COMPARATIVE STUDY OF THE EFFICACY OF A NEW ANTISCHISTOSOMAL DRUG RO-15-5458 HOFFMAN LAROCHE, BILTRICIDE AND DISTOCIDE ON EXPERIMENTAL SCHISTOSOMIASIS MANSONI

By

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Thesis

Submitted for partial fulfillment of M.D. degree in Parasitology

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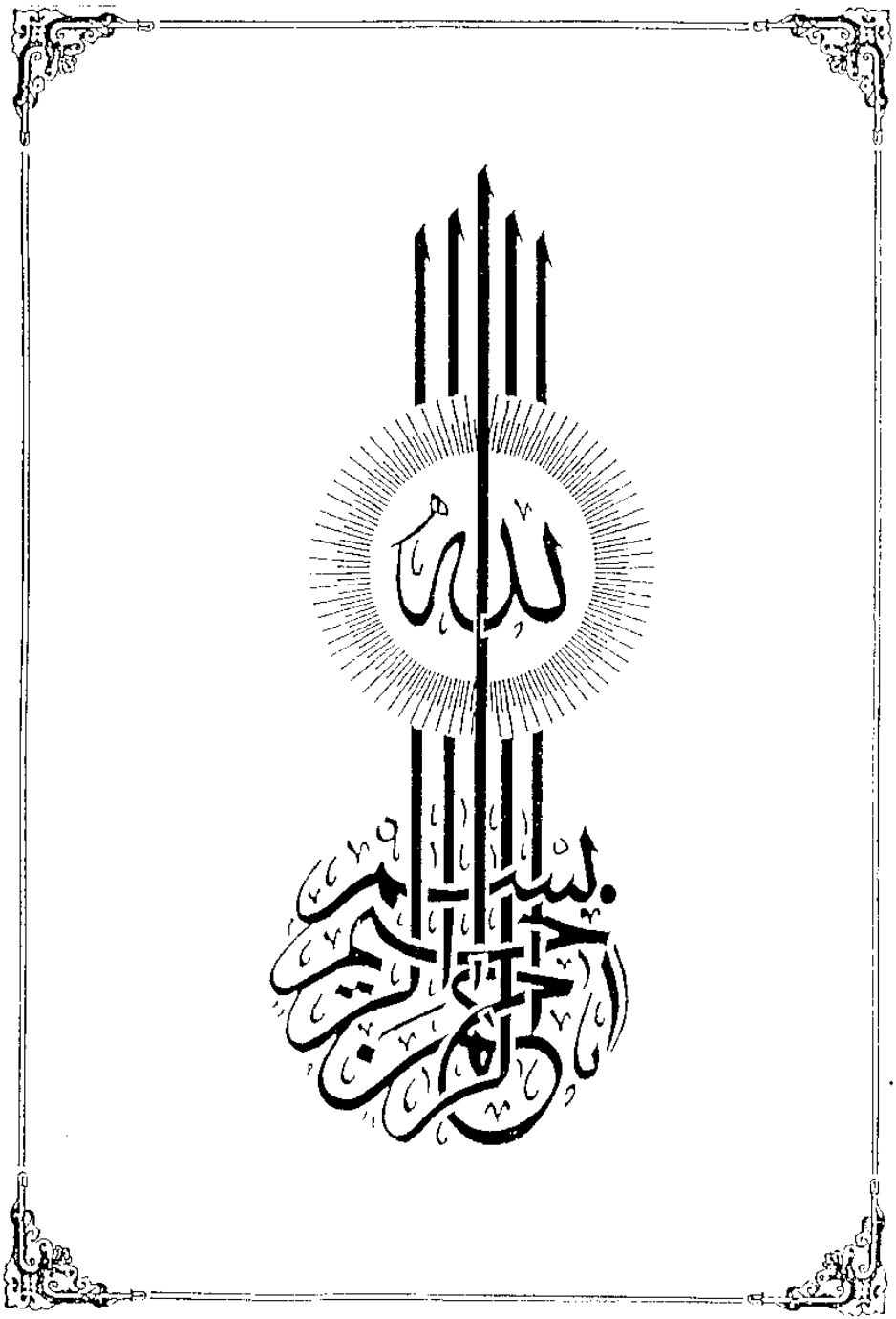
(1994)

I wish to express my profound gratitude and sincere appreciation to **Dr. Magda Youssef.** Assis. Prof of Parasitology, Faculty of Medicine, Ain Shams University, for her kind help, instructive guidance and valuable suggestions and supervision.

To **Prof. Dr. Tosson Morsy** Prof and head of Parasitology Department, Faculty of Medicine Ain Shams University, I express my deep thanks for his great help and the support he offered.

I owe a particular Dept to my colleague Samiya William, who offered me her endless assistance and advice althrough my work.

In fact I owe much to the staff of Parasitology and Pharmacology Departments in Theodor Bilharz Research Institute for the facilities so freely placed at my disposal.



CONTENT

INTRODUCTION AND AIM OF WORK

INTRODUCTION

Schistosomiasis is generally acknowledge to be the major chronic helminth infection of mankind (Warren et al., 1974). It is estimated that more than 200 million people are infected by schistosomiasis (bilharziasis) and about three times this number are threatened by the infection (Iarotiski and Davis, 1981; WHO, 1985; WHO, 1990).

The disease is endemic in about 76 countries most wide spread in tropic and subtropic areas of Africa, South America, the Carribian Islands, Eastern Mediter-reanean and the Arabian peninsula, and South east Asia. It is essentially an infection of areas usually rural and agricultural, where there exists poverty, ignorance, poor housing and standard hygienic practices. Schistosomiasis ranks second to malaria in terms of socioeconomic and public health importance (WHO, 1985). Despite the availability of praziquatel as a safe effective drug, schistosomiasis is still and perhaps increasingly a matter of concern (Butterworth, 1992).

Schistosomiasis is caused by a digenetic trematodes of the genus Schistosoma, among which *S. mansoni*, *S.haematobium* and *S. japonicum* are the principal causative agents of the human disease. Human subjects are exposed to the infective form of the parasite in water during occupational or

recreational activities; agricultural work in irrigation schemes constitutes one of the schistosomiasis risks (Hunter, 1982; Kloos, 1985; WHO, 1985).

In most endemic areas, children 6-15 years of age have been identified as the most highly exposed and heavily infected age group and are the ones that also contribute more to water contamination (Dalton and Pole, 1978; Kloos et al., 1983).

Once the invasive form of the parasites finds its way into the system of the ultimate host; the resulting larvae migrate until the parasites grow sexually mature. The male and female worms copulate and depending on the species of the schistosome, parasites differ in geographical snail host infectivity, response to drugs, pathogenicity and immunogenicity (Rifaat, 1976).

The pathology of schistosome infection involves many organs and is mainly due to vigorous host response against the parasite eggs. The egg output is closely related to the numbers of worm pairs that the host carries. A direct relationship between the intensity of infection and clinical disease was reported (Webbe, 1981). The egg is considered to be the main pathogenic agent (WHO, 1966). It is also the origin of extrinsic cycle.

Therefore, treatment has two main aims, namely to prevent or reduce further tissue damage in infected individuals and to reduce egg excretion and thus transmission in the community (Cook et al., 1977; Mc Mahob, 1978; Pugh and Teesdale, 1984; Sleigh et al., 1986).

Numerous approaches have been implemented in attempt to reduce the transmission of infection and morbidity due to schistosomiasis (WHO, 1985; Jordan, 1986; Sleigh et al., 1986; Klumpp and Chu, 1987). Health education, improved sanitation and water supply with focal mollusciciding and chemotherapy have been recommended as an effective means of controlling the disease (WHO, 1985). However, such strategies have suffered various limitations and have therefore been marginally successful (Jordan et al., 1978; Polderman, 1984; Fenwick, 1987).

Vaccine development has been proposed as a cost effective means of controlling the transmission of the disease. Although prospects for the development of schistosome vaccines are high (Metwally et al., 1984 Smithers, 1986; Butterworth and Hagan, 1987; Capron et al., 1987; Butterworth, 1992), there is a little chance that the vaccine will be available in the foreseeable future. The complexity of host-parasite relationship, lack of knowledge of the host immune effector mechanisms against the parasite

and possible evasion of the host immune system by the parasite have further shadowed the optimism towards schistosome vaccines (Mitchell, 1989).

At present chemotherapy is the most effective method for the short term control of schistosomiasis (WHO, 1983; Liese, 1986). Currently, however, few chemo-therapeutic agents are available for the treatment of schistosomiasis and the future of this approach is threatened by the possible emergence of drug resistant strains of the parasites (Bruce et al., 1987; Coles et al., 1987a). Thus, research has to be continued towards the development of few antischistosomal drugs to complement existing drugs or to replace those that cease to be effective.

Praziquantel, an isoquinoline-pyrazine derivative has become accepted as the antischistosomal agent of choice for *S.mansoni, S.japonicum, S.mekongi, S. intercalatum* and *S.haematobium* (King and Mahmoud, 1989). In addition, praziquantel has become accepted world wide as an agent of choice for clonorchiasis, opisthorchiasis (liver fluke), paragonimiasis (lung fluke), cysticercosis and many intestinal tape worms (Medd Lett Drug therapy, 1988).

Praziquantel has also been used successfully in the treatment of severe fascioliasis (Schiappacasse et al., 1985). However, the cost of praziquantel continues to limit

its use in developing countries. The possi-bility of appearance of drug tolerant or resistant parasites may not also be overruled when treatment reaches a large sector of the infected population.

Another broad spectrum antschistosomal agent that is in the process of development is Ro15-5458. The antischistosomal activity of this compound has been demonstrated to be superior to many standard antischistosomal drugs against the three principal species of the parasites that infect humans (Stohler and Montavon, 1984).

AIM

The objectives of the present work

1. Study the efficacy of Praziqua brands namely Biltricide (from Eipico Egypt).
2. Study the efficacy of a newly RO15-5458 (from La Roche).
3. Study the efficacy of Biltrici mice infected with different d cercariae at different time in

REVIEW OF LITERATURE

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Life Cycle of Schistosomes :

The three species of schistosomes commonly affecting man, have similar life cycles and develop over successive stages, egg miracidium, first stage sporocyst, second stage sporocyst, cercaria, schistosomule and adult worm.

Adult worms live in the pelvic, vesical and pudendal plexuses, less commonly in the portal blood stream. The female schistosome neither attain sexual maturity (Armstrong, 1965), nor migrate out of the liver (Standen, 1953) until the male clasps it in the gyneacophoric canal. They mate in the small vasculature of the liver and make a paired migration against the flow of venous blood to the predestined mesenteric plexus. When the vessel caliber impedes further paired migration, the female progresses further alone and lays her eggs receding backwords in doing so. Egg laying starts 30-40 days from the date of infection (Pellegrino *et al.*, 1962). The favoured eventual location of the adult worms and consequent egg deposition varies according to the species (Laughlin, 1984).

S. haematobium lives principally in the veins of the urinary bladder plexus, while *S. mansoni* prefers the inferior mesenteric vessels of the large intestine. *S. japonicum* is more concentrated in the superior mesenteric vessels of the large and small intestine (Schmidth and Roberts,1981). Incompletely embryonated eggs are laid, with approximately 50% being swept upstream, where they become lodged in the micro- vasculature of the liver and other organs and 50% become attached to and embedded in the mesenteric venule wall. The penetration to the host lumen by the egg, is mediated by the release of lytic enzymes from the egg and is assested by host muscular contractions (Rifaat, 1976; Laughlin,1984). The penetration takes approximately 8-12 days, coincident with egg maturation. In a certain percentage of eggs, the process of penetration is arrested and a granuloma is formed. Death and calcification of the egg follows, then it is eventually absorbed by the host (Laughlin,1984). Eggs that reach the lumen of the intestine or bladder are passed out in the stool or urine (Laughlin,1984), their extrusion causing injury to the epithelium with bleeding (Pellegrino et al., 1962).