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RECENT ADVANCES IN IMMUNITY TO HUMAN SCHISTOSOMIASIS

PAUL HAGAN & FREDERICO G. C. ABATH

Division of Parasitology, National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, UK

For many years the epidemiological significance of immunity in human schistosomiasis has been the subject of inconclusive debate. Recently, the results of studies from Brazil and Kenya, on Schistosoma mansoni *and from Zimbabwe and The Gambia on* S. haematobium *have confirmed the importance of protective immunity. In communities in endemic areas the development of immunity to infection only occurs after many years of exposure. In part this is due to the slow development of antibodies which are protective but also to the earlier development of antibody isotypes which lack protective capacity and which are capable of interfering with the functioning of protective antibodies. Protective antibodies appear to be of the IgE class but some IgG subclasses may also be important. Initially, blocking antibodies were thought to be predominantly IgM and IgG2 but IgG4 also seems to possess blocking activity. The early production of blocking antibodies and late production of protective antibodies may be indicative of cytokine induced immunoglobulin class switching caused by the sequential involvement of different lymphokines.*

Key words: schistosomiasis – immunity – man

Examination of the association between schistosome infection prevalences and intensities in relation to age reveals a characteristic pattern. Prevalence and intensity are both high in children and decline to lower levels in adults. This pattern may be explained in a number of ways but two interpretations have dominated the literature. The first is that the high levels of exposure to infection of children lead to high levels of infection. Adults have low levels of exposure to infection and therefore remain lightly infected or even uninfected. The second explanation is that after several years of exposure to infection adults develop an immunity which prevents infection even though they have continued exposure. Up until 1987 several studies had been reported but none of them allowed a clear statement to be made on the relative importance of exposure to infection and resistance to infection. The data of Kloetzel & Da Silva (1967) on *Schistosoma mansoni* infection patterns in immigrants to an endemic area have been interpreted as favouring a role for immunity to infection. They concluded that the infection patterns of the immigrants were related to the length of residence and not to age and this has led others to suggest that the cumulative history of exposure to infection is important. Bradley & McCullough (1973) also favoured an important role for immunity when interpreting their studies of *S. haematobium* infection in Tanzanian schoolchildren in terms of the "concomitant immunity" model proposed by Smithers & Terry (1967). But others, notably Dalton & Pole (1978) found no requirement for immunity, attributing *S. haematobium* infection patterns in a Ghanaian community solely to the pattern of water contact (exposure to infection). The results of Dalton and Pole have since been reevaluated (see Barbour, 1985), but there is now convincing evidence supporting a role for immunity in the epidemiology of schistosome infection.

In the last few years a number of approaches have been used to address the "exposure" versus "immunity" dichotomy. Woolhouse et al. (1991) used mathematical modelling. Their model based on that of Anderson and colleagues (Crombie & Anderson, 1985; Anderson & May, 1985) predicts that if immunity is

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important in controlling infection then with any increase in transmission the infection curve should become more convex, the peak intensity of infection should increase and the age at which the peak intensity of infection is reached should decrease. By examining 2185 schoolchildren in 17 primary schools in Zimbabwe they were able to show that where the prevalence of infection was high, reflecting high transmission, the age of peak prevalence was lower than in areas where the peak prevalence was low. These data are consistent with their model and with the idea that the development of immunity is, in part, dependent upon cumulative exposure to infection and that immunity plays a significant role in controlling infection levels. A more conventional approach to this problem involves the use of a reinfection study design. By eliminating infection with chemotherapy levels of subsequent reinfection can then be related to any exposure to infection which has taken place in the intervening period and to parallel assessments of immunological reactivity.

Butterworth et al. (1985) pioneered this approach. They identified two groups of children, one with low levels of exposure and high levels of reinfection and one with high levels of exposure and low levels of reinfection. They could not find immunological correlates with resistance to reinfection but were able to show that "susceptibility" to reinfection was associated with high levels of IgM antibodies against egg antigens. They postulated that slow development of resistance to reinfection was a result of the early production of these IgM "blocking" antibodies which interfered with the protective effects of other antibody types. A reinfection study design was also used in investigations on *S. haematobium* in The Gambia, West Africa. In this case classification of the individuals in the study on the basis of their exposure to infection revealed that in children levels of exposure to infection were important in determining their levels of reinfection but in adults this was not the case. In particular, adult women remained uninfected despite levels of exposure to infection which were as high as those of the most heavily reinfected children. As a result Wilkins et al. (1987), concluded that in the adults factors other than exposure to infection were important in determining levels of reinfection and postulated that the immune system of the adults had acquired the ability to destroy an increased proportion of migrating immature parasites before they reached egg-laying maturity. The question then remained, could any relationship be demonstrated between reinfection and exposure data and the immunological parameters which were measured in this study group?

Measurement of antibody responses revealed no evidence of IgM "blocking" activities but high IgG4 antibody levels were found in children and these were associated with high levels of reinfection. IgG4 is known to interfere with IgE-mediated mast cell degranulation and may therefore reduce the harmful consequences of any schistosome induced allergic reactivities but IgG4 will also block IgG1- and IgG3-mediated killing of schistosomula by human eosinophils *in vitro* (Khalife et al., 1989). In contrast, low levels of reinfection, ("resistance"), were associated with high levels of specific anti-worm IgE. Specific IgE levels were low in children and reached their highest levels in adults. Statistical analysis revealed that this effect was significant even after allowances were made for age and exposure to infection (Hagan et al., 1991). IgE has been shown to participate in a number of anti-schistosome responses allowing monocytes, eosinophils and platelets to kill larval schistosomes *in vitro*. Set against the weight of evidence gathered from studies of the rat model of schistosomiasis these data lend considerable support to the hypothesis, that responses involving IgE have evolved as an important immune defence targeted against helminth infection. It is possible to speculate that in an exposed individual the balance between the levels of antibodies which mediate protection and those which interfere with protective functions may determine whether or not they become infected.

Although the evidence of the development of immunity to schistosome infection is now fairly convincing we do not know, as yet, which of the many parasite antigens are important in stimulating immunity to infection. One way to identify potential candidates is to examine reactivity to a given antigen on a population basis. The results of three such studies are described below. King et al. (1989) examined serological reactivity of Eyptian villagers to a 68 Kd antigen derived from *S. mansoni* adult worms (SmW68) and showed a significant increase in the response with the age of their study population. Isotype analysis revealed that resistance of infection was associated with IgM antibodies but not with IgG. Although IgM

antibodies are often viewed in terms of their blocking capacities, their protective capacity has been demonstrated in passive transfer experiments with monoclonal anti-schistosome IgM antibodies. In Brazil, resistance to reinfection with *S. mansoni* was shown to be associated with IgG reactivity to the 37Kd antigen identified as a schistosome glyceraldehyde-3P-dehydrogenase, an antigen present in larval and adults worms (Dessein et al., 1988; Goudot-Crouzel et al., 1989). Confirmation of the association of IgG4 antibodies with susceptibility to reinfection has come from studies in Kenya. Auriault et al. (1990) examined the responses of "immune" and "susceptible" groups to (P28) recombinant glutathione-S-transferase and reported that IgG4 levels were higher in the "susceptible" than in the "resistant" groups. This difference was also seen in the responses of the groups to two of three synthetic peptides (amino acids 115-131 and 140-153) which were derived from the primary sequence of P28. The IgA response of the "immune" group was two-fold higher than that of the "susceptible" group. Recent evidence (see Capron et al., this volume) supports an anti-schistosome role for IgA antibodies. Presumably, in conditions of natural exposure to infection the situation is much more complex and individuals may respond to any or all of these antigens and to many others. The antigens they recognise and the responses they mount against them will determine whether or not they become infected. An important consideration must then be the factor or factors which determine the capacity for individuals to respond to schistosome antigens. Although they did not directly address the question of immunological reactivity to defined schistosome antigens Abel et al. (1991) concluded from their segregation analysis of 20 Brazilian pedigrees (269 individuals) that a major codominant gene controls human resistance to infection. They classified 60% of people as resistant, 35% of people with intermediate resistance and 5% as predisposed to high infection. As yet there are no data showing an association of impaired immunological reactivities with this predisposition to high infection but nevertheless the genetic predisposition of a proportion of a population to high infections could have important implications for control programmes.

In conclusion, whilst exposure and genetic factors contribute to the pattern of schistosome infection in communities in endemic areas there is now overwhelming evidence that there is immunity to infection. The acquisition of this immunity appears to be dependent on the cumulative effects of repeated exposure. One reason for the slow development of immunity is the early production of "blocking" antibodies, particularly IgM and IgG4 which may interfere with protective functions. The slow development of immunity may also reflect the delay in the production of protective IgE, IgG and perhaps IgA antibodies. Several potential vaccine candidate antigens have been identified. With the supporting data on human immunity to schistosome infection it is likely that they will soon be used to attempt to artificially induce resistance to infection.

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