

ADOPTIVE TRANSFER OF LYMPHOCYTES AND ITS ROLE IN

PROTECTION AGAINST Schistosoma mansoni

INFECTION IN Arvicanthus sp RATS.

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Adoptive Transfer of Lymphocytes and Its Role in Protection  
Against Schistosoma mansoni Infections in Arvicanthus species

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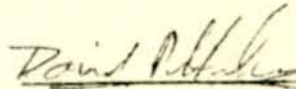
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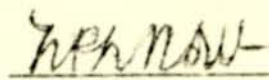
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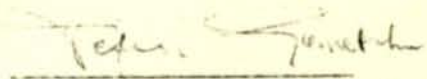
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## ABSTRACT

Adoptive transfer of protection from infected donor Arvicanthus sp rats to uninfected recipients was attempted by varying some parameters such as the infection period of donor rats and the time of transfer relative to challenge. Concurrent investigation on the effect of heterologous infection and fractionation of cells was also carried out.

It was found that cells from 2 month-infected donors had high ability to transfer resistance to recipient rats, while cells from 1.75 and 3 month-infected donors showed partial ability and those from 2.5 month-infected donors showed an unexpected inhibitory effect on transfer recipients. Transfers done close to challenge day confer almost complete immunity to recipient rats, while

Heterologous cestode infection in these rats appear to play a secondary role in protecting against S. mansoni infections, while it was also found that unfractionated cells have more ability to transfer resistance than fractionated cells.

Possible immunological mechanisms involved during these events and the practical significance of the work are briefly discussed.

## 1. INTRODUCTION

Schistosomiasis is a disease caused by trematode flukes of the genus Schistosoma. The parasite undergoes a succession of stages - egg, miracidium, first-stage sporocyst, second-stage sporocyst, cercaria, schistosomulum and adult. This cycle alternates with the adult schistosomes in the definitive vertebrate hosts which include man and other animals ( Von Lichtenberg, 1977), and an asexual multiplicative stage in snails. The cercaria shed by the snails are the infective stages; when these enter the skin after penetration, they change morphologically into the schistosomulum stage in the lungs and finally to the adult stage in the mesenteric veins. The adults lay eggs, most of which become trapped in the host's tissues and cause overt disease ( W.H.O. memoranda, 1974).

Schistosomiasis is a world health problem and it affects some 200 to 300 million people ( Forsyth & Bradley, 1966, Capron et al. 1982 ). Moreover the population infected and those at high risk are located overwhelmingly in the poor underdeveloped countries of Asia, Africa, the Middle East and Latin America ( Andreano, 1978 ).

The economic losses due to schistosomiasis are attributed to factors such as reduced work productivity, reduced performance of schoolchildren and to a lesser extent mortality cost from premature death of young children and work-fit adults. It is estimated that there is an annual world economic loss from disability and lowered production of roughly U.K. £ 400 million ( Weisbord et al. 1973 ).

Present methods of control largely focus on molluscicides, chemotherapy and other environmental and chemical means. But these methods are generally inadequate in the total control of the disease ( Bradley & Webbe, 1978 ). For example, biological control of snails has little prospect of success in view of the wide variety of snails that can act as vectors under diverse ecological conditions ( Warren, 1962). Chemotherapy and molluscicides have also been found to have a major drawback, especially on the larger scale required for effective control in large parts of Africa where reintroduction is always likely ( Vaksman & Cook, 1975). The cost of molluscicides is usually very high, requiring much-needed foreign currency and decidedly beyond the means of most developing countries ( Weisbord et al. 1973 ). The presence of different kinds of reservoir animal hosts for the different schistosome species further complicates control efforts ( Warren, 1962 ).

Immunologic approaches seem to be promising in the control of schistosomiasis, a belief that led Kloetzel ( 1962 ) to exclaim that " any prospect, however remote, of decreasing the severity of schistosomiasis by prophylactic means deserves a trial " . Evidences suggest that some sort of immunity is acquired by man against schistosomiasis ( Newsome, 1956; Warren, 1977 ), thus attempts to produce vaccines have been one prospective means that might lead to a better control of the disease.

Two types of responses are manifested in schistosomiasis, which are of practical interest in terms of prospects for immunological control. The first is the host's response to the schistosome eggs and this is responsible for the major pathology of the disease. By manipulating this response immunologically, one might be able to alleviate or prevent the occurrence of the disease.

The second response prevents the maturation of subsequent infections in the host (concomitant immunity) (Smithers & Terry, 1969). A better understanding of the effector mechanisms of this response would help in the design of vaccines. Vaccine production against schistosomiasis may take one of several lines.

The identification and characterization of 'protective antigens' to be used as vaccines is the first step. However with the exception of some soluble egg antigens (Pelley et al. 1976) and a cercarial antigenic preparation (Bogitsch & Stephan, 1976) few promising results have been documented in this line. Use of irradiated cercariae for immunization is another step and results in this line are anomalous. Heterologous infections, such as the infection of man by bird schistosomes (W.H.O. memoranda, 1974), or S. bovis (Warren, 1962) have been considered, but it has been warned that worm migration in the lungs can cause severe complications during such infections.

Other protective immunological methods have also been considered. It has been suggested that stage and species-specific SEA's may be used to simulate egg granuloma modulation in vivo (Warren, 1977).

Passive immunization with immune serum and cells has been considered but results obtained are as varied as the methodology and hosts used.

Many workers believe that until the overall pattern of the immune mechanism(s) against schistosomiasis is understood, the search for a vaccine is perhaps premature ( Waksman & Cook, 1975; Sher et al. 1975; Phillips et al. 1978; Hoffman et al. 1979 ).

Although laboratory animals are used in research studies, there appears to be wide species variation in responses to schistosomal infections ( Smithers & Terry, 1976 ), and there is no evidence that any experimental animal provides an accurate model of the situation in man ( Butterworth et al. 1982 ). Although many animals can be infected with the schistosomes ( Von Lichtenberg et al. 1962 ), the rat and the mouse have been the laboratory animals most widely used. It has however been suggested that extensive differences in immunologic competence exist between different strains of both ( Colley, 1972; Ramalho-Pinto et al. 1976; Knopf et al. 1977 ). Thus it appears that the use of an appropriate ' laboratory model ' may to a large extent eliminate such 'host factors' and present a better picture of the immunological situation in man.

Arvicanthus niloticus is a susceptible species for both S. mansoni and S. haematobium and shows a pathological picture typical in experimental situations of schistosomiasis ( Kuntz & Malakatis, 1955 ).

Mansour ( 1973 ) maintains that the heavy worm load and excretion of viable eggs in both natural and experimental infections suggest that A. niloticus can serve as a natural reservoir host under natural conditions. Polderman ( 1974 ) also found natural infection with S. mansoni in these rats from N.W. Beghemder, Ethiopia.

It was felt that use of Arvicanthus rats as animal models of S. mansoni for immunological investigation may give more relevant information that can be related to man. This is in accordance with W.H.O. recommendations ( 1974 ) to use animal schistosomes within their natural hosts. Accordingly Arvicanthus sp was chosen to investigate the protective effect of adoptive transfer of cells ( predominantly lymphocytes ) by varying a number of parameters such as the degree of sensitization of cells, transfer time , and the concurrent influence of heterologous infections and fractionation of lymphocytes. At the same time this investigation may indicate how far this rat model can serve as an ' animal model ' for further immunological studies on S. mansoni .

## 2. REVIEW OF THE LITERATURE

### A. IMMUNOLOGICAL AND IMMUNOPATHOLOGICAL ASPECTS OF SCHISTOSOMIASIS.

Many interesting mechanisms of damage and killing of the schistosome parasite have been described in vitro and there are evidences to suggest that the same mechanisms may also operate in vivo ( David et al. 1980; Benteley et al. 1981 ). In general it is believed that effector mechanisms of acquired resistance to S. mansoni is an antibody-dependent cell-mediated cytotoxicity ( ADCC ) reaction ( Sher, 1977; Capron et al. 1980 ) involving a variety of cellular and humoral factors.

The main pathological effects of schistosomiasis have been shown to be due to immunological reaction against different parasite antigens; thus schistosomiasis is truly an 'immunologic disease' ( Warren, 1962 ).

Inflammatory hypersensitivity reactions to penetrating cercariae ( Ramalho-Pinto et al. 1976 ) or the schistosomula ( Warren et al. 1972 ) cause dermal infiltration and pulmonary granulomata respectively. Splenomegaly has been shown to be due to reactions in the reticulo-endothelial system ( R.E.S. ) against parasite antigens ( W.H.O. memoranda, 1974 ), while colonic polyposis, which results in damage to the muscularis mucosa, has been shown to be due to tissue granulomata around highly localised eggs ( Smith et al. 1977 ). The hepatosplenic

form of schistosomiasis mansoni has frequently been associated with glomerulonephritis ( Andrade et al. 1971 ).

The most important sequelae of schistosomiasis - hepato - splenomegaly and portal hypertension - are the result of an immunopathological process in the liver due to a delayed type hypersensitivity reaction to the schistosome eggs ( Warren, 1962; Warren, 1967; Boros et al. 1975 ). This hypersensitivity reaction is mediated by T-cell reactions to soluble egg antigens ( Domingo & Warren, 1968 ) and the inflammation is composed usually of macrophages, lymphocytes and eosinophils ( Von Lichtenberg, 1964).

In mice it is observed that during chronic schistosomiasis, egg granuloma size decreases progressively. This endogenous desensitization ( Domingo & Warren, 1968 ) or spontaneous modulation ( Boros et al. 1975 ) has been assumed to be due to immunoregulatory processes which involve suppressor cells ( Pelley et al. 1976; Ellner et al. 1980 ) or blocking antibodies ( Rocklin et al. 1980; Houba, 1977 ).

Many workers have tried to protect against the damage caused by tissue granulomata using different methods. Domingo et al. ( 1968 ) used immunosuppressive drugs, while Mahmoud et al. (1975) used anti-lymphocytic serum (ALS). However during such suppression of cell-mediated reactivity, severe complications result which involve liquefactive necrosis around granulomata and bacteraemia ( Fine et al. 1973 ). Thus it has not been possible to protect the host against the deleterious reactions it generates against itself. However Pelley et al. ( 1976 ) and Warren ( 1977 )

believe that induction of modulation by highly specific egg antigens may be possible in the future.

Part of the problem in the present situation of lack of protection by immunological means is due to inadequate knowledge of the exact immunological reactions involved during active infection ; the complexity of the immune responses to large parasites such as the schistosome parasite is understandable. Experiments done in vitro implicate a variety of cells and antibodies as possible candidates for the effector mechanisms against the schistosome parasite.

#### The Role of Cells.

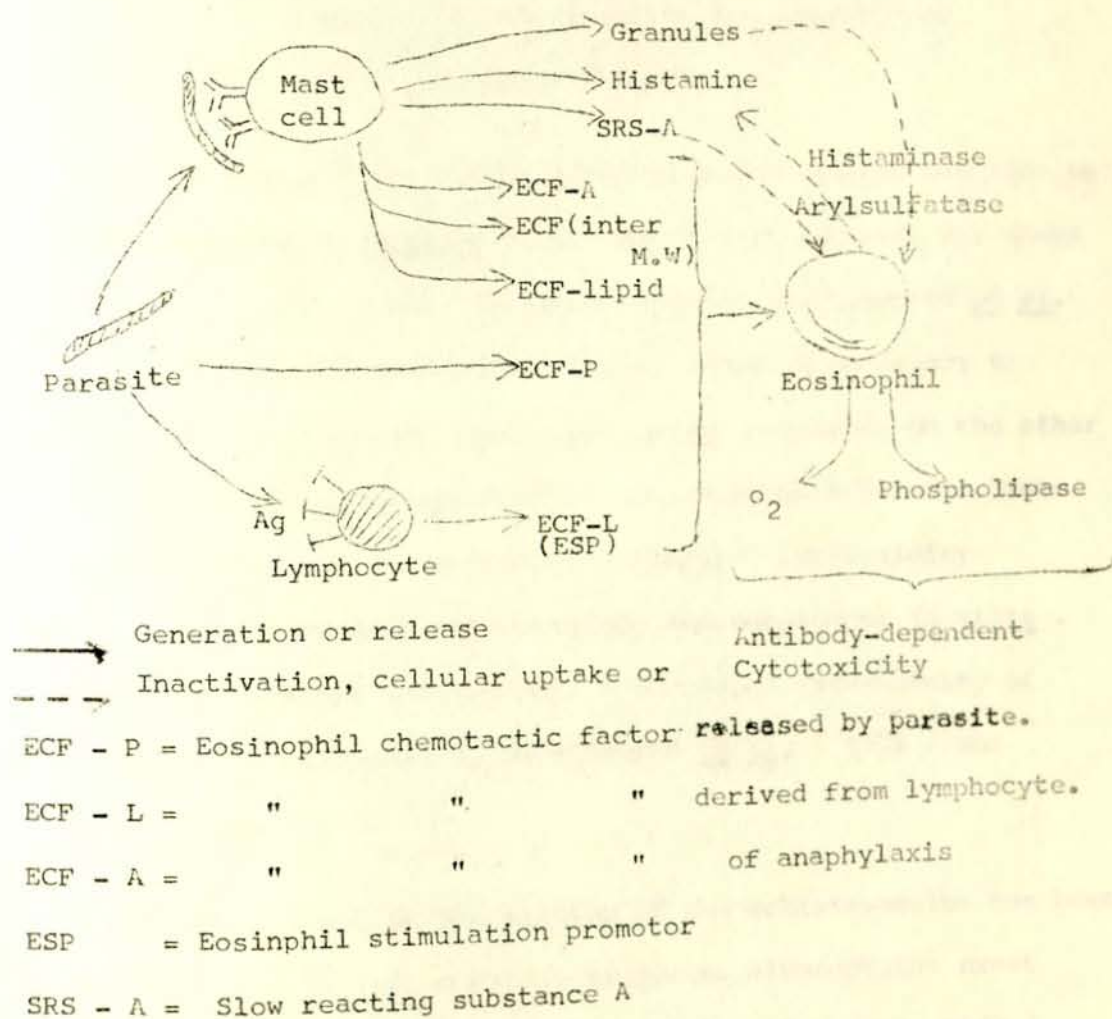
There is no description of damage to the schistosome parasite mediated directly by cytotoxic T-cells ( Butterworth, 1977 ). Even so there is extensive evidence to suggest that immunity against S. mansoni is at least in part dependent on thymic-influenced lymphocyte function ( Phillips et al. 1975 ).

Various cells have been shown to effectively kill the schistosome parasite in vitro. Gloetzel and Austen ( 1977 ) attach importance to mast cell - eosinophil interaction as a possible killing mechanism during helminth infections, including schistosomiasis ( Fig 1 ).

Capron et al. ( 1978 ) and Sher ( 1976 ) have shown in vitro interaction between mast cells and schistosomula, although the immunologic significance of such cytoadherence is not clear.

Other workers have elegantly demonstrated that neutrophils are important in immunity against *S. mansoni* ( Dean et al. 1974, 1975 ), while human monocytes have also been shown to kill schistosomula, independent of antibody or complement, in vitro ( Ellner & Mahmoud, 1979 ).

Fig. 1. Schematic representation of eosinophil response to parasitic infections.



However the eosinophil in combination with antibody and/or complement and macrophages in cooperation with IgE are the systems that have received much attention as possible effector mechanisms operating against the schistosomes both in vitro and in vivo.

There is significant increase in blood and tissue eosinophil level during invasive parasitic infestation in man ( Mahmoud et al. 1975 ). Eosinophils attracted to the tissue sites of parasitic invasion potentially fulfill at least two roles in defending the sensitized host, namely directly damaging the parasite or inhibiting mast cell - derived mediators.

That eosinophils can act as effector cells against the eggs or schistosomula of S. mansoni in the absence of antibody was shown by James & Colley ( 1976 ) in mice. However, Butterworth et al. ( 1977 ) are of the belief that immune serum is necessary to effect killing, although complement is not required. On the other hand, Ramalho-Pinto et al. (1978 ) and MacLaren & Ramalho-Pinto ( 1979 ) found that the effect of eosinophil cytotoxicity increased on incubation with antibody and complement in vitro . Further evidence for the antibody - dependent cytotoxicity of eosinophils is presented by Butterworth et al. ( 1975 ) and Mahmoud et al. ( 1975 ).

Eosinophil action in the killing of the schistosomulum has been shown to be due to degranulation products. Although the exact nature of these substances is not known ( Butterworth, 1977 ),

some workers believe that they are enzymatic in nature, probably lysosomal ( David et al. 1980 ) or perhaps peroxidase ( MacLaren et al. 1975 ). Gloetzel and Austen ( 1977 ) maintain that the eosinophil is endowed with specific enzymes capable of rapidly degrading mast cell-derived mediators ( Fig 1 ). Butterworth et al. ( 1979 ) and Gleich et al. ( 1973 ) suggest that the association of eosinophils with high quantities of " major basic protein " ( MBP ) may have some implications, as prompt killing of the parasite after discharge of MBP is observed. Eosinophils also release another protein called eosinophil cationic protein ( ECP ) and this is also found to be toxic to schistosomula at low concentrations. Another protein classified as a lymphokine, the eosinophil stimulation promoter ( ESP ), has been shown to be released from SEA - sensitized T-cells on stimulation ( Greene & Colley, 1976 ). ESP has also been shown to increase the migration of eosinophils collected from mice ( Colley, 1973 ) and in some instances to stimulate the generation of bone marrow eosinophils ( Gloetzel & Austen, 1977 ).

These in vitro mechanisms of eosinophil - dependent killing of the schistosome parasite are difficult to prove in vivo ( David et al. 1980 ). However they have been impressively corroborated with in vivo studies in models of both S. mansoni ( Mahmoud et al. 1975 ) and T. spiralis ( Grove et al. 1977 ) and also in man ( Bentley et al. 1981 ). Von Lichtenberg and co-workers ( 1976 ) also showed that eosinophil adherence and degranulation occur in the skin of immune animals.

The macrophage is another cell that has been intensively investigated as a possible effector cell against the schistosome parasite in vitro . Perez & Smithers ( 1977 ) , for example , showed that peritoneal exudate cells from normal SD or PVG rats, when sensitized with immune serum showed cell adherence reactions to the schistosomula in vitro . This reaction did not appear to require complement and resulted in tegumental damage.

Although Capron et al. ( 1979 ) have shown that macrophage activation needs complement, Kassis et al. ( 1979 ) are of the opinion that complement - independent opsonizing IgG may also activate macrophages into cytoadherence and killing reactions. Perez et al. ( 1974 ) have also observed that macrophages interact with IgG in killing the schistosome parasite in the rat. On the other hand, a cytophilic event involving either antibody or immune complexes appears to be responsible for the activation of macrophages ( Capron et al. 1975 ). Capron et al. ( 1980 ) have demonstrated this impressively by showing that IgE molecules , when aggregated , bind to a specific receptor on the surface of macrophages distinct from the Fc receptor of IgG.

Despite these demonstrations, it has not been possible to show granular secretions as in the case of the eosinophil. Macrophages most probably kill the schistosome parasite in the conventional non-specific phagocytic reactions ( Capron et al. 1975 ) .

## The Role of Antibodies

From various experiments on murine and simian hosts, many workers have arrived at the conclusion that the humoral arm plays a significant role in immunity against schistosomiasis ( Smithers, 1968 ).

As early as 1936, it was recognized that many animals have in their sera a cercaricidal fraction ( Culberston, 1936 ). Clegg and Smithers ( 1972 ) also showed that in the presence of highly immune rhesus monkey serum, some schistosomula die within the first 24 hours in vitro. They conclude that this lethal factor is specific antibody which is dependent for its action on complement. Capron et al. ( 1980 ) also showed that, in the rat, immunity is antibody - dependent in that it is abolished in anti- $\mu$  treated neonate rats. Concurrently Phillips et al. ( 1975 ) and Smithers ( 1976 ) demonstrated that immunity is effected by participation of cytophilic antibody in the rat.

Although the exact mechanism(s) by which antibodies exert their lethal effect is not entirely understood, some possibilities emerge. Newsome ( 1956 ) believes that antibodies cause precipitates around the orifices of adult worms or interfere with enzyme activity in worm tissue. Ogilvie ( 1970 ) postulates that inhibition of essential metabolic pathways of the parasites may be facilitated by antibodies. Suppression of the immune response may be effected by blocking antibodies, as in the case of the shut-off of early immunity seen in rats and modulation of the

granuloma size during chronic schistosomiasis ( Waksman & Cook, 1975 ). Antibodies may also function locally to facilitate antigen sequestration ( Von Lichtenberg, 1964 ).

Opsonizing antibodies cooperate with cells in the killing of the schistosome parasite. For instance, Hillyer ( 1969 ) and Mussulman et al. ( 1980 ) observed high production of IgG during S. mansoni infections in man and the mouse. Capron et al. ( 1978 ) demonstrated that IgG of rabbit hyperimmunized with soluble extracts of S. mansoni is toxic to adults of the same species grown in vitro. Clegg and Smithers ( 1972 ) observed that serum of infected rhesus monkeys, when cultured in vitro with schistosomula, had lethal activity. They conclude that this lethal action is due to the IgG class and is dependent for its action on complement in fresh serum.

Schistosomiasis is frequently found associated with high production of reaginic antibodies ( Maddisson et al. 1970 ). The fact that these antibodies are evoked only in animals that show a marked degree of natural or experimental resistance to S. mansoni, and not in those that have a low degree of resistance ( for example, the mouse ), prompted some workers to consider if these antibodies are involved in protection in some way ( Ogilvie & Jones, 1971 ). Thus for example, Ogilvie ( 1964 ) found a close correlation between immunity to infection and the presence of reagins in the nematode Nippostrongylus brasiliensis and the trematode S. mansoni in the rat.

Capron et al. ( 1980 ) also found that a close correlation exists between the evolution of specific IgE molecules and immunity to reinfection. Sadun & Gore ( 1970 ) found positive correlation between resistance to reinfection and the production of reagin - like homocytotropic antibodies in S. mansoni - infected hosts.

How these anaphylactic antibodies are involved in the killing of the schistosome parasite is not clear. Ogilvie ( 1970 ) is oversimplifying the issue when she states in broad terms that IgE may be involved in the sudden elimination of parasites seen in some helminth infections. It has also been suggested that these antibodies may play an important role in stunting the development of adult schistosomes, reducing egg production and mediating resistance to reinfection ( Ogilvie et al. 1966; Sadun & Gore, 1970 ). Capron et al. ( 1980 ) believe that, because of their production during schistosome infections, anaphylactic antibodies may play an important role in triggering phagocytic cell activity, thus revealing a new role for these antibodies classically implicated in adverse anaphylactic reactions only. This finding has important implications. For example, the injection of antigens which would stimulate the production of protective gamma E antibodies is one prospective means of protection ( Ogilvie, 1964 ).

B. MECHANISMS OF EVASION OF THE HOST'S IMMUNE REACTIONS BY THE PARASITE.

In schistosomiasis a paradoxical situation occurs in which parasites from a primary infection elicit a response which eliminates parasites from subsequent infections. This phenomenon of acquired resistance to reinfection in the presence of a continued primary infection was referred by Smithers and Terry ( 1969 ) as ' concomitant immunity '.

The mechanism(s) by which the parasite disguises itself from the immune attack of the host is not completely understood. It is believed that the adult schistosome of a primary infection has on its surface antigens which mimic those of the host and thus fool the host's immune system from recognizing it as non-self. The nature and origin of these surface antigens is also a matter of controversy.

Various workers contend that the surface antigens which disguise the parasite are of host origin. Clegg and Smithers ( 1972 ) proved this by showing that, in vitro, the early stages of the parasite which had no time to become protected are rapidly eliminated by complement-dependent antibody, whereas older worms are protected from the effect of same. Clegg et al. ( 1971 ) used a different approach. They transferred worms grown in mice directly into the portal circulation of rhesus monkeys previously immunized with mouse red blood cells and found that the schistosomes were rapidly destroyed whereas worms transferred to normal

monkeys survived. Coelho et al. ( 1980 ) arrived at the same conclusion by portal transfer experiments in rats, hamsters , Mastomys natalensis and Cebus monkeys. By using the sensitive enzyme - antibody bridge technique, MacLaren et al. ( 1975 ) also showed that 3-hours schistosomula do not possess mouse red blood cell antigens on their surface and are susceptible to attack by immune rhesus monkey immunoglobulin, whereas 4-day worms are not. Sher et al. ( 1978 ) also believe that the surface antigens are definitely acquired from host tissue, rather than synthesized by the parasite.

Equally convincing evidence is presented by many workers to show that antigens present on the surface of the schistosomulum are of parasite origin. Sprent (1959 ) and Dinnen ( 1963 ) believe that the surface antigens, although of parasite origin, have evolved under selection pressure to resemble those of the host. This in general reduces the overall immunogenicity of the parasite and favours its survival in the host.

Capron et al. ( 1968 ) speculate that the schistosomes possess the genetic capacity to synthesize antigens of several host types and that specific selection for a given mimicking antigen takes place when the worm enters the particular host. Other workers, ( Damain et al. 1973; Damain, 1967 ) have given more proof that the surface antigens are synthesized by the parasite itself.

The nature of these surface antigens is also not agreed upon. Smithers & Terry ( 1976 ) assume that antigens synthesized by the parasite are pure proteins while those acquired from the host are glycolipids. Similarly, Waksman & Cook ( 1975 ) have stated that host antigens taken by the parasite include the A,B,H and Lewis glycolipid antigens of human erythrocytes. However, Sher et al. ( 1978 ) have convincingly shown that non-glycolipid molecules such as the K and I gene products of murine MHC may also associate themselves with the schistosome surface and help to disguise the parasite from the host's immune attack.

Whatever the nature or origin of these surface antigens, how do they act to effect escape of the parasite from the deleterious action of the host's immune response?

The target of the host's immune attack is the schistosomular surface and Smithers et al. ( 1977 ) have shown that in vitro there is rapid turnover of plasma membrane layers into culture media. They believe that such turnover may be responsible for counteracting antibody attack by the parasite. Kusel et al. ( 1975 ) also showed the same turnover phenomenon using radioactive labelling.

It is generally assumed that immunologic disguise occurs as the schistosomulum matures to the adult stage. This loss of antigenicity has been associated with the loss of ability to activate complement via the alternative pathway and the

redistribution of intramembraneous particles ( IMP ) on the schistosome surface ( Smithers et al. 1977 ). The release from the schistosomular surface of a variety of products which may affect immune effector mechanisms, such as proteolytic enzymes which cleave IgG ( Auriault et al. 1981 ) and factors which inhibit lymphocyte and mast cell functions ( Capron et al. 1980 ) have been suggested.

Smithers and Terry ( 1976 ) bridge the various assumptions by concluding that antigens of parasite origin may serve to reduce the overall immunogenicity of the parasite, while antigens of host origin attaching to the parasite surface complete the immunologic disguise of the adult worm and protect it from immune attack. Recently, MacLaren and Terry ( 1982 ) have shown that the escape of the schistosomulum from the host's lethal reaction may involve mechanisms quite different from those involving the parasite surface.

C. SOME PROBLEMS ENCOUNTERED IN THE  
IMMUNOLOGICAL STUDY OF SCHISTOSOMIASIS.

Although many immunological mechanisms against the schistosome parasite have been understood, there are still a lot of unanswered questions and this might be responsible for the lack of prospect for a vaccine in the near future ( Hoffman et al. 1979 ).

Part of the problem resides in the very nature of the study of helminth immunology itself. For example, the demarcation of cellular and humoral immunity in helminthiasis is a complex process. The difficulties encountered in dissociating multiple overlapping host mediator systems activated by a polyantigenic metazoan parasite is enormous ( Von Lichtenberg, 1977 ). This is the case of schistosomiasis, where the host, exposed to cercariae, schistosomula, adults and eggs, is given the opportunity to react to each of these antigenic varieties with a wide range of immune responses ( Butterworth et al. 1982 ).

The lack of a convenient and realistic laboratory animal model has encumbered immunological study of schistosomiasis to a great extent ( Smithers & Terry, 1976 ). Laboratory hosts are known to differ in their responses to S. mansoni. For example, differences of about 20% in yield of adult worms exist between C57/BL6 and A/J mice exposed to the same number of cercariae ( Sher, 1977). The most widely-used laboratory models are the rat and the mouse; however both animals have some inherent characters that is undesirable for immunologic study.

The high susceptibility of the mouse is disadvantageous in its use as an immune model since it is difficult to dissociate the effects of protective immunity from those of the disease itself ( Sher, 1977 ). The high intrinsic resistance of the rat has been exploited to demonstrate immunologically-mediated resistance mechanisms ( Phillips et al. 1977 ) but it has been cautioned that direct analogy cannot be drawn between this resistant species and the more sensitive species man. Thus results obtained from laboratory animals are not necessarily applicable to man ( Newsome, 1956; Warren et al. 1972; Butterworth et al. 1982 ) .

Variation in the parasite itself is another parameter that may affect results. Saoud ( 1966 ) and Warren ( 1967 ) found that the prepatent period, number of maturing worms, distribution of eggs in host's tissues and pathology differed with varying strains of S. mansoni. El Hassan et al. ( 1977 ) also found differences between geographical strains of S. mansoni.

The lack of correlation between protection and immunological manifestations has long been recognized. Phillips et al. ( 1977 ) observed that serum IgG level increases dramatically, despite granuloma diminuation, in CDF rats during chronic schistosomiasis. No correlation between in vitro titres of antibody activity and in vivo resistance was observed by Phillips et al. ( 1978 ) in studies on mice, while Sher et al. ( 1974 ) found resistance to be unrelated to antibody titre or PMN-dependent cytotoxicity. It is assumed that such lack of relation is observed because the

antibodies or cells measured may simply be unrelated to those responsible for transfer of immunity. This has undesirable consequences. For example, although many serological tests are available for the diagnosis of schistosomiasis; since they detect antibodies which bear little relationship to the course of the disease, they cannot be used to assess the intensity of infection, prognosis or cure ( Sadun & Gore, 1970)

In vitro methods of analysis of immune mechanisms have their advantages and drawbacks ( Butterworth, 1977 ). Phillips et al. ( 1977 ) contend that no in vitro method, including both humoral and cellular techniques, have been shown to accurately mirror in vivo resistance. It has also been reported that reactions which damage schistosomula in vitro may not necessarily be operative in vivo. For example, a complement-dependent antibody from rats, although lethal to schistosomula in vitro, has no effect on the parasite in vivo ( Sher et al. 1974 ); thus direct application of in vitro results to the in vivo situation is not fully reliable

Cross reactive antigens have been reported between S. mansoni and other parasites such as S. bovis and Trichinella spiralis ( Sadun et al. 1962b ), S. haematobium ( Smith et al. 1976 ). While advantageous in conferring some degree of heterologous immunity, such cross reactions also complicate the analysis and interpretation of results. Perez et al. (1974) also found that results obtained using different methods such as lung assay, liver assay, etc are not concordant sometimes.

### 3. MATERIALS AND METHODS

#### Experimental animals

##### Rats

Wild Arvicanthus sp rats were collected from Debre Berhan, Ambo and Bole International Airport areas using conventional traps. These areas are not endemic for schistosomiasis; therefore the rats are in all likelihood schistosome - free prior to challenge in the laboratory. 15 - 18 rats were put in one cage and maintained on rat feed, bread and occasionally carrots for about 2 months, after which rats that had contracted disease from the field died. The rest were used for the experiment. Weight - matched rats were put in each cage so as to be used as a unit for the different parameters considered.

##### Snails

Infected Biomphalaria pfeifferi snails were obtained from the collection of the Pathobiology Institute from Kemisse, Wollo. Others were collected from canal sites from the Wonji Sugar Plantation. Cercariae were shed by photic exposure for about 45 minutes. Cercaria collected from different snails were pooled together in order to increase the sex ratio proportion of female:male towards 1:1. However different number of snails were used for the different groups of rats; this is reflected fairly in that rats of different groups ( parameters ) show differences in egg loads ( See Table I ).

### Infection of rats with schistosome cercariae

The lowest number of cercariae needed to maintain infection without being lethal was determined by exposing rats to 100, 200, 300, 400, 600, 800 and 1,000 cercariae and it was found to be 300 cercariae. Drops of water containing the cercariae were counted under 100X objective after immobilizing the cercariae with Lugol's Iodine. The number of drops adding up to 300 cercariae was then added at the tail and leg regions of rats immersed in 100 ml of aged water. Rats were kept thus for about 45 minutes after which the water was checked for any remaining cercariae. As a routine, about 80% penetration was observed.

### Transfer times

The time of challenge with cercariae was denoted as day 0 and cell transfers were done either before challenge ( negative days ) or after challenge ( positive days ). The choice of the transfer days is arbitrary, hence there is no consistent pattern either in the number of rats used in each group or in the transfer dates themselves.

### Fractionation of lymphocytes and transfer procedure

Donors were sacrificed at the end of 1.75, 2, 2.5 and 3 months infection and their mesenteric lymph nodes, hepatic lymph nodes and spleens excised and put in Hank's balanced salt solution ( HBSS ) supplemented with 5% fetal bovine serum ( Sher et al. 1975 ). Individual cells were collected

by pressure sieving using slight modification of the methods of Corba ( Personal communication, 1981 ). Briefly, lymph nodes and spleen were first minced into small pieces, then gently crushed using modified rubber stoppers on a sieve of mesh size 0.2 mm. Cells were washed with HBSS and left to stand for about 15 min. The supernatant was sucked out while the remaining cells were gently shaken to form uniform cell suspension ( Weir, 1978 ). Such concentrated cell suspensions were pooled and resuspended in 2 ml HBSS for injection.

Fractionation was done in columns of glass wool fibre as of Greaves et al. ( 1976 ), and the cells layered into a total volume of 2 ml HBSS. Since fractionation was run only once, the presence of cells other than T-cells in the eluate cannot be ruled out.

Before injection the viability of the cells was checked by the Trypan Blue dye exclusion test ( Wakelin & Llyod, 1976 ). As a routine about 80% viable cells were noted. The number of transferred cells was estimated using slide gridding and further verified with counting chambers. An estimated  $3 - 5 \times 10^6$  cells were present in 2ml HBSS.

#### Assessment of protection

Egg load of the liver and the intestines was estimated following the method employed at the Pathobiology Institute ( IPB Handbook, 1969 ) and also according to Smith et al. ( 1977 ).

Briefly, weighed amounts of liver, small and large intestines ( corresponding to the ileum and colon in rats ) were put in 10 times their volume of 4% KOH and incubated at 55°C for 2 hours or 40°C for 3 hours. This mixture was homogenized using magnetic stirrer. 1 or 2 ml samples were counted under gridded petridishes using 20X objectives. As many as 6 counts were done for each sample and each was done twice by different people. The average number of eggs per square of the grids was obtained and the number of eggs per gram of organ calculated using this information.

Adults were perfused with a 50 gauge needle according to the usual method ( IPB Handbook, 1969 ). Sometimes this was not very efficient, so that physical search in the mesenteric and portal veins had to be undertaken to recover as many adults as possible.

#### Statistical treatment

Student's t-test was employed to determine the significance of the differences in mean egg loads and adult burdens between experimental and control groups ( Snedecor & Cochran, 1967 ).

#### 4. RESULTS AND DISCUSSION

Outbred Arvicanthus sp rats were used to assess the effect of adoptive transfer of cells ( mostly lymphocytes ) during S. mansoni infections. One possible limitation of such a study is allogeneic rejection of transferred cells between histo - incompatible strains.

Experiments done for other parasites ( for example T. spiralis ) indicate that allogeneic cell transfers between different strains of mice ( for example NIH and B.10 ) has a positive effect on worm fecundity in recipients ( Wakelin & Donachie, 1980 ). In guinea pigs, it is also observed that passive transfer of immunocompetent allogeneic cells results in prolonged survival and protection in recipient animals ( Katz, 1977 ). Thus although no previous information on cell transfer using Arvicanthus rats is available, it is envisaged that adoptive transfer may also lead to protection in some way, either through effect of transferred cells or GVH reaction.

It is not exactly clear how transferred cells act in conferring immunity to recipient animals. It has been suggested that transferred mesenteric lymph node cells ( MLNC ) do not act directly on parasites but cooperate with other components of the host's immune system ( Wakelin & Wilson, 1977 ). Weir ( 1978 ), for example, says that cell - mediated immunity can be adoptively transferred either by sensitized cells or their

products. Thus, one area of cooperation may be between sensitized T-cells which release lymphokines and other effector cells which are accordingly stimulated. It is not hard to think of the situation where lymphokines released from egg-sensitized cells such as eosinophil stimulation promoter (ESP), macrophage activating factor (MAF), etc, may lead to an enhanced response and to killing of the schistosome parasite during adoptive transfer, even allowing for their elimination some time after introduction. On the other hand, T-cells could elevate circulating anti-egg antibody responses, thereby blocking the afferent arm of the granulomatous response (Chensue & Boros, 1979). Sensitized lymphocytes also function in the induction of immunologic competence to uncommitted blast cells (Weir, 1978).

- (i). Effect of transfer of schistosome - sensitized cells on resistance of recipient rats to S. mansoni infection

Cells from donors infected for 1.75, 2, 2.5 and 3 months previously were transferred into recipients which were then challenged with schistosomes and sacrificed 3 months post-infection. The ability to resist infection was assessed by egg load and adult burden in these rats compared to control rats which were only infected. Results are given in table I.

It can be seen that some protection is transferred by cells from donors infected 1.75 months previously (  $P < 0.05$  ). Oviposition starts 1.5 months post - infection ( W.H.O. memoranda, 1974 ) and it appears that one week after egg - laying, there is some stimulation by egg antigens and this can be transferred adoptively. However, the rather smaller protection observed may be due to inadequate sensitization of the cells, since the post-oviposition period is short. It can be seen that cells from 1.75 months have a deleterious effect even on adult schistosomes. It is reported that adult antigens are detectable as early as 2 - 4 weeks after infection ( Houba, 1980 ), and it is attractive to speculate that such antigens may sensitize circulating lymphocytes.

On the other hand, cells from 2 month - infected donors give almost complete protection to recipient rats (  $P < 0.001$  ). It appears that 2 weeks post-oviposition there is enough stimulation by egg antigens which may sensitize lymphocytes to produce lymphokines in abundance. This is further supported by the fact that cells were not fractionated for this group of rats. Thus the lymphokines produced may have a stimulatory effect in the recipients as, for example, in mobilizing eosinophils ( ESF ) or macrophages ( MAF ) to effectively kill the parasite at an early stage ( Kazura et al. 1975 ). The almost complete attrition of parasites before they reach the adult stage further supports this view.

Transfer of cells from donors infected for 2.5 months affords no protection to recipient rats (  $P < 0.5$  ). It is probable that suppression of cell - mediated response may have occurred at this stage of infection. This concept of suppression of cell - mediated reactivity which results in granuloma modulation during chronic infections of S. mansoni has been well established ( Chensue & Boros, 1979 ). However the early suppression in Arvicanthus sp rats ( 10 weeks ) may be a reflection of its high susceptibility to infection by S. mansoni. For instance, serosuppressive factors are readily formed in susceptible hosts ( Todd et al. 1980 ). The higher egg load and adult burden in these recipients as opposed to controls is puzzling, but this may be due to the small size of the controls used for comparison, or the heterologous effect of the cestode: infection in these controls. On the other hand the involvement of mechanisms quite unrelated to suppression should also be considered.

Partial transfer of immunity is acquired from cells obtained from donors infected for 3 months (  $P < 0.01$  ). It is possible that blocking mechanisms against egg antigens are uplifted at this time of infection while those against adult antigens apparently are not.

There are adequate reports of adoptive transfers from chronically -infected cells and serum ( Sher, 1977 ) and splen cells ( Chensue & Boros, 1979 ). Such transfers usually affect the later modulatory phase of hepatic granulomata ( Phillips et al. 1977 ) as is further supported by the performance of Arvicanthus rats in this case too.

Table I. Protection in recipient rats that had received sensitized cells from donors infected for different periods of time

Infection period of donors (months)	Sites examined and adults no.	Mean epg+SD (Rats) (Recipients)	Mean epg +SD (Rats) (Controls)**	% protection
1.75	Liver	13,102 <sub>+</sub> 8,277(6) <sup>0</sup>	39,287 <sub>+</sub> 23,113(5) <sup>⊕</sup>	66.6
	Small intest.	15,111 <sub>+</sub> 4,016(5)	36,148 <sub>+</sub> 36,767(5)	58.2
	Large intest.	12,794 <sub>+</sub> 5,452(6)	33,889 <sub>+</sub> 26,883(5)	65.2
	Adults	15 <sub>+</sub> 13 <sup>0</sup> (4)	19.2 <sub>+</sub> 12.8 (5)	21.8
2	Liver	1.201 <sub>+</sub> 2,657(13)	8,443 <sub>+</sub> 2,940 (7)	85.7
	Small intest.	34.9 <sub>+</sub> 67 (12)	2,315 <sub>+</sub> 1,404 (5)	98.5
	Large intest.	24.4 <sub>+</sub> 45 (12)	8,088 <sub>+</sub> 5,717 (7)	99.7
	Adults	2.5 <sub>+</sub> 3 (5)	11 <sub>+</sub> 7 (3)	77.0
2.5	Liver	13,024 <sub>+</sub> 13,170(5)	7,078 <sub>+</sub> 3,354 (3)	-84
	Small intest.	8,074 <sub>+</sub> 7,129 (5)	7,461 <sub>+</sub> 4,970 (3)	-8.2
	Large intest.	15,819 <sub>+</sub> 27,035(5)	5,987 <sub>+</sub> 2,946 (3)	-164.2
	Adults	27.2 <sub>+</sub> 24.9 (5)	15.6 <sub>+</sub> 4.5 (3)	-74

3	Liver	7,052 $\pm$ 9,395 (13)	39,237 $\pm$ 23,113(5) @	82.0
	Small intest.	7,005 $\pm$ 9,897 (13)	36,148 $\pm$ 36,767(5)	80.6
	Large intest.	6,359 $\pm$ 9,054 (13)	33,889 $\pm$ 26,883(5)	81.2
	Adults	9.3 $\pm$ 14.8 (11)	19.2 $\pm$ 12.8 (5)	51.5

\* Rats in each group received cells before and after challenge infections.

Recipients of cell from donors infected for 1.75 months had challenges ( 0d,+2d,+6d ), those of 2 months on ( -21d, -4d, -2d, -1d, +2d ), those of 2.5 months on ( -4d, +6d ) and those of 3 months on ( -17d, -3d, -1d, +1d, +5d ). epg= eggs per gram

\*\* Controls were challenged at the same time as respective recipients but recieved no cells

Ø Different animals are represented because some samples wre not considered, in cases like inadequate perfusion of adults, breakage of vials..etc.

@ Same controls used because infected from same pool of snails.

% protection expressed as 
$$\frac{\text{Mean eggs/gm of controls} - \text{Mean eggs/gm of experimental} \times 100}{\text{Mean eggs/gm of controls}}$$

However it is interesting to determine what causes uplifting of effector mechanisms against egg antigens, as opposed to adults, in such 3 month-infected donors. Perhaps some egg antigen-sensitized lymphocytes from chronic infections may stimulate "memory cells" in recipients and these act selectively against target egg antigens later.

Experiment was done to investigate if infection was required for the cells to adoptively transfer resistance. Although no test for sensitization was done, it is assumed that repeated egg excretion from the schistosome parasite into the host's tissues results in 'sensitization' of the host ( Domingo & Warren, 1968 ). If sensitization can be transferred by cells from 3 month-infected donors, then the effect of sensitization per se can be evaluated by comparing recipients of normal cells and those of sensitized cells. A selection is shown in table II.

It can be seen that recipients of sensitized cells have on the average lighter infections than recipients of normal cells. No definite conclusion must be hastily drawn from this result, however. It is likely, for example, that immunity is transferred by the eosinophils that are transferred with the other cells, or the GVH reaction may be responsible for the observed immunity. Takelin and Donachie (1980) however also found that transfer of mesenteric lymph node cells from uninfected donors had no effect upon worm populations in recipient rats.

Table II. Effect of transfer of cells from normal, versus infected donors on ability of recipient rats to resist challenge infection with S. mansoni.

Transferred cells	Rat No.	Egg Load in			Adults
		liver	small intestine	large intestine	
Normal cells	1	22,800	11,435	6,612	7
	2	28,900	13,722	33,333	13
	3	87,762	59,633	10,795	16
	4	18,419	55,727	1,900	9
Sensitized cells**	1	17,784	26,839	25,334	6
	2	0	0	0	0
	3	0	0	0	0
	4	16,000	10,795	8,708	N.D
	5	400	156	80	N.D
	6	540	80	120	2

\* Eggs per gram of organ \*\* 3 months infection ( both cestode infected and non-infected rats are considered, hence the obvious variation observed ). N.D Not done

It appears that cells from 2 months post-infected donors give maximum protection against S. mansoni infections in recipient rats. In mice infected with T. spiralis, Wakelin and Wilson ( 1977 ) also found that only MLN cells of mice infected for 4, 6 or 8 days are capable of transferring immunity, while Corba ( pers. comm ) found that only lymphocytes from rats infected 8 - 10 weeks previously with F. hepatica conferred protection to syngeneic recipients.

- (ii). Effect of variation in the time of transfer  
( relative to challenge ) on resistance of  
recipient rats.

Table III shows result of protection obtained from transfer of cells at different times relative to challenge day. It can be seen that transfers done as early as, or later than, 2-3 days of challenge are protective. This is not surprising since the host's immune system is mainly directed against the early stages of the parasite ( Phillips et al. 1978 ). As demonstrated by in vitro experiments, such killing involves mobilization of effector cells such as eosinophils and macrophages against the early schistosomulum by transferred cells ( Capron et al. 1982; Butterworth, 1977 ). Like serum transfer regimens, which are usually effective if transferred before 2 days of challenge ( Knopf, pers.comm. Sher, 1977 ), the transfer of sensitized cells also appears to be effective when transferred on days near the day of challenge. This is also supported by Wakelin and Wilson's ( 1977 ) work, in which they showed that only cell transfers made close to the challenge date are effective in transferring resistance against T. spiralis infections in recipient mice.

It is surprising that even transfers done 2 or 3 weeks previously afford protection to recipients. Although elimination of lymphocytes after long periods of introduction is likely, the possibility of induction of resistance even after such elimination is borne out well by results of recipient rats of cells transferred

Table III. Protection in recipient rats by adoptive transfer of cells at different times relative to challenge.

Transfer time	Donors' infection per (mon)	Parameter	epg organ $\pm$ SD (Experimental)	epg organ $\pm$ SD (Controls)	%protection
-21d	2	Liver	313 $\pm$ 280 (3)	8,586 $\pm$ 3,056 (7)	N.C. (See text)
		Small int.	118 $\pm$ 54 (2)	2,315 $\pm$ 1,404 (5)	
		Large int.	100 $\pm$ 28 (2)	8,088 $\pm$ 5,717 (7)	
		Adults	N.D.	11.3 $\pm$ 6.6 (3)	
-17d	3	Liver	47,914 $\pm$ 53,114 (3)	48,245 $\pm$ 27,535 (6)	6.8
		Small int.	44,804 $\pm$ 42,489 (3)	51,861 $\pm$ 42,148 (6)	13.6
		Large int.	46,841 $\pm$ 46,807 (3)	43,233 $\pm$ 30,606 (6)	-8.3
		Adults	17 $\pm$ 15.5 (3)	25.6 $\pm$ 10.9 (4)	36
-4d	2	All parameters	0 (3)	control 1	100
-3d	3	"	0 (4)	control 2	100
-2d		"	0 (3)		
+1d	2	"	0 (5)	control 1	100
+2d	2	Liver	1,315 $\pm$ 2,682 (3)	control 1	84.6
		Small int.	36 $\pm$ 81 (3)		98.4
		Large int.	18.6 $\pm$ 41 (3)		99.7
		Adults	N.D.		N.D.
+5d	3	Liver	19,072 $\pm$ 3,166 (3)	control 2	60.4
		Small int.	16,663 $\pm$ 5,117 (3)		67.8
		Large int.	13,368 $\pm$ 4,597 (3)		67.7
		Adults	34.5 $\pm$ 6.4 (3)		-30.0

Effect of heterologous vaccine infections on  
three weeks ( -21d ) or 2½ weeks ( -17d ) previously. As  
Resistance of recipient rats against challenge  
expected, the level of immunity conferred is not high. The  
Infections with schistosome antigen  
high attenuation of infection in recipients of cells that  
were transferred 21 days before ( -21d ) is puzzling, but  
such an anomaly is probably due to some methodological error  
and to the small number of rats used for comparison; the  
result is therefore not considered ( N.C ).

Transfers done 5 days post-infection ( +5d ) also give  
protection. It is known that cercariae metamorphose into the  
schistosomula in the lung by days 5-6 post-infection ( W.H.O.  
memoranda, 1974 ), where the host's immune system traps them  
in a lethal inflammatory reaction ( Von Lichtenberg et al. 1977 ).  
Thus transfers done at this time may augment and enhance the  
killing reactions, accounting for the protection seen in these  
rats.

From these results it appears that adult and egg antigen -  
sensitized cells may be transferring resistance against the  
early stages, of cercariae and schistosomula. In view of common  
antigenic determinants between the different stages of the  
schistosome parasite, this is not strange ( Kagan & Pellegrino,  
1961 ). For example, Bogitsch and Stephan ( 1976 ) have shown  
that protection can be effected against challenge infections by  
cercarial antigenic preparation ( CAP ). In other cases it has  
been documented that portal transfer of adults also results in  
protection against challenge infections ( Smithers, 1976 ).

- (iii). Effect of heterologous cestode infections on resistance of recipient rats against challenge infections with Schistosoma mansoni

This investigation was carried out due to the frequent observation that rats which had concomitant cestode infections ( Hymenolepis sp ) contracted from the field usually had more attenuated S. mansoni infections when compared to cestode - free rats. Accordingly , selected rats from recipients of cells from 2 and 3 month-infected donors were used to see the effect of heterologous immunity. Results are recorded in table IV.

Recipients of transfer cells and cestode-infected rats have lighter infections as compared to the other categories in table IV. Rats which were cestode-free but had received transfer cells also developed only moderate infections, while non-transfer but cestode-infected rats develop severe infections on challenge with S. mansoni cercariae. Thus it is safe to conclude that the main protective effect is due to transferred cells and whatever effect is obtained from cestode infections is only of secondary importance.

Closer examination of the data in table IV will show that egg distribution in the liver and intestines is affected by cestode infection. For example, recipients of cells and at the same time cestode-infected rats have more eggs in the liver than in the intestines, while the reverse is true for recipients of cells from 3 month-infected donors. The overlapping of cestode

Table IV. Effect of cestode infections on ability to resist Schistosoma mansoni infections in Arvicanthus rats.

Donors' infection period(months)	Category of rats		eggs/gm liver + SD ( Rats )	eggs/gm intestines + SD ( Rats )	Adults
	cells rec.	Cestodes			
2	+	+	94+200 (10)	43+92 (10)	N.D.
	+	-	4,891+3,954 (3)	265+127 (3)	4.6+1.5(3)
	-	+	9,865+2,379 (3)	4,299+2,187(3)	N.D
3	+	+	4,826+8,258 (7)	10,239+19,865 (7)	N.D
	+	-	14,474+9,925(4)	25,519+17,316 (4)	24.5+16(4)
	-	+	43,231+28,233(7)	65,491+46,404 (7)	18+10 (7)

infections in these recipients thus appears to cause a shift in egg distribution. Interestingly enough, this condition is also observed in cestode-infected rats which had not received any protective cells. It is thus probable that the shift in egg distribution is caused by the physical presence of the cestodes in the intestine.

The appearance of more eggs in the liver of maximally - protected rats ( recipients of 2 month-sensitized cells ) may probably be because of the effect of the transferred cells on the early stages of the parasite. The higher egg load in the intestines as opposed to the liver in recipients from 3 month - infected donors is likewise because of the effect of cells from chronic infections on the later modulatory phases of hepatic granuloma ( Maddisson & Kagan, 1979 ).

It is interesting to determine how cestodes cause immunity against infections of S. mansoni and how they affect egg distribution. Do such phenomena involve immunological enhancement or mechanical obstruction of egg sites? Ishaak et al. ( 1975 ) found that in mice, the elimination of Hymenolepis diminuta is thymus-dependent. If the immune reactions against the cestode infection in Arvicanthus rats also involves cell-mediated responses, then it is possible that cross immunity between S. mansoni and Hymenolepis sp. develops during concurrent infections. It has been reported that S. mansoni shares many common antigens with other parasites ( See Literature Review ).

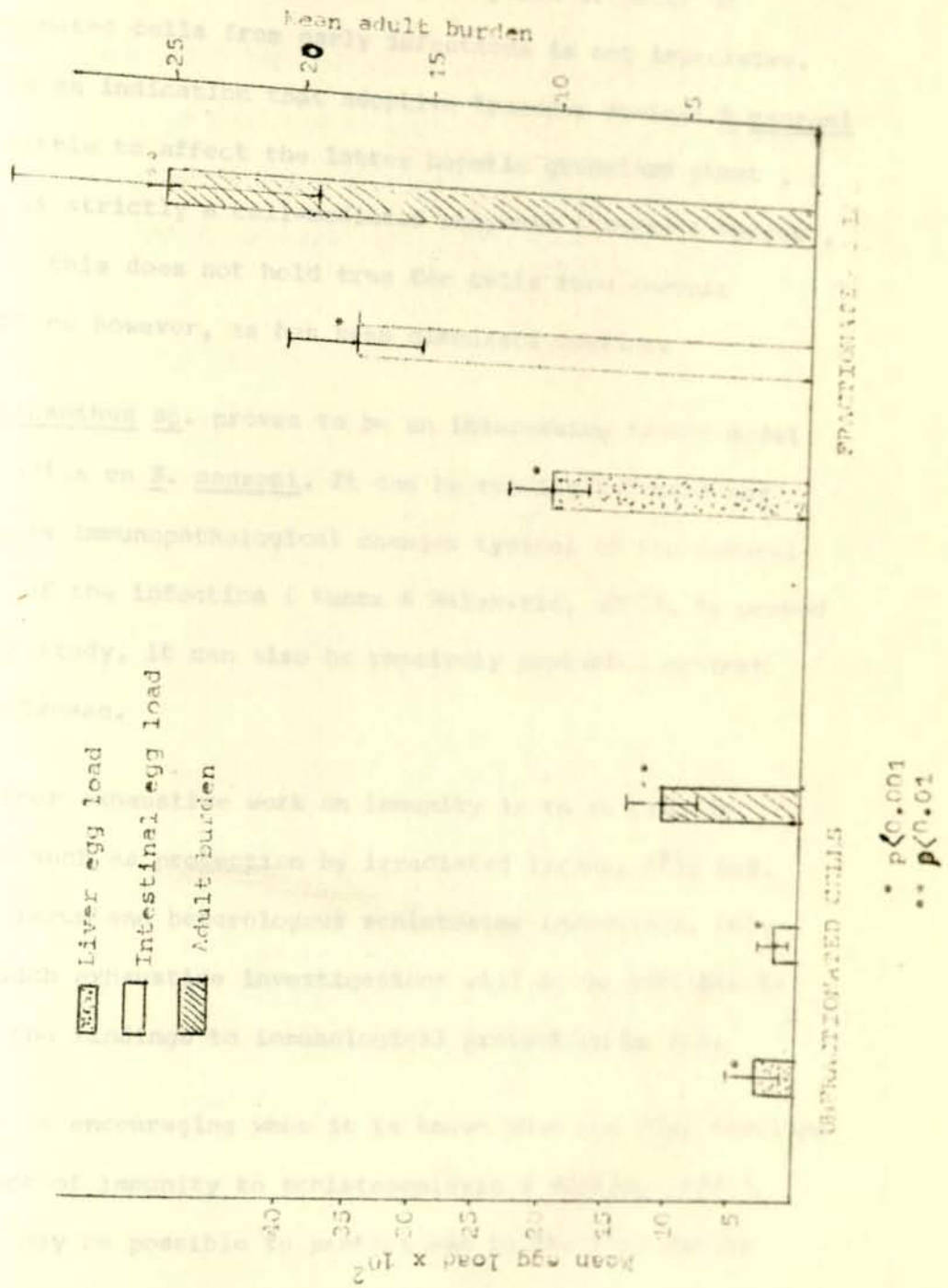
Attempts to demonstrate cross-reactive antigens between the two parasites did not give conclusive result. However it was demonstrated that both share some antigens with Cysticercus teniculus and that antiserum of each precipitated some factor in the somatic antigenic preparation of the other. It is thus probable that S. mansoni and Hymenolepis sp. may also share some common antigens and thus evoke cross immunity during concurrent infections.

- (iv). Fractionation of cells : Ability to transfer resistance to recipient rats.

Fig 2 gives a summary picture of the effect of fractionation of cells on columns of glass wool fiber before transfer to recipient rats.

It can be seen that recipients of unfractionated cells have lighter infections (  $P < 0.001$  ). It appears that in the situation where different cells are involved, better killing reactions against the schistosome parasite result. This is acceptable in that the effector mechanisms against the schistosome parasite involve the ADCC system, whereby both cells and antibodies are involved ( See Literature Review ); hence the transfer of unfractionated cell populations such as B-cells, macrophages, etc with the T-cells , naturally enhances the level of immunity in recipients.

Fig 2. Effect of fractionation of cells on ability to transfer resistance to recipient rats ( 5/group)



The ability to transfer CMI by adoptive transfer of fractionated cells from early infections is not impressive. This is an indication that adoptive transfer against S. mansoni does little to affect the latter hepatic granuloma phase , which is strictly a cell-mediated response ( Boros & Warren , 1975 ), this does not hold true for cells from chronic infections however, as has been discussed earlier.

Arvicanthus sp. proves to be an interesting immune model for studies on S. mansoni. It can be readily infected and undergoes immunopathological changes typical of the natural course of the infection ( Kuntz & Malakatis, 1955). As proved by this study, it can also be passively protected against overt disease.

Further exhaustive work on immunity in these rats is desired such as protection by irradiated larvae, SEA, ALS, immune serum and heterologous schistosome infections. Only after such exhaustive investigations will it be possible to relate the findings to immunological protection in man.

This is encouraging when it is known that man also develops some sort of immunity to schistosomiasis ( Warren, 1977 ). Thus it may be possible to protect man in the long run by immunological manipulation of the results obtained from good immune laboratory models such as Arvicanthus rats.

If, and when, such immunological methods prove to be feasible, it may be possible to protect short-term residents visiting endemic sites which are important from some point of view; for example, tourism, irrigation.

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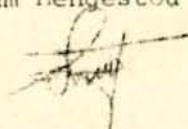
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DECLARATION SHEET

I, the undersigned, declare that this thesis is my work and that all sources of material for the thesis have been duly acknowledged.

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Signiture



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