Cercariae of *Schistosoma mansoni* and *S. haematobium* invade the definitive mammalian host by penetrating intact skin. The cercariae adhere to the skin surface with the oral sucker and then penetrate the epidermis with the aid of muscular movement and lytic secretions derived from the acetabular glands, losing their tail in the process and transforming into schistosomula. The schistosomula need 48–96 hr to negotiate the different layers of the stratified epidermis (Wilson, 1987; Sturrock, 1993, 2001). In this context, one wonders about the in vivo relevance of immunological data obtained with the in vitro–favored model of 3- and 24-hr schistosomula because in vivo parasites of this age are still in the epidermis, well protected from the effect of blood components and cells. In the blood and lymphatic capillary-free, immunologically privileged environment of the epidermis, schistosomula shed the glyocalyx and undergo metabolic changes that end with replacement of the original, trilaminate tegumental membrane by a heptalaminate, double bilayer. Larvae merge into the dermis after acquiring resistance to the effect of complement- and cell-mediated cytotoxicity (Dean, 1977; Samuelson et al., 1980). Dessein et al., 1981; Wilson, 1987). Focal inflammatory reactions elicited in the dermis may impede larval movement within the connective tissue, yet likely facilitate exit into the blood capillaries by increasing wall permeability. Until arrival in the liver, migrating larvae cannot feed as adults do because they lack a functional gut. They depend for their survival on energy obtained through the metabolism of reserve food and glucose and amino acids they obtain from the host via the apical tegumental glucose and amino acid transporter, respectively (Skelly et al., 1994, 1999; Skelly and Shoemaker, 1996). Inflammatory cellular foci, induced by inflammatory mediators such as interferon-gamma (IFN-γ) or tumor necrosis factor-alpha, and nitric oxide (Crabtree and Wilson, 1986; Wilson et al., 1999, 2001). Indeed, IFN-γ-dependent cellular immunity has been invoked as an important arm in defense against challenge infection with schistosomes in mice, immunized once or twice with radiation-attenuated larvae. Firm evidence supports the possibility of developing an effective vaccine against human schistosomiasis. Persons classed as “endemic normals” are continuously exposed to infective cercariae of *S. mansoni* and yet have no record of previous or current infection and appear uninfected as judged by repeated stool examination. There are numerous examples of lack of reinfection in adult humans that cannot be attributed solely to reduction in exposure to cercaria-infested water or to age-related factors. In such resistant humans, both T-helper 1 (IFN-γ) and T-helper 2 (interleukin-4 and interleukin-5)-derived cytokines were found to be associated with the protective immune response to schistosomes (reviewed in McManus, 1999; Dunne and Mountford, 2001).

Regarding the antibody arm of immunity, several studies have suggested that immunoglobulin E (IgE) is not required for the protective immune response in mice (Sher et al., 1990; El Ridi, Ragab et al., 2001). In contrast, a build up of IgE antibodies has been correlated with vaccine-induced protection in the radiation vaccine model, using mice that lack functional FcγRI, FcγRIII, and FcεRI, and RI/RIII, and RI/RIII mice (Jankovic et al., 1999). On the basis of the aforementioned points, it has been suggested that optimal immunization against schistosomes involves both cell- and antibody-mediated mechanisms. Accordingly, any candidate vaccine for schistosomiasis should activate cell-mediated and humoral immune effector arms (reviewed in McManus, 1999; Dunne and Mountford, 2001; James and Colley, 2001).

Professional antigen-presenting cells (APCs) such as macrophages and dendritic cells are stimulated to take up vaccine antigens formulated with appropriate adjuvants. Exogenous antigen processing is followed by presentation of peptides bound to host MHC class II molecules. Restrictions in protease-mediated antigen processing (Manoury et al., 2002) and peptide binding to the MHC molecules (Lanzavecchia, 1993) greatly restrict the number of vaccine antigen–derived peptides that are presented on the APC surface. As a result of the schistosome and host proteins homology, several of the presented peptides will fail to elicit T-helper-cell responses. But a few peptides can induce immune responses, which, if effective, might interfere with larval migration and development. The peptide-activated T-helper lymphocytes do not interact with the parasite. Impairment of vital functions is mediated through recruitment of inflammatory cells and release of inflammatory mediators and cytokines. Accordingly, any candidate vaccine antigen–derived peptide bearing immunogenic T-helper-cell epitope(s) should be able to stimulate an effective cell-mediated immunity, regardless of its location in the cognate protein or the parasite. Yet, such T-cell responses seem insufficient to induce significant protective immunity. In support, some “unexposed” nonsurface antigens were found to elicit in vitro immunological responses, which may well reflect protective mechanisms (reviewed in McManus, 1999; Dunne and Mountford, 2001; James and Colley, 2001).

B-lymphocytes can interact directly with the candidate vaccine antigen via the clonally distributed surface immunoglobulin receptors. After more than one immunization, B-cells of a given host are expected to recognize most, but certainly not all, of the vaccine antigen conformational and linear epitopes. The host Ig repertoire will be a major factor in determining the array of epitopes recognized, which will vary largely among genetically diverse hosts. Because of the schistosome–host proteins homology, many antibody specificities will actually be autoantibodies that will have little chance to encounter the parasite. The remaining antibody species may interact with the parasite only if the immunogen is associated with the outer membrane. Antibody-dependent complement-mediated cytotoxicity and ADCC are not expected to play a major role in parasite attrition. Yet, binding of antibody to an important molecule may interfere with its function and impair parasite viability, provided a critical site(s) of the molecule is targeted. If the host is unable to produce antibodies against this (these) critical site(s), even a copious humoral response will be ineffective. The humoral response can even be protective for the parasite, rather than the host, if the antibody specificities are directed to sites near the critical ones, and thus hinder or reduce binding of the antibody to an important molecule may interfere with its function and impair parasite viability, provided a critical site(s) of the molecule is targeted. If the host is unable to produce antibodies against this (these) critical site(s), even a copious humoral response will be ineffective. The humoral response can even be protective for the parasite, rather than the host, if the antibody specificities are directed to sites near the critical ones, and thus hinder or reduce binding of the...