Parasites and the Immune System

Conflict or compromise?

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One of the distinctive characteristics of all organisms, however simple or complex, is that they can distinguish the components of their own bodies—self—from those of genetically unrelated organisms—nonself. This capacity rests on complementary interactions between molecular structures, often located at cell surfaces, and is used by different species in many different ways. In animals, these include activities as diverse as feeding by phagocytosis, maintenance of the separate identities of colonial animals, and recognition of gametes in reproduction. In addition, all species use self/nonself discrimination to defend themselves against invasion by parasites.

The mechanisms by which this discrimination is achieved exist in some form at all levels of animal organization but show a phylogenetic increase in sophistication, culminating in the adaptive immune system (Turner 1994). As animals become larger and more complex, as their individual life spans increase, and as their internal environments become regulated more precisely—in other words, as they provide better environments for invaders—so the threat from parasitism becomes more severe. Birds and mammals are particularly at risk, because they provide ideal habitats for a wide variety of invading organisms. Not only are the members of these classes structurally complex, often large and long lived, but their internal environments are maintained at a high temperature. They therefore provide a diversity of stable, nutritionally rich niches in which parasites can establish, develop, and reproduce with maximal efficiency. Not all of these infections result in frank dis ease, but many do, and all carry a fitness cost to the host.

With these considerations in mind, it seems axiomatic that the sophistication and complexity of the mechanisms for self/nonself discrimination found in the avian and mammalian adaptive immune systems must in part represent an evolutionary response to the threats posed by parasitism. If this view is accepted, how successful is the immune system as a countermeasure? As far as humans are concerned it is difficult to provide a clear answer, because data must come largely from observation rather than experiment, but the problem can be highlighted by two observations. Parasitic infections of all types remain a common cause of mortality and morbidity in populations living in tropical and subtropical regions of the world, suggesting that antiparasite immunity is inefficient. However, when the immune system is severely depressed, as in patients treated with immunosuppressant drugs or suffering from AIDS, opportunistic parasitic infections become more frequent and can be life threatening, implying that in immunologically normal individuals the prevalence and severity of these infections are well controlled. It is unlikely that humans differ fundamentally from other animals in their capacity to respond immunologically to parasites; therefore, the wider question of the relationship of the immune system to the control of parasitic infections remains.

In this article I look at this issue by examining what is currently understood about the role of the immune system in regulating the interactions between hosts and parasites, using data relating to infections in humans and in experimental animals. I then focus on whether immu-
Parasites

The term parasites can be defined inclusively, to cover all pathogens from viruses onward, or it can be used more conventionally to refer specifically to eukaryote animal pathogens—the single-celled protozoans and the multicellular worms and arthropods. I use the more restricted definition here. Table 1 lists examples of the major eukaryote parasite groups of greatest importance in humans. Fuller accounts of these parasites can be found elsewhere, for example, in Despommier et al. 1994, Muller and Baker 1990, and Zaman and Keong 1989, which deal with human infections, and in Schmidt and Roberts 1989 and Smyth 1994, which also provide a broader animal parasitology approach.

Several important distinctions can be made between the different groups of parasites in terms of their size, structure, reproduction, mode of transmission, and location in the host, all of which are relevant to their relationship with the host immune system. One important distinction is between micro- and macroparasites. Protozoa, like the other major groups of microparasites (viruses and bacteria), are small in relation to host cells, and many take advantage of their small size to live intracellularly. All protozoans share the capacity to replicate within the host, so that parasite load and infection severity are potentially independent of the number of infection events. If immunity is to provide effective protection it must therefore control the infection as it develops.

Worms and arthropods are macroparasites. Not only are they large in relation to host cells, but characteristically (with some important exceptions) they do not replicate within the host. In contrast to the micro-parasites, levels and severity of infection with macroparasites reflect the total of infection events, that is, how many infective stages enter the host on how many occasions. Immunity against these parasites may therefore have a more important role in controlling reinfection than in dealing with an initial infection.

Protozoan organisms are limited by a conventional plasma membrane, which functions as the interface with the host. In species living extracellularly this interface is readily accessible to potentially damaging immune-mediated effector mechanisms, such as those involving antibody, complement, or cytotoxic cells. If the cell membrane is damaged sufficiently and loses its integrity, the parasite is effectively destroyed. Uptake of extracellular parasites by phagocytic cells, assisted by prior immune recognition, is also a potent means of control. Intracellular protozoans are protected from many immune effectors by virtue of their location, but they can be damaged by the defense mechanisms of the host cell, especially those involving production of reactive oxygen or nitrogen metabolites.

Worm parasites present a much more complex surface to the host. Flatworms and tapeworms are essentially bounded by a plasma membrane that is potentially vulnerable to immune-mediated damage, especially in those worms or developmental stages that live within the tissues of the body. Nematode worms, by contrast, are covered by a collagenous cuticle. This cuticle is not invulnerable, but it certainly offers considerable protection, although smaller larval stages in tissues can be killed by effector mechanisms directed against this surface.

A majority of arthropod parasites live on the outside of their hosts and can be directly affected by immunity only via their feeding behavior. Feeding on blood or tissue fluids results in close contact with components of the host response, particularly antibodies, which may then interact with released secretions, such as saliva, or with cells of the arthropod’s intestine.

Immunity does not need to kill parasites to protect the host. Although complete elimination of a parasite may seem desirable, simply reducing its feeding, its movement, or its replication may be as effective. There are therefore many different ways in which the immune system may operate to minimize the deleterious effects of parasitism. However, producing an immune response is metabolically costly, and hosts may have to compromise in budgeting their resources between defense and their own growth or reproduction (Behnke et al. 1992).

Immune system

To understand the relationships of parasites to host immunity it is necessary to give a brief outline of the immune system. (Many excellent texts provide more detailed accounts; see, for example, Benjamin and...

The central feature of the adaptive immune response is that it is initiated by the recognition of specific non-self molecules—antigens. Recognition is achieved through interactions of antigens with receptors on, or released by, lymphocytes. There are two major classes of lymphocytes present in the body, T (thymus-derived) and B (bursa-derived), which play separate roles in the immune system. The former recognize antigens through their membrane T cell receptors (TCRs), release hormone-like molecules (cytokines) that coordinate the immune response, and act as effector cells. B cells recognize antigens through membrane immunoglobulin (Ig) molecules and secrete Ig in large quantities to provide the body with circulating recognition molecules (antibodies). A particular antigen receptor can recognize only one antigen. The ability of the adaptive immune system to recognize an almost infinite number of antigens reflects genetic mechanisms that allow the generation of a corresponding diversity of receptor molecules.

Almost all immune responses relevant to the control of parasites are initiated by the interaction of antigens with TCRs carried by a subset of T cells known as T helper (TH) cells. Before this interaction can occur, antigens must be processed by specialized cells, and fragments of the antigen (epitopes) must then be made available on the surface of the presenting cell in the form of a complex with molecules coded by genes of the major histocompatibility complex (MHC). In this form, the epitope can be recognized by the appropriate TCR. Correct presentation and recognition therefore requires conformational compatibility between epitope and MHC molecule and between epitope and TCR.

Once recognition is achieved, the T cells involved are activated: they enlarge, release cytokines, and proliferate to give clones of cells bearing identical TCRs. If antigen persists, as it does during infection, clonal expansion continues, giving rise to large populations of antigen-specific T cells. Some of these will be actively involved in the immune response, whereas others will become memory cells capable of providing an accelerated response on re-stimulation. Activated TH cells release cytokines that initiate, coordinate, and regulate the activities of other T cells, B cells, and of inflammatory cells, all of which may contribute to immunity (Table 2).

Antiparasite responses involve a wide range of immune and inflammatory mechanisms. Some T cells are cytotoxic and have the potential to kill cells infected with intracellular pathogens; B cells release antibodies that can combine with parasite antigens; inflammatory cells (which include several cell types) can actively phagocyte parasites or adhere to them and release a wide range of powerfully destructive mediators such as oxygen and nitrogen metabolites, enzymes, biologically active amines, and cytokines. The combination of antibody and antigen triggers the activation of complement, a complex series of serum proteins that operate as a cascade system, each component activating the next by enzymatic cleavage. Products of the cascade can bind to parasite surfaces or form lytic complexes that become inserted into cell membranes. Adherence of inflammatory cells to parasites is enhanced when antibodies or complement components coat the surface of target organisms because cells such as macrophages and eosinophils have membrane receptors for these molecules. Binding of these receptors to their ligands both increases the degree of contact with the target and activates the adhering cell. One consequence of this enhanced adherence may be more effective phagocytosis; another is release of damaging mediators onto the parasite's surface.

One group of inflammatory cells, the amine-containing cells (basophils and mast cells), have receptors for a particular class of antibody (IgE). When molecules of IgE bound to these receptors are cross-linked by their specific antigens, the cells discharge potent biologically active mediators (e.g., histamine, serotonin, or leukotrienes) that initiate hypersensitivity responses in local tissues. These responses result in changes in the tissues, such as increased permeability of vessel walls and cell junctions, altered muscle contractility, and increased fluid secretion. The mediators themselves can be directly harmful to parasites in the locality, but the changes they induce can also affect parasites indirectly by altering their environment; they may also damage the host. Hypersensitivity responses in the skin are a common consequence of ecto-parasite feeding activities. Again, the mediators released may affect the parasite directly, but they also induce itching sensations that cause the host to scratch and possibly dislodge the parasite.

Clearly, the immune response can unleash powerful effector mechanisms that can, if misdirected, cause considerable damage to the host as well as to the parasite. Consequently, there is always the danger of immunopathology accompanying antiparasite responses.

### Table 2. Immune and inflammatory mechanisms in antiparasite responses.

<table>
<thead>
<tr>
<th>Component</th>
<th>Functions</th>
<th>Mechanisms</th>
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<tr>
<td>Antibody</td>
<td>Recognizes antigen</td>
<td>Agglutination, opsonization, internalisation, lysis</td>
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<tr>
<td>T Cells</td>
<td>Binds to host cells</td>
<td>ADCC&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Macrophages</td>
<td>Cytotoxicity</td>
<td>ADCC&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Phagocytosis</td>
<td>ADCC&lt;sup&gt;c&lt;/sup&gt;, extracellular killing</td>
</tr>
<tr>
<td>Mast cells and basophils</td>
<td>Release of mediators</td>
<td>ADCC&lt;sup&gt;d&lt;/sup&gt;, inflammation</td>
</tr>
<tr>
<td>Complement</td>
<td>Binds to parasites</td>
<td>Hypersensitivity</td>
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<tr>
<td></td>
<td>Binds to host cells</td>
<td>ADCC</td>
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<sup>a</sup>Antibody-dependent cellular cytotoxicity.

The eukaryotic parasites are complex organisms that present their
hosts with several antigens. In species that have complex life cycles involving progression through a sequence of developmental stages, this array may change over time, with antigens often showing strict stage specificity. Certain protozoans, notably the trypanosomes, can vary their antigens more or less continuously (Barry and Turner 1992). Antigenic variation is an effective survival strategy, keeping the parasite one step ahead of the host’s response.

For all parasites the antigens that are of greatest importance in terms of host responses are those that are most accessible to the immune system, that is, those present at the parasite surface and those released into the host, the so-called excretory/secretory (ES) antigens (Maizels 1990). ES antigens include molecules released by surface turnover, those secreted during feeding or invasion, and those released as a consequence of metabolic activities. When parasites are described as targets for the immune response, it is these surface and ES antigens that are targeted, both by the molecules that are involved in identifying and labeling the parasite as nonself and by those that act as effectors.

During the course of an infection several antigens may be recognized and a spectrum of responses made against them. In many cases these responses may have no effect on the parasite—they are irrelevant to its survival. Only when the molecules recognized by the host play a critical role in the biology of the organism (e.g., in invasion, location finding, nutrition, metabolism, or reproduction), are vital for defense against immunity or inflammation, or effectively act as a focus for destructive effector activities will the host response adversely affect the parasite. These critical antigens are almost always proteins or glycoproteins, and many have enzymatic activity.

Analysis of immunity to parasites

Our present knowledge of antiparasite immunity comes from three basic approaches: in vitro studies, in vivo studies using defined models in experimental animals, and correlative and immunoepidemiological studies using human populations living in areas where parasites are endemic. These approaches have allowed us to define several features of immunity to parasites:

- Under laboratory conditions, experimental animals can develop strong protective immune responses that control or eliminate initial infections and provide high levels of immunity to reinfection. Protective immune responses are almost always initiated and coordinated by TH cells but can be mediated through virtually any component of the host’s immune and inflammatory repertoire.
- Some parasites have the ability to subvert or evade the immune response and, as a result, are able to establish long-term chronic infections.
- Antiparasite responses carry a cost to the host, not only in use of resources but often in terms of the damage that may result from immunopathological responses.
- In contrast to the situation seen in many experimental models, immunity to parasites in humans is often slow to develop and rarely gives complete protection. However, epidemiological studies often show that within populations living in areas where a particular parasite is prevalent, there are individuals who are negative on parasitological examination even though they show immunological evidence of having been exposed to infection.
- The ability to express effective immunity is determined by many genotypic and phenotypic factors. There are strong genetic influences that control both quantitative and qualitative aspects of the immune response. The genotypically determined immune response capacity is also heavily influenced by external factors, such as age, concurrent infection, hormonal status, nutrition, and stress.

Experimental studies

The most informative laboratory animals for experimental studies involving parasitic infections are the mouse and rat. Both are well defined immunologically and genetically and provide easily manipulable hosts. Few of the species responsible for the major parasitic infections of humans can be maintained in these hosts, but most can be modeled using taxonomically related species or species whose biology and host–parasite relationships are similar to those of the target parasite (Table 3).

With those parasites that induce a strong protective response, it is common to find that the initial infection is controlled or eliminated and that subsequent infections are either suppressed completely or that immune control is accelerated. The immune basis and T cell dependency of such responses is easily demonstrated by using selectively immunosuppressed animals or by using naturally T cell–deficient hosts such as nude mutant mice or rats (Figure 1a). Restoration of protective immunity in such hosts by transfer of T cells or antibodies can pinpoint the mechanisms that underlie this immunity (Figure 1b).

Over the last decade, attention has been focused on the roles of particular TH cell subsets in regulating antiparasite responses. In mice and humans, TH cells can be categorized into two major subsets, TH1 and TH2, on the basis of the cytokines they produce (Mosmann and Coffman 1989). Because different cytokines regulate particular components of the immune system, acti-
viation of a given subset may be necessary for full expression of a protective response. The TH1 subset regulates protective mechanisms involving phagocytic cells and controls formation of particular antibody classes (isotypes), whereas the TH2 subset controls other antibody isotypes and regulates inflammatory responses, particularly those involving amine-containing cells. It is not fully understood why a particular immune response involves one subset of TH cells rather than the other, but in the case of parasitic infections, there is abundant evidence that differential subset involvement can determine whether the host expresses protective responses or whether it remains susceptible because inappropriate or blocking responses are induced (Figure 2). In general terms, microparasites that live within cells are controlled by TH1-dominated responses, whereas macroparasites are controlled by TH2-dominated responses.

Protective responses

It is not possible to do more here than touch on the range of protective responses that have been identified in experimental work, but some idea of this range can be given in a brief summary of current views of immunity to the parasites responsible for the most important human infections. Although these parasites are associated with chronic infections, it is possible under experimental conditions to identify specific mechanisms that can provide the host with significant protection. (Fuller accounts of immunity to particular groups of parasites can be obtained from several recent texts, such as Kierszenbaum 1991, Sher and Coffman 1992, Wakelin 1993, and Warren 1993.)

Malaria. Malaria, transmitted by the Anopheles mosquito, is prevalent in many warmer countries of the world and is arguably one of the most important infectious diseases of humans. The parasites that cause this disease, species of the genus Plasmodium, are human specific, but there are several primate and rodent malarial that can be used for experimental study. Plasmodium is an intracellular protozoan that during its development occupies two distinct sites in the mammalian host. After infection, which is acquired as a mosquito takes a blood meal, the parasite invades the hepatocytes of the liver to complete its initial division stages. These give rise to the merozoite stages, which then invade the red blood cells, in which all subsequent development occurs. The cycle is completed when mosquitoes take up red cells containing the sexual stages of the parasite.

The existence of immunity against the intraerythrocytic stages has been known for many years, although there have been fundamental disagreements about the mechanisms involved. In part this is because there are multiple immune mechanisms operating—against the stages in the red cell; against the altered red cells themselves, which display parasite antigens on their surface; and against the invading merozoite stages. Antibodies play a significant role against the merozoites, combining with their surface antigens to interfere with red blood cell invasion; but they can also operate against infected cells, facilitating their phagocytosis in spleen and liver as well as reducing parasite nutrient uptake. Other T cell-mediated responses can provide protection against the red cell stages (see Figure 1b). It has been recognized only recently that the liver stages can also be affected by immunity. Infected hepatocytes express parasite antigens on their surface and can be the target of T cell-mediated cytotoxicity. The parasites present within the cells can also be damaged directly by mediator molecules that cross the host cell membrane and act intracellularly.

In addition to the protective responses that operate to reduce parasite numbers, immunity can help to prevent some of the pathological consequences associated with sequestration of parasites in capillaries, a major cause of the severe and often fatal illness (cerebral malaria) associated with infection by P. falciparum in children.

Leishmaniasis. Leishmaniasis is a disfiguring and debilitating infection that is widespread in warmer
countries, where it is transmitted by sandfly vectors. Several species are involved in this disease, each causing a distinctive pathology, and all of these can be studied in experimental animals. *Leishmania* parasites are intracellular. They selectively invade and reproduce by asexual division in macrophages and related cells. Most species cause cutaneous lesions, which develop at the site where the vector has bitten, but some, notably *Leishmania donovani*, invade visceral macrophages and can cause a fatal condition. Much of the biology of leishmaniasis as a disease is bound up with the biology of the macrophage. Although these cells should have the capacity to break down ingested particulate material, *Leishmania* parasites prevent their own digestion by a variety of strategies. However, if the macrophages can be correctly activated, that is, by T cell–derived cytokines, they can destroy parasites internally. Experiments in mice with cutaneous leishmaniasis have shown that activation of the correct TH subset is critical to the outcome of infection (Sher and Coffman 1992). Strains of mice that are susceptible to this infection make a TH2-dominated response, whereas resistant strains make a TH1-dominated response in which there is the release of macrophage-activating cytokines such as interferon-γ (see Figure 2). There is strong genetic control of the ability to make a particular TH response.

### African trypanosomiasis

Trypanosomes are extracellular protozoans transmitted by the bite of the tse-tse fly. After inoculation into the skin, as the insect takes a blood meal, the trypanosomes move into the blood and, later, into the cerebrospinal fluid and deep tissues. Because of these locations in the host they can be exposed directly to the action of antibodies and white cells as well as to complement. Under defined laboratory conditions in rodent hosts, using organisms closely related to those infecting humans, it is possible to show that immunity can eliminate infection through a combination of antibody recognition of surface antigens and phagocytic uptake in spleen and liver (Vickerman et al. 1993). However, trypanosomes have a seemingly unlimited capacity to change their surface antigens, so that although the majority of trypanosomes in a particular population may be removed by the host’s immune response, some survive because their changed antigens are not recognized. These then increase their numbers to form a recrudescence population, before this is again affected by immunity (Figure 3). In humans infected with *Trypanosoma rhodesiense* or *Trypanosoma gambiense*, this process can go on almost indefinitely, and the infection remains chronic.

### Schistosomiasis

Schistosomes, or blood flukes, are widely distributed in tropical and subtropical regions, where climatic conditions favor the development of the aquatic snail vectors and socioeconomic factors often result in contamination of water by human urine and feces. This combination allows the parasite to complete its life cycle, the infected snails releasing larval parasites that can reinvoke humans directly. After invasion (through the skin), the larvae migrate to the lungs and then to the liver before finally

![Figure 3. Time course of trypanosome infection in a mouse showing repeated waves of parasitaemia (log number of trypanosomes/ml of blood; data from Barry 1986).](https://academic.oup.com/bioscience/article-abstract/47/1/32/232450)

![Figure 4. Granuloma formation around an egg (thin arrow) of Schistosoma mansoni that has become trapped in the liver of an infected mouse. The accumulation of cells (indicated between the two wide arrows) represents an immunemediated inflammatory reaction to antigens released by the larva inside the egg. Such granulomas, which are the major cause of the pathology associated with schistosomiasis, illustrate one of the negative features of the capacity of hosts to respond immunologically to parasite infection, that is, the immune response itself is the cause of the pathology.](https://academic.oup.com/bioscience/article-abstract/47/1/32/232450)
maturing in blood vessels around the intestine (Schistosoma mansoni or Schistosoma japonicum) or bladder (Schistosoma haematobium). The long-lived adult female worms release eggs that must move through tissues to escape with feces or urine if the cycle is to continue. The eggs are highly immunogenic and stimulate powerful T-cell-mediated hypersensitivity responses. As a result, many become trapped in the intestine or bladder in extensive inflammatory foci. Other eggs are carried by the blood into organs such as the liver, in which the hypersensitivity reactions that form around them cause the characteristic pathology of the disease (Figure 4).

Work in animals infected with species of schistosomes that infect humans has shown clearly that immunity is stimulated primarily by exposure to antigens released by the adult worms. This immunity may have little or no effect on the continuing survival of the initial population of adult worms; it does, however, act against larvae from subsequent infections—a situation known as concomitant immunity. In immune hosts, invading larval stages can be killed in the skin or lungs (Capron et al. 1992). The mechanisms involved include direct antibody-mediated cellular cytotoxicity (ADCC) and indirect killing as a result of exposure to mediators released in the inflammatory foci that form around migrating larvae.

Filarisis. Filarial worms, of which there are two main groups (those living in lymphatic tissues and those living in the skin), are arthropod-transmitted nematodes that are distributed widely wherever the climate is warm enough to support vector populations. Their development in the human host is usually a lengthy process, often taking a year or more. The females release live embryos (microfilaria), which circulate in the blood or the skin, from which they can be taken up by the vector. Of the three major species that infect humans, two (Wuchereria bancrofti and Onchocerca volvulus) are human specific, and the third (Brugia malayi) infects humans and a limited range of additional hosts. Most data relating to immunity have therefore come from in vitro studies or from experimental models using related species. Filarial worms have relatively delicate cuticles and can make use of these for direct nutrient uptake. Like schistosomes, they are vulnerable to ADCC, which seems to be one of the most important means by which they can be killed in immune hosts. This vulnerability applies mainly to the larval stages, the adults being capable of prolonged survival.

Gastrointestinal nematodes. Humans are frequently infected by several genera of nematodes, all of which are transmitted as a consequence of fecal contamination of the environment. Some, the hookworms and Strongyloides, have larvae that can invade directly through the skin; others, the large roundworm Ascaris and the whipworm Trichuris, establish infection when eggs are swallowed. As with the filaria, the species that infect humans are highly host specific and develop poorly if at all in laboratory animals. Experimental studies of immunity to such parasites have therefore used related species or rodent parasites with a similar biology. Immunity against these species often involves the development of acute inflammatory changes in the intestine that effectively “flush out” the worms and so eliminate the infection (Wakelin et al. 1993). Antibodies can also interact directly with antigens to inhibit feeding or location finding. When the life cycle involves a tissue migration, such as from skin to lungs to intestine, the migrating larvae may be trapped in immune-mediated inflammatory foci. Not all experimental models show clear-cut immunity, and host genetic factors clearly have a strong influence on the response to infection. Lack of effective immunity appears to be characteristic of gastrointestinal nematode infections in humans. These infections are acquired early in life, worms may survive for prolonged periods, and reinfection occurs easily. In regions where these parasites are endemic, the prevalence of infections peaks in childhood and then remains high throughout adult life (Figure 5).

It is striking that five of the major parasitic infections listed above are transmitted by vectors. Does vector transmission favor the evolution of parasite virulence? Or is it simply more difficult to prevent exposure to vectors than it is to prevent contact with directly transmitted parasites, such as the gastrointestinal nematodes? Certainly the latter are a major problem only where extrinsic ecological factors such as overcrowding, malnutrition, and poor sanitation increase the chances of exposure to the infective stages.

Conflict or compromise

From the brief account of immunity in host–parasite relationships given here, it is possible to conclude that although hosts can develop levels of immunity that are effective in regulating, or even completely eliminating, parasitic infections, this does not occur in all cases. Effective immunity is not seen against all infections, hosts that are able to express protective responses do not always do so, and in particular, development of immunity seems slow and incomplete in many human infections.

Of course, the infections that are most often recorded and that cause the most severe disease are precisely those in which immunity is not effective. The view that immunity is often ineffective may therefore result from a bias in observation. In addition, expression of immunity is heavily influenced by physiological and environmental factors (Wakelin...
quences of responses relevant to in turn, may be "irrelevant" consequences of the ability to recognize and respond to any not-self molecule, analogous to the occurrence of allergic responses to environmental antigens such as pollen and animal dander. Although these, in turn, may be "irrelevant" consequences of responses relevant to immune protection against helminths (Moqbel 1992). Irrelevancy is also a result of the ability of parasites to evade immune responses.

- All responses to infection, whether relevant, in the sense of providing protection, or irrelevant, carry a cost to the host because of the demand they place on the use of metabolic resources. In addition, other responses, again both relevant and irrelevant, can be harmful because they are associated with immune-pathological damage.

The question of whether or not hosts and parasites always remain in conflict or whether, when relationships develop over long periods of evolutionary time, they move toward a compromise, is one that has exercised parasitologists for many years. It is now accepted that there is always conflict, but that there may be a compromise over the extent of that conflict (Dawkins 1990, Read 1994). Both conflict and compromise inevitably involve the immune system, because it is potentially the most important host influence on the outcome of infections with natural parasites, that is, those that are well adapted to survive in the structural, biochemical, and physiological environment of a given host species. There must therefore be complex checks and balances on this aspect of host-parasite relationships, and these must operate within several competing demands.

Hosts must strike a balance between beneficial and potentially harmful consequences of immune responses to infection and must do so without unduly diverting resources away from growth and reproduction. Resource diversion must not, however, be minimized at the cost of uncontrolled parasite development. Moreover, hosts must optimize their responses to the total spectrum of parasites and other infectious organisms that they encounter in their environments. Directional selection that maximizes resistance to infection by a parasite of particular virulence may incur loss of fitness in terms of the response to other parasites.

Parasites must strike a balance between optimizing their own growth and reproduction and limiting the harmful consequences of infection to the host. Unless transmission requires host debility or host mortality, parasite reproduction will be promoted by host survival because existing infections have a greater fitness value than potential future infections. Ironically, a degree of host immunity may be a good thing for the parasite, not only in preventing overinfection and possible host death, but also because some facets of the host response may directly benefit the parasites. For example, in schistosomiasis the host's immune response may increase female worm fecundity and facilitate movement of the eggs through tissues (Hagan et al. 1993).

The balances struck can be expressed as a series of "trade-offs." For the host the trade-off is between resistance, pathology, and loss of resources, whether through the immune response or from the activities of the parasite; for the parasite the trade-off is between reproduction, immunogenicity, and pathogenicity. These can be reduced to the question of conflict or compromise between host fitness and parasite fitness. If "fitness" is interpreted only in terms of levels of parasite reproductive success and minimal loss of host resource, then fitness gain for one inevitably means fitness loss for the other, and balanced host-parasite relationships could never evolve. However, if fitness is taken to include the costs of damage to host tissues, however caused, and the consequences this damage may have for both host and parasite, then the concept of compromise becomes more acceptable.

Therefore, in the complex associations formed by hosts and their parasites, immunity may often be partial and limited in effect. The dangers of immunopathology as a correlate of protection may have led to selection of genes that down-regulate rather than up-regulate responsiveness (Mitchison and Oliveira 1986), thus contributing to the genetic heterogeneity seen in natural populations. The need to maintain protective capacity against a broad spectrum of pathogens will promote immunogenetic diversity, of which MHC polymorphism may be an extreme example (Klein 1986), and an associated diversity of immune re-
sponsiveness. Correlations between particular MHC alleles and resistance to specific infections provide evidence of the strong selection pressures parasites can exert, as in the case of *falciparum* malaria in Africa (Hill 1992). Parasites may be selected for intermediate virulence (Read 1994), but because virulence is often determined as much by the level of host response as by the biological characteristics of the parasite, intermediate virulence may be the outcome of a complex and dynamic interplay between the two members of the host–parasite relationship (Wakelin 1993) that may well involve sophisticated mechanisms of parasite evasion or modulation of the host's response.

Together, these considerations suggest that immunity to the eukaryote parasites will often be qualitatively different from that seen in some prokaryote and viral infections, in which strong, lifelong immunity is a consequence of infection. Acceptance of this view may well assist the conceptual development of prophylactic approaches designed to tilt the balance of host–parasite relationships more toward the host and thereby overcome the evolutionary accumulation of host and parasite strategies that promote a stable compromise rather than conflict. It also suggests, however, that disruption of the stable equilibria that have been established between many parasites and their hosts may have unanticipated results, one of which may be greater, rather than reduced, costs to the host concerned.

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