Articles

Immunity to Schistosomes: Progress Toward Vaccine

ANDRÉ CAPRON, J. P. DESSAINT, M. CAPRON, J. H. OUMA, A. E. BUTTERWORTH

Among the major parasitic infections, schistosomiasis may be the most promising candidate for human vaccination. Information about mechanisms of immunity, gained mainly from experimental models but likely to be relevant to human infection, indicates a dynamic balance between protective and regulatory (blocking) mechanisms. Besides cell-mediated responses leading to macrophage activation, antibody-dependent cell-mediated cytotoxicity systems involving precise antibody isotypes and nonlymphoid cells (mononuclear phagocytes, eosinophils, and platelets) appear to be essential effectors of immune attack. The slow development of immunity in humans seems related to the production of antibodies that cross-react with schistosomulum surface antigen and block the binding of antibodies of the effector isotype. Schistosomes that survive in the bloodstream and produce chronic infections may evade the immune system as a result of intrinsic changes in membrane susceptibility and of transient expression of target antigens; at other stages of the parasite life cycle, cross-reactive molecules may be secreted that play an essential role in the induction of immunity. Several schistosome proteins have been characterized as candidates for vaccination. Among these, an antigen of 28 kilodaltons has been cloned and shown to be immunogenic in humans and protective in mice, rats, and baboons.

SCHISTOSOMIASIS IS A CHRONIC AND DEBILITATING PARASITIC disease affecting 200 million people throughout the world and responsible for 800,000 deaths per year, according to recent estimations of the World Health Organization. Infection is characterized by the presence of adult worms (*Schistosoma*, class Trematoda, phylum Platyhelminthes) in the portal and mesenteric veins of humans and various mammalian species as part of a complex migratory cycle initiated by cutaneous penetration of infective larvae (cercariae) shed by infected freshwater snails. The infective larvae transform into schistosomula in the skin of appropriate hosts and, over several weeks, develop into sexually mature, egg-laying worms. It is generally agreed that pathological reactions to schistosome infection are related to the deposition of numerous parasite eggs in host tissues (*1*). Unlike protozoan parasites such as *Plasmodium*, schistosomes are nonreplicating organisms in their vertebrate hosts; therefore, a partial, nonsterilizing, naturally acquired, or vaccine-induced immunity can strongly decrease human pathology and transmission levels in endemic areas.

Among the parasites used as models by immunologists, schistosomes have probably provided the broadest experimental approach. They have illustrated the existence of novel effector and regulatory mechanisms that may be of interest not only in the field of parasitic diseases but also as more general immunological processes. Much interesting work has been done by many different investigators, but here we offer primarily a personal account of what we have learned from studying immunological processes in schistosomiasis. We suggest that an understanding of the basic mechanisms of the immune response in humans and in experimental animal models is essential for the development of antischistosome vaccines. Enormous progress has been made during the last decade and, in terms of human vaccination, schistosomiasis may now be the most promising candidate among the major parasitic infections.

Immunity in Humans and Experimental Animals

It has been recognized for many years that a variety of experimental hosts develop an acquired immunity to schistosome infection after either a natural primary infection or immunization with irradiated larvae or, as shown recently, with isolated antigens. However, the existence of a comparable immunity in humans has remained controversial. The continued presence of adult worms of a primary infection, dying at an unknown and possibly variable rate, makes it difficult to determine the extent to which an individual is becoming superinfected, and hence the degree of immunity to these new infections. More important, it is also difficult to distinguish between immunity and lack of exposure as possible reasons for a lack of superinfection or of reinfection after treatment. Although several workers have argued that the decline in prevalence and intensity of infection observed in older people may be attributable to the slow development of a partial immunity (*2*), others have suggested that the observed effects may be ascribed to changes with age in patterns of contact with cercariae in water (*3*).

Recent studies of both *Schistosoma haematobium* and *S. mansoni* infections have helped to resolve this issue (*4*). In both cases, investigators studied intensities of reinfection after treatment of individuals whose frequency and duration of exposure to water from known infective sites were monitored by direct observation. Although frequency of water contact was found to decline in older children and adults, this decline was insufficient to account for the marked reduction with age in intensities of reinfection after treatment. In addition, there was good evidence for the development of

A. Capron, J. P. Dessaint, and M. Capron are at the Centre d'Immunologie et de Biologie Parasitaire, Unité Mixte INSERM 167-CNRS 624, Institut Pasteur, 1 rue du Pr. A. Calmette, 59019 Lille Cédex, France. J. H. Ouma is with the Division of Vector-Borne Diseases, Ministry of Health, Nairobi, Kenya. A. E. Butterworth is in the Department of Pathology, Immunology Division, Cambridge University, United Kingdom.

an age-dependent acquired resistance to reinfection that depends also on previous experience of infection (*5*), strongly indicating an immunological component rather than simply some age-related physiological change. However, the cellular and humoral components of such protective responses remain uncertain. Studies on the cellular and humoral components of such protective responses have allowed the demonstration and characterization of a range of possible effector mechanisms, including a novel effect of eosinophils (*6*). A possible role for the eosinophil in mediating immunity to *S. haematobium* infections is indicated by the demonstration of increased eosinophil counts in immune individuals (*4*). In *S. mansoni* infections, preliminary evidence has been obtained for a correlation of cell-mediated responses to schistosome antigens with resistance to reinfection after treatment (*1*), whereas blocking antibodies may play a role in limiting the expression of immunity in young children, as discussed below. However, analysis of the role in vivo of the various mechanisms that have been identified in human infections, although important, is difficult and time-consuming and is still in its early stages. Instead, much information about effector and regulatory mechanisms of immunity that may be relevant to human infections has come from the study of rodent (and to a lesser extent, primate) models of infection.

The rodent models most commonly used have been the mouse and the rat, and these differ strikingly in their capacity to mount a protective response against the parasite. They also appear to have different mechanisms of resistance and have therefore provided complementary information. The mouse, studied extensively by many investigators, is a permissive host, allowing the maturation of adult worms and the deposition of eggs, which subsequently elicit strong immunopathological reactions. In this respect, the mouse model has some characteristics in common with human infections. Chronically infected mice develop a resistance to superinfection; this resistance was shown to be a consequence of a nonspecific trapping or shunting of larvae of a challenge infection around areas of egg-induced pathology (*1, 7*), rather than a specific immune response to the larva itself. Since the density of pathology is dependent both on the worm burden and on the mass of the host, the relevance of this phenomenon to human infection is not immediately apparent. Instead, therefore, investigators have concentrated more recently on the specific immunity that is induced by immunization either with irradiated larvae (*8*) or with isolated antigens, procedures that circumvent the confounding influence of egg-induced pathology. After such immunization, a specific immunity is expressed that is associated primarily with cell-mediated responses leading to macrophage activation (*9*), although the demonstration that murine monoclonal antibodies with specificity for schistosomulum surface antigens can mediate protection (Table 1) suggests that antibody-dependent mechanisms may be involved in some circumstances. Such activated macrophages may kill the larvae at some stage during their migration to the hepatic portal system, probably later than was previously supposed: the consensus now is that the main attrition of schistosomula in immunized mice occurs after their migration through the lungs (*10*), by which time they are no longer expressing surface antigens accessible for antibody-dependent attack, as discussed below.

In contrast to the mouse, the rat is a nonpermissive host exhibiting unique characteristics of immunity. Although the course of parasite migration and the development of the primary infection are roughly similar in rats and mice during the first 3 weeks, a dramatic decrease in parasite burden appears in rats approximately 1 month after the infection. After this "self-cure" phenomenon, in which T cell responses (*11*) and nonimmune factors appear again closely interwoven, the rat develops a strong and long-lasting resistance to secondary infections. Numerous studies in the last 10 years have shown that this high resistance to reexposure is attributable to immunologically mediated pathways and support the view that resistance is primarily mediated through antibody-dependent mechanisms. For instance, serum transfer passively confers resistance on naïve rats, and contrarily neonatal rats treated with anti–μ chain antibodies fail to acquire immunity against schistosomes (*12*). As far as the humoral response is concerned, rats and humans have common characteristics: antibody specificity, isotype restriction, high immunoglobulin E (IgE) antibody responses, and the formation of blocking antibodies, which may justify the particular emphasis we have put on this model.

Protective Immune Response to Schistosomes

Our present concepts concerning the immunology of schistosomiasis are largely dependent on the biological characters of the parasite itself. After skin penetration, the infective larvae (schistosomula) undergo a complex migratory cycle in the vertebrate host before they settle, in the case of *S. mansoni*, in the blood vessels of the portal and mesenteric system. In this intravascular situation, the adult worms release a large amount of excretory or secretory material, which elicits a strong antibody response and which may be found in the serum and various body fluids in the form of free antigens and more generally as immune complexes (*13*). This continuous release of soluble antigens has important implications in the regulation of the immune response, both in terms of antigenic competition and as direct factors of immunosuppression or tolerance. The major role of

Table 1. Protective antigens of schistosomes. *Sm, S. mansoni*; *Sj, S. japonicum*; *Sh, S. haematobium*; *Sb, S. bovis*.

Species	Size (kD)	Identified by	Protection (%)	References
Sm	26	Rat IgE monoclonal antibody	40 to 60 (rat)	*82*
Sj	26		30 (mouse)	*83*
Sm	28 (glutathione transferase)	Rat and human IgE antibody	43 (mouse)	*78, 79*
Sh	28 (glutathione transferase)	Rat and human IgE antibody	65 (rat)	*78, 79*
Sb	28 (glutathione transferase)	Rat and human IgE antibody	50 (hamster)	*78, 79*
Sm	28	Rabbit antibody		*84*
Sm	38	Rat IgG2a monoclonal antibody	53 to 63 (rat)*	*39, 77*
			50 to 75 (rat)†	*76*
Sm	38	Mouse antibody		*85*
		Mouse monoclonal antibody	50 (mouse)	*57*
Sm	97 (paramyosin)	Mouse antibody	60 to 77 (mouse)	*86, 87*
Sm	130 to 160	Mouse IgG1 monoclonal antibody		*88*

*By anti-idiotypic immunization. †By immunization with the cross-reacting oligosaccharide of KLH.

antibodies in protective immunity is to induce cytotoxic destruction of schistosomulum targets, and, although the significance of complement-fixing antibodies is not yet resolved, antibody-dependent cell-mediated cytotoxicity (ADCC) appears to be the main parasite-killing mechanism both in rat and human schistosomiasis (*14*).

Even though the adult worm population represents the major source of antigenic stimuli, it is totally unaffected by the cytotoxic response that it elicits, and schistosomula, which rapidly lose their susceptibility to immune attack, appear during reinfection to be the privileged target of effector pathways, a phenomenon known as concomitant immunity (*15*). In addition to the role of circulating antigens already mentioned, numerous processes have been described that potentially account for this insusceptibility. The worm membrane, which undergoes a continuous and rapid turnover, acquires numerous host molecules ranging from various serum proteins or glycolipids to major histocompatibility antigens (*16*). This phenomenon has been considered as an essential escape mechanism. Although there is evidence that antisera to these host antigens strongly reduce the survival of the parasite both in vitro and in vivo, a clear demonstration of the functional importance of such host molecules in the course of natural infection is still lacking. However, the acquisition of such host antigens proceeds concomitantly with intrinsic changes in membrane susceptibility to antibody-dependent killing (*17*) and with the loss of expression in the adult worm membrane of the major target antigens that are expressed on the schistosomulum surface (*18, 19*). Moreover, in the general framework of the modulation of the immune response in schistosome infection, other mechanisms have been proposed. Factors of parasite origin, including schistosome-derived immunosuppressive factor (SDIF), or those derived from cleavage by parasite enzymes of host immunoglobulins, such as an anti-inflammatory tripeptide (*20*), may contribute to the regulation of effector functions. Finally, there is now much evidence for immune regulation by antibody isotype and also by idiotype–anti-idiotype interactions in human and experimental infections, as discussed later.

These complexities of the immune response to schistosomes may help to explain the partial inefficiency of immune defense leading to stage-specific susceptibility to immune attack and to nonsterilizing immunity after either primary exposure or immunization by schistosome antigens.

Effector Mechanisms Against Schistosomes

Immunity to reinfection by schistosomes is clearly thymus-dependent, as indicated by the marked reduction in immunity in athymic animals. Yet, schistosomula do not appear to be susceptible to cytotoxic mechanisms involving effector cells of the lymphoid lineage at least in experiments in vitro. Although cytotoxic T cells can specifically adhere to schistosomula in vitro, they are unable to kill them (*21*). This is true even when target parasites have been collected from infected hosts and thus have acquired the major histocompatibility products of the host, therefore fulfilling the restriction conditions for recognition by syngeneic T cells. Lymphokine-activated and natural killer cells (*22*) have been reported to damage schistosomula in vitro, but the percentage of killing is low, and these results await confirmation. Moreover, although ADCC systems appear as potent in vitro correlates of immunity, conventional lymphoid K cells do not seem to be involved. In contrast, antischistosome antibodies and various nonlymphoid effector cells have been demonstrated to cooperate both in rats and in humans.

By mixing, in one- or two-step experiments, purified cell populations from uninfected donors, antibody-containing serum, and target schistosomula, the cytotoxic killing of the larvae was obtained

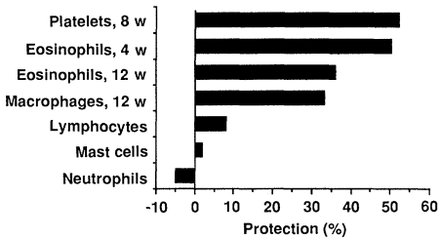

Fig. 1. Protection of naïve rats against schistosome infection by passive transfer of cells from immune donors. Purified cell preparations were collected from infected rats at 4 and 12 weeks after infection (eosinophils), at 12 weeks (macrophages), and at 8 weeks (platelets). Immunity was assessed in recipient syngeneic rats after challenge infection by liver perfusion: the percentage of protection was calculated from the reduction in collected worms in comparison with control animals receiving cells from uninfected donors [data from (*27* and *33*)].

with monocytes, macrophages (*23, 24*), eosinophils (*6, 25, 26*), and platelets (*27*). The exact nature of the cytocidal factor or factors responsible for damaging the metazoan target in these unusual ADCC reactions is still under investigation. Each of the three nonlymphoid effectors produces and releases reactive oxygen intermediates (*28*). Depending on the cell type, more specialized mediators might also contribute to the observed cytotoxicity. Monocytes/macrophages sensitized with antibodies to schistosome and exposed to schistosomulum antigen or to appropriate antibodies to immunoglobulin or $F(ab')_2$ fragments therefrom, release lysosomal enzymes and interleukin-1 (*28, 29*). Emphasis has also been put on the schistosomicidal properties of the cationic proteins from eosinophil granules. Purified major basic protein (MBP) and eosinophil cationic protein (ECP) can damage schistosomula in vitro, and the specific eosinophil peroxidase (EPO), which is deposited at the interface between target larvae and eosinophils in the ADCC reactions, might cause parasite attrition directly or through its enzymatic activity (*30*).

One of the major drawbacks of in vitro assays is that they give a valid but isolated and perhaps oversimplified picture of the components of the immune effector mechanisms. The in vivo relevance of ADCC reactions involving nonlymphoid cells can be supported by data showing the accumulation of eosinophils and macrophages around dead schistosomula in immune animals, including monkeys (*31*), and by the effect of injecting antisera to eosinophils into mice, which apparently reduces their level of immunity to a challenge infection (*32*). More direct evidence of the effector mechanisms has been gained in the rat model by passive transfer of cells to naïve recipients (Fig. 1). Nonadherent, eosinophil-enriched and adherent, macrophage-rich peritoneal cell preparations from immune rats, injected at the site of exposure to the challenge infection, are able to confer a significant resistance. Confirming the in vitro findings, rosette assays have revealed surface-bound immunoglobulins arming eosinophils and macrophages from the donor rats. In addition, in vitro sensitization of normal eosinophils or macrophages with serum from an immune rat also results in the passive transfer of resistance (*33*). Likewise, the intravenous injection of platelets from immune rats confers to normal rats a highly significant degree of protection (*27*).

These in vivo or ex vivo experiments are fragmentary, but they have confirmed, in experimental infections, a biological role for the three cell populations identified by in vitro assays both in experimental and human schistosomiasis, although the final test of relevance has to come from human studies. These experiments have also demonstrated the participation in immune defense against metazoan parasites of hitherto unsuspected effector cells such as eosinophils and platelets.

Besides the killer cell, another essential factor of these unusual ADCC systems is the class and the specificity of the antibody. In the

rat model, normal mononuclear phagocytes, eosinophils, and platelets each acquire cytotoxic capability against schistosomula when incubated with unheated serum collected from rats resistant to a challenge infection, that is, a few weeks after the self-cure of their primary infection. Heat-inactivation of serum from immune rats abolishes the ADCC at this time of the infection, and it cannot be restored by the addition of fresh complement. Absorption by antibodies to the various rat isotypes or by schistosome antigen has clearly identified the essential participation of IgE antibody in the cytotoxicity mediated by macrophages, eosinophils, and platelets. This can be confirmed by the opposite experiment, showing that aggregated, nonschistosome-specific myeloma E protein inhibits cytotoxicity by each of the three cell types exposed to unheated serum from immune rats (*23, 25, 27*). A more positive proof of an IgE antibody–dependent cell-mediated killing has been obtained by the use of a rat IgE monoclonal antibody against schistosomula, which can turn normal rat macrophages, eosinophils, and platelets into potent cytotoxic effectors (*34*).

A hallmark of infection by helminth parasites is the massive production of IgE. By using rat ε chain–specific antibody in a radioallergosorbent test (RAST)–elution technique or by inducing passive cutaneous anaphylaxis, high levels of IgE antibodies to schistosomes have been detected in serum from immune rats at the time when IgE antibody–dependent cytotoxicity can be induced, antischistosome IgE being found both as free antibody and in immune complexes (*35*). Circumstantial evidence for the involvement of IgE antibody in protective immunity was available from the observation of a direct connection between the resistance of various animal species to the parasite and their level of production of reaginic (IgE) antibodies (*36*). Evidence has also been obtained by injecting neonatal rats with antibodies to ε chain, which suppress their IgE responses and reduce their immunity to schistosomes (*37*). Further evidence of IgE involvement has been obtained by transfer of serum from immune rats: selective depletion of IgE significantly decreases the ability of such serum to confer passive immunity (*14*), and, in contrast, injection of the IgE monoclonal antibody to schistosomes (which triggers ADCC in vitro) confers on naïve rats significant resistance to a challenge infection (*34*) (Fig. 2). It should be noted also that in the cell transfer experiment reported above, cytophilic IgE was detected on macrophages, eosinophils, and platelets from 8 week–infected donors, and these cells passively protected the naïve recipients (*27, 33*).

Since other antibody isotypes are also produced during infection, their participation has also been investigated. In the case of macrophage and platelet-mediated cytotoxicity, however, only IgE antibody has been shown to be involved (*34*). With eosinophils, experiments with serum from rats infected from 5 weeks onward have allowed the identification of two distinct ADCC mechanisms. After 8 weeks of infection, the necessary participation of IgE antibody in eosinophil-mediated cytotoxicity was clearly identified. During the early period of immunity, however, heat-inactivated rat serum could trigger eosinophils to kill schistosomula, and the responsible antibody was identified by absorption or inhibition experiments as IgG2a (*38*). This isotype, which is the major IgG subclass of the rat and has anaphylactic activity, can be detected by rosette assays on the surface of eosinophils at the early stage (4 to 6 weeks after infection) of immunity. At this period, such IgG2a-bearing eosinophils but no other cells can passively confer resistance (*33*). Conversely, selective IgG2a depletion of serum from rats infected for 6 weeks significantly reduces the passive transfer of resistance (*14*). A confirmation has been provided by the use of a rat IgG2a monoclonal antibody to schistosomes, which triggers normal rat eosinophils to kill schistosomula in vitro and passively confers protection in vivo (*39*) (Fig. 2). Indirect support for the essential

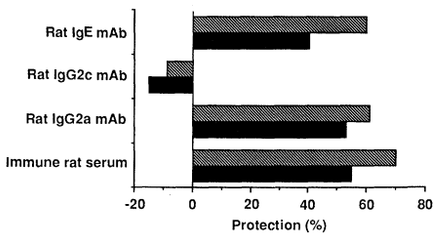

Fig. 2. Protection of naïve rats against schistosome infection by passive transfer of antibody. Naïve rats received either immune rat serum (8 weeks after infection) or rat monoclonal antibody of the indicated isotype. Immunity was assessed in recipient rats after challenge infection by liver perfusion: the percentage of protection was calculated from the reduction in collected worms in comparison with control animals receiving normal rat serum (slashed bars) or nonschistosome-specific monoclonal immunoglobulin of the corresponding isotype (solid bars) [data from (*12, 34, 39, 40*)].

role of an anaphylactic antibody isotype has been provided by the observation that another rat monoclonal antibody specific for the same surface schistosomulum antigen as the protective IgG2a monoclonal, but of the nonanaphylactic IgG2c subclass, can neither induce eosinophil-mediated killing nor passively confer protection (*40*).

It is of interest in this context that in human schistosomiasis, IgE ADCC against schistosomula has also been demonstrated. Human infection is indeed associated with a strong IgE antibody response, and as much as 1 μg of specific IgE may be found per milliliter of serum as free antibody and in immune complexes (*41*). In the presence of IgE-rich serum from infected individuals, human monocytes or baboon peritoneal macrophages, human eosinophils, and human platelets (*24, 26, 27*) damage schistosomula in vitro. As in the rat model, human eosinophils, but not monocytes or platelets, can be activated into cytotoxic effectors by IgG antibody from human serum, although the subclass involved is unknown (*6*).

These findings in experimental and human infections, pointing to the key role of anaphylactic antibodies in defense against schistosomes, have led to a reevaluation of the general biological significance of anaphylactic antibody responses hitherto considered only in the context of allergy. The late appearance of IgE in phylogeny and the complex immunological network controlling its production, as well as the high rate of evolution of the ε chain, suggest that nature has selected for the continuous existence of this fifth class of immunoglobulin. If so, then a major biological function of IgE and anaphylactic antibodies in general might well be to represent an essential participant in the complex response to parasitic infections (Fig. 3), and a number of clinically significant allergic responses to environmental antigens may reflect the inappropriate activation of immunologic circuits or effector pathways ordinarily initiated by helminths, and which confer resistance to infections against which other effector mechanisms appear to be of low efficiency.

These novel interactions between IgE antibody and non–mast cell or nonbasophil populations also raise the possibility that hitherto unsuspected receptors for IgE might exist on such cells. Investigations by our group and several others have now unequivocally established that subpopulations of monocytes, macrophages, eosinophils, and platelets from rodents and humans carry specific IgE Fc receptors (*23, 26, 27, 42*). The determination of their binding parameters has allowed their distinction from those on mast cells and basophils (FcεRI), and we have proposed that they may be designated FcεRII. The lower affinity of FcεRII for monomeric IgE might explain why IgE-immune complexes isolated by ultracentrifugation from infected rat or human serum were found to be more efficient than free IgE antibody to schistosomes at inducing cell-mediated schistosome killing (*24, 43*).

Another indication of the distinct nature of the receptors for IgE

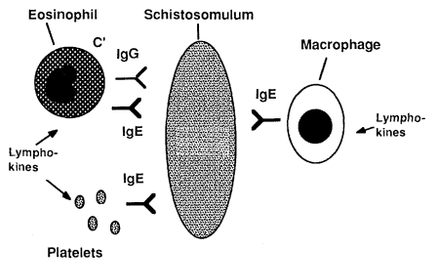

Fig. 3. Effector mechanisms against schistosomes. Effector cells so far identified by in vitro assays are eosinophils, platelets, and monocytes/macrophages. These cells are activated into cytotoxic effectors by antibodies to schistosomes of the appropriate isotype and by several lymphokines secreted by activated T cells. Most of these in vitro cytotoxic mechanisms have been demonstrated both in rats and humans. C', complement.

on mononuclear phagocytes, eosinophils, and platelets has been provided by the use of polyclonal and monoclonal (BB10) antibodies to the receptor. These antibodies bind similarly to the receptors of these cells and inhibit their interaction with IgE, contrary to antibodies specific for mast cell/basophil receptors. Polyclonal or monoclonal (BB10) antibody to FcεRII has been shown to induce a marked inhibition of IgE antibody–dependent cytotoxicity by monocytes/macrophages, eosinophils, and platelets (*26, 27, 34*), a clear indication of the triggering function of FcεRII in ADCC against schistosomula.

The selectivity of the signals delivered to the cell through the FCεRII is demonstrated in the case of platelets, which produce oxygen metabolites but do not release serotonin upon IgE-dependent activation, whereas the reverse is found after exposure to IgG (*44*). Likewise, in IgG-dependent reactions, eosinophils liberate significant amounts of their granule proteins, including ECP; but after activation by complexed IgE (or IgG2a in the rat), these cells release predominantly EPO, MBP, and platelet-activating factor (paf-acether), whereas ECP is hardly detected (*45*). Another possibility that may account for this apparent selectivity of the response to anaphylactic and nonanaphylactic immunoglobulin isotypes might be related to the existence of specialized cell subpopulations. A particular subset of human eosinophils, characterized by its low density on metrizamide gradients, which preferentially expresses FcεRII and bears cytophilic IgE, has been shown to release EPO and paf-acether by IgE-dependent activation, together with a preferential capacity to kill schistosomula in vitro (*26, 45*).

The prominent role played by IgE and more generally anaphylactic antibody in defense against schistosomes does not exclude the participation of alternative effector mechanisms or the contribution of other activating pathways. Investigations made mainly in the mouse model have shown that newly transformed schistosomula were killed in vitro by macrophages activated as a consequence of the infection. Analysis of this mechanism has led to the demonstration that lymphokine-activated macrophages have strong schistosomicidal capacities, and the genetic factors controlling such macrophage effector function against schistosomes have been evaluated (*9*). This finding might be related to the resistance induced in mice by various immunostimulants like bacille Calmette-Guérin. However, BALB/c mice that are protected after administration of irradiated cercariae but not by nonliving larval or adult worm antigens plus mycobacterial adjuvant show no obvious defect in delayed-type hypersensitivity reaction at the time of challenge (*46*). In rat schistosomiasis, however, a strong depression of delayed-type hypersensitivity reactions, which are usually correlated with macrophage activation by T cell–derived lymphokines, is observed at the very period of acquisition of resistance (*47*). Experiments with polyclonal or monoclonal antibodies have also suggested the participation of complement components in eosinophil-mediated cytotoxicity and the involvement of the complement receptor type 3 (CR3) of FcεRII$^+$ low-density eosinophils (*48*). Complement components have been reported either to trigger eosinophil attack nonspecifically or to act in synergy with IgG antibodies (*49*). Other non–antibody-dependent factors, including several cytokines, contribute to the induction or potentiation of eosinophil cytotoxic capacity (*50*).

Control of the effector activity of platelets might depend also on several lymphokines found in conditioned medium from mitogen-activated T cells or antigen-specific T cell lines. In the case of human lymphocytes of the cluster of differentiation 4 (CD4$^+$), several molecules with potentiating activity have been identified, including γ-interferon and tumor necrosis factor β. In contrast, CD8$^+$ cells release a 20-kD platelet activation–suppressive lymphokine (*51*). The cytotoxic activity of platelets against schistosomula, which is triggered by specific IgE antibody, can therefore be modulated by balance between lymphokines with antagonistic activities, reflecting the balance between regulatory CD4$^+$ and CD8$^+$ T cells.

Finally, we should stress that the parasite itself, or its metabolic products released in the host, contribute to negative or positive regulation of the effector mechanisms of immunity, for instance, by activating complement at its surface, by excreting proteases or inhibitors of lymphocyte proliferation or of mast cell degranulation (*19*), and more generally by potentiating IgE responses (*34*).

Collectively, these studies indicate that schistosome-specific T cells can stimulate or modulate numerous effector mechanisms against schistosomes. Immunity to reinfection appears thus to be a multifactorial process involving several antibody isotypes, complement components, T cells, and various effector cell populations not necessarily acting together at a given time, and with relative contributions of the effector pathways varying according to the host species.

In human *S. haematobium* infections, the expression of resistance has been found to be associated with both raised peripheral blood eosinophil levels and the presence of antibodies with specificity for adult worm antigens. Studies on resistance to *S. mansoni* infections have revealed a more complicated picture (*4, 52*). In an attempt to understand the slow development of resistance during childhood, blood samples have been taken from a group of 129 children, aged 9 to 16 years, before treatment with oxamniquine and at various intervals after treatment, and the levels of various immune responses have been related to subsequent susceptibility or resistance to reinfection. Initially, it was anticipated that the continued susceptibility of the younger children would be attributable to the lack of one or more potentially protective responses that developed slowly among the older individuals. However, no evidence has been obtained that supports this simple hypothesis. All of these heavily exposed subjects, including the younger children who remained susceptible to reinfection after treatment, have shown a range of potentially protective immune responses including, for example, high levels of IgG antibodies mediating eosinophil-dependent killing of schistosomula in vitro, or IgE antibodies capable of triggering ADCC by monocytes, eosinophils, and platelets. Thus, the possible modulation of putative effector mechanisms in the course of the infection had to be investigated.

Blocking Antibodies and Expression of Immunity

Evidence for the selective production of defined antibody classes during the course of experimental schistosome infection in rats, as already mentioned, raised questions about the function of isotypes not directly implied in killing mechanisms. It was first shown in rats

that the decrease in immunity observed at certain periods of infection is not related to a sharp decrease in antibody production, but is concomitant with the appearance of non-anaphylactic IgG subclasses. It was later shown that a representative IgG2c monoclonal antibody can prevent the capacity of an IgG2a monoclonal antibody both to induce eosinophil-dependent killing of schistosomula in vitro and to confer passive protection in vivo. The concept of blocking antibody was supported by the observation that the IgG2c monoclonal antibody can inhibit the recognition by the IgG2a monoclonal antibody of the carbohydrate moiety of a major surface glycoprotein of schistosomula described as gp38 (*40*). A similar observation was made in the mouse model: greater binding to the schistosomulum surface of antibodies to carbohydrate epitopes, including those expressed on gp38, was demonstrated with serum from chronically infected mice than with serum from animals immunized with irradiated cercariae (*53*).

The possibility that a similar phenomenon might be important in humans was indicated initially by the observation that susceptibility to reinfection after treatment is significantly correlated with the presence of high levels of antibodies with specificity for egg antigens, including a major egg polysaccharide (K3) that bears carbohydrate epitopes that are also expressed on the young schistosomulum (*52*). This leads to the hypothesis that, during early natural infections, the main immunogenic stimuli are carbohydrate-rich antigens released from eggs (present in greater mass than either the larval or adult stages). Such antigens elicit antibody responses that cross-react with schistosomulum surface antigens and block the binding of antibodies of an "effector" isotype against the same or sterically adjacent epitopes. In support of this hypothesis, it was also found that susceptibility to reinfection is associated with the presence of antibodies that inhibit the binding to a major gp38 schistosomulum surface antigen of the monoclonal IgG2a antibody with specificity for a carbohydrate epitope described above (*39*). In addition, IgM antibodies isolated from the sera of various individuals directly block the eosinophil-dependent killing of schistosomula mediated by IgG antibodies from the same sera, and IgM antibodies with specificity for schistosomulum surface antigens are present in higher levels in the young, susceptible children than in the older, resistant subjects (*54*). More recent experiments with the same human sera have also demonstrated a role for IgG2 antibodies to egg antigens in mediating the blocking effect. Such antibodies cross-react primarily with carbohydrate epitopes, both on the surface of the schistosomula and in the antigenic material, largely polysaccharide in nature, that is released during the transformation of the cercaria after penetration of the skin (*55*). There is also evidence that other IgG isotypes against the same antigens may mediate protection, as revealed by an inverse correlation with susceptibility to reinfection after treatment: the isotype involved and its specificities remain to be determined (*55*). Although isotype restriction of protective and blocking antibodies is clear in rats and possibly in humans, such restriction is not evident in mice (*56, 57*). The production of blocking antibodies does not appear, however, to be restricted to carbohydrate moieties, and recent evidence suggests that IgG4 antibody to peptide epitopes is highly correlated with susceptibility.

The main message from these studies is that in schistosomiasis, and possibly in other chronic transmissible diseases, blocking antibodies are important components of the expression of immunity and that the definition of immune versus susceptible populations might rely more on the identification of potential markers of susceptibility than on putative indicators of protection (*34*).

Along with the production of blocking antibodies, other mechanisms might contribute to the regulation of the expression of immunity. Idiotype–anti-idiotype interactions might influence ongoing immune responses in conditions of chronic infection, with continuous exposure of the host to the many antigens presented by adult worms, their excretory or secretory material, and soluble egg antigens. Indeed, the development of chronic murine infection with *S. mansoni* was shown to be correlated with production of anti-idiotype antibody related to soluble egg antigen (*58*). Increasing concentrations of IgG1 specific for idiotypes of antibodies to soluble egg antigen were also detected in mice infected with *S. japonicum*, and these anti-idiotypic antibodies were shown to be highly suppressive of granuloma formation in vivo. This suppressive activity could be confirmed with an anti-idiotypic IgG1 monoclonal antibody (*59*). These network interactions related to the reactivity to soluble egg antigens from schistosomes have also been characterized at the T cell level. Anti-idiotypic T lymphocyte responses to antibodies against soluble egg antigens were indeed detected both during active human infection or in former schistosomal patients (*60*) as well as in the $L3T4^+$, $Lyt\text{-}2^-$ subpopulation of mice with chronic *S. mansoni* infection (*61*). Evidence for the regulatory function of such anti-idiotypic responses can be drawn from the identification of anti-idiotypic suppressive T cells that modulate egg-induced granuloma formation (*62*). Cross-reactivity between egg and schistosomulum stages (*52, 63*) suggests that these observations, made in the study of immune regulation of granulomatous inflammation around schistosome eggs, might also be relevant to the control of resistance or susceptibility. Anti-idiotypic responses were indeed shown in the control of expression of resistance to murine infection with *S. mansoni* (*64*). Accordingly, waning of resistance during chronic murine infection was attributed to the modulation of macrophage activation by suppressive T lymphocytes of the $Ly\text{-}1^-$, $Lyt\text{-}2^+$ phenotype (*65*). Furthermore, in vivo depletion of $Lyt\text{-}2^+$ cells was shown to augment resistance and decrease morbidity in infected mice (*66*) while depletion of $L3T4^+$ T cells in mice (*66*), or $W3/25^+$ T cells in rats (*67*), produced opposite changes. However, whereas T cell clones specific for soluble egg antigen augmented granuloma formation around eggs in mice (*68*), various T-cell lines or clones specific for schistosomulum antigens conferred a significant level of protection by passive transfer as well as enhanced the production of antibodies in rats (*69*).

As for the antibody response, therefore, both the specificity and the T cell subset activated by schistosome antigens appear essential factors of the function of T cells in the control of resistance, susceptibility, or granulomatous hypersensitivity. An additional factor to be considered is antigen presentation, and indeed changes in resistance induced by nonliving vaccine were found to depend strongly on the route of antigen administration (*70*).

Resistance, granulomatous hypersensitivity, and morbidity due to schistosomes appear thus as distinct although interrelated components of the immune response (*1*), and it was feared that a strong immune response elicited against developing schistosomes could, in increasing immunopathology, have adverse consequences. Indications of stage-specific immunity and the demonstration that the control of the intensity of the infection leads to decreased rather than enhanced granulomatous hypersensitivity and egg-induced morbidity (*66*), together with similar findings in primates (*71*), are strong indications that vaccination in schistosomiasis would result in decreased morbidity.

Molecular Targets and Prospects for Vaccine

The multifactorial components of potential effector mechanisms against schistosomes might lead to the prediction of a corresponding diversity in the expression of target antigens. In fact, immunoprecipitation of surface-radioiodinated molecules has shown that *S.*

mansoni schistosomula display at their outer surface a limited number of antigenic components. The importance of a group of 30- to 40-kD antigens has been demonstrated during infection of various animal species, including rats, mice, monkeys, and humans (*72*). One of the major immunogenic components of this group of antigens is the already mentioned gp38, defined by the protective rat IgG2a monoclonal antibody (*73*). The corresponding epitope is also characterized on a 115-kD molecule in the excretory/secretory products of adult worms (*18*), thus providing a molecular support for concomitant immunity in schistosomiasis. This epitope is also expressed not only on high molecular weight components of cercariae and miracidia (eggs), but more strikingly in the intermediate host, *Biomphalaria glabrata* (*73, 74*). Confirming our early observations of the existence of common determinants between schistosomes and their intermediate hosts (*75*), it was possible to show that this surprising cross-reactivity could be related to an oligosaccharidic structure, the phylogenic origin of which has been found in the hemocyanin of an ancestral marine mollusk named *Megathura crenulata* and commonly known by immunologists as keyhole limpet hemocyanin (KLH) (*76*).

The evidence that the carbohydrate moiety of the schistosomulum gp38 or its cross-reacting homologs at other parasite stages could elicit both protective and blocking antibodies led us to consider two different strategies for the use of this major immunogen as a potential vaccine. First, anti-idiotypic antibodies were produced against the protective IgG2a monoclonal antibody, and such internal image-bearing anti-idiotypes were shown to induce strong protection in rats (*77*). Since the potential use of such an idiotypic vaccine in humans appears limited at present, advantage has been taken of the cross-reactivity between the schistosome antigens and KLH to induce protection by KLH-immunization (*76*) and to purify and to define the chemical structure of the KLH oligosaccharide. Knowledge of the precise structure of this protective carbohydrate may allow the production of synthetic oligosaccharides bearing the protective epitope but lacking the blocking determinant(s), which would constitute an original model for the study of the isotype-epitope relation.

The cloning and expression in *Escherichia coli* of the complementary DNA encoding for a 28-kD antigen (P28) has recently been reported and the full sequence of the protein determined in collaboration with Transgene. The recombinant protein induces similar levels of protection as the purified native protein in rats, mice, and hamsters (*78–80*).

One of the major interests of this protective antigen is the existence in P28 of epitopes cross-reactive not only with two other human schistosome species, *S. haematobium* and *S. japonicum*, but also with the bovine parasite *S. bovis*. This has encouraged us to undertake immunization experiments in cattle, which have already demonstrated the good immunogenicity of the recombinant P28 expressed either in *E. coli* or in yeast.

More recently, in two series of immunization experiments in baboons, a mean protection of 40 percent (which is quite significant in this animal model), with individual levels rising up to 80 percent, could be obtained. Although rather large individual variations in the protection induced by immunization can be observed, the present results seem quite promising and have allowed us to undertake larger experiments in order to optimize the potential use of such a candidate vaccine.

The response to this highly protective antigen in rats and baboons also included a strong production of IgE antibodies, which could induce in vitro cytotoxicity by platelets and eosinophils. Naturally infected humans exhibit a marked response to the recombinant P28, including a major IgE antibody response (*81*). The recent use of synthetic peptides constructed from the P28 sequence has shown that human IgG4 antibodies, which are strongly correlated as mentioned above with susceptibility to reinfection, can also be produced (*81*).

Although a good candidate for immunization, P28 is only one of several antigens that have been characterized and cloned in several laboratories (Table 1), some of these being found protective in mice or rats (*57, 82–88*).

Although it would be unreasonable to claim at this stage that a potential vaccine against human schistosomiasis is now available, major progress has been made in the identification and biosynthesis of protective molecules, and evidence for their immunogenicity in humans has been obtained.

Concluding Remarks

It is now clear from studies both in experimental animals and in humans that immunity to schistosomes cannot be anything other than multifactorial. In this respect, the demonstration of both protective and regulatory (blocking) mechanisms has led to more general concepts that might be applicable to other chronic transmissible diseases: antibody isotype selection, effector function of minor antibody classes or subclasses, production of blocking antibodies, and effector function of nonlymphoid cells. Such studies have also revealed that integral membrane components might not necessarily be the sole targets of immune response in the case of infections characterized by their chronicity and partial immunity. Recent evidence that a highly protective antigen of schistosomes, the P28, is not an integral membrane protein but is an enzyme excreted by the parasite and transiently expressed at the surface of schistosomula (*79*) points to the essential role that could be played by excretory and secretory antigens in the induction of immunity. Because many parasites including schistosomes occur in the vertebrate hosts at various developmental stages, it is likely that cross-reacting molecules expressed at these various stages, but with different locations on or in the parasite, are more suitable candidates for the permanence of effector mechanisms that are the components of concomitant immunity than the stage-specific antigens. The recent observations made both in experimental and human schistosomiasis provide at least one explanation for the slow development of immunity in humans, although not necessarily the only explanation, and they offer some hope that an approach to vaccination with recombinant peptides as described above, or synthetic neoglycopeptides, may prove successful.

REFERENCES AND NOTES

1. S. M. Phillips and D. G. Colley, *Prog. Allergy* **24**, 49 (1978); K. S. Warren, *Immunol. Rev.* **61**, 189 (1982).
2. K. Koetzel and J. R. da Silva, *Am. J. Trop. Med. Hyg.* **6**, 167 (1967); D. J. Bradley and F. S. McCullough, *Trans. R. Soc. Trop. Med. Hyg.* **67**, 491 (1973).
3. K. S. Warren, *J. Infect. Dis.* **127**, 595 (1973); P. R. Dalton and D. Pole, *Bull. WHO* **56**, 417 (1978).
4. P. Hagan *et al.*, *Parasite Immunol.* 7, 617 (1985); H. A. Wilkins, U. J. Blumenthal, P. Hagan, R. J. Hayes, F. Pulloch, *Trans. R. Soc. Trop. Med. Hyg.* **81**, 29 (1987); A. E. Butterworth *et al.*, *ibid.* **78**, 108 (1984); A. E. Butterworth *et al.*, *ibid.* **79**, 393 (1985).
5. R. F. Sturrock *et al.*, *Trans. R. Soc. Trop. Med. Hyg.*, in press; A. E. Butterworth *et al.*, in preparation.
6. A. E. Butterworth, R. F. Sturrock, V. Houba, P. Rees, *Nature (London)* **252**, 503 (1974); A. E. Butterworth *et al.*, *J. Exp. Med.* **145**, 136 (1977); A. E. Butterworth *et al.*, *J. Immunol.* **118**, 2230 (1977); A. E. Butterworth, D. W. Taylor, M. C. Veith, *Immunol. Rev.* **61**, 5 (1982).
7. R. A. Wilson, P. S. Coulson, S. M. McHugh, *Parasite Immunol.* **5**, 595 (1983).
8. P. Minard *et al.*, *Am. J. Trop. Med. Hyg.* **27**, 76 (1978); O. D. Bickle *et al.*, *Parasitology* **79**, 209 (1979); S. M. Phillips and M. A. Reid, *Int. J. Nucl. Med. Biol.* 7, 173 (1980); A. Sher *et al.*, *J. Immunol.* **128**, 1880 (1982).
9. D. Bout *et al.*, *J. Immunol.* **127**, 1 (1981); S. L. James *et al.*, *ibid.* **128**, 1535 (1982); C. A. Peck, M. D. Carpenter, A. A. F. Mahmoud, *J. Clin. Invest.* **71**, 66 (1983); S. L. James, *J. Immunol.* **136**, 3872 (1986); R. Correa-Oliveira *et al.*, *ibid.* **137**, 2014 (1986).
10. Q. D. Bickle and M. J. Ford, *J. Immunol.* **128**, 2101 (1982); K. L. Miller and S. R.

Smithers, *Exp. Immunol.* **50**, 212 (1980).
11. S. M. Phillips *et al.*, *J. Immunol.* **131**, 1466 (1983).
12. A. Capron *et al.*, *Am. J. Trop. Med. Hyg.* **29**, 849 (1980); M. J. Ford *et al.*, *Parasitology* **89**, 461 (1984); B. L. Mangold and P. M. Knopf, *ibid.* **83**, 559 (1981); H. Bazin *et al.*, *J. Immunol.* **124**, 2373 (1980).
13. F. Santoro *et al.*, *Clin. Exp. Immunol.* **32**, 435 (1978); T. E. Nash, B. Prescott, F. A. Neva, *J. Immunol.* **112**, 1500 (1974); V. Houba *et al.*, *ibid.* **117**, 705 (1976); A. M. Deelder *et al.*, *Exp. Parasitol.* **50**, 26 (1980); Y. Carlier *et al.*, *J. Immunol.* **124**, 2442 (1980); W. J. Stevens *et al.*, *Clin. Exp. Immunol.* **52**, 142 (1983).
14. A. Capron, M. Capron, J. P. Dessaint, in *Immunology 80, Progress in Immunology IV*, Fourth International Congress of Immunology, M. Fougereau and J. Dausset, Eds. (Academic Press, New York, 1980), pp. 782–793.
15. S. R. Smithers and R. J. Terry, *Trans. R. Soc. Trop. Med. Hyg.* **61**, 517 (1967); S. R. Smithers and R. J. Terry, *Ann. N.Y. Acad. Sci.* **160**, 826 (1969); J. A. Clegg and S. R. Smithers, *Int. J. Parasitol.* **2**, 79 (1972); A. Dessein *et al.*, *Parasitology* **82**, 357 (1981).
16. J. A. Clegg, S. R. Smithers, R. J. Terry, *Nature (London)* **232**, 653 (1971); R. T Damian, N. D. Greene, W. J. Hubbard, *J. Parasitol.* **59**, 64 (1973); D. A. Dean, *ibid.* **63**, 418 (1977); G. Torpier, A. Capron, M. A. Ouaissi, *Nature (London)* **278**, 447 (1979); A. Sher, B. F. Hall, M. A. Vadas, *J. Exp. Med.* **148**, 46 (1978).
17. G. Moser, D. L. Wassom, A. Sher, *J. Exp. Med.* **152**, 41 (1980).
18. C. Dissous and A. Capron, *FEBS Lett.* **162**, 355 (1983).
19. A. J. G. Simpson *et al.*, *J. Immunol.* **133**, 2725 (1984).
20. J. P. Dessaint *et al.*, *Eur. J. Immunol.* **7**, 624 (1977); C. Mazingue *et al.*, *Int. Arch. Allergy* **72**, 22 (1983); C. Auriault *et al.*, *Parasite Immunol.* **3**, 33 (1981); C. Auriault *et al.*. *FEBS Lett.* **153**, 11 (1983).
21. A. E. Butterworth *et al.*, *J. Immunol.* **122**, 1314 (1979); M. A. Vadas, A. E. Butterworth, S. Burakoff, A. Sher, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 1982 (1979); B. D. Gitter, S. L. McCormick, R. T. Damian, *J. Parasitol.* **68**, 513 (1982).
22. A. M. Attalah *et al.*, *Int. Arch. Allergy* **13**, 351 (1980); J. J. Ellner *et al.*, *J. Clin. Invest.* **70**, 369 (1982).
23. A. Capron, J. P. Dessaint, M. Capron, H. Bazin, *Nature (London)* **253**, 474 (1975).
24. M. Joseph, A. Capron, A. E. Butterworth, R. F. Sturrock, V. Houba, *Clin. Exp. Immunol.* **33**, 45 (1978).
25. M. Capron, H. Bazin, G. Torpier, M. Joseph, A. Capron, *J. Immunol.* **126**, 1764 (1981).
26. M. Capron *et al.*, *ibid.* **132**, 462 (1984).
27. M. Joseph, C. Auriault, A. Capron, H. Vorng, P. Viens, *Nature (London)* **303**, 810 (1983).
28. M. Joseph, A. B. Tonnel, A. Capron, C. Voisin, *Clin. Exp. Immunol.* **40**, 416 (1980); M. Joseph *et al.*, *C. R. Acad. Sci. (Paris)* **298D**, 55 (1984).
29. C. Mazingue *et al.*, *Clin. Exp. Immunol.* **67**, 587 (1987).
30. A. E. Butterworth *et al.*, *J. Immunol.* **122**, 221 (1979); E. C. Jong, A. A. F. Mahmoud, S. J. Klebanoff, *ibid.* **126**, 468 (1981); D. J. McLaren *et al.*, *Parasite Immunol.* **3**, 359 (1981).
31. S. Y. L. Hsü, G. L. Lust, H. F. Hsü, *Proc. Soc. Exp. Biol. Med.* **136**, 727 (1971); F. Von Lichtenberg *et al.*, *Am. J. Pathol.* **84**, 479 (1976); P. M. Knopf, *Exp. Parasitol.* **47**, 232 (1979).
32. A. A. F. Mahmoud, K. S. Warren, P. A. Peters, *J. Exp. Med.* **142**, 805 (1975).
33. M. Capron *et al.*, *Cell. Immunol.* **3**, 60 (1984).
34. A. Capron and J. P. Dessaint, *Annu. Rev. Immunol.* **3**, 455 (1985).
35. A. Rousseaux-Prevost *et al.*, *Immunology* **35**, 33 (1978).
36. E. H. Sadun and R. W. Gore, *Exp. Parasitol.* **28**, 435 (1970).
37. E. P. Kigoni *et al.*, *Eur. J. Immunol.* **16**, 589 (1986).
38. M. Capron *et al.*, *ibid.* **8**, 127 (1978).
39. J. M. Grzych, M. Capron, H. Bazin, A. Capron, *J. Immunol.* **129**, 2739 (1982).
40. J. M. Grzych, M. Capron, C. Dissous, A. Capron, *ibid.* **133**, 9998 (1984).
41. J. P. Dessaint *et al.*, *Clin. Exp. Immunol.* **20**, 427 (1975).
42. D. S. Findbloom and H. Metzger, *J. Immunol.* **129**, 2004 (1982); H. L. Spiegelberg, *Adv. Immunol.* **35**, 61 (1984).
43. A. Capron *et al.*, *Eur. J. Immunol.* **7**, 315 (1977).
44. A. Capron *et al.*, *Int. Arch. Allergy* 77, 107 (1985).
45. J. Khalife *et al.*, *J. Immunol.* **137**, 1659 (1986).
46. S. L. James and L. A. DeBlois, *ibid.* **136**, 3864 (1986).
47. D. Camus *et al.*, *Eur. J. Immunol.* **9**, 341 (1979).
48. M. Capron and T. Jouault, *Ann. Inst. Pasteur Immunol.* **137C**, 371 (1986); M. Capron *et al.*, *J. Immunol.* **139**, 2049 (1987).
49. A. R. E. Anwar, S. R. Smithers, A. B. Kay, *J. Immunol.* **122**, 628 (1979); F. J. Ramalho-Pinto, D. J. McLaren, S. R. Smithers, *J. Exp. Med.* **147**, 147 (1978).
50. D. G. Colley, *J. Immunol.* **110**, 1419 (1973); A. J. Dessein, H. L. Lenzi, J. R. David, *Monogr. Allergy* **18**, 45 (1983); R. Sher, A. Wadee, M. Joffe, *Clin. Exp. Immunol.* **51**, 525 (1983); M. C. Veith and A. E. Butterworth, *J. Exp. Med.* **157**, 1828 (1983); S. H. Pincus *et al.*, *Cell. Immunol.* **87**, 424 (1984); K. J. I. Thorne *et al.*, *Eur. J. Immunol.* **15**, 1083 (1985); G. J. Gleich and C. R. Adolphson, *Adv. Immunol.* **39**, 177 (1986); M. Veith *et al.*, *Dev. Comp. Immunol.* **10**, 144 (1986).
51. V. Pancré *et al.*, *J. Immunol.* **137**, 585 (1986); unpublished observations.
52. A. E. Butterworth *et al.*, *Parasitology* **94**, 1626 (1986); D. W. Dunne *et al.*, *ibid.* **94**, p. 269.
53. P. Omer-Ali *et al.*, *J. Immunol.* **137**, 3601 (1986).
54. J. Khalife *et al.*, *J. Exp. Med.* **164**, 1626 (1986).
55. D. W. Dunne *et al.*, *Eur. J. Immunol.*, in press; A. E. Butterworth *et al.*, *Biochimie*, in press.
56. D. A. Harn *et al.*, *J. Cell. Biochem. Suppl.* **11A**, 151 (1987).
57. D. A. Harn *et al.*, *Mol. Biochem. Parasitol.* **16**, 345 (1985).
58. M. R. Powell and D. G. Colley, *J. Immunol.* **134**, 4140 (1985).
59. R. T. F. Kresina and G. R. Olds, *Infect. Immun.* **53**, 90 (1986); G. R. Olds and T. F. Kresina, *J. Clin. Invest.* **76**, 2338 (1985); A. B. Stavitsky, *Immunol. Today* **8**, 228 (1987).
60. M. S. Lima *et al.*, *J. Clin. Invest.* **78**, 983 (1986).
61. M. R. Powell and D. G. Colley, *Cell. Immunol.* **104**, 377 (1987).
62. T. Abe and D. G. Colley, *J. Immunol.* **132**, 2084 (1984).
63. D. A. Harn, M. Mitsuyama and J. R. David, *J. Exp. Med.* **159**, 1371 (1984); D. A. Harn *et al.*, *J. Immunol.* **138**, 1571 (1987).
64. S. M. Phillips *et al.*, *J. Immunol.* **137**, 2339 (1986).
65. G. R. Olds and J. J. Ellner, *ibid.* **133**, 2720 (1984).
66. S. M. Phillips *et al.*, *ibid.* **139**, 919 (1987).
67. F. Mendlovic, R. Tarrab-Hazdai, R. Arnon, *Eur. J. Immunol.* **17**, 1151 (1987).
68. N. K. Mak and C. J. Sanderson, *Immunology* **54**, 625 (1985); P. J. Lammie, G. P. Linette, S. M. Phillips, *J. Immunol.* **134**, 4170 (1985).
69. J. Pestel *et al.*, *J. Immunol.* **134**, 4132 (1985); C. Auriault *et al.*, *Infect. Immun.* **55**, 1163 (1987); M. Damonneville *et al.*, *Clin. Exp. Immunol.* **69**, 299 (1987).
70. S. L. James in (*9*).
71. R. T. Damian *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 3552 (1984).
72. C. Dissous, C. Dissous, A. Capron, *Mol. Biochem. Parasitol.* **3**, 215 (1981); C. Dissous and A. Capron, *Protides of the Biological Fluids*, Proceedings of the 29th Colloquim on Protides of the Biological Fluids, Brussels, Belgium, May 1981, H. Peeters, Ed. (Pergamon, New York, 1982), pp. 179–182; A. J. G. Simpson, S. L. James, A. Sher, *Infect. Immun.* **41**, 591 (1983).
73. C. Dissous, J. M. Grzych, A. Capron, *J. Immunol.* **129**, 2232 (1982).
74. ———, *Nature (London)* **323**, 443 (1986).
75. A. Capron *et al.*, *Ann. Inst. Pasteur (Paris)* **109**, 798 (1965).
76. J. M. Grzych *et al.*, *J. Exp. Med.* **165**, 865 (1987).
77. J. M. Grzych *et al.*, *Nature (London)* **316**, 74 (1985).
78. J. M. Balloul *et al.*, *ibid.* **326**, 149 (1987); J. M. Balloul *et al.*, *J. Immunol.* **138**, 3448 (1987), J. M. Balloul *et al.*, *Molecular Paradigms for Eradicating Helminthic Parasites* (Liss, New York, in press).
79. J. B. Taylor *et al.*, in preparation.
80. J. M. Balloul *et al.*, in preparation.
81. A. Capron *et al.*, in preparation.
82. M. Damonneville *et al.*, *Int. Arch. Allergy Appl. Immunol.* **79**, 320 (1986).
83. D. B. Smith *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 8703 (1986); E. J. Pearce *et al.*, *J. Immunol.* **137**, 3593 (1986).
84. J. S. Cordingley *et al.*, *Mol. Biochem. Parasitol.* **18**, 73 (1986).
85. J. P. Dalton *et al.*, *J. Immunol.* **136**, 4689 (1986).
86. A. Sher *et al.*, *ibid.*, p. 3878.
87. D. E. Lanar, E. J. Pearce, S. L. James, A. Sher, *Science* **234**, 593 (1986).
88. D. M. Zodda and S. M. Phillips, *J. Immunol.* **129**, 2326 (1982); R. H. Barker, Jr., *et al.*, *Eur. J. Immunol.* **18**, 73 (1986).
89. Research of the authors is supported by INSERM, CNRS, and Medical Research Council, and grants from Edna McConnel Clark Foundation, European Economic Community, the WHO-UNDP (United Nations Development Program) Special Program for Research and Training in Tropical Diseases, and with practical support of the government of Kenya.