HUMORAL IMMUNE RESPONSE IN PARASITIC INFECTIONS

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The fact that clinical evidence for acquired immunity in parasitic infections is often absent or equivocal at best has prompted the belief that parasites, unlike bacteria and viruses, are poorly immunogenic, and are not effective in inducing the immune response in affected hosts. However, it has been shown that both humoral and cellular immune components are stimulated during the course of infection by most parasitic agents that have been thoroughly investigated (Ogilvie, 1970; Soulsby, 1972; Porter and Knight, 1974; Mauel and Behin, 1974; Cohen and Sadun, 1976). Both types of responses however correlate poorly with protection, suggesting that neither antibodies nor sensitized cells could damage the parasites. Such a conclusion is largely supported by the data showing that passive serum or cell transfer often fails to induce immunity in recipients (Ogilvie, 1970; Mauel and Behin, 1974; Porter and Knight, 1974; WHO, 1975). However, because both parasiticidal antibodies and sensitized cells can also be demonstrated *in vitro* in those infections which induce poor immunity to reinfections, it appears that parasites are also able to evade the host immune mechanism that they themselves induce, thus allowing them to survive for long periods in the immune hosts (Soulsby, 1972; Porter and Knight, 1974; Cohen and Sadun; 1976; Ogilvie and Wilson, 1976).

Following an active infection, 3 different categories of immune response can be distinguished.

Sterilizing immunity: This type of immunity is associated with a complete elimination of the parasite and with a life-long specific immunity to reinfection (Porter and Knight, 1974). This situation occurs in certain forms of human cutaneous leishmaniasis, trypanosomiasis in rats and cattle, and rodent malaria. However, the pattern of acquired immunity is not constant for a given parasite but often exhibits wide variation in different hosts. *Plasmodium berghei*, for example, produce sterilizing immunity in rats, but a rapidly fatal infection in mice (Porter and Knight, 1974). The extent to which acquired immunity determines these different responses to the same pathogen has not been adequately investigated.

Nonsterilizing immunity: This is associated with persistence of the parasite in the host at relatively low density (Porter and Knight, 1974). In this type of immunity, established parasites are resistant to the immune mechanisms which are capable of eliminating establishing parasites. There are many suggestions as to how the parasites could survive in the immune host. Among these suggestions are antigenic variations of the parasites, acquisition of host or host-like antigens on their surfaces, or production of factors that counteract the action of the immune components of the hosts (Ogilvie and Wilson, 1976). This situation is consistently observed in a majority of helminthic infections and also occasionally in protozoal infections, e.g., human and simian malarias, trichomoniasis in cattle and coccidiosis in birds.

Absence of effective immune response: Many parasitic infections in human fall into this category and this includes African trypanosomiasis, amoebiasis and many nematode infections (Jarrett and Urquhart, 1971; Cohen and Sadun, 1976).

Regardless of the type of the immune response developed, acquired immunity to parasites is, in general, species- and strain-specific. Furthermore, with some parasites, malaria for instance, it is also stage-specific (WHO, 1975; Cohen and Sadun, 1976).

There are a few distinctive features that characterize the humoral immune response in parasitic infections that should be mentioned before discussing the biological effect of antibodies on the parasites. These include:

Hyperglobulinemia: The circulating level of the various classes of immunoglobulins in many parasitic infections is often elevated and this is mainly the result of enhanced immunoglobulin synthesis rather than decreased catabolism (Ogilvie, 1970; Soulsby, 1972; Porter and Knight, 1974; Cohen and Sadun, 1976). It is possible that this is due to a chronic nature of the infection itself or to an extensive tissue migration by some parasites, thereby allowing continuous antigenic stimulation on the part of the host. However, only a small proportion of the elevated immunoglobulins in the circulation has any activity specific for the parasite involved (Porter and Knight, 1974).

Class specificity of the newly synthesized immunoglobulins: In addition to a diffuse hyperglobulinemia which results in an increase of many immunoglobulin classes, some parasites are known to induce elevation of only a certain class of immunoglobulin (Ogilvie, 1970; Porter and Knight, 1974). For example, elevated IgM has been observed in African trypanosomiasis, chronic schistosomiasis and malaria. Such an elevation is rather non-specific as only a small proportion of the IgM produced has antibody to the parasite involved (Ogilvie, 1970). The mechanism responsible for the preferential stimulation of a particular class of immunoglobulin over another is not known. One possibility is that some parasites have extensive antigenic variation and IgM antibody has to be made continuously against new antigens that emerge. It is also possible that these parasites may elaborate factor(s) that interferes with the regulation of the host immune response, e.g., mechanism for the switching over from IgM to IgG production.

Association of enhanced IgE production and eosinophilia with helminthic infections. Some parasites, particularly the intestinal and tissue helminths, induce a marked elevation of IgE (Table 1) that is most frequently associated with eosinophilia. The following observations regarding the relationship between IgE and parasites have been made:

Table 1

Examples of helminthic infections with increased IgE level.

Ascariasis
Capillariasis
Schistosomiasis
Strongyloidiasis
Toxocariasis
Nippostrongylus infection
Hookworm infection

(1) There is a demonstrable increase of total IgE level in parasitized subjects and this returns to normal when parasites are eleminated (Ito *et al.*, 1972; Grove *et al.*, 1974; Ishizaka *et al.*, 1976 a, b).

(2) Only a small fraction of the increased IgE has demonstrable activity to parasites (Ishizaka *et al.*, 1976 a, b).

(3) IgE antibody to parasite appears after the circulating IgE has reached the peak (Ishizaka *et al.*, 1976 a, b; Jarrett *et al.*, 1976);

(4) Appropriately timed infection by some parasites potentiates the production of IgE antibody to unrelated antigens (Bloch, 1973;

Ishizaka *et al.*, 1976 a, b; Jarrett *et al.*, 1976). Such a potentiation is almost always observed in active infection as artificial immunization with the parasite extract has no effect (Soulsby, 1972; Cohen and Sadun, 1976). Exceptions to this statement are *Ascaris* and *Trichinella* extracts (Cohen and Sadun, 1976).

Depending on the species of the animals involved, the potentiation effect is observed only when infection occurs after animals have been sensitized and begun to make IgE. The degree of potentiation usually parallels preexisting IgE level (Cohen and Sadun, 1976).

Although a close association between enhanced IgE production and parasitic infections has been observed in both natural and experimental infections, neither the mechanism of induction nor the action of IgE antiparasite are well understood. From the several hypotheses that have been proposed, the adjuvant-like effect of parasitic antigens is most credible and is consistent with the limited evidence that are currently available (Cohen and Sadun, 1976; Ishizaka *et al.*, 1976 a, b). These parasitic components can act directly on IgE-B eclls, and not on IgG-B cells. On the other hand, they may act on specific T cells thus resulting in a release of soluble factor that stimulates only IgE-B cells. Infection of rats with *Nippostrongylus brasiliensis* is known to induce differentiation and proliferation of IgE-bearing cells in the mesenteric lymph nodes (Ishizaka *et al.*, 1976 a). Nevertheless, it is also possible that these substances may act indirectly on the suppressor T cells which regulate IgE production. These substances however have never been characterized but, in the case of intestinal parasites, it is most likely associated with the metabolic products elaborated by the intestinal phase of the parasites (Jarrett and Steward, 1973). The adjuvant-like effect of these subtances on IgE-B cells is also consistent with the currently available data on the potentiation of the IgE antibody response to unrelated antigens during the course of parasitic infections.

Specific antibody production that is not related to protection: Parasites are antigenically much more complex than other infective agents, not only because they are larger as some are multicellular, but many of them exist in different developmental stages within the same host. Although some of the antigens that exist in different developmental stages may be similar to one another, stage-specific antigens do exist (Cohen and Sadun, 1976). Under appropriate conditions, all of these antigens should be antigenic and induce antibody response that is heterogeneous with regards to its specificity. The serological tests (Table 2) in parasitic infections have not been as useful as in bacterial or viral infections as the former is rather non-specific for the reason just mentioned.

Table 2

Common serological tests used in diagnosis of parasitic infections.

Test	Disease
Complement fixation, agglutination, immunofluorescence	Amoebiasis, Malaria, Leishmaniasis, Trypanosomiasis, Toxoplasmosis, Trichinosis, Schistosomiasis, Filariasis
Immunodiffusion, immunoelectrophoresis	Amoebiasis, Malaria, Trypanosomiasis, Trichinosis
Circumoval precipitation	Trichinosis, Schistosomiasis

The following discussion will be focussed on protective antibodies as they are immediately more relevant to the host-parasite relationship. Knowledge of the immune mechanisms and antigens involved in protective immunity should provide the most satisfactory solutions for the control of some parasitic infections. However, protective antigens have never been completely defined and characterized for any parasites and this make it difficult to understand the mechanisms involved in acquired immunity and almost impossible therefore to design effective immunoprophylaxis against these agents. Due to the fact that only acitve infection, and not artificial immunization with killed parasites, induces resistance to reinfection (Porter and Knight, 1974; Cohen and Sadun, 1976), it appears therefore that the antigens involved are associated with the metabolic activities of living parasites. Instead of using somatic antigens, excretory and secretory products (ES antigens) have been recently used to immunize animals in attempt to induce protective immunity but the results were variable (Richard and Bell, 1971; Kowalski and Thorson, 1972; Richard and Outteridge, 1974; Kwa and Liew, 1977). Improved techniques for the *in vitro* cultivation of parasites will definitely contribute to a progress in designing a safe and effective vaccine for some of these parasitic diseases.

Although information on the nature of the protective antigens is limited, protective antibodies have been frequently demonstrated in the serum of subjects who recovered from active infection (Ogilvie, 1970; Porter and Knight, 1974; Cohen and Sadun, 1976; WHO, 1975). The presence of such an antibody has been demonstrated most often by a classical method of passive serum transfer. Although it is difficult to generalize the finding obtained from the limited results that are currently available, it appears that successful serum transfer (Table 3) is mediated primarily by

Table 3

Immunity conferred by passive serum transfer.

Ascariasis
Malaria
Schistosomiasis
Trichinosis
Toxoplasmosis
Trypanosomiasis
Coccidiosis

IgG class of antibody and is observed more often in cases which are associated with sterilizing immunity. Even in this situation, very often a large quantity of serum is required to give a complete protection, particularly in the case of helminthic infections (Soulsby, 1972; Armour and Dargie, 1974; Porter and Knight, 1974). Nonetheless, it has been reported that if appropriate serum is available, only a small quantity of antibody is required to give complete protection as, for example, in the case of malarial infection in rodents (WHO, 1975). Frequently the quantity of serum required for protection can be reduced if both serum and sensitized cells are used in the transfer, suggesting that both humoral and cellular components are required for protective immunity (Dineen *et al.*, 1973; Maddison *et al.*, 1976; Wakelin and Lloyd, 1976).

What are some of the possible ways that antibodies can damage, interfere with metabolic activities or kill the parasites? It is known that the immune defence could reduce infectivity, motility, reproductive potential, enzyme activity and oxygen consumption of the parasites (Table 4), thereby resulting in retardation of development, reduction of worm burden or complete protection against reinfection (Porter and Knight, 1974). How does the antibody do this? Does it act directly on the parasite or indirectly by creating conditions unfavorable for parasite survival? Does the antibody act alone or require cooperation with other humoral and cellular components?

Table 4

Direct effect of antibodies on parasites.

Biological Effects	Parasites
Neutralization (reduction of infectivity)	*Trypanosoma* sp., Hookworms, *Plasmodium* sp., *Nippostrongylus braziliensis*, *Trichinella spiralis*
Activation (induction of antigenic variation)	*Plasmodium* sp., *Trypanosoma* sp.
Enzyme inactivation	*Trypanosoma* sp.
Immobilization	*Entamoeba coli*
Reduction of reproductive potential	*N. braziliensis*, *Schistosoma* sp.
Interference with migration	*Schistosoma* sp.
Inhibition and retardation of larval development	*Trichostrongylus* sp., *Ascaris* sp.
Interference with growth regulatory mechanism (stunting)	*Schistosoma* sp., *Angiostrongylus cantonensis*
Decreased oxygen consumption	*N. braziliensis*, *Trypanosoma* sp., *A. cantonensis*
Damaging the gut cells	*N. braziliensis*
Change in permeability	*Trypanosoma lewisi*

Antibody alone is known to exert a diverse effect on the parasite (Table 4), although its action may be potentiated by activation of complement (Porter and Knight, 1974). Theoretically all classes of antibodies must be able to react with and damage the parasites directly one way or another, similarly to antitoxic effect in bacterial infections or neutralization of infectivity of viruses. Antibody of different immunoglobulin classes except IgE and IgD have been found on the surface of parasites removed from an immune host (Kemp *et al.*, 1976; Seesee *et al.*, 1976; Befus, 1977). IgE antibody to parasites has never been shown to exert any direct damage to the parasites but accumulating evidence suggest that it may affect the parasites indirectly by creating environments unfavorable for them to live and survive (Jarrett and Urquhart, 1971; Ogilvie and Parrott, 1974; Cohen and Sadun, 1976). Secretory antibody of the IgA class is known to protect mucosa against surface infections by bacteria and viruses (Hereman, 1974). Its action on parasites has never been demonstrated directly although it has been shown that the intestinal secretion of immune host has anti-parasite activity, but whether or not this plays a role in protection is uncertain. Anti-parasite-activity has been demonstrated in the intestinal secretions of *N. brasiliensis*-infected rats or *Coccidia*-infected birds (Cohen and Sadun, 1976; Poulain *et al.*, 1976 a,b.), and in the vaginal secretion of human infected with *Trichomonas vaginalis* (Ackers *et al.*, 1975). It is not unreasonable to expect that SIgA antibody could react with the secreted and excreted products of the parasites and thereby interfering with their food intake and waste elimination. Anchorage of the parasites to the intestinal wall may also be affected by SIgA class of antibody. Only limited information is currently available on IgD and its biological activity and nothing is known about IgD antibody and parasite.

In addition to these direct actions, antibodies can also collaborate with other humoral and cellular components to accentuate the damage induced by the direct mechanism

Table 5

Specific and nonspecific immune effector mechanisms in some parasitic diseases.

Effector Immunoglobulin	Effector Cell	Complement	Biological Effect	Parasite or Disease
All classes	—	–	Neutralization	Malaria
IgG, IgM	—	+	Cytolysis	Trypanosomiasis Schistosomiasis Malaria
IgG, IgM	Macrophage	±	Immune adherence	Trypanosomiasis Malaria
IgG	K cell, Eosinophil	–	Antibody-dependent cell-mediated cytolysis	Schistosomiasis Malaria?
IgE	Mast cell	–	Immediate hypensensitivity	Worm expulsion
—	T cell	–	Cell-mediated cytolysis	Leishmaniasis, Worm expulsion?
—	T cell and macrophage	–	Non-specific cytotoxicity	Malaria Toxoplasmosis

(Table 5; Soulsby, 1972; Porter and Knight, 1974; Cohen and Sadun, 1976). Expulsion of *N. brasiliensis* from the intestine of rats is a good example of a collaboration between antibody and cells. It is generally accepted that the expulsion in this model is a 2-step immunological process involving the sequential action of antibodies which damage the worms and sensitized lymphocytes which cause the actual expulsion of the damaged worms (Jarrett and Urquhart, 1971; Dineen *et al.*, 1973; Ogilvie and Parrott, 1974). It is not known however why antibody-damaged worms are more easily expelled than undamaged worms or how the cells expell these damaged worms. Nevertheless, recent data suggest that animals seemingly lacking potential to produce antibody can still expell the worms from the intestine. The presence in trace quantity of antibody in these animals has never been ruled out.

There are many possibilities as to how IgE antibody might play a role in acquired immunity in parasitic infections (Ogilvie and Parrott, 1974). Some of these include:

(1) **Direct action:** This is by reacting directly with the ES antigens and thereby interfering with their metabolic functions. The IgE antibody may also interfere with the attachment and penetration of the parasites.

(2) **Indirect action:** This may occur as a result of different mechanisms which include the following:

(a) Recruitment of eosinophils: Eosinophils are attracted to the site of infection when eosinophil chemotactic factor of anaphylaxis (ECFA) is released from IgE sensitized mast cells or through activation of the complement system via an alternate pathway (Despommier *et al.*, 1974; Zucker-Franklin, 1974; Kay, 1976). Why eosinophilia occurs or why ac-

cumulation of eosinophils in the tissue is more prevalent in parasitic infections than in bacterial or viral infections are not clearly understood.

Esoinophils may participate in an antibody-dependent cell mediated cytolysis reaction (Butterworth *et al.*, 1976; James and Colley, 1976; Kay, 1976; Jacobson *et al.*, 1977). The action of IgE antibody is to provide environment that would be more favorable for the parasite destruction by IgG antibody and eosinophils. This reaction is more intense when eosinophil-rich leukocyte preparation is used and is nullified in the presence of antiserum to eosinophils (Butterworth *et al.*, 1976; Butterworth *et al.*, 1977). It is possible that eosinophils are attracted to antibody-coated parasites by the receptors on the surface. At least in the schistosome infection in mice, this reaction may play an important role in acquired immunity because elimination of eosinophils from immune rat abrogates its resistance to reinfection (Mahmoud *et al.*, 1975).

(b) Induction of local anaphylactic reaction: This reaction induces non-specific inflammatory response that provide environmental condition not suitable for parasite survival. This "leak-lesion" effect allows protective antibodies to accumulate at the site of infection. The following evidence are consistent with the contention that the local anaphylactic response mediated by IgE class of antibody may have some protective value (Soulsby, 1972; Cohen and Sadun, 1976).

(1) Correlation between the onset of inflammation and worm expulsion.

(2) Inflammation appears quicker, and it is more intense and more prolonged in immune host.

(3) Reduction of the intensity of inflammatory response by cortisone, antihistamine or irradiation prolongs worm retention.

(4) Worm expulsion occurs when intestinal anaphylaxis is induced by unrelated antigen-antibody reaction.

(5) Immediately before and during worm expulsion, there is an accumulation of vasoactive amines and mast cells at the site of worm expulsion.

On the other hand, there are some evidence that are inconsistent with this contention and these include worm expulsion in the absence of IgE antibody and in animals lacking antibody production potential (Jacobson *et al.*, 1977).

These evidence, though still somewhat controversial, favor the idea that IgE antibody somehow plays a role in acquired immunity in some parasitic infections. The inability to induce IgE antibody and acquired immunity with artificial immunization and the ability to induce IgE antibody and acquired immunity following active infection add more weight to the protective role of IgE antibody. Regardless of its role in protection, enhanced IgE antibody production is valuable in immunodiagnosis as the immediate type of skin reaction is useful in providing a presumptive diagnosis for many parasitic infections in human (Table 6).

Table 6

Immediate skin reaction used as presumptive diagnosis of parasitic infections in human.

Ascariasis
Filariasis
Trichinosis
Echinococcosis
Schistosomiasis
Clonorchiasis
Strongyloidiasis
Diphyllobothriasis
Hookworm Infection

These various mechanisms mainly demonstrated by *in vitro* techniques, indicate that

the host immune components can damage the parasites or interfere with their development and survival. Whether or not these mechanisms are effective *in vivo* is not certain because there are many factors that can interfere with these mechanisms. For instance, blocking antibody, soluble antigens, or soluble immune complexes can interfere with the expression of the cell-mediated response to parasites (Ogilvie and Wilson, 1976). Certain parasites may also decrease the phagocytic and killing action of the macrophages or release anti-complementary factor that nullifies the action of complement (Ogilvie and Wilson, 1976).

In summary, there are several possible mechanisms that the antibody, either by itself or in collaboration with other humoral or cellular components, might participate in acquired immunity in parasitic infections. However, it should be stressed that there are many other factors that will influence the outcome of these interactions. Furthermore, many parasites have the ability to evade immune mechanisms, thus allowing them to survive for a long period in the immune host. With these points in mind, it may seem a long way yet before a safe and effective immunoprophylaxis for parasitic infections will be available for human use. Attenuated vaccines using irradiated larvae or chemically treated larvae have been used in some animals and proved to be rather safe and effective (Silverman, 1970; Soulsby, 1972; Cohen and Sadun, 1976; Poulain *et al.*, 1976 b). The ideal preparation for human use is to have purified protective antigen, either of metabolic or somatic origin, available for use as vaccine but this is not yet possible. It has been shown recently however that a purified antigen obtained from somatic extract or metabolic products from *Taenia taeniaeformis* is effective in inducing acquired resistance to infection by this parasite (Kwa and Liew, 1977). It has been shown that malate dehydrogenase and aminopeptidase enzymes from *Ascaris suum* have some protective value when immunized into guinea pig (Rhodes *et al.*, 1965, 1966). Metabolic antigens from *N. brasiliensis* (Poulain *et al.*, 1976 b) *Trichinella spiralis*, *Ancylostoma caninum*, *Dictyocaulus viviparus*, *Trichostrongylus colubriformis* and *Strongyloides papillosus* (Thorson, 1970) could induce a certain degree of protective immunity in experimental animals, but the nature of these antigens is not known as they have never been fully characterized and investigated. Our group has been interested in using *Angiostrongylus cantonensis* as a model system to study acquired immunity to infection by tissue nematode. The limited data that are currently available show that artificial immunization of rats with the *in vitro* culture fluid from adult females is effective in protecting rats from a lethal challenge infection by infective third-stage larvae (Uahkowithchai *et al.*, 1977).

It is hoped that advance in this area of investigation will be forthcoming in the near future as techniques for the *in vitro* cultivation of parasites are improving and investigators with diverse background and experience, e.g., biochemists, immunologists, and parasitologists, collaborate in their effort to solve the same common problem. When this task is accomplished, it will be a great contribution to the well-being of our society, especially for people living in this part of the world where parasitic infections are still prevalent.

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