Concomitant infections, parasites and immune responses

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SUMMARY

Concomitant infections are common in nature and often involve parasites. A number of examples of the interactions between protozoa and viruses, protozoa and bacteria, protozoa and other protozoa, protozoa and helminths, helminths and viruses, helminths and bacteria, and helminths and other helminths are described. In mixed infections the burden of one or both the infectious agents may be increased, one or both may be suppressed or one may be increased and the other suppressed. It is now possible to explain many of these interactions in terms of the effects parasites have on the immune system, particularly parasite-induced immunodepression, and the effects of cytokines controlling polarization to the Th_1 or Th_2 arms of the immune response. In addition, parasites may be affected, directly or indirectly, by cytokines and other immune effector molecules and parasites may themselves produce factors that affect the cells of the immune system. Parasites are, therefore, affected when they themselves, or other organisms, interact with the immune response and, in particular, the cytokine network. The importance of such interactions is discussed in relation to clinical disease and the development and use of vaccines.

Key words: Concomitant infections, cytokines, protozoa, helminths, bacteria, viruses.

INTRODUCTION

The term concomitant infections, alternatively called mixed infections, traditionally refers to a situation in which two or more infectious agents coexist in the same host. In the light of modern concepts of biology this definition is insufficiently precise and the definition that will be used here is one in which the two (or more) concomitant infectious agents are specifically designated as being genetically different. This definition permits the inclusion of agents belonging to different species, the commonly accepted view of concomitant infections, and members of the same species that are genetically different, for example those belonging to a different strain or population. In nature, concomitant infections are the rule and this has been recognized since the earliest recorded times; for example, multiple infections of helminth eggs have been detected in human coprolites and other human remains from prehistoric sites (see Brothwell & Sandison, 1967; Cockburn, Cockburn & Reyman, 1998). What is less well known is that there are numerous interactions, both gross and subtle, between different kinds of organisms. This fact has been long recognized by experimental scientists, including parasitologists, who go to great lengths to use animals that are germ free, specific pathogen free (SPF) or harbour a known fauna or flora (gnotobiotic). Despite the widespread acceptance that different organisms commonly occurring together in the same hosts can, and do, influence one another directly or indirectly, field workers and other parasitologists seldom consider more than the single organism that directly concerns them. The standard parasitological text books are silent on this subject and there is virtually nothing about concomitant infections in the more specialized texts on epidemiology (Anderson & May, 1991; Grenfell & Dobson, 1995; Isham & Medley, 1996), parasitism and host behaviour (Barnard & Behnke, 1990; Beckage, 1997), helminth infections and nutrition (Stephenson, 1987), evolution (Brooks & McLennan, 1993), immunology (Wakelin, 1996) or even host-parasite relationships (Toft, Aeschlimann & Bolis, 1991). There is some tangential reference to hormonal changes induced by parasites and possible effects on other parasites by Hillgarth & Wingfield (1995) but this is not pursued in any depth. There is, therefore, a major gulf between the well defined world of text book parasitology, with everything laid out in neat self-contained sections, and the nicely controlled conditions that exist in a laboratory, where there is usually a one to one parasite-host relationship, and the real world in the field where there may be many infections interacting with one another. There are many examples of concomitant infections in humans and animals (see for example Christensen *et al*. 1987; Ashford, 1991; Petney & Andrews, 1998; Viera *et al*. 1998). The infectious agents concerned may be those of the same species, related species or distantly related species. Among the best known examples of the interactions between parasites of the same species are the schistosomes where the presence of an ongoing infection of adult worms inhibits the establishment of a subsequent infection by larval forms, a phenomenon known as concomitant im-

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Parasitology (2001), **122**, S23–S38. © 2001 Cambridge University Press
https://doi.org/10.1017/S003118200001698X Published online by Cambridge University Press
DOI: 10.1017/S003118200001698X Printed in the United Kingdom

munity (Smithers, Terry & Hockley, 1969). This phenomenon is also seen in other helminth infections, for example, cestodes (see Heath, 1995). In malaria, an ongoing infection is thought by many workers not only to induce, but also to be necessary for immunity to a superimposed infection of parasites with the same or different genotype, a phenomenon called premunition (Sergent, 1937; Smith *et al*. 1999). Well known examples of interactions between more distantly related organisms are those that exist between the Epstein Barr virus and malaria parasites (Burkitt, 1969) and between the Human Immunodeficiency Virus (HIV) and several parasites of which the best known examples are *Cryptosporidium* and *Leishmania* spp. (see Ambroise-Thomas, this supplement).

One of the reasons why so little attention has been paid to concomitant infections is that the interactions involved are complex and difficult to understand. Briefly, such interactions can either be ecological, in which case the rules of ecology, particularly competition for space or resources, apply or immunological where the rules immunology apply. Anderson (1994) has stated, in another context, that 'the interaction between the variables that determine the typical course of infection in an individual patient and those that determine the typical course of infection in communities of people is often complex and very non-linear in form'. Everything that is said and implied here is made even more complex in the case of mixed infections. A number of ecologists, particularly those working with helminths, have begun to appreciate and take cognizance of mixed infections and their implications and a considerable amount of progress has been made in this area (Dobson, 1985, 1990; Poulin, 1998) and some of these aspects will be discussed further in this supplement by Dobson, Poulin, and Kennedy. However, the more subtle interactions that occur in hosts co-infected with more than one infectious agent, particularly those involving immunological responses, have been less well investigated and this is the area that will be considered in this article.

THE NATURE OF THE INFECTED HOST

It is a truism that a host harbouring any infectious agent is not the same as one that is not infected. Furthermore, hosts harbouring large numbers of parasites are not the same as those harbouring small numbers, those harbouring viruses are not the same as those harbouring bacteria and so on. It is not appropriate here to discuss in detail the nature of all the host's immune responses to infectious agents but it is important to appreciate the significance of T lymphocyte subsets and the cytokine network.

Essentially, from the moment an immunologically intact host is infected with any infectious agent, the host begins to mount an appropriate protective immune response. The key cells are the Th (T helper) lymphocytes. At first these cells are uncommitted but they gradually differentiate into Th_1 and Th_2 cells, each characterized by the cytokines they produce, until eventually they become fully differentiated and, when this happens, they are mutually exclusive. The Th_1 cells produce T_1 cytokines, particularly IL-2 that drives the immune response towards the production of cytotoxic T (T_c) cells and IFN-γ that drives the immune response towards the activation of macrophages. Th_2 cells, on the other hand, produce IL-4, IL-5, IL-10 and IL-13 that lead to the activation of B cells and the subsequent production of antibody, and to the proliferation and differentiation of eosinophils. In shorthand, the Th_1 responses represent the cell-mediated arm of the immune response and the Th_2 responses represent the humoral arm. For further information, there is an excellent account of this subject in Klein & Hořejší (1997). T_c cells are ideally suited for the destruction of virus-infected cells, IFN-γ-activated macrophages are involved in the killing of intracellular pathogens and the antibody produced by B cells is most effective against extracellular pathogens such as helminths. The role of Th_1 and Th_2 cells in a number of infectious diseases is well discussed in the various contributions in Romagnani (1996) and, with particular relevance to helminths, by Pritchard, Hewitt & Moqbel (1997). Parasites are no different from other pathogens in that they inevitably induce some kind of immune response except that T_c cells are less involved in parasitic infections than in viral infections (see Cox & Wakelin, 1998 and Wakelin, 1996 for general accounts of the immune responses to parasites). In general, it is widely accepted that protective Th_1 responses predominate in infections caused by protozoa whereas Th_2 responses are more important in immunity to helminth infections. In addition, the mutual exclusivity mentioned above frequently results in extreme polarization in which one arm of the immune response is protective and the other counter protective. However, these are generalisations and the details of each individual immune response can differ from time to time or from stage to stage of an infection (Allen & Maizels, 1997).

The polarization of T cells towards cell-mediated or antibody-mediated responses does not depend entirely on the infectious agent involved but can be modulated by pre-existing factors including cytokines. For example, the presence of IL-12 drives the immune response towards the T_1 pole whereas the presence of IL-4 drives it towards the T_2 pole (Ma *et al*. 1997). Initial or subsequent polarization involves the interaction of a number of regulatory cytokines some of which act as growth and differentiation factors. What is important here is that these cytokines, and also effector molecules, act non-

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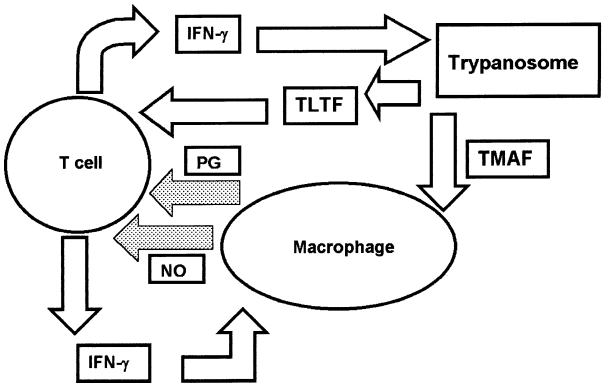


Fig. 1. Diagrammatic representation showing some of the interactions that exist between African trypanosomes and cytokine network. Trypanosomes produce a number of factors including trypanosome macrophage activating factor (TMAF) and trypanosome-derived lymphocyte triggering factor (TLTF) that stimulate macrophages and lymphocytes respectively. IFN-γ, a product of stimulated lymphocytes, can act as a trypanosome growth factor but prostaglandins (PG) and nitric oxide (NO) produced by macrophages inhibit lymphocyte activity and hence the production of IFN-γ. Trypanosomes are therefore enmeshed in a network of cytokines and effector molecules that both stimulate and inhibit their growth and development. In this diagram, positive signals are indicated by open arrows and inhibitory ones by stippled arrows.

specifically. It is therefore possible for any infectious agent to be caught up in the cytokine network. It is now becoming clear that this is what happens in the case of any agent acquired previously, concurrently or subsequently in the majority of concomitant infections at least under controlled laboratory conditions.

EFFECTS OF CYTOKINES AND PARASITE-DERIVED MOLECULES ON PARASITES

Although directed at other cells involved in the immune response certain molecules such as transforming growth factor-beta (TGF-β) and interferon-gamma (IFN-γ) can act directly or indirectly on parasites. For example, IFN-γ acts as a growth factor for *Trypanosoma brucei* (Bakhiet *et al*. 1996*b*) and TGF-β is required for the invasion of mammalian cells by *Trypanosoma cruzi* (Ming, Ewen & Pereira, 1995). Other examples are given by Barcinski & Costa-Moreira (1994) and Omer *et al*. (2000).

In addition to the molecules of the immune system, all parasites produce secreted or excreted products some of which can themselves affect cells of the immune system (see Kaye, 1999). The best studied molecules are those produced by African trypanosomes, particularly *T. brucei brucei*; trypanosome-derived lymphocyte triggering factor (TLTF) and trypanosome macrophage activating factor (TMAF). TLTF induces lymphocytes to produce IFN-γ which both activates macrophages and promotes trypanosome growth and TMAF also stimulates macrophage activity (see Sternberg, 1998; Hamadien, Bakhiet & Harris, 2000). The production of TLTF is not restricted to *T. b. brucei* but has also been found in *T. b. gambiense*, *T. b. rhodesiense* and *T. evansi* (Bakhiet *et al*. 1996*a*). All the African trypanosomes are, therefore, potentially caught up in a series of interactions in which trypanosome-derived factors activate both T lymphocytes and macrophages. The net effect is that lymphocyte-produced IFN-γ enhances trypanosome growth while other trypanosome-derived molecules induce macrophages to produce molecules that inhibit lymphocyte activation (Fig. 1). Among other parasite-derived molecules there are some of protozoan origin that induce the synthesis of IL-12 by macrophages (Gazzinelli *et al*. 1997) and an IFN-γ-like molecule produced by the nematode *Trichuris muris* (Grencis & Entwistle, 1997). The precise role of these molecules is unclear but what is important here is that these parasite-derived factors can interact with the other molecules of the immune system and may be involved in enhancing or depressing the immune response to other organisms and cannot be ignored in any consideration of concomitant infections.

INTERACTIONS BETWEEN INFECTIOUS AGENTS

There have been numerous reports of interactions between parasites and between parasites and other infectious agents (see Christensen *et al*. 1987). This is not intended to be a comprehensive review of the subject and many of the examples cited by Christensen *et al*. will not be reiterated here. However, this is an attempt to collate and categorize some examples of the various interactions that have been recorded and to try to explain them in terms of what is happening in an infected host. In this respect, the Christensen *et al*. paper represents the end of an era. 1986 in an important watershed in our understanding of the interactions that occur between infectious agents because it was in that year that the Th_1/Th_2 dichotomy was suggested, first in mice (Mosmann & Coffman, 1989) then in humans (Romagnani, 1991) and subsequently in all species of mammals studied. This concept has dominated thinking about immune responses ever since (see Romagnani, 1996). Prior to this discovery, the various interactions between parasites and other infectious agents had been difficult to explain and mainly centred on attempts to implicate ill-defined mechanisms of immunodepression, often referred to as immunosuppression, brought about by molecules produced by parasites which facilitate their own

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survival. The best studied examples of immunodepression are infections with African trypanosomes (Greenwood, 1974; Hudson & Terry, 1979), malaria parasites (Greenwood, 1974; Del Giudice, Grau & Lambert, 1988) and nematode worms (Behnke, 1987). According to the theory of immunodepression, any concomitant infection that is acquired while the host is experiencing a phase of parasite-induced immunodepression should be able to establish itself more readily and possibly become more virulent or pathogenic. There is, for example, a correlation between the occurrence of Burkitt's lymphoma, caused by infection with the relatively harmless Epstein-Barr virus, and the presence of malaria (Burkitt, 1969). On the other hand, HIV does not seem to have much effect on malaria infections or vice versa (Butcher, 1992).

Not all factors that affect the outcome of concomitant infections are immunological. Other factors responsible for a particular outcome include changes in the microenvironment. The induction of reticulocytosis in experimental rodent malaria infections, for example, should, and does, disadvantage species such as *Plasmodium vinckei* and *P. chabaudi* that require mature erythrocytes resulting in lower parasitaemias. However, this explanation does not account for the fact that infections with *P. berghei*, which prefers reticulocytes, are similarly affected (see Cox, 1975*a*, 1978 and below).

These situations described above illustrate some of the problems inherent in seeking explanations for the interactions between the different agents in concomitant infections because there seem to be as many exceptions to the 'rules' as there are examples. It is, therefore, necessary to consider the nature of the possible outcomes. It is best to start with the simplest examples where a host that is harbouring, or has harboured, one organism A, is infected with a different organism, B. There are three outcomes with respect to B: the ensuing infection may be enhanced, suppressed or not affected in any way. However, there is also the reciprocal situation with respect to the infection caused by A, which may also be enhanced, depressed or neutral. Thus in this simple situation, there are a number of different possible outcomes. However, this example only takes into account a subsequent infection acquired at a specific point in time during the course of the ongoing infection. The outcome of infection B may well be different if the host harbouring A is infected with B at the beginning of the infection, at its peak or during a chronic phase. For example, the outcome of dual infections with of *Babesia microti* and *T. b. brucei* in mice varies according to when the piroplasm is administered in relation to the trypanosome (Millott & Cox, 1985). In this situation, the piroplasm infection is always inhibited when the trypanosome is given beforehand but the inhibition increases with the interval between the two infections until at −21 days it is absolute (Millott & Cox, 1985). In passing, it must be pointed out that these results are counterintuitive as it might be expected that superimposing a piroplasm infection on an ongoing trypanosome infection, during a period of what should be trypanosome-induced immunodepression, should result in higher rather than lower piroplasm infections.

There are, therefore, many different outcomes resulting from concurrent infections and, from the examples cited above, it is clear that these may be unpredictable. In searching for the truth in any complex situation it is advisable to adopt the advice of William of Ockham (or Occam) as perpetuated in the maxim, Ockham's razor, which states that in seeking an explanation, various assumptions need not be multiplied needlessly; in other words, if there is a simple explanation there is no need to seek a more complicated one. However, this implies that all the knowledge necessary to produce a feasible explanation is available but, unfortunately, it is not. Therefore, the sensible approach is to seek simple explanations wherever possible, to look for exceptions and to modify the original explanation in terms of the exceptions and new knowledge.

In the sections below, selected examples of interactions between protozoa and viruses, protozoa and bacteria, protozoa and protozoa, protozoa and helminths, helminths and viruses, helminths and bacteria and between helminths and helminths will be discussed. It must be pointed out, however, that virtually all the information available comes from carefully controlled laboratory studies, usually with mice, that are sometimes very contrived. However, it is likely that these interactions will eventually be shown to apply to natural human and animal diseases and examples of such situations will also be discussed.

Protozoa and viruses

Viral infections are usually extremely difficult to detect and, therefore, the amount of information we have on interactions between protozoa and viruses is limited. Much of what we know comes from experiments involving *Plasmodium* spp. and other intraerythrocytic protozoa in mice and rats but there is no coherent pattern that emerges (see the reviews by Cox, 1975*a*, 1978). The intensity of *P. berghei* infections is suppressed in mice infected with West Nile virus (Yoeli, Becker & Bernkopf, 1955) or Newcastle Disease virus (Jahiel *et al.* 1968*b*) suggesting that virus-induced IFN-α might be protective against malaria parasites (Jahiel *et al.* 1968*a*). However, there is no direct evidence that this is the case but, in this context, it is interesting to note that, in humans, infections with *P. falciparum* are lower in patients co-infected with measles or influenza viruses (Rooth & Bjorkman, 1992). Thus

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viral infections may ameliorate malarial infections but, on the other hand, the non-lethal strains of *P. yoelii* and *P. chabaudi* become lethal in mice infected with the Rowson Parr virus (Cox, Wedderburn & Salaman, 1974) and infections with the Rowson Parr or urethane leukaemia virus also enhance *Babesia microti* infections in mice (Cox & Wedderburn, 1972). These results might be due to immunodepression caused by the viruses which, as a group, tend to be immunosuppressive (Salaman, 1969) but these conflict with those cited above in which infections in virally infected animals or individuals were actually suppressed.

Turning now to other combinations of protozoa and viruses (other than HIV), there are a number of observations that can be attributed to the immunodepressive effects of the virus infections and explained in terms of the consequent down regulation of cytokines required for immunity to the protozoan. *Cryptosporidium parvum* infections are enhanced in mice experimentally infected with the murine leukaemia retrovirus LP-BM5 (Darban *et al*. 1991) and this enhancement correlates with decreased IFN-γ and IL-2 production in the virus-infected mice (Alak *et al*. 1993). In naturally infected chickens, infections with *C. baileyi* are enhanced in animals co-infected with the chicken anaemia virus, CAV (Hornok *et al*. 1998). *Trypanosoma cruzi* infections are also more severe in mice co-infected with viruses; for example, infections with the murine leukaemia virus, MuLV, results in the enhancement of *T. cruzi* infections in mice (Silva *et al*. 1993) and this is also the case in mice co-infected with the mouse hepatitis virus type 3 (Verinaud *et al*. 1998). In the MuLV-infected mice, T cells do not respond to trypanosome antigens, suggesting immunodepression on the part of the virus (Silva *et al*. 1993), and this is also the proposed explanation of the observations seen in the mouse hepatitis-infected animals (Verinaud *et al*. 1998).

There are very few studies on the effects of protozoan parasites on infections caused by viruses but those that have been described all indicate that viral infections are enhanced in animals harbouring parasitic protozoa. For example, infections with the murine oncogenic viruses, Murine Sarcoma virus or Moloney virus, are more severe in mice co-infected with *P. yoelii* (Salaman, Wedderburn & Bruce-Chwatt, 1969; Wedderburn, 1970, 1974) and mice co-infected with *T. cruzi* and MuLV develop a murine form of AIDS which does not occur in animals infected with either of these agents alone (Silva *et al*. 1993). The best documented evidence that protozoan infections can enhance viral infections in humans is that relating to the Epstein Barr virus which normally causes mild or inapparent infections but can contribute to the development of Burkitt's lymphoma in individuals exposed to malaria (see De The, 1985). Immunodepression is characteristic of malaria infections in mice and humans (McGregor & Barr, 1962, see also Houba, 1988) and the enhancement of viral infections in co-infected animals can be explained in these terms. What is not so easy to explain, however, is the finding that the feline immunodeficiency virus (FIV) causes changes to the activity of macrophages but this does not affect co-infection with *Toxoplasma gondii* (Lin & Bowman, 1992). Other interactions between *T. gondii* and immunosuppressive viruses are reviewed by Lacroix *et al*. (1996).

Protozoa and bacteria

Most of the information we have about interactions between protozoa and bacteria comes from studies on infections with intraerythrocytic protozoa. Early studies were mainly concerned with the spirochete, *Borrelia duttoni* which has little effect on infections with *P. berghei* (Colas-Belcour & Vervent, 1954) and *B. hispanica* which causes a slight enhancement of *P. berghei* infections in rats (Sergent & Poncet, 1957). As mentioned above, rickettsiae have a dramatic effect on rodent malaria infections and there is a considerable literature on the effects of *Eperythrozoon coccoides* and *Haemobartonella muris*, which both cause anaemia, and the consequent reticulocytosis that should favour the development of parasites like *P. berghei* that preferentially invade reticulocytes. In fact, the reverse is the case and *P. berghei* infections are suppressed in mice co-infected with *E. coccoides* (Peters, 1965). Infections with *P. chabaudi* and *P. vinckei*, that preferentially invade mature erythrocytes, are milder in mice harbouring *E. coccoides* which is easier to explain (Cox, 1966). *Haemobartonella muris* has received less attention but rats co-infected with this organism and *P. berghei* harbour higher infections of the malaria parasite than do uncontaminated controls, which is what one might expect in hosts with an increased proportion of the preferred host cells (Hsu & Geiman, 1952; Smalley, 1975). The interactions between rickettsial infections and rodent malaria parasites are important because of serious problems inherent in interpreting results obtained in laboratory mice infected with *E. coccoides* (see Cox, 1978).

A well explored but essentially experimental aspect of the possible interactions between bacteria and protozoa arises from studies in the 1970s that demonstrated that BGC, *Corynebacterium parvum* and other bacteria and bacterial products protect mice against malaria parasites and piroplasms (see Cox, 1975*a*). In fact, the number of bacteria and bacterial products that protect mice non-specifically against blood parasites is very large (Cox, 1981) and it is very likely that, in the field, bacterial infections play an important role in modulating infections with intraerythrocytic protozoa. The most likely explanation of the protection is the production of

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mediators, probably tumor necrosis factor (TNF) and nitric oxide (NO) by macrophages. This topic is discussed more fully elsewhere in this volume by Clark.

There are very few reports of interactions between bacteria and protozoa in humans but there are a number of reports of enhanced bacterial infections, particularly in children, suffering from severe malaria. Increased prevalence and parasite densities of *P. falciparum* appear to correlate with pertussis in children in contrast to the suppression of parasitaemias seen in those suffering from viral infections mentioned above (Rooth & Bjorkman, 1992). It is also well known that bacterial pneumonia is sometimes associated with malaria (Bygbjerg & Lanng, 1982; Mabey, Brown & Greenwood, 1987; Walsh *et al*. 2000) and there has been a report of enhanced tuberculosis in a patient with malaria (Hovette *et al*. 1999) but the reasons for this are not known. Given the importance of malaria it is surprising that the interactions between this disease and bacterial infections has not received much attention even in epidemiological studies (see Greenwood, 1997).

Protozoa and other protozoa

There is a massive literature concerned with the various interactions reported between protozoa and it is only possible here to draw on a few selected examples. These interactions can be divided into two main groups, interactions between parasites belonging to the same species and interactions between different species ranging from closely related to distantly related forms. The phenomenon of premunition in malaria infections has already been touched on and will not be discussed further here as it is more fully explored by Smith *et al*. (1999). Mixed infections with different species of malaria parasites are common (see Tanner & Baker, 1999) and all four species that infect humans have been found in a single individual (Purnomo *et al*. 1999). Much of what we know about the situation in humans comes from cross-sectional surveys and these indicate the involvement of both immunological and density-dependent factors in the regulation of parasitaemias (Bruce *et al*. 2000). Such studies are at the descriptive stage and it is not possible to speculate on the mechanisms involved without entering into the massive literature concerned with malaria immunology. The concept of specific immunity underlies much of our understanding of the epidemiology and control of malaria infections and this assumption appeared to suffer a major setback when it was demonstrated that there was a certain degree of heterologous immunity between different species of malaria parasites in rodents (reviewed by Cox, 1978). This was later extended to the discovery of protective immunity between different genera of intraerythrocytic protozoa, *Plasmodium* and *Babesia* (Cox, H. W. & Milar, 1968; Cox, F. E. G., 1968). Attempts were initially made to explain these findings in conventional immunological terms, such as the presence of cross-reacting antigens, but it soon became clear that what happens is that the superimposed infection becomes involved in non-specific responses involving a number of mediators of inflammation, a topic that is discussed in more detail elsewhere in this supplement by Clark. Heterologous immunity is not restricted to the parasites of rodents and there is also convincing evidence that there is cross-immunity between the malaria parasites of non-human primates (Voller, Garnham & Turner, 1966) and some evidence that infections with *P. vivax* might reduce the severity of *P. falciparum* infections in humans (Maitland, Williams & Newbold, 1997).

In addition to the blood parasites, there are other examples of unexpected interactions between related protozoa belonging to different species. For example in mice infected with the coccidians *Eimeria falciformis* and *E. pragensis*, in that order, the cyst output of the latter is enhanced but in the reverse order there is no such effect (Shehu & Nowell, 1998).

There are also examples of dramatic interactions between distantly related species of protozoa, the most studied being those involving trypanosomes and other blood parasites. Some of the earliest investigations were concerned with co-infections with *T. lewisi* and *P. berghei* in rats in which the parasitaemias due to both infections, particularly the trypanosomes, were enhanced (Hughes & Tatum, 1956; Shmeul, Golensa & Spira, 1975). Experiments in mice infected with *T. musculi* provided similar results in mice co-infected with *P. berghei* (Büngener, 1975), *P. yoelii* (Cox, 1975*b*) or *Babesia microti* (Cox, 1977). *Trypanosoma cruzi* infections are also enhanced in mice infected with *P. berghei* (Krettli, 1977). Although difficult to explain at the time, these results can now be explained in terms of immunologically significant molecules, such as IFN-γ, acting as trypanosome growth factors as has been discussed above. However, this cannot be the whole story as *T. b. brucei* infections are not enhanced in mice co-infected with *B. microti* whereas the babesial infections are (Millott & Cox, 1985). In rats, infection with *T. lewisi* enhances *Toxoplasma gondii* infections (Guerrero, Chinchilla & Abrahams, 1997), although the mechanism is not at all clear and could be due to immunodepression or to the effects of trypanosome-derived molecules.

There are a number of reports of reciprocal enhancements of protozoan infections in mice, for example, *P. yoelii* and *Leishmania mexicana* (Coleman, Edman & Semprevivo, 1988) and *P. yoelii* and *L. amazonensis* (Coleman, Edman & Semprevivo, 1989). *P. berghei* infections are enhanced in rats co-infected with *Toxoplasma gondii*

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(Rifaat *et al*. 1984) but there is no information about any effects on the toxoplasma infection. There are also examples of other one-sided interactions. The cyst output in mice infected with the intestinal flagellates *Spironucleus muris* and *Giardia muris* is reduced in animals also infected with *B. microti*, *P. berghei* or *P. yoelii* but the blood infections are not affected (Brett & Cox, 1982). These authors attribute the reduction in cyst output to physiological changes in the gut rather than to any immunological factors and this also seems to apply in the case of mice co-infected with *G. muris* and *Trichinella spiralis* (Roberts-Thomson *et al*. 1976 and see below). Interactions between protozoan infections in humans are not at all easy to assess but, with the increased use of more sensitive and specific diagnostic methods, it is likely that in the future there will be a number of such reports.

Protozoa and helminths

Intuitively, it would seem unlikely that there could be any interactions between single celled protozoan and multicellular helminths, particularly as most of them occupy different sites in the body and elicit very different kinds of immune responses. In fact, in virtually all situations where protozoa and helminths occur together that have been investigated experimentally, there is some degree of interaction, sometimes very dramatic (Christensen *et al*. 1987; Chieffi, 1992; Petney & Andrews, 1998; see Behnke *et al*. this supplement) Some of these interactions are now beginning to be subjected to the kind of analysis involving Th_1 and Th_2 cells referred to at the beginning of this review and this topic is discussed elsewhere in this supplement with relevance to nematode worms in rodents (see paper by Behnke *et al*.). The most studied interactions are those between trypanosomes and the intestinal nematode worm *Trichinella spiralis*. Mice infected with *T. spiralis* experience considerably increased *Trypanosoma musculi* infections when the nematode infection is initiated 5–10 days before the trypanosome and this enhancement is still obvious after 45 days (Bell, Adams & Ogden, 1984*a*). Similar enhancement of the trypanosome infection occurs in strains of mice differing in resistance to *T. spiralis* suggesting that this phenomenon is a general one that overrides the inherent susceptibility or resistance to the nematode (Chiejna & Wakelin, 1984). There are also reciprocal effects and the expulsion of *T. spiralis* is inhibited by infections with *T. musculi* also indicating a suppressive effect on the host's immune response, this time in the other direction (Bell, Adams & Ogden, 1984*b*). Thus it would seem that, in this model of doubly-infected animals, both the trypanosome and the nematode benefit although the details of the actual outcome vary from strain to strain of mouse. However the trypanosome also reduces the fecundity of the worms which, therefore, suffer from the relationship in a different way (Bell, Adams & Ogden, 1984*b*). Rats infected with *T. b. brucei* also fail to expel the nematode worm *Nippostrongylus brasiliensis* (Urquhart *et al*. 1973), as is the case in another combination of trypanosome and nematode, *T. b. brucei* and *Trichinella spiralis*, in mice where the presence of the trypanosome also has an inhibitory effect on immunity to the worm (Onah & Wakelin, 1999). These authors measured IFN-γ and IL-4 levels, markers for Th_1 and Th_2 responses respectively and found that in the doubly-infected animals levels of IFN-γ were increased and levels of IL-4 were reduced and they conclude that in the doubly-infected animals the immune response is biased to the T_1 pole thus inhibiting immunity to *T. spiralis* which relies on the activation of T_2 responses.

The findings that trypanosome infections are enhanced in animals co-infected with nematodes relate to laboratory systems but there is some evidence that in domesticated animals the outcome is likely to be similar. In a natural situation, N'dama cattle in The Gambia are more susceptible to infection with *T. congolense* or *T. vivax* if they are infected with trichostongyle nematodes (Dwinger *et al*. 1994) and sheep infected with *Haemonchus contortus* and *T. congolense* are able to tolerate either infection but not both (Goossens *et al*. 1997). However, it is impossible to generalise from these findings and those discussed above and conclude that in dual infections with nematodes and trypanosomes the trypanosome infection will always be enhanced. For example in mice infected with *Heligmosomoides polygyrus* and *T. musculi* the trypanosome infection is not enhanced (Bell, Adams & Ogden, 1984*a*).

Schistosome infections interact with a variety of protozoa, at least in experimental models (see Chieffi, 1992). Infections with the rodent malaria parasites are affected in different ways by the presence of *Schistosoma mansoni*. For example, in the vole *Microtus guentheri*, *P. berghei* infections are enhanced if the two infections are given within 2 weeks of each other but depressed if the malaria infection is given seven weeks after the schistosome infection when the immune response to the worm is most active (Yoeli, 1956). There are also reciprocal interactions and *P. yoelii* actually inhibits the development of schistosome granulomas in experimentally infected mice (Abdel-Wahab *et al*. 1974). There have been some attempts to explain the complex and interdependent interactions between schistosomes and malaria parasites in terms of the Th_1/Th_2 dichotomy. In mice infected with *S. mansoni*, infections with the malaria parasite *P. chabaudi* are enhanced in animals infected with the worm 8 weeks previously while Th_2 responses to soluble egg antigens are reduced for 4 weeks after the malaria infection (Helmby, Kullberg & Troye-Blomberg, 1998), a finding that also applies in other situations that will be discussed below.

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Schistosomes also interact with a number of other protozoa and infections with *T. cruzi* are much more severe in mice previously infected with *S. mansoni* (Kloetzel, Faleiros & Mendes, 1971) as are infections with *Toxoplasma gondii* (Kloetzel *et al*. 1977). *Schistosoma mansoni*-infected mice also experience more intense infections with the intestinal protozoa *Entamoeba muris*, *Trichomonas muris* and *Spironucleus muris* (Higgins-Opitz *et al*. 1990) but not *Leishmania major* (Yoshida *et al*. 1999) although *L. infantum* infections are more severe in hamsters infected with *S. mansoni* (Mangoud *et al*. 1998). Turning to the effect of protozoa and schistosome infections, *L. infantum* in hamsters delays *S. mansoni* granuloma formation (Morsy *et al*. 1998), a finding similar to that recorded for malaria parasites discussed above although when mice infected with *S. mansoni*, and undergoing an ongoing Th_2-inducing infection, are infected with *Toxoplasma gondii*, an infection that is responsive to Th_1 cytokines, there is a considerable reduction in schistosome granuloma size but there is no evidence of uncontrolled toxoplasma replication (Marshall *et al*. 1999). Taken together, these results suggest that infections with protozoa that stimulate a Th_1 response actually downregulate Th_2 responses with the result that the development of schistosome granulomas, a Th_2 phenomenon, is inhibited.

There is some indication that schistosomes interact with protozoa in the field and, from epidemiological studies in Egypt, it appears that the schistosomes interfere with the acquisition of immunity to *Entamoeba histolytica* and/or *E. dispar* (Mansour *et al*. 1997).

The expulsion of nematode infections is inhibited in mice infected with blood parasites, for example in mice infected with *B. microti* or *B. hylomysci* and *Trichuris muris* the expulsion of the worm is delayed, the suggested explanation being the immunodepression induced by the piroplasms (Phillips & Wakelin, 1976) and mice infected with *Plasmodium berghei* suffer from prolonged infections with *Nippostrongylus brasiliensis* and the self-cure mechanism is suppressed (Modrić & Mayberry, 1994). These authors attribute the results to decreased eosinophil production in the doubly-infected mice. Infections with intraerythrocytic protozoa, therefore, have an adverse effect on concomitant nematode infections. On the other hand, *B. microti* infections are not enhanced or prolonged in mice co-infected with *Heligmosomoides polygyrus* (Behnke, Sinski & Wakelin, 1999).

Among other records of interactions between protozoa and helminths is the observation that infections of *Entamoeba histolytica* are enhanced in mice infected with *Syphacla obvelata* (Vinayak & Chopra, 1978). There have been conflicting results from studies involving *T. spiralis* and *Eimeria* spp. In one study in mice, the outcome of infections with *T. spiralis* and *E. vermiformis* or *E. pragensis* differed according to the eimerian species; *E. vermiformis* delayed the expulsion of the worm whereas *E. pragensis* did not and the replication of *E. vermiformis* was enhanced in the presence of the worm whereas that of *E. pragensis* was reduced (Rose, Wakelin & Hesketh, 1994). These authors explain the results in terms of inflammation and immunological responses. In rats infected with *T. spiralis* and *E. nieschulzi* there were decreases in the number of adult worms and muscle parasitism and also in the numbers of oocysts produced by the protozoan (Stewart, Reddington & Hamilton, 1980). It is possible to interpret these last results in terms of changes to the architecture of the gut as the worms reach the gut when it has been severely damaged by the eimerian. A number of other examples of interactions between *T. spiralis* and *Eimeria* spp. are cited and discussed by Rose *et al*. (1994) who conclude that it is not possible to predict the outcome of the interactions between these parasites. Staying with intestinal infections and another combination involving *T. spiralis* and the intestinal flagellate, *Giardia muris*, the output of protozoan cysts is decreased in doubly-infected mice but the worm infection is not affected (Roberts-Thomson *et al*. 1976). The authors attribute this decrease in cyst output to changes in the gut rather than to any immunological factors, a conclusion also reached in the experiments using *G. muris* and the intraerythrocytic protozoa mentioned above (Brett & Cox, 1982).

Among other interesting interactions between helminths and protozoa are those between *Taenia crassiceps* and *T. cruzi* where, if the two are given to mice together, there is a slight delay in the onset of the trypanosome parasitaemia whereas if the trypanosome infection is initiated later during the cestode infection there are decreases in the levels of both IFN-γ and IL-4 and susceptibility to the trypanosome infection is markedly enhanced. In mice infected with *T. spiralis* and *L. infantum* 7 days later, when IFN-γ levels are already elevated, the subsequent leishmania infection is milder and the parasite load is reduced (Rousseau *et al*. 1997) and in mice infected with *T. spiralis* and *T. gondii*, also 7 days later, the protozoan infection is also milder (Afifi *et al*. 1999). In these experiments infection with *T. gondii* also protects against the nematode.

Helminths and viruses

Although concurrent infections of helminths and viruses are common the literature on the subject is rather limited and it is interesting to note that there are very few reports on the effects of immunosuppressive viruses on the outcome of helminth infections (see Markell, John & Krotoski, 1999). The best studied examples are those of the human

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lymphotropic virus type 1 (HTVL-1) that enhances infections with *Strongyloides stercoralis* (see Genta & Walzer, 1989). There is little evidence to suggest that HIV and schistosomes interact with one another despite the fact that they occur together in many parts of the world. However, there is some evidence that human infections with the hepatitis B virus contribute to liver damage caused by *S. mansoni* (Strauss & Lacet, 1986). There is also evidence that the viral infection is actually enhanced by the presence of the schistosomes and that there is an association between hepatitis B and the severity of schistosomiasis in Brazil (Strauss & Lacet, 1986) and Egypt (Madwar, El Tahawy & Strickland, 1989). Taken together, these findings indicate that infections with helminths can increase the severity of viral infections.

Helminths and bacteria

Some of the earliest reports of interactions between bacteria and helminths are concerned with a phenomenon called 'prolonged septicemic salmonellosis' in which patients infected with *S. mansoni* experienced prolonged bacteraemias due to several species of *Salmonella*. This finding was subsequently extended to other bacteria and the term 'prolonged septicaemic enterobacteriosis' was coined for this condition (see Chieffi, 1992). It has been suggested that this phenomenon is due either to immunodepression induced by the schistosomes or by the provision of some sort of protection to the bacteria (see Chieffi, 1992). There are, however, interactions between *Escherichia coli* toxins and schistosomes in mice in which the lethality caused by both agents is increased (see Chieffi, 1992). Much of the current interest in the effects of bacterial infections on helminths is indirect and is concerned with what happens in individuals vaccinated against *Mycobacterium tuberculosis*, the causative agent of tuberculosis, with BCG, particularly the purified protein derivative (PPD). BCG stimulates Th_1 immune responses and there is some concern that this might bias the response away from protection which, in the case of the helminths, tends to be Th_2 dependent. In fact, there is no evidence that this happens but there is evidence that the reverse is the case and in children sensitized *in utero* with *S. haematobium* or *Wuchereria bancrofti* the bias is away from the Th_1 responses required for protection against mycobacterial infections (Malhotra *et al.* 1999). Similarly, there is evidence that infection with *Onchocerca volvulus* may have an inhibitory effect on the immune responses to *M. tuberculosis* or *M. leprae*, the causative agent of leprosy (Stewart *et al.* 1999). These authors also comment on the significance of these findings with reference to reports of increased incidences of lepromatous leprosy in individuals with onchocerciasis. *Fasciola hepatica* is another helminth that suppresses the protective Th_1 immune response against a bacterial infection, in this case *Bordetella pertussis* (Brady *et al.* 1999). It would appear from these examples that helminth infections that induce protective Th_2 immune responses can also downregulate Th_1 responses and that this might bring about the exacerbation of concomitant infections or a failure to respond to vaccination in infections that are controlled by Th_1 responses.

Helminths and other helminths

There are numerous examples of interactions between helminth worms (see Christensen *et al.* 1987) and those involving nematodes of rodents are discussed elsewhere in this supplement by Behnke and others. The best studied example of interactions between helminths is the phenomenon of concomitant immunity in which the adults of an ongoing infection prevent the establishment of another infection with larvae of the same species by eliciting an immune response which the adult worms can evade but the new larvae cannot. This seems to be a common phenomenon in helminth infections and is best exemplified by schistosomes (Smithers, Terry & Hockley, 1969) and by *Echinococcus granulosus* (see Heath, 1995). These interactions between worms belonging to the same species will not be discussed further here. Different species of helminth do, however, frequently occur in the same host and can interact with one another. The ecological aspects of such concurrent infections are discussed elsewhere in this supplement by Poulin and some of the immunological aspects of interactions between nematode worms are discussed by Behnke and his colleagues. It is only possible to discuss a few examples of different kinds of interactions here. In mice concurrently infected with the nematodes *Trichuris muris* and *Heligmosomoides polygyrus* the trichurid infection is rejected more slowly than in animals harbouring this parasite alone and the authors consider that this is due to a raising of the immune threshold necessary for the expulsion of the worms (Behnke, Ali & Jenkins, 1984). However, in most other systems investigated, the superimposed infection is suppressed by the presence of the original agent. In mice infected with *S. mansoni* and the cestode *Mesocestoides corti*, there is a reduction in the number of *M. corti* tetrathyridia and in the intensity of infection in the animals harbouring dual infections (Chernin *et al.* 1988). In mice infected with *S. mansoni* and the cestodes *Hymenolepis diminuta* or *Rodentolepis microstoma* there is an accelerated expulsion of the cestodes (Andreassen, Odaibo & Christensen, 1990). In mice co-infected with *S. mansoni* and *T. muris*, the Th_2 response to schistosome eggs appears to be involved in the elimination of the nematode infection (Curry *et al.* 1995) and in

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mice infected with *S. mansoni* and *Strongyloides venezuelensis* there is a decrease in the numbers of the nematode which the authors attribute to the effects of the immune response on the migrating larvae (Yoshida *et al*. 1999). There is also evidence from the field that infection with *S. mansoni* is in some way protective against infection with the geohelminths *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms (Chamone *et al*. 1990). Thus, from these few examples it is clear that, in most combinations, infection with one worm can protect against others but that there are some circumstances in which infection with one helminth can enhance infection with another. Dual infections may also have synergistic effects on the pathology of some infections, for example children co-infected with hookworms and *Trichuris trichiura* have significantly less haemoglobin than children harbouring only one of these nematodes (Robertson *et al*. 1992).

DISCUSSION

This review, which of necessity is very selective, is intended to indicate the range of interactions between infectious agents that might affect the outcome of parasitic infections. It should be clear that mixed infections are the rule in natural situations and that protozoan infections are affected by other protozoa, helminths, bacteria and viruses while helminth infections are affected by protozoa, bacteria, viruses and other helminths. In virtually every combination that has been examined one or other of the concomitant agents is affected by the presence of the other and in many cases both are affected. In addition to these infectious agents, there are also fungi and prions to consider and virtually nothing is known about how these interact with parasites. The outcome of any interaction is not necessarily predictable and can vary from stage to stage of the infection. The age and sex of the host, factors that have not been considered here, can also influence the outcome of an infection. The important thing to be borne in mind is that these interactions do occur and cannot be ignored.

Immunodepression

The most common outcomes in dual infections are that the infection caused by one or other of the agents may be enhanced or depressed, both may be affected, one may be enhanced and the other depressed or vice versa. In addition, the presence of one agent can increase or decrease the severity of the pathology caused by the other. With all these possibilities the outcomes of any combination might be unpredictable but there are a number of patterns that seem to be consistent and a beginning has been made in unravelling these patterns. The most common situation is one in which one agent causes immunodepression and a superimposed infection is able to take advantage of this situation. Essentially this is no different from the situation in which many immunocompromised hosts are susceptible to intercurrent infections with a range of microorganisms. However, it is too simplistic to assume that any parasitic infection in an immunocompromised host is likely to be enhanced and, in this context, it is interesting to note that very few parasitic infections are actually significantly enhanced in individuals infected with HIV (see Ambroise-Thomas, in this volume). Some degree of immunodepression is common, if not universal, during the course of infections with parasites and microorganisms but the methods used to assess the immune status of the host need not necessarily reveal those aspects that are relevant to the superimposed infection. For example, many of the early observations on immunodepression in parasitic infections were based on counting antibody-producing cells, which is no longer appropriate given our present knowledge of the roles of T cells in immune responses. Immunodepression during parasitic infections may be due to by-products of an ongoing protective immune response or to factors induced by the parasites themselves in order to ensure their own survival or to damp down immunopathological changes. Various aspects of these processes are discussed in more detail in the various contributions in Doenhoff & Chappell (1997). What is important to understand here is what the essential elements of a particular immune response are that render the host more or less susceptible to infection. There may be other alternatives to explain the enhanced infections seen during concomitant infections such as factors that enhance the growth or development of the parasite produced as part of the normal immune response or alterations to the cells required for the survival of a particular parasite.

The Th_1/Th_2 dichotomy

The second important factor in determining the outcome of an infection is whether or not the established infection is inducing a Th_1 or a Th_2 response. The Th_1 immunological milieu involves a number of molecules and the cells that produce them, in particular, NK cells, IL-12 and IFN-γ. The initiation of a new immune response in such a situation is gradually forced towards the Th_1 pole and, if the superimposed agent is controlled by Th_2 responses, it is at an advantage in such a situation. The reverse applies if IL-4 predominates in the immunological milieu at the time of the second infection. There is now a considerable amount of solid work going on in this area and from the experiments that have been described it looks as if the pattern described above is of general application. However, it is important to bear in mind that the

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Th_1/Th_2 paradigm is not a rigid set of rules (Allen & Maizels, 1997) and that there may be switches in the patterns of Th_1 and Th_2 cytokines during the course of an infection as has been clearly demonstrated in the case of rodent malarias (Taylor-Robinson & Phillips, 1998).

Immune effector molecules

A number of molecules involved in the immune response act on a variety of cells and can affect parasites directly. Mention has already been made of IFN-α which, although important in viral infections, does not seem to play any significant part in the immune responses induced by, or otherwise involved in, parasitic infections. There are, however, a number of molecules that are relevant, the most studied being the lymphocyte product, IFN-γ, and the macrophage products TNF, TGF-β, NO and reactive oxygen intermediates. Regardless of how a particular immune response was initiated these molecules act non-specifically and thus a superimposed parasite may be affected by effector molecules the production of which it itself has not initiated, in other words, the bystander effect.

Parasite-derived immunomodulatory factors

It is now clear that a number of parasites produce molecules that affect cells of the immune response directly or indirectly and thus exert immunomodulatory effects. The best characterized are trypanosome macrophage activating factor (TMAF) and trypanosome lymphocyte triggering factor (TLTF) and it is almost certain that a number of others will be described. The presence and effects of such molecules will have to be taken into account when considering concomitant infections.

The significance of studies on concomitant infections

It has been the purpose of this review to give some indication of the range of interactions that occur when a host is infected with more than one infectious agent. These interactions cover the whole spectrum from the enhancement to suppression of one or other or both of the co-infecting agents and from the augmentation to the amelioration of the pathology of the infection. This means that the nature of any specific parasitic infection in a host concurrently infected with another infectious agent may be very different from an infection caused by the same parasite in a host co-infected with another agent or in a host that is otherwise uninfected. This has a number of implications that relate to the epidemiological and clinical aspects of human and veterinary parasitology and to the development of vaccines and the use of chemotherapy. The best known example of the clinical implications of interacting infections is Burkitt's lymphoma, resulting from an interaction between the Epstein-Barr virus and malaria (Burkitt, 1969; De The, 1985) where the host appears to lose the T cell control of the virus infection (Whittle *et al*. 1984). There are also other examples including the increased incidence of lepromatous leprosy in patients with onchocerciasis (Stewart *et al*. 1999) and more severe strongyloidiasis in patients harbouring the virus HTVL-1 (Genta & Walzer, 1989). There is now a vast amount of evidence from experimental studies to suggest that the clinical picture in many infections may be markedly influenced by the presence of unrelated organisms and it is probable that such influences will prove to be the rule rather than the exception.

Concomitant infections are also likely to affect the efficacy of vaccines and will influence the design of new vaccines. It is already known that it is difficult to vaccinate children with malaria against tetanus, typhoid or bacterial meningococcus (Williamson & Greenwood, 1978, and see Björkman, 1988). Children sensitized to helminth antigens also appear to have an impaired response to mycobacterial antigens (Malhotra *et al*. 1999). New antiparasitic vaccines will have to take account of the possibility of inhibiting the immune responses to antimicrobial and antiviral vaccines by triggering inappropriate immune responses. Such inappropriate responses might also result from chemotherapy which causes the death of the parasites and the release of sequestered antigens as occurs in some autoimmune diseases. It has been suggested that new antiparasitic vaccines should be designed to trigger the appropriate T_1 or T_2 response (Cox, 1997) but care will also have to be taken to ensure that the efficacy of such vaccines is not impaired by concomitant infections.

Concomitant infections have long been ignored by parasitologists but the time has now come to accept that such infections may be the rule and not the exception and to test laboratory findings in the field. Our understanding of the totality of the immune response, particularly its cytokine control, has now provided us with tools to analyse what is happening during the course of mixed infections and it would be remiss of us not to take advantage of these tools and to apply the findings to the rational control of parasitic infections in animals and humans.

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https://doi.org/10.1017/S003118200001698X Published online by Cambridge University Press