzial patients infected with Schistosoma mansoni and/or Schistosoma haematobium, using an enzyme-linked immunosorbent assay.

The levels of these two immunological parameters were correlated with intensity of infection and with the level of immune complexes present in the circulation. Their levels were also studied in relation to the clinicopathological condition of the patients, wether intestinal or hepatosplenic cases.

REVIEW OF LITERATURE

SCHISTOSOMIASIS

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Human Schistosomiasis is one of the major health problems of increasing importance in different parts of the world, affecting more than 200 million people by one or other forms of the disease and 500 million under exposure *(Ayad, 1974).*

It heads the list of communicable diseases in Egypt, both as regards its prevalence, its gravity and its great repercussions on national economy of our country. Schistosoma heamatobium infection is prevalent all over the country with an average prevalence rate of 50%, while Schistosoma mansoni infection is limited to Nile Delta with 5-40% prevalence rate *(Shoeb, 1976).*

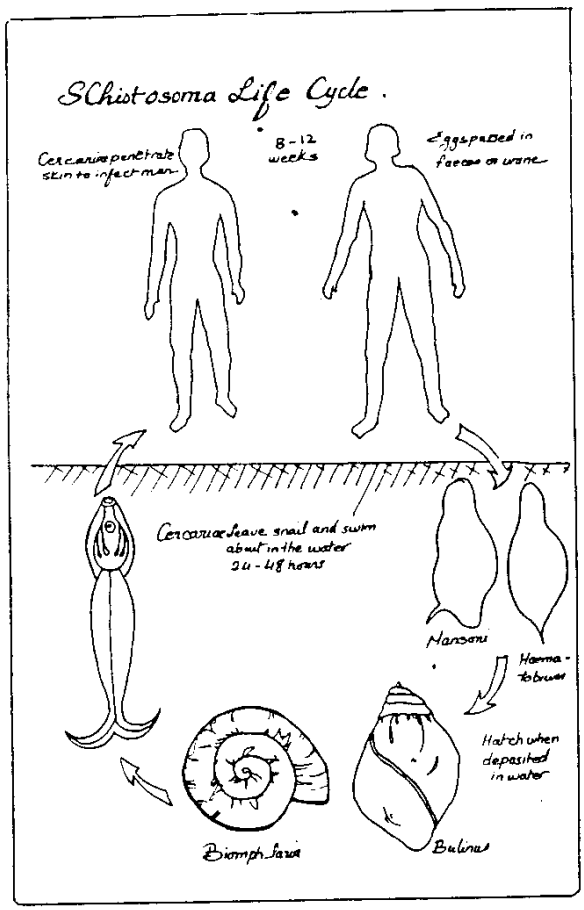

Fig. 1: Showing Schistosomal life cycle (Rady and Rady, 1987).

IMMUNITY IN SCHISTOSOMIASIS

1. Concomitant immunity

In the majority of experimental hosts, it is believed also in man *(WHO, 1974)* that there is a gradual development of immunity to reinfection despite the continuing presence of a healthy population of adult worms. Immunity in the presence of an active infection was first described in rhesus monkeys, where adult Schistosoma mansoni (S. mansoni), derived from a primary infection persisted long after resistance to a challenge infection had developed *(Smithers and Terry, 1965)*. This is now recognized as an established characteristic of schistosome infection in baboons, mice, rats and almost certainly occurs in man *(Bradly and Mc Cullough, 1973)*. It has now been established both in vivo and in vitro that young schistosomulae lose their susceptibility to immune effector mechanisms within the first few days of their transformation from cercariae *(Smithers et al., 1977 and Sher, 1977)*.

Concomitant immunity has the obvious biological advantage of preventing the overcrowding of parasites and allowing the extended survival of both the host and the schistosome. This phenomenon can be explained by the hypothesis that the host antigens on the surface membrane of adult worms protect them against the immune response of the host, and the developing stages of the parasite which are susceptible to immune attack should lack host antigens *(Smithers and Terry, 1976)*.

2. Heterologous immunity

A number of workers have shown that animals infected with schistosomiasis developed varying degrees of resistance to a challenge infection with a different schistosome species; *(Eveland et al., 1969; Hussein et al., 1970; Preston et al., 1972 and Taylor et al., 1973).* The degree of cross protection does not appear to be related to the phylogenetic relationship of the schistosomes. The development or severity of immunizing infection in the host is probably a more important factor.

3. Immunity induced by live attenuated schistosomes

A considerable level of immunity is induced in a variety of experimental animals following exposure to live cercariae or schistosomulae which are without the ability to develop into adult worms. The lack of egg deposition by the immunizing infection results in the absence of the pathology normally seen in patent Schistosomiasis and there is therefore much interest in the potential of these attenuated schistosomes as living vaccines *(Bushara et al., 1978; Majd et al., 1980).*

Attenuated schistosomes can occur naturally as a strain or species which is unable to develop to maturity in the host to be immunized *(Hsu and Hsu, 1961);* or attenuation can be achieved by exposure of the cercariae (or schistosomulae) of a pathogenic strain to irradiation from an X-ray or ^{60}Co source *(Minard et al., 1978).*

The resistance to infection induced by vaccination is indeed the result of a specific immune response, as suggested by the failure of S. mansoni vaccinated mice to develop high levels of protection against challenge with

Schistosoma japonicum (S. japonicum) *(Cheever et al., 1983).* Furthermore, resistance to S. mansoni infection fails to develop in vaccinated mice deprived of B or T lymphocytes *(Sher et al., 1982).*

Finally, vaccination with irradiated cercariae has been shown to induce a prolonged state of sensitization in host B and T lymphocytes *(James et al., 1981).* This immunological memory is recalled upon infection *(Correa-Oliveira et al., 1984).*

4. Non specific immunity

Activated macrophages are involved in non-specific immunity. Using B cell-deficient mice, *Maddison et al. (1978)* found that pretreatment of the deficient mice or age and sex-matched control mice with BCG, suppressed infection with S. mansoni to similar levels in both groups, indicating that B cells do not play a major role in the immunity stimulated by BCG. The authors suggest that this mechanism may involve a T cell activation of macrophages. Macrophages obtained from Corynbacterium parvum-treated mice have the capacity to kill schistosomula in vitro. The killing is mediated by soluble factors released into the culture media after incubation with S. mansoni schistosomula or non specifically, with Trichinela spiralis larvae *(Mahmoud et al., 1979).*

MECHANISMS OF IMMUNE PROTECTION AGAINST SCHISTOSOMIASIS

Role of eosinophils

Eosinophilia was noted in patients infested with S. mansoni and more evident in the hepatomegalic phase *(Ata, 1962; Cailey, 1972; Mahmoud et al., 1975; Knopf, 1979; and Shobhi et al., 1981).* The study done by *Arafa et al., (1985)* indicated that high eosinophilia occurs in heavy infection with urinary or intestinal Schistosomiasis especially in patients presenting with hepatomegaly rather than with splenomegaly.

The relation between eosinophilia and increased serum IgE level could be looked at as an allergic condition, i.e. IgE mediated activation of mast cells would lead to production of pharmacologically active mediators, including an· eosinophil chemotactic factor. The latter would lead to congregation of eosinophils in the local tissue sites *(Parish, 1972; Wasserman et al., 1974).*

a. Activity against schistosomula

Mahmoud et al., (1975) exposing partial immune mice (previously challenged with cercaria) to antieosinophil serum, observed complete block of immunity as detected by marked increase in the number of schistosomulae recovered from the lungs after 6 days. Control mice exposed to antilymphocyte, antineutrophil, antimacrophage serum did not reveal such response. They concluded that eosinophils were the main effector cells in acquired resistance to Schistosomiasis.

The interaction of eosinophil with the surface of schistosomula may be initiated by antibody molecules or complement fragments (C3), tight

adherence follows and the contents of eosinophil granules can be seen evacuating on the parasite surface *(Mc Laren, 1980)*. Parasite destruction is thought to be achieved by the activity of the highly reactive products of O_2 reduction such as superoxide or hydrogen peroxide *(Jong et al., 1981; Kazura et al., 1981)* or the release of cationic or major basic proteins from the granules *(Gleich et al., 1980; Venge et al., 1980)*.

The adherence of eosinophils to antibody-coated schistosomula is through Fc-Fc receptor interaction *(Mackenzie et al., 1977; Vadas et al., 1980)*. The antibody responsible in human serum is an IgG *(Butterworth et al., 1977)*, the antibody subclasses are IgG_{2a} and IgG_1 respectively.

Eosinophils will also adhere to schistosomula in the absence of antibody but in the presence of complement. This activity is the result of the activation of the alternative pathway of complement at the schistosomular surface. Cell adherence is through C3-C3 receptor interaction *(Ramalho-Pinto et al., 1978)*. Eosinophil chemotactic factors are released at the parasite surface, as a result of complement activation, and these may be responsible for increasing the number of cells at the target surface *(Ramalho-Pinto et al., 1978)*.

b. Activity against eggs

James and Colley (1978) have reported that in vitro damage to S. mansoni eggs by eosinophils was complement independent and directed by specific antibody against egg antigen, and derived from serum of S. mansoni infected hosts.

Mice treated with antiserum to eosinophils had a cumulative mortality of 88% at 9 weeks compared with 5% among those treated with