

## IMMUNOLOGICAL ASPECTS OF HOST-SCHISTOSOME RELATIONSHIPS

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*The complex immunological relationships between schistosomes and their vertebrate hosts are considered to be conveniently divisible into four distinct, though interrelated categories: the parasite's vulnerability to, its evasion of, and its exploitation of the host's immune response, and its stimulation of the host's immune response to produce immunopathology. Some significant recent advances in the first three categories are discussed, as well as their relationships to the fourth category of immunopathology.*

The immunological relationships between schistosomes and their vertebrate hosts are complex and imperfectly understood. For convenience, they can be divided into several aspects:

1. schistosome vulnerability to host immunity
2. schistosome evasion of host immunity
3. schistosome exploitation of host immunity
4. schistosome induced immunopathogenesis.

Obviously, the boundaries between and among these categories are not sharp, as was earlier emphasized (Damian, 1984). Since the fourth category, immunopathogenesis, is covered by others in great detail elsewhere in this volume, I will discuss it only in relation to its boundaries with the first three categories identified above.

### VULNERABILITY TO IMMUNITY

The classic description of schistosome immunity as concomitant immunity by Smithers & Terry (1969) contained within it the idea of stage-specificity of anti-schistosomal immunity. Although it is well accepted among workers in the field that the *major* targets of host immunity are the invading and migrating larval

stages or schistosomula (Smithers & Doenhoff, 1982; Capron & Dessaint, 1985), there exists a developing appreciation that adult worms may also be targets of host immunity, at least under certain circumstances. Therefore, this topic can be considered as follows:

1. vulnerability of schistosomula
  - a. newly transformed schistosomula
  - b. migrating, older schistosomula
2. vulnerability of worms
  - a. effects of immunity on worm survival
  - b. effects of immunity on reproduction.

With respect to the vulnerability of schistosomula, numerous *in vitro* studies have identified schistosomulocidal effector systems (reviewed by Smithers & Doenhoff, 1982; Butterworth, 1984; Capron & Dessaint, 1985). Claims, sometimes exaggerated, have been made with respect to the *in vivo* relevance of one or another of these systems in different host species, including man. Other areas of contention relate to the age and location of the invading or migrating larvae when they are most vulnerable. Earlier work (reviewed by Damian, 1984) allowed the conclusion that it is the newly transformed schistosomulum which is maximally vulnerable *in vitro*, but *in vivo* experiments were controversial on this point. Several more recent studies in vaccinated mice have shown that most schistosome attrition occurs in the skin (Kamiya et al., 1987). However, other recent work in the same model (but using a different strain of mouse) shows the major loss of parasites to take place in or beyond the lungs (Mangold et al., 1986; Coulson & Wilson, 1988). At the moment, this issue is unresolved. Different mechanisms may be inherent in the different host/parasite strain combinations used or the discrepancy may be traceable to methodological differences. Excel-

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lent morphological evidence for the involvement of eosinophils in the cutaneous death of schistosomula (in the guinea pig) was recently provided by Pearce & McLaren (1986).

Radiotracking experiments using  $^{75}\text{Se}$ -methionine-labeled parasites had been somewhat disappointing, since apparently doomed parasites often seemed to be surviving beyond the resolving power of the method, and their immediate fate remained unknown. The latest work using these techniques, however, suggests that lung stage parasites may actually be exteriorized into the lung alveoli by a normal route of elimination that becomes enhanced in immunized mice (Coulson & Wilson, 1988).

The influence of the pathology of schistosomiasis in mimicking concomitant immunity in the chronically infected mouse model has already been reviewed (Damian, 1984). Still to be determined is the relative role of nonspecific pulmonary inflammation in the elimination of pulmonary phase schistosomula in the various models (Smith et al., 1975). This impinges upon schistosome-induced immunopathogenesis when the inflammation in question is the result of schistosome eggs shunted into the lungs by portacaval anastomoses arising from the portal hypertension of chronic schistosomiasis (Dean et al., 1981; Wilson et al., 1983).

The vulnerability of adult worms was also reviewed (Damian, 1984). They are not as completely safe from the host immune response as is often implied. Their *potential* vulnerability to cytotoxic mechanisms was shown both *in vivo* (Smithers et al., 1969) and *in vitro* (McCormick & Damian, 1987). Both studies used the approach of artificially increasing the density of surface epitopes on the worms, thereby raising their vulnerability to cytotoxic antibodies and complement. This approach thus lends support to the concept of surface epitope paucity as a major evasion mechanism in adult schistosomes. This concept is also consonant with the recent suggestion (Brindley & Sher, 1987) that the synergy of praziquantel with the immune response (Sabah et al., 1985) results from tegumental damage by the drug and exposure of normally inaccessible epitopes.

Adult worms may be vulnerable to immunity when weakened by development in non-permissive hosts or may be slowly eliminated by unknown mechanisms in permissive hosts

(reviewed by Damian, 1984). Anti-reproductive or anti-fecundity effects may be more subtle manifestations of host immunity (reviewed in Damian, 1984). But as for other facets of anti-schistosomal immunity, the evidence remains ambiguous, particularly when garnered from both *in vitro* and *in vivo* experiments. Recent studies in *Schistosoma mansoni*-nonhuman primate systems both support and deny a role for the immune response in controlling oviposition. Bosshardt & Damian (1986) found that serum factors from chronically infected baboons had two anti-fecundity effects *in vitro*: inhibition of oviposition and unpairing of the sexes. On the other hand, Damian et al. (1986) found no support for the immune anti-fecundity hypothesis from *in vivo* experiments in which worm pairs were transplanted from chronically infected into naive primates.

#### EVASION OF HOST IMMUNITY

Many mechanisms have been proposed to account for the worm's ability to exist for long periods of time in immunologically competent hosts. None is definitely established as being relevant to successful parasitism, to the degree that antigenic variation in African trypanosomes is established in this regard. These putative mechanisms may be summarized as follows:

1. Reduced antigenicity
  - a. Molecular mimicry
  - b. Antigen masquerade
  - c. Antigen shedding/modulation
  - d. Epitope inaccessibility
  - e. non-MHC associating peptides
2. Immunosuppression
3. Effector cell blockade
4. Fabulation
5. Schistosome-derived anti-inflammatory molecules
6. Immunological misinformation
7. Resistant membranes.

This is not intended to be an exhaustive review of them all. Rather I will select for discussion certain of these which are of particular interest to me or which have been recently reviewed elsewhere.

Molecular mimicry in schistosomiasis is a subject in which I have long been interested (Damian, 1964). The current status of this field was the subject of a recent review (Damian, 1987b), which reemphasized the importance of oligosaccharide epitopes in the phenomenon,

and also discussed the possible importance of host-mimicking immunodominant peptides in T-cell clone ablation.

Effector cell blockade as an evasion tactic used by schistosomes (Capron & Dessaint, 1985) has recently come to the fore, as a result of accumulating evidence that blocking antibodies, mostly of the IgM and IgG2 isotypes, may interfere with anti-schistosomicidal mechanisms in humans (Dunne et al., 1987; Butterworth et al., 1987).

Schistosome-derived anti-inflammatory molecules as possible evasion agents were also discussed in the heuristic review of Capron & Dessaint (1985).

Despite these exciting advances, it is clear that full understanding of this fascinating and important aspect of the schistosome's relationship with its host depends upon progress in our understanding of the biochemical make-up and dynamics of the tegumental surface, particularly as it matures into the definitive double outer membrane of the worm stage (Simpson & Cioli, 1982), as well as upon our knowledge of the immunoregulation of anti-worm responses. A great deal of activity is taking place in the definition of the molecular components of the double outer membrane, facilitated by newer technologies including hybridomas, recombinant DNA, and oligosaccharide structural analysis (reviewed in Simpson & Cioli, 1987). For example, the first direct structural analysis of actual schistosome glycoprotein oligosaccharides was recently published (Nyame et al., 1987). Of equal importance are studies aimed at understanding membrane dynamics; for example, antigen shedding (Pearce et al., 1986), membrane fluidity (Foley et al., 1986), and tegumental repair processes (McCormick & Damian, 1987).

#### EXPLOITATION OF HOST IMMUNITY

Recently, workers in the field of host-parasite relationships have begun to wonder if host immune and immunopathogenic responses to parasites function solely in negative ways towards them, as was commonly thought (reviewed in Damian, 1987a). The possibility that some host responses may actually facilitate parasite survival and propagation seems especially strong for the schistosomes, where much evidence has accumulated for immune

system involvement in egg passage through the tissues (Doenhoff et al., 1985), and for immune granuloma mediation of egg extravasation (Doenhoff et al., 1986) and egg translocation through the tissues (Damian, 1987a). This concept has recently been referred to as parasite exploitation of host immunity (Damian, 1987a).

With respect to granuloma-mediated egg translocation, observations were made in *S. mansoni* infections in baboons which suggested that the egg granuloma carries the egg from its site of formation in the intestinal submucosa to the luminal border of the intestine, a process that might be especially relevant in those species whose intestinal wall thickness is great in relation to the diameter of the egg-granuloma unit (Damian, 1987a).

#### POSTSCRIPT

The above discussion points out that there are several ways by which it is at least theoretically possible for the immunological status of the host to influence the number of *S. mansoni* eggs in the feces. These include direct anti-reproductive effects, effects on egg destruction rates, and effects on the rate of egg passage through the tissues. Epidemiologists have at the present time only quantitative fecal egg counts from which to try to deduce human worm burdens for such important considerations as (1) reinfection rates after chemotherapy and the meaning of such rates for the question of the development and mechanism of human anti-schistosome immunity and (2) the immunizing potential of drug-killed adult worms as an "endogenous" vaccine. Both of these important considerations were discussed at this conference. They serve to emphasize the importance which should be attached to the development of some independent criterion of worm burden, perhaps the measurement of circulating worm products.

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