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# Th2–mediated host protective immunity to intestinal nematode infections

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# Th2-mediated host protective immunity to intestinal nematode infections

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Despite many years of study, relatively little is known about the effector mechanims that operate against intestine-dwelling nematodes. Most of the current understanding comes from studies of laboratory model systems in rodents. It is clear that when an intestinal helminth infection takes place the immune system generates a strong Th2-mediated response, which regulates a variety of responses characteristic of helminth infections such as eosinophilia, intestinal mastocytosis and elevated IgE production. The ability to modulate the host's immune response *in vivo* with cytokine-specific monoclonal antibodies and recombinant cytokines, together with the use of animals with disruption of key genes involved in the immune reponse, have provided powerful tools with which to dissect the potential effector mechanisms operating. In the absence of a T-cell compartment the host is unable to expel the parasite. If a Th1-dominated response is generated, protective immunity is almost universally compromised. Thus, it would appear that some aspect of a Th2-mediated response controls effector mechanisms. Although it is clear that for some infections the mast cell appears to be involved in protection, probably through the generation of a non-specific inflammatory response, how these cells become activated remains unclear. Data from infections in transgenic animals suggest that activation is not through the high-affinity receptor for IgE. Such studies also call into doubt the importance of conventional interactions between effector leucocytes and antibody. There is little evidence to support a protective role for eosinophilia in any system. New data also imply that, although interleukin 4 (IL-4) is generally important (and can exert effects independent of an adaptive immune response), it is not always sufficient to mediate protection; other Th2 cytokines (e.g. IL-13) may warrant closer investigation. It is apparent that a number of potential Th2-controlled effector mechanisms (some of which may be particularly important at mucosal surfaces) remain to be explored. Overall, it is likely that worm expulsion is the result of a combination of multiple mechanisms, some of which are more critical to some species of parasite than to others.

## 1. INTRODUCTION

Intestinal nematode infections of humans and animals are some of the most prevalent infections worldwide (Chan *et al.* 1994). A spectrum of infection intensities is often a feature in the natural situation, and many infections are chronic (Behnke *et al.* 1992). Nevertheless, studies from controlled situations in the laboratory and from immunoepidemiological investigations in the field show that host protective immunity can operate (reviewed in Maizels *et al.* 1993). It is clear, however, that despite study for many years we are only now beginning to understand the immunoregulatory mechanisms underlying the variation in worm burden and resistance status between infected individuals. Our knowledge of definitive effector mechanisms operating against these parasites is far from complete.

The major part of current understanding of the regulation of the protective mechanisms mediating resistance to intestinal nematodes has come from the study of laboratory model systems, particularly in the rat and the mouse. Recent studies have concentrated on a number of species of intestinal nematode, including *Nippostrongylus brasiliensis*, *Trichinella spiralis*, *Heligmosomoides polygyrus*, *Trichuris muris* and to a lesser extent *Strongyloides venezuelensis*. Each of these models has its own advantages and disadvantages with the common feature in that in all of them the host mounts a protective response and expels the worm from the gut or can be induced to do so relatively easily. This has allowed the dissection of both the immuoregulatory mechanisms and the host's protective responses under controlled conditions impossible to achieve in the field.

The analysis of the immune response to infection essentially began in the 1930s with the pioneering work of Taliaferro & Sarles working with *N. brasiliensis* in the rat. These workers made a number of key observations and suggested a role for both antibody and cells in resistance alongside key changes in pathology including eosinophilia (Taliaferro & Sarles 1939). These data were extended in the 1960s and 1970s by Ogilvie and coworkers, who suggested that the dual action of lymphocyte and antibody- (possibly IgE-) mediated damage to the parasite resulted in worm expulsion from the gut

(Ogilvie & Jones 1968; Ogilvie & Love 1974). A hypothesis was put forward (the 'leak lesion hypothesis') suggesting that an immediate-hypersensitivity type of response in the intestine allowed antibody into the gut lumen, where it could attack vital worm functions such as feeding (see Murray 1972).

## 2. CONTROL OF IMMUNITY BY T HELPER CELL SUBSETS

Adoptive cell-transfer studies from both *T. spiralis* and *N. brasiliensis* sytems proved beyond doubt that T cells, particularly CD4+ T cells, were the important subset (Grencis *et al.* 1985; Katona *et al.* 1988, Ramaswamy *et al.* 1994). This observation was also confirmed for *H. polygyrus* (Urban *et al.* 1991*a*) and *T. muris* (Koyama *et al.* 1995).

With the division of CD4+ T cells into functionally distinct subsets based on the secretion of different sets of cytokines (Mosmann & Coffman, 1989; Mosmann & Subach, 1996) a closer analysis of the involvement of particular subsets in the host's protective response to nematodes became possible. Two basic subsets were described: Th1 cells, secreting predominately interferon gamma (IFN-$\gamma$); and IL-2 and Th2 cells secreting interleukin (IL) -4, IL-5, IL-6, IL-9, IL-10 and IL-13. Measurement of cytokine production by T cells during intestinal nematode infection after stimulation *in vitro* or by analysis of cytokine mRNA expression showed a predominance of Th2-type responses. This response has been shown for *N. brasiliensis* (Finkelman *et al.* 1997; Lawrence *et al.* 1996), *T. spiralis* (Grencis *et al.* 1991), *H. polygyrus* (Wahid *et al.* 1994; Behnke *et al.* 1993) and *T. muris* (Else & Grencis 1991; Else *et al.* 1992).

It also became possible to determine the role of specific cytokines in the host's protective response. Of particular importance were a number of observations from the *H. polygyrus* and *T. muris* systems. Treatment of animals infected with *H. polygyrus* with a neutralizing anti-IL-4 or anti-IL-4-receptor monoclonal antibody inhibited the protective immunity generated in the challenge model (Urban *et al.* 1991*a*). After *T. muris* infection, the host's protective immunity was blocked by treatment of infected animals with anti-IL-4 receptor monoclonal antibodies (Else *et al.* 1994). In this latter system, such treatment was accompanied by a downregulation of Th2-mediated immune responses (such as IgE production, IgG1 production, eosinophilia and intestinal mastocytosis) and an upregulation of Th1 responses (such as IFN-$\gamma$ and IgG2a production). These animals went on to exhibit chronic infection with *T. muris*.

In a number of intestinal nematode systems the induction of a Th1 response has been found to inhibit the host's protective response. Treatment of mice infected with *N. brasiliensis* with IL-12 (a non-T-cell-derived cytokine that promotes the development of a Th1 response) extended the normal period of intestinal infection as long as treatment persisted. This effect was mediated predominantly through IFN-$\gamma$ production (Finkelman *et al.* 1994). Similar observations have been made in the *T. muris* system, although in this case IL-12 administration to resistant strains of mouse induced chronic infection. The effect was again mediated through the production of IFN-$\gamma$ but in this model, to induce this effect, the IL-12 could be administered for a short period only during the first two weeks of infection (Bancroft *et al.* 1997).

The importance of Th2 cytokines in resistance has also been investigated in transgenic mice that have had a deletion (knockout—KO) of the IL-4 gene (IL-4 KO mice). Such mice have a dramatically reduced capacity to generate a Th2 response owing to the major role played by IL-4 in the production of this subset of cells (Kopf *et al.* 1993; Kühn *et al.* 1991). These animals are unable to mount a protective response against *H. polygyrus* (see Finkelman *et al.* 1997). Such mice are, however, able to expel *N. brasiliensis* over a time course similar to that of wild-type controls. These data imply that in the absence of IL-4 (and presumably of 'classical Th2 cells') the host can still mount a protective response. Interestingly, recent data have implicated IL-4-independent pathways for the induction of responses previously thought to be exclusively under this cytokine's control, such as the role of CD40 in IgE production (Morawetz *et al.* 1996).

Data from experiments in IL-4 KO mice and *T. muris* provide a somewhat more complicated picture. In this system, early experiments with IL-4 KO mice on a mixed genetic background (after only a few generations of interbreeding) suggested that the parasites could be expelled in the absence of IL-4, although there was some evidence of a delay in expulsion compared with wild-type mice (A. J. Bancroft, A. E. Bianco and K. J. Else, unpublished data). More recent work, however, with IL-4 KO mice on a mixed genetic background (after many more generations) or on a defined inbred genetic background suggests that IL-4 *is* important: these mice are completely susceptible to infection and allow patent infections to develop whereas the wild-type mice expel their worm burdens efficiently (A. J. Bancroft *et al.*, unpublished data). Such variations between parasite systems and within the same system are difficult to explain, although differences in immune responsiveness to helminths between IL-4 KO mice on different genetic backgrounds have been reported (E. J. Pearce, personal communication; M. Kopf, personal communication).

Recent data, however, suggest that although Th2 cells (and particularly IL-4) are important they may not be sufficient to bring about worm expulsion. Mice with a targeted disruption of the IL-13 gene are highly susceptible to *T. muris* infections when compared with wild-type controls (A. J. Bancroft *et al.*, unpublished data). It is clear that infected IL-13 KO mice are able to secrete Th2 cytokines and mount characteristic Th2 responses, such as intestinal mastocytosis. These data open up interesting new avenues for exploration of IL-13-controlled effector mechanisms.

## 3. EFFECTOR CELLS

The relatively tight control of particular immune responses by particular cytokines has provided the opportunity to examine their contribution to defined effector mechanisms by neutralization of cytokines *in vivo* or by the use of KO mice. An example is provided by

the investigation of the role of eosinophils in mice given anti-IL-5 antibodies or in IL-5 KO mice. For *N. brasiliensis* (Coffman *et al.* 1989), *T. spiralis* (Herndon & Kayes 1992), *H. polygyrus* (Urban *et al.* 1991*b*) and *T. muris* (C. J. Betts and K. J. Else, unpublished observations), treatment of infected animals with anti-IL-5 monoclonal antibodies ablated eosinophilia but failed to affect the normal expulsion of the parasites from the intestine. These data strongly imply that eosinophils are unlikely to be a major effector cell against intestinal nematodes.

Another granulocyte prominent in gut nematode infections is the intestinal mast cell. It is well established that mast cells are functonally active during infection around the time of worm expulsion. This has been demonstrated for a number of parasites, most notably *N. brasiliensis* and *T. spiralis* in rats and mice, by the measurement of intestinal mast-cell-specific proteases released into the gut and circulation (Woodbury *et al.* 1984; Tuohy *et al.* 1990).

IL-3 has long been thought to play a major role in the development of this intestinal mast-cell response. This opinion is largely based on studies of bone marrow cultures *in vitro* in the presence of IL-3 (Rennick *et al.* 1985). Indeed, treatment of mice infected with *N. brasiliensis* with anti-IL-3 monoclonal antibodies depressed the intestinal mast-cell response, but only partly. A combination of anti-IL-3 and anti-IL-4 monoclonal antibodies depressed the normal mast-cell response by approximately 85%, although this had no effect on the normal progress of worm expulsion (Madden *et al.* 1991). This result suggests that, for *N. brasiliensis*, the mast cell is not a major effector-cell type; this conclusion reinforced earlier studies of infections of the mutant mouse strain $W/W^v$, which is deficient in mast cells and expels an infection with *N. brasiliensis* quite efficiently (Crowle & Reed 1981).

The observations from the *N. brasiliensis* system are quite different from those from the *T. spiralis* system. Infection of $W/W^v$ mice with the latter nematode shows a delayed expulsion of the worm from the gut (Alizadeh & Wakelin 1984). $W/W^v$ mice have a defect in *c-kit* (the receptor for stem-cell factor, SCF) a growth factor important in haemopoiesis, including mast-cell development (see review by Galli *et al.* (1994)). Treatment of mice infected with *T. spiralis* with monoclonal antibodies to either the receptor for SCF or SCF itself completely depresses the normal mast-cell response observed (by more than 99%) without having a major effect on the CD4+ T-cell response (Donaldson *et al.* 1996). Moreover, these mice exhibit a dramatic inhibition in the expulsion of the worm from the gut as long as the treatment persists (Donaldson *et al.* 1996). These latter observations strongly implicate the mast cell as an important component of the expulsion of *T. spiralis* from mice.

Interestingly, expulsion of *T. spiralis* from IL-3 KO mice is similar to that from wild-type mice. Although there are differences in the magnitude and kinetics of the mast-cell response, IL-3 KO mice do mount a strong functional mastocytosis: this response suggests that IL-3 is not essential *in vivo* and that other cytokines can compensate for this particular factor in this respect (R.K. Grencis and V. Tybulewicz, unpublished data).

The data for *T. spiralis* also highlight the importance of both the T-cell and haemopoietic arms of the host's protective response to intestinal nematode infection. This is typified by recent work on IL-9, a Th2 cytokine that has been shown to influence mast-cell production *in vitro* (Hültner *et al.* 1990). IL-9 transgenic mice (overexpressing this cytokine) infected with *T. spiralis* expel their worms extremely rapidly compared with normal wild-type mice (Faulkner *et al.* 1997). Indeed, IL-9 transgenic mice exhibit an overall enhanced Th2-type response to parasite challenge (including intestinal mastocytosis). However, treatment of infected IL-9 transgenics with anti-SCF receptor monoclonal antibodies dramatically depressed intestinal mastocytosis and worm expulsion was delayed (Faulkner *et al.* 1997). This result implies that Th2 responses are important, that there is a role for IL-9 in the generation of this response, and that there is additional involvement of a non-T-cell-derived factor (SCF) in the production of mast cells, resulting in worm expulsion. The source of SCF after infection is unknown, but one possibility could be the intestinal epithelial cells themselves (Puddington *et al.* 1994).

There are also data to suggest that the mast cell may play a role in the expulsion of *H. polygyrus*. In most strains of mouse, infection with *H. polygyrus* results in a chronic infection, although some strains do eventually expel their worm burden (Wahid *et al.* 1994). A primary infection is accompanied by an elevated serum IgE response, peripheral eosinophilia and parasite-specific IgG1 response: all hallmarks of Th2-cell activity (reviewed by Wahid & Behnke 1993; Wahid *et al.* 1994). An intestinal mastocytosis is, however, generally absent, although it begins to develop in those strains that do eventually expel their worms (Behnke *et al.* 1993). An analysis of Th2 cytokine secretion after primary infection demonstrates that those strains that do eventually expel their parasites are able to maintain a sustained IL-3 and IL-9 response compared with those strains that do not expel (Behnke *et al.* 1993). These data are also suggestive of a selective immunomodulatory effect by *H. polygyrus*, which can affect the mast-cell response. This can be shown *in vivo* by co-infection studies of mice with *T. spiralis* and *H. polygyrus*. Such mice show a marked depression of the pronounced intestinal mastocytosis induced by *T. spiralis* and a delay in expulsion of *T. spiralis* from the gut (Dehlawi *et al.* 1987).

Although these data do imply a role for the mast cell as a component of the effector response operating against at least some species of intestinal nematode, the precise mechanism whereby they do so is still unknown. A reasonable hypothesis, which was discussed many years ago, is that the mast cell generates an inflammatory response within the intestine and that this response makes the gut unsuitable for worm survival (Wakelin 1978). The release of mucosal mast-cell-specific proteases (especially mouse mast-cell protease 1 (MMCP1) and rat mast-cell protease 2 (RMCP2)) may be an important component of this process. Interestingly, these proteases are secreted from the cells in the absence of 'classical' degranulation. The role of these proteases (at least some of which are known to be under T-cell cytokine regulation (Ghildyal




PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

*et al.* 1992)) in the inflammatory response is largely undefined. However, recent data from the rat have suggested that RMCP2 production is associated with the rapid development of macromolecular permeability through the epithelium of the intestine (Scudamore *et al.* 1995); it is possible that MMCPl may operate in a similar way. These changes may well contribute to an environment unfavourable for worm survival.

Other mast-cell-derived products have also been implicated in resistance, including leukotrienes. In the rat, secondary *T. spiralis* infections are expelled rapidly within 24 h (the so-called rapid expulsion phenomenon); the production of leukotrienes has been demonstrated during this process (Moqbel *et al.* 1987). Leukotrienes have also been shown to be produced during *N. brasiliensis* infections (Perdue *et al.* 1989). Again, the release of inflammatory mediators such as these will contribute to overall intestinal inflammation.

Although the above evidence clearly demonstrates a role for mast cells in worm expulsion, their mode of activation during infection remains to be defined. Classically, IgE has been implicated, based on the elevated concentrations produced during infection (e.g. with *N. brasiliensis*) and its role in immediate-type hypersensitivity responses. In the rapid expulsion response to *T. spiralis*, there is evidence from passive transfer studies that implies a role for IgE (Ahmad *et al.* 1984; Harari *et al.* 1987). Others, however, have suggested that an elevation of serum IgE is in fact a mechanism for survival of intestinal nematode infections (Pritchard 1993). Much of the serum IgE generated during intestinal nematode infection is non-specific (Jarrett & Bazin 1974); it has been postulated that such non-specific immunoglobulin may bind to the high-affinity IgE receptors (Fc$\epsilon$RI) on mast cells, thus preventing parasite-specific IgE from attaching.

There is new evidence, however, to suggest that during intestinal nematode infection activation of the mast cell can occur by mechanisms not involving the Fc$\epsilon$RI. This has come from studies of mice with a disruption of the gene encoding the $\gamma$ chain of the Fc receptor (Fc$\gamma$ KO mice lack several Fc receptors including Fc$\epsilon$RI (Takai *et al.* 1994)). *T. spiralis* infections in such mice are expelled efficiently and are coincident with a strong intestinal mast-cell response, including secretion of MMCPl; secretion by these cells reflects their activation (figure 1) (R. K. Grencis and J. V. Ravetch, unpublished data). These data strongly suggest that neither IgE nor other isotypes operating through Fc receptors are crucial in expulsion of a primary infection of the worm from the intestinal tract of mice. Other mechanisms involved in activation of mast cells during infection remain to be defined. It is known that mast cells are multifunctional cells secreting and responding to a variety of cytokines (see review by Gordon *et al.* (1990)).

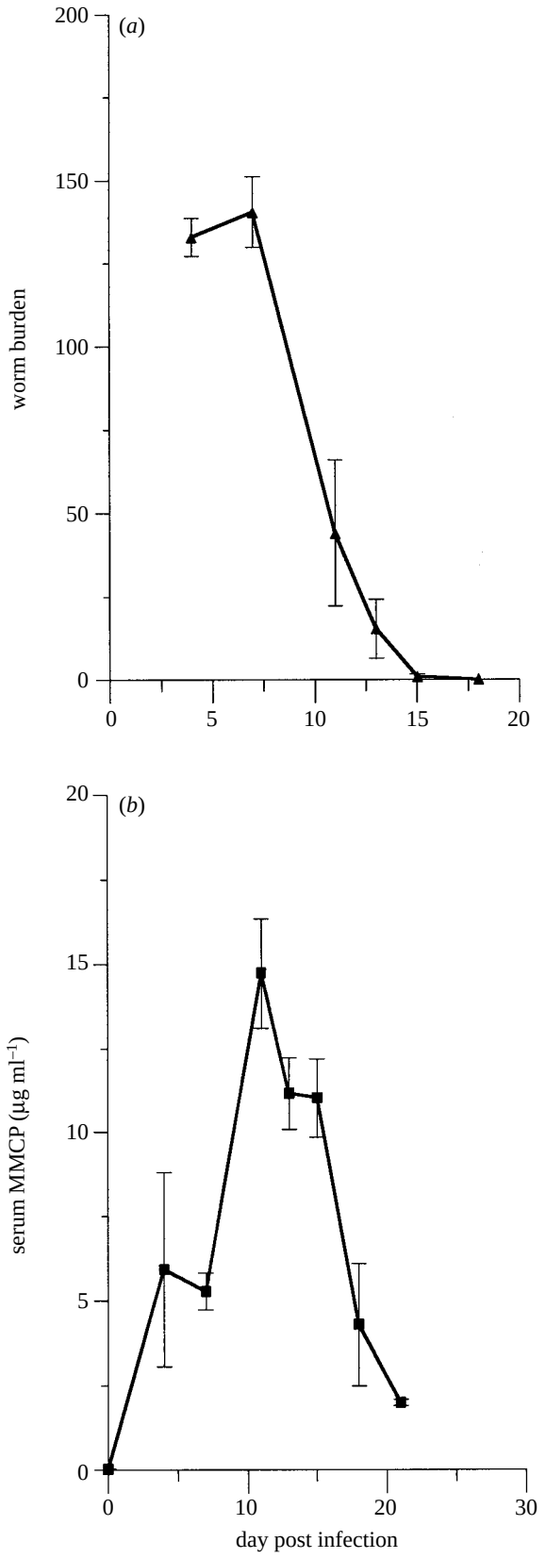


Figure 1. (*a*) Worm burden (±s.e.) and (*b*) serum MMCP levels (±s.e.) of Fc$\gamma$ chain KO mice infected with *T. spiralis*. Mice were infected with 300 *T. spiralis* muscle larvae on day 0; $n = 5$ animals per time point.

## 4. EFFECTOR MOLECULES

Recently, a series of experiments has been conducted by F. D. Finkelman, J. F. Urban and colleagues to investigate the protective mechanisms mediated by IL-4. These experiments were based on the ability to deliver recombinant IL-4 *in vivo*. Investigations have been carried out in the *H. polygyrus*, *N. brasiliensis* and *T. muris* systems. Administration of IL-4 during *H. polygyrus* infection induces worm expulsion and several changes in

intestinal physiology, such as smooth-muscle contractility and increased fluid secretion (Urban *et al.* 1995; Finkelman *et al.* 1997). Such changes are not observed in infected W/W$^v$ mice; this observation suggests that mast cells are involved in this response. Infections of *N. brasiliensis* in severe combined immunodeficient (SCID) mice are also completely expelled after IL-4 administration (Urban *et al.* 1995). This effect is independent of mast-cell activity (F. D. Finkelman, personal communication). The mechanism of action in this case is unknown but is unlikely to be a direct effect of IL-4 on the worms, as IL-4 treatment of STAT6 KO mice fails to induce expulsion of the parasites from the gut. STAT6 is an IL-4 signal transduction molecule (see Keegan *et al.* 1996); STAT6 KO mice are unable to expel *N. brasiliensis* from the gut (F. D. Finkelman, personal communication). Administration of IL-4 to SCID mice infected with *T. muris* causes partial expulsion when an established adult infection is present in the gut but is unable to induce expulsion when given during the larval stages of infection (K. J. Else, C. J. Betts and F. D. Finkelman, unpublished data). It still remains to be proved, however, that the IL-4 induced changes described are causally related to worm expulsion in normal immunocompetent animals.

The importance of antibody as an effector molecule is also still essentially unclear, although a number of older studies implicated antibody in the expulsion of nematodes after the passive transfer of relatively large amounts of serum before and during the early stages of infection (see review by Wakelin (1978)). Relatively few studies have transferred purified immunoglobulin, although the *H. polygyrus* system is a notable exception in this regard, with data implicating IgG1 as a protective isotype (Pritchard *et al.* 1983). IgE has also been postulated to play a role in the rapid expulsion response to *T. spiralis* in the rat; this response can be transferred by thoracic-duct lymphocytes together with IgE (Ahmad *et al.* 1984). Indeed, a novel mechanism for the intestinal transport of IgE has recently been described (Ramaswamy *et al.* 1994). It is noteworthy that there are very few data to imply a protective role for IgA, an antibody class often thought to play a major role in protection at mucosal surfaces, although this lack of data may reflect the relatively scant attention secretory antibodies have received with regard to these infections.

Various approaches have been used to depress the host's capacity to mount an antibody response and hence investigate the importance of antibody in resistance. Mice infected with *N. brasiliensis* have been treated with anti-IgM, although this had little effect on their ability to expel their worm burden (Jacobson *et al.* 1977). Mice that are μ-chain-deficient (antibody-deficient) are also able to expel a secondary challenge of *H. polygyrus* (see Finkelman *et al.* 1997). It is also apparent that the classical interaction between cells and antibody is unecessary: mice with a disrupted γ chain of the FcR can expel *T. spiralis* efficiently (see above). Fcγ KO mice are also highly resistant to *T. muris* infections (K. J. Else, C. J. Betts and J. V. Ravetch, unpublished observations). Moreover, the inability of SCID mice to expel *T. muris* can be rectified by the adoptive transfer of highly purified CD4+ T cells. Expulsion occurs in the absence of any detectable antibody response (Else & Grencis 1996). Protection operates against the larval stages of the parasite (K. J. Else and C. J. Betts, unpublished data) and this is clearly different from that induced by administraion of IL-4 to SCID mice, which induces expulsion of adult but not larval parasites (see above).

## 5. OTHER EFFECTOR RESPONSES

Other Th2 cytokine-controlled gut responses that may be involved in worm expulsion remain to be explored fully. These include changes in the mucus and intestinal goblet-cell responses. Goblet-cell hyperplasia is a feature of most intestinal nematode infections, including those with *N. brasiliensis* (Ishikawa *et al.* 1993), *T. spiralis* (Garside *et al.* 1992) and *T. muris* (D. Artis, personal communication). Although it is clear that the production of goblet cells is, at least in part, independent of the immune response (for example, SCID mice have goblet cells) the hyperplasia observed on infection is influenced by T cells (Miller & Nawa 1979). Recent work from the *N. brasiliensis* system has also shown a CD4+ T-cell (and, based on other work, presumably Th2-cell) influence on the mucus response during infection (Khan *et al.* 1995).

Interestingly, a series of co-infections with *N. brasiliensis* and *S. venezuelensis* in the gerbil have suggested that, whereas resistance to *S. venezuelensis* is correlated with intestinal mastocytosis, resistance to *N. brasiliensis* is more closely related to the goblet-cell response (Horri *et al.* 1993; Nawa *et al.* 1994). Mucus has been suggested to play a role in the rapid expulsion response to *N. brasiliensis* (see Miller 1987). Thus, for *N. brasiliensis*, the goblet-cell response and mucus production remains attractive as an important effector mechanism. Based on the discussion, it is reasonable to suppose that the hyperplasia may be controlled by particular Th2 cytokines, which do not absolutely rely on IL-4 for their production, although this remains to be proven.

A number of studies have also observed major changes in the turnover of the intestinal epithelium in response to infection by nematodes, resulting in crypt hyperplasia and villous atrophy (Manson-Smith *et al.* 1979; Symons 1965, 1978). These changes may contribute to a situation that is suboptimal for parasite survival and hence promote expulsion. Data from non-parasite systems of intestinal inflammation clearly implicate a role for T-cell-derived cytokines in the regulation of intestinal cell turnover (Mowat 1989); recent experiments from the *T. muris* system suggests that this may be the case in gut nematode infections (D. Artis, unpublished observations).

## 6. CONCLUSIONS

From the previous discussion, it is clear that it is difficult to make broad generalizations about effector mechanisms that operate against intestinal nematodes. It does appear that in immunocompetent animals expulsion generally requires the generation of a Th2-mediated response. These cells, through the secretion

of cytokines such as IL-3, IL-4, Il-5, IL-6, IL-9, IL-10 and IL-13, control the changes that are most often associated with worm expulsion, including intestinal mastocytosis, eosinophilia and IgE production. It is likely, however, that other responses are regulated by these cytokines but as yet are unappreciated in terms of potential effector mechanisms.

It appears that immune effector mechanisms differ considerably between infections with different species of nematode and, indeed, between primary and secondary infections and between different stages of infection (for example, larval or adult stages of the parasite). Eosinophils do not appear to be involved in host protection against any of the intestinal stages of the nematodes so far studied. A protective role for the mast cell appears much stronger for infections with some species of parasite, yet it is clear that these cells are not critical for others. The role of antibody in host protection is also variable and there is only scant evidence of a role for IgE in activation of mast cells in those systems where mast cells appear to be important. It is likely that less well-explored effector responses may be involved. For example, this appears to be the case in *N. brasiliensis* infections, the expulsion of which is closely associated with a goblet-cell response and changes in mucus production.

Investigations of infections in immunocompromised animals, including those with selective deletions of cytokine genes, tend to reflect the observations made from conventional approaches although they have highlighted the critical nature of particular factors in the host's protective response. These studies have also discovered potential effector mechanisms, such as IL-4 in *N. brasiliensis* infections, that can act in the relative absence of a conventional adaptive immune system.

It has also become clear that in certain cases resistance could occur in the absence of a 'classical' Th2-cell response. It does appear to be true, however, that even in these cases there is no evidence to show that a Th1 response mediates resistance. In all cases of intestinal nematode infection where a Th1 response is promoted, resistance is depressed or abrogated. It is feasible that a number of Th2-type cytokines are not strictly dependent on IL-4 for their production and can function in the absence of IL-4-induced Th2 cells.

A reasonable hypothesis to put forward is that the host responds to intestinal nematode infection by generating an innate (about which we know very little) and subsequently a Th2-dominated adaptive response. The cytokines produced by these cells control a diverse set of potential immune effector mechanisms, some (but not all) of which will be protective against any one particular parasite. Indeed, it is reasonable to suggest that multiple coincident effector mechanisms contribute to the overall response observed. The aim of these responses is to alter the environment in which the parasite lives to make it unsuitable for continued survival. The worms will become damaged indirectly via inflammation or possibly directly via antibody through interference with activities such as feeding and mating.

Set against this scenario is the evolution by the parasite of mechanisms for evasion of the host's immune response, designed to downregulate the particular aspects of the Th2 response that are harmful to it. These mechanisms will differ between species of parasite and between life-cycle stages of the same parasite. It is clear that a number of important innate and Th2-controlled effector responses remain to be defined before we have a complete understanding of the complex interactions occurring between these parasites and the host's immune system.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES