REVIEW ARTICLE

The beneficial helminth parasite?

D. M. McKAY*

Intestinal Disease Research Programme, McMaster University, Hamilton, Ontario, Canada

(*Received 4 April 2005; revised 6 June and 18 July 2005; accepted 19 July 2005; first published online 21 September 2005*)

SUMMARY

There is unequivocal evidence that parasites influence the immune activity of their hosts, and many of the classical examples of this are drawn from assessment of helminth infections of their mammalian hosts. Thus, helminth infections can impact on the induction or course of other diseases that the host might be subjected to. Epidemiological studies demonstrate that world regions with high rates of helminth infections consistently have reduced incidences of autoimmune and other allergic/inflammatory-type conditions. Here I review and assess the possible ways by which helminth infections can block or modulate concomitant disease processes. There is much to be learned from careful analysis of immuno-regulation in helminth-infected rodents and from an understanding of the immune status of acutely and chronically infected humans. The ultimate reward from this type of investigation will likely be a more comprehensive knowledge of immunity, novel ways to intervene in the immune response to alleviate autoimmune and allergic diseases (growing concerns in economically developed areas), and perhaps the development of helminth therapy for patients suffering from specific inflammatory, autoimmune or allergic disorders.

Key words: allergy, inflammation, immunomodulation, *Hymenolepis* spp., nematode, *Schistosoma* spp.

INTRODUCTION

Parasitism by definition is a malevolent condition: the parasite survives at some cost to the health and/or nutritional status of the host. Thus, as elegantly stated in the Red Queen hypothesis (Castrodeza, 1979; Sasaki, 2000), the host-parasite relationship can be considered a complex evolutionary arms-race. The host evolves to better recognize, and then neutralize or destroy the parasite, while the parasite attempts to stay one step ahead by developing ways of avoiding or suppressing the host's immune response. The successful parasite is one that reaps the required benefits from its host, completes its life-cycle, and is not fatal to the host. While the latter may not be a prerequisite for a parasitic life-style it offers the advantages of allowing greater time for parasite eggs/larvae to be produced, and host reproduction that will maintain the host population for subsequent generations of the parasite to infect.

The concept of a 'harmonious' parasite appears paradoxical, but it is not new and makes sense if one accepts that while exploiting the host, the parasite would benefit by providing some advantage to the host over non-infected individuals (Desowitz, 1981). Caution must be exercised when attempting to assign evolutionary significance to host-parasite relationships: evolution operates in a random fashion to optimize the organism's fitness in terms of survival and reproduction. For instance, increased pathology in the host species leading to greater dissemination of eggs or larvae would be advantageous to the parasite. Alternatively, should the parasitic infection result in reduced susceptibility of the host to other diseases and increase survival of the host, then the parasite would benefit from a stable relationship with the host that could allow for increased reproduction by the parasite. In contrast, host fatality as a result of adding the burden of a parasitic infection to an existing condition might offer no advantage to the parasite. In simple book-keeping terms, immune responses can be considered as energy expensive and a number of mechanisms have evolved in an effort to target immune responses appropriately (e.g. major histocompatibility class I and II processing pathways in the recognition of cytosolic- and extracellular-derived antigen, respectively) (Bradley and Jackson, 2004). Theoretically, the well-adapted parasite would not be fatal to the host, would limit anti-parasite immune responses and might protect the host from other diseases or immunopathologies. Indeed, there are numerous examples, some more anecdotal that others, of parasitic infections being

* Address correspondence to: Intestinal Disease Research Programme, HSC-3N5C, McMaster University, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5. Tel: 905-525-9140 ext. 22588. Fax: 905-522-3454. E-mail: mckayd@mcmaster.ca

Parasitology (2006), **132**, 1–12.
doi:10.1017/S003118200500884X Printed in the United Kingdom

associated with reduced incidences of other diseases, such as inflammatory bowel disease (Elliott *et al*. 2000).

The aims of this article are to review and critique the current literature on modulation of disease by helminth parasites, identifying gaps in the field and to provide an opinion on the areas that require clarification and further study. This commentary is complemented by recent excellent reviews of the immune response to helminth parasites and the subversion of host immunity by the parasite (Gause, Urban and Stadecker, 2003; Maizels and Yazdanbakhsh, 2003; Finkelman *et al*. 2004; Hayes, Bancroff and Grencis, 2004; Maizels *et al*. 2004).

Epidemiology studies indicate an inverse relationship between endemic helminthiasis and autoimmune and allergic diseases

A number of authoritative and convincing review articles have documented increasing incidences of diseases such as inflammatory bowel disease (IBD), insulin-dependent diabetes mellitus, multiple sclerosis, celiac disease, asthma and atopic/allergic conditions in economically developed regions of the world (Elliott *et al*. 2000; Araujo *et al*. 2004*a*; Cooper, 2004; Hunter and McKay, 2004; Wilson and Maizels, 2004). These disorders are too diverse and their emergence too rapid to support an exclusively genetic explanation for their increased incidence. Thus, one is drawn to a consideration of changes in environmental or nutritional factors as risk factors in the occurrence of, for example, IBD. Indeed, the geographical distribution of the aforementioned diseases is remarkable as it virtually excludes areas where helminth infections are endemic. In fact, Weinstock and colleagues presented a very elegant case for the association of de-worming with increasing incidence of Crohn's disease, a major form of IBD (Weinstock *et al*. 2002). However, correlative studies must always be viewed with caution as the data can be confounded by study bias, differences in the criteria used to include patients in the study, under or misdiagnosis of the disease in question (Farrokhyar, Swarbrick and Irvine, 2001), and really cannot disentangle the issues of cause and effect: a strong significant relationship between one continuous variable and another does not mean that that the two events are causally linked. So while the epidemiological data are supportive of the postulate that infection with parasitic helminths could prevent or reduce the severity of specific diseases, evidence in support of a causative relationship must be sought and the mechanisms that account for any benefit derived from helminth infections defined.

In presenting the case for helminth infections providing a concomitant health benefit to their hosts, the deleterious effects of parasitic infections must not be overlooked. Helminth infections cause severe morbidity and mortality, are detrimental to physical and cognitive development and, among other concerns, are a leading cause of neurological disorders in developing nations (Oberhelman *et al*. 1998; Oyewole *et al*. 2002; Ito, Nakao and Wandra, 2003; Udani, 2005). Thus, 1470 million people are infected with the nematode whipworm *Trichuris trichiura*, and as a consequence suffer from dysentery, anemia, malnutrition and rectal prolapse (Compton, 1999; Saldiva *et al*. 1999).

The T helper (Th) cell paradigm

In the mid-1980s Mosmann and colleagues unequivocally showed that murine $CD4^+$ T helper cell clones developed *in vitro* could be classified as Th1 or Th2 based on mitogen-evoked production of interferon-γ (IFNγ) and interleukin (IL)-4, respectively (Mosmann *et al*. 1986; Reiner, 2001). The Th1-Th2 paradigm is readily demonstrable in murine systems, and while a similar dichotomy likely exists in humans (Turner *et al*. 2003; Romagnani, 2004), a definite designation of Th1 or Th2 can be obscured depending on when the analysis is performed during the course of the infection (Allen and Maizels, 1997). Moreover, Th1 and Th2 cells are reciprocally cross-inhibitory; activation of a Th1 response (e.g. IFNγ production, activation of macrophages and $CD8^+$ cytotoxic T cells, and generation of IgG_{2a}) would be accompanied by inhibition of the mobilization of Th2-dominated responses, such as IgG_1 and IgE production.

It is now clear that Th1 and Th2 cells are but two phenotypes among a spectrum of T cell types and that the generation and resolution of adaptive immune responses involves multiple types of T cell (McGuirk and Mills, 2002). Recognition of $CD8^+$ T cells as a source of cytokines and identification of the regulatory B cell adds another layer of complexity to the adaptive arm of the immune system (Mosmann, Li and Sad, 1997; Velazquez, Wei and Braun, 2005). Thus any immune response, and particularly that against parasitic helminths, requires analysis from an integrated immunophysiological perspective, where the theme of connectedness between cells and systems is emphasized (Perdue and McKay, 1994). While definition of adaptive immunity as Th1- or Th2-type can be restrictive, the Th1-Th2 paradigm does nevertheless provide a convenient conceptual framework to begin to assess immune responses. In this context, assessment of serum, tissue or *in vitro*-stimulated immune cells from helminth-infected animals consistently reveals increases in Th2-type cytokines (i.e. IL-4, IL-5, IL-13 and IL-10) and Th2-driven immune effector systems (e.g. increased mucus-producing goblet cells in the intestine) (Grencis, 2003). However,

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

with the exception of intestinal helminth infections, where the Th2-driven responses are clearly anti-helminthic, the relative value of Th2 responses to limiting immunopathopathology and tissue injury, helminth eradication, or contrarily helminth survival need to be viewed in a species-specific manner, with consideration given to the various life-cycle stages of the different parasites (Allen and Maizels, 1996). For instance, the cytokine response in mice infected with the parenteral cestode, *Taenia crassiceps* (a widely accepted model of human cycticercosis caused by *Taenia solium*), is of a Th1 or mixed Th1/Th2 following infection, and converts to Th2-dominated responses in older infections characterized by the presence of granuloma-encased cysticerci (Toenjes and Kuhn, 2003). Furthermore, serum measurement of cytokine levels in helminth-infected humans does not universally reveal an overtly Th2-skewed pattern. This may be a reflection of the time of cytokine determination after infection (i.e. acute verses chronic), or indicative of mixed parasite infections (and/or bacterial infections), and, of course, tissue levels of cytokines may not be the same as serum levels of cytokines. However, recent data from a study involving Cameroonians suggests that assessment of Th2 responsiveness from stimulated peripheral blood mononuclear cells can predict susceptibility to gastrointestinal nematodes (Jackson *et al*. 2004).

Parasitic helminths and the modulation of disease

Cytokine profiles in patients with Crohn's disease have led to the wide-spread acceptance of this disorder as a Th1-dominated condition (Sawa *et al*. 2003) Thus, helminth infections by mobilizing Th2-cyokine responses would be predicted to be of value in blocking Crohn's disease. As proof-of-principal in support of this postulate, mice infected with nematode (*Heligmosomoides polygyrus*, *Trichinella spiralis*), cestode (*Hymenolepis diminuta*) or trematode (*Schistosoma mansoni*) parasites, or treated with *S. mansoni* egg antigen, are protected from colitis induced by direct intra-rectal administration of tri- or dinitrobenzene sulphonic acid (TNBS, DNBS) or by addition of dextran sodium-sulphate (DSS) to their drinking water: these models of colitis are associated with increased Th1 cytokine levels (Reardon *et al*. 2001; Khan *et al*. 2002; Elliott *et al*. 2003; Moreels *et al*. 2004; Hunter *et al*. 2005). Similar experimental data can be found in support of parasitic helminths blocking other Th1-type diseases in mice, such as *Helicobacter*-induced gastritis and experimental autoimmune encephalomyelitis (a model of multiple sclerosis) (Fox *et al*. 2000; La Flamme, Ruddenklau and Backstrom, 2003). So, are these studies relevant to human disease? In a recent small non-blinded study, Summers and coworkers reported that consumption of ova from the porcine whipworm, *Trichuris suis*, led to disease remission, or significant symptom relief, for patients with Crohn's disease (Summers *et al*. 2005*a*). While preliminary, these data are intriguing and generally fit the Th1-Th2 paradigm.

These studies generate 2 important areas for discussion. The beneficial effects of helminth parasites in murine models of inflammation or Crohn's disease have, with the exception of *H. polygyrus*, been observed in non-permissive systems, suggesting that the immune response mobilized to evict the worm is of sufficient magnitude to block the initiation of colitis or reduce established disease. Indeed, unlike infection of the non-permissive murine host, rats develop a patent *H. diminuta* infection and are not protected from DNBS-induced colitis (Hunter *et al*. 2005). In the same study, mice deficient in the transcription factor, signal transducer and activator of transcription (STAT)-6, which do not expel *H. diminuta* (McKay and Khan, 2003), were not protected from DNBS-induced colitis by prior infection with *H. diminuta*. However, the possibility that STAT-6 is important in the anti-colitic effect has not been unequivocally excluded and indeed exogenous IL-4 (STAT6 is an important intracellular mediator of IL-4 bioactivity) has been shown to block TNBS-induced colitis (Hogaboam *et al*. 1997). To extrapolate these data to human disease, where helminth infections are often chronic, one can hypothesize that the immune response against the worm, while incapable of eliminating the parasitic burden is able to reduce Th1-mediated disease and pathology (I will return to the issue of humans with chronic helminth infections later). In the context of the therapeutic benefit gained by the patients with Crohn's disease who ingested *T. suis* eggs, it should be noted that these patients are unlikely to have a history of helminth infections and that *T. suis* will not establish a chronic infection in humans.

The corollary of the hypothesis that parasitic helminths will block Th1-driven disease by promoting an antagonizing Th2 response is that the helminth infections would predispose to Th2-dominated disorders. This in fact appears not to be the case: enhanced IgE production is characteristic of individuals with helminth infections, but this is not associated with increased allergic or atopic-type disorders (Yazdanbakhsh, van den Biggelaar and Maizels, 2001). Indeed, and seemingly paradoxically, asthma and allergy (Th2- and IgE-dominated conditions) are significantly less prevalent in areas of endemic helminth infections (Bashir *et al*. 2002; Yazdanbakhsh, Kremsner and van Ree, 2002). Also, in an assessment of *H. diminuta* amelioration of DNBS-induced colitis it was found that infected mice simultaneously sensitized to ovalbumin were not hypersensitive to subsequent ovalbumin challenge as gauged by mast

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

cell-mediated responsiveness compared to animals only sensitized by ovalbumin (Hunter *et al*. 2005). Equally provocative are recent data showing that patients with ulcerative colitis, a disorder associated with Th2 cytokines, obtained some symptomatic relief after ingestion of *T. suis* eggs (Summers *et al*. 2005*b*) (in an accompanying editorial the novelty of this approach and the small therapeutic benefit that was achieved were highlighted (Mayer, 2005)). How then does one rationalize Th2-promoting infections with reduced incidence or development of diseases driven by Th2-type cytokines?

Helminth-evoked interleukin-10 production

Since strict adherence to the Th1-Th2 paradigm or the hygiene hypothesis does not universally explain the down-regulation of many diseases or immunopathological states by helminth infections, other explanations have been sought. A concept presented by a variety of investigators from diverse disciplines is that of creation of an immuno-suppressed or immuno-regulatory environment as a consequence of helminth infections. A variety of model systems suggest that IL-10 is important in the immune-regulation that accompanies helminth infection and is important for host survival (Schopf *et al*. 2002). Thus, the protection against DNBS-induced colitis afforded by *H. diminuta* infection is lost if the mice are simultaneously treated with an IL-10 neutralizing antibody (Hunter *et al*. 2005). Similarly, the anti-colitic effect of *S. mansoni* eggs correlated with increased tissue levels of IL-10 mRNA (Elliott *et al*. 2003). Furthermore, the protection that nematode or *S. mansoni* infection provides against atopic, allergic and autoimmune conditions can be associated with increased IL-10 levels and ablated by blocking IL-10 activity (van den Biggelaar *et al*. 2000; Araujo *et al*. 2004*b*; Wohlleben *et al*. 2004). Ramaswamy and coworkers extended the focus on IL-10, and suggested that part of the immuno-modulatory effect of IL-10 following *S. mansoni* infection was due to the subsequent production of prostaglandin (PG) E_2, which is generally immuno-suppressive (Ramaswamy, Kumar and He, 2000). T helper 2 cells could be the source of the IL-10, but it is also likely that regulatory T cells (T_{regs}) in helminth-infected individuals are a significant source of IL-10 (O'Garra and Vieira, 2004). In the intestine, T_{regs} have been shown to limit inflammation and tissue injury (Groux *et al*. 1997). Moreover, recent findings suggest that inhibition of fatal anaphylaxis in mice infected with *S. mansoni* was due to IL-10 from B cells (Mangan *et al*. 2004); and, there is an increasing body of literature concerning the regulatory B cell and more recently how B cells might modulate the activity of T_{regs} (Wei *et al*. 2005). A considerable amount of data can be presented in favour of IL-10 as a major player in helminth-evoked beneficial health effects; however, this is certainly not the full story. Interleukin-10 deficient mice develop a spontaneous colitis the severity of which can be reduced by *H. polygyrus* infection (Elliott *et al*. 2004). In this instance, IL-10 cannot be mediating the nematode-evoked effect. Also, the promise of IL-10 therapy for IBD as predicted by murine models of colitis has not been fulfilled in clinical trails, leaving one with the unsatisfactory explanations that either the recombinant IL-10 is not being administered in the appropriate manner or that Crohn's disease is not amenable to IL-10 therapy (Li and He, 2004).

*Regulatory T cells and transforming growth factor-*β

As mentioned above, the regulatory T cell is an important source of IL-10 but other phenotypically distinct T cells exist that exert their effects by direct cell-cell contact or soluble factors, notably IL-10 and TGFβ (O'Garra and Vieira, 2004). It is likely that analysis of the host immune response to all classes of helminth parasite will reveal increases in T_{regs} during the infection (and/or rejection). Given the ability of these cells to control immune reactions, it is conceivable that T_{regs} mobilized in response to helminth infections could, in a bystander manner, limit other pathophysiological reactions. To date, a limited number of studies have been presented in support of this hypothesis. For instance, IL-10 producing $CD4^+CD25^+$ T_{regs} have been described in *S. mansoni* infected mice, FoxP3 (a T_{reg}-specific transcription factor) has been shown in *S. mansoni* or *H. polygyrus*-infected mice and, a regulatory T cell designated as type 1 (Tr1) has been identified in patients with chronic onchocerciasis (Satoguina *et al*. 2002; Elliott *et al*. 2004; Hesse *et al*. 2004; McKee and Pearce, 2004).

Increases in TGFβ have been associated with immunomodulation following infection with protozoan parasites (Omer, Kurtzhals and Riley, 2000), and while recent reports have documented TGFβ production following infection with helminths, the contribution of this cytokine to inhibition of concomitant disease has not been tested (Omer *et al*. 2003; Paalangara, McClure and McCullagh, 2003).

Given the intense current interest in T_{regs} and TGFβ in the control of mucosal immunity, it is reasonable to speculate that substantial evidence in support of T_{regs} and TGFβ involvement in the amelioration of disease by helminth infections will be forthcoming. However, as is the case with IL-10 (and PGE_2), findings relating to mobilization of T_{regs} and TGFβ in helminth infections and any concomitant health benefits for human hosts must be placed in the context of infections followed by spontaneous cure, chronic infections and/or polyparasitism (see below).

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

Antigen-presenting cells: dendritic cells and macrophages

It has already been noted that B lymphocytes can be responsible for some of the effects that accompany helminth infections, and it would be naïve to exclude consideration of other immune cells. For example, primary immune responses are in large measure dependent on dendritic cells (DC). The activity of the DC, and the subsequent polarization of the immune cell response is dependent on the nature of the antigen, the expression of co-signals (e.g. B71 (CD80) verses B72 (CD86)) and other molecules (e.g. CD40), and the nature of the cytokine milieu (Maldonado-Lopez and Moser, 2001). The ability of DC to cause the differentiation of Th2 cells is increased by exposing the DC to products from *Acanthocheilonema vitaea* or *S. mansoni* (Whelan *et al.* 2000; Thomas *et al.* 2003). In addition, using gene-microarray analysis it was recently shown that soluble egg antigen from *S. mansoni* affected the expression of >100 LPS-regulated genes in DCs (Kane *et al.* 2004). These findings led the authors to conclude that helminth-derived products could affect toll-like receptor (TLR: LPS binds TLR-4) signalling and this would certainly impact on the nature of innate immunity and subsequent adaptive immune responses. However, while highly probable, direct involvement of DC subtypes in the modulation of disease by helminth infections has not been shown and needs to be specifically addressed.

Macrophages are important scavengers of abnormal/damaged self-tissue and foreign antigen, and while the respiratory burst associated with the phagocytic activity of macrophages can damage host tissue there is increasing evidence of additional macrophage phenotypes that can influence T cell polarization and may be more immunologically 'quiet' (Mills *et al.* 2000). Helminth infections have been associated with an 'alternatively activated macrophage' (AAM) that develops under the influence of IL-4 and IL-13 (Gordon, 2003). These cells are characterized by increased expression of arginase-1 compared to inducible nitric oxide synthase (iNOS) in conventional macrophages, and by the expression of Fizz1 and Ym1 genes (Loke *et al.* 2000; Donnelly *et al.* 2005). Arginase-1 is active in tissue remodeling, since L-arginine metabolites are consumed during cell division and collagen deposition. Little is known of the activity of the Fizz1 or Ym1, but both have been implicated in tissue repair processes and Ym1 may be a chemoattractant for eosinophils (Welch *et al.* 2002; Liu *et al.* 2004; Nair *et al.* 2005). Thus, differentiation of AAMs could be a reaction to the tissue damage caused by migrating helminths or the abrasion/destruction associated with nematode feeding. Moreover, the AAMs that develop in response to *Brugia malayi* block lymphocyte proliferation by a cell-to-cell contact that is not due to the induction of apoptosis (Loke *et al.* 2000), while *S. mansoni*-induced T cell anergy was associated with up-regulation of programmed death ligand-1 on macrophages (Smith *et al.* 2004). Also, peritoneal macrophages that develop in chronically *T. crassiceps*-infected mice display increased PGE_2 production but dampened nitric oxide synthesis upon stimulation: these cells promoted the development of IL-4-producing $CD4^+$ T cells (Rodriguez-Sosa *et al.* 2002). A similar non-classical macrophage phenotype has been identified in airways tissue following *T. spiralis* infection (Dzik *et al.* 2004). Thus, AAMs could contribute to the suppression of concomitant disease in helminth infected individuals; while this is a reasonable speculation, there is currently no data to support the supposition.

Major challenges in assessing helminth infections as a benefit to blocking other diseases in their hosts, will be to provide a precise evaluation of the relative individual contributions of the immune cells and the collective effect of mobilizing multiple immuno-regulatory cells (plus their respective mediators), and understanding how the cells/mediators interact to combat helminth infections and provide additional health advantages for the host.

The neuroimmunophysiological perspective

Pioneering work by Castro in the 1980s drew attention to the fact that the host response to a parasitic infection is an integrated one, involving a variety of effector cells and communication between cells that hitherto had not been well appreciated (Castro, 1989). In this context one must look beyond the 'classical' components of the immune system and ask, what other cells or mediators might be involved in the response to helminth infections?

Increased mucus production and water secretion are characteristic of intestinal helminth infections, particularly those in which spontaneous cure is evident (McKay *et al.* 1990*b*; Masson *et al.* 1996). For example, *H. polygyrus*-induced IL-4 in mice had direct and indirect (via nerves) effects on epithelial ion transport especially following secondary worm infection (Shea-Donohue *et al.* 2001). Enhanced mucus and water secretion would reduce the contact time between luminal agents (e.g. microbial or food antigens) and the gut epithelium, 'wash' the surface of the enterocyte and contribute to the flushing of noxious agents from the gut. As a consequence, aggravated intestinal disease evoked by luminal stimuli would be reduced. Similarly the altered muscle contractility and increased peristalsis that accompanies enteric helminth infections would result in enhanced caudally-directed movement and expulsion of antigen and parasites from

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

the body (Vallance, Blennerhassett and Collins, 1997; Zhao *et al*. 2003).

Muscle contraction is under neuronal control and there is abundant information on bi-directional communication between nerve cells and all classes of immune cells. Some neurone-derived molecules enhance immune responses (e.g. substance P) (Suzuki *et al*. 1999) and others dampen immune reactivity (e.g. vasoactive intestinal peptide (VIP)) (Delgado and Ganea, 2001). In fact, descriptions of neuronal changes following helminth infections are common; however, the functional significance of the altered neuronal activity is often less clear (McKay and Fairweather, 1997). Nerve growth factor (NGF) affects not only neuronal growth but also a variety of immune functions (Bonini *et al*. 2003). Murine recombinant Fizz1 can inhibit NGF-mediated survival of rat dorsal root ganglion neurones *in vitro* (Holcomb *et al*. 2000). This AAM/Fizz1-Neuron/NGF relationship is intriguing and allows for the possibility that macrophage-nerve communication could influence neurogenic inflammation or the participation of nerves in mucosal immune responses. Similarly, *T. spiralis* infection has recently been shown to block up-regulation of iNOS expression via an IL-4/STAT6-dependent, T cell-independent mechanism (Bain *et al*. 2005): a predicted consequence of this would be reduced enteric inflammation. Juxtaposition of the facts that neuronal changes accompany helminth infections and that immune responses can be modified by neurochemicals/neuropeptides leads to the testable hypothesis that amelioration of inflammatory or autoimmune disease by helminth infections is due in part to changes in the local or systemic nervous system.

Similarly, enteroendocrine cells (EC) are a source of mediators that can affect mucosal immunity (e.g. serotonin, neurotensin). Increases in EC numbers can accompany helminth infection (McKay *et al*. 1990*a*) but the relevance of this to altered immune reactivity or the suppression of concomitant disease has not been determined. Enteroendocrine cells are potentially excellent surveillance cells: their luminal aspect is exposed to the gut lumen and they contain a variety of amines and neuropeptides that can be quickly released to act at both local (autocrine, paracrine) and distant (endocrine) sites. The role of enteroendocrine cells in enteric helminth infections deserves greater research efforts.

Active parasite involvement

To this point the beneficial effects of helminth infections have been considered as components of the hosts' response to the parasite, the inference being that this is solely an active host response. This is clearly not the case. At the outset it was noted that the successful parasite is one that survives the host's attempts to quickly identify and destroy/eradicate it. Behnke and colleagues presented some of the seminal observations on immuno-suppression caused by acute and chronic helminth infections (Behnke, Barnard and Wakelin, 1992) and there are innumerable examples of how specific species of helminths modulate host immunity and irrefutable evidence that helminths subvert host immune responses (Maizels *et al*. 2004). In the latter instance, active modulation of host immune cell activity could be a major contributor to any subsequent health benefits that coincide with helminth infections. For example, many helminth-derived excretory/secretory products have general immunosuppressive properties (Arechavaleta, Molinari and Tato, 1998). Other helminth-derived molecules seem to preferentially influence the development of a restricted spectrum of immune events or cytokines – inhibition of IL-4 or potentiation of IFNγ, for example (Lawrence, Allen and Gray, 2000; Rigano *et al*. 2001). Finally, and of particular relevance in the light of immuno-regulation, protein components from *Onchocerca volvulus*, *A. viteae*, and *H. diminuta* and a lipid-based molecule from *S. mansoni* appear to specifically promote IL-10 production from host immune cells (van der Kleij *et al*. 2002; Hartmann and Lucius, 2003; Wang and McKay, 2005). So, unlike systems that assess the implications of delivering purified antigen (with or without adjuvant), the host's immune response, whether anti-helminthic, beneficial to the helminth, or advantageous to the host by limiting concomitant disease, must always be viewed from the perspective of host-parasite interactions.

Finally, there is increasing evidence that helminths can actively manipulate their hosts' immune response by the production of cytokine, or neuropeptide, analogues, including IFNγ, IL-12 (p40 chain), macrophage migration inhibitory factor (MIF), TGFβ, and vasoactive intestinal polypeptide (VIP) (Foster and Lee, 1995; Grencis and Entwistle, 1997; Gomez-Escobar, Lewis and Maizels, 1998; Zang *et al*. 2002; Wang and McKay, 2005).

Human helminthiasis

The host response to parasitic infection can often be presented from an immunologists' perspective, overlooking the parasitiological context. In areas with high prevalence of parasitic infections, individuals are often infected with multiple species of helminth and/or protozoal parasites. However, laboratory models (particularly rodents infected with gastrointestinal helminths or *S. mansoni*) that have been so instrumental in defining the stereotypic host immune responses to helminths almost exclusively use a single species of parasite. Indeed, it is known that concurrent infection of *Nippostrongylus*

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

brasiliensis-infected rats with *H. polgyrus* prevents the spontaneous cure of *N. brasiliensis*, converting it to a chronic infection (Wescott and Colwell, 1980). This issue of polyparasitism is intriguing and has implications for worm fecundity (which is often higher in mixed helminth infections) and for immune responses in the host (Tchuem-Tchuente *et al*. 2003). Specific helminth co-infections have been assessed in mice (Behnke *et al*. 1992) but not in the context of how this would impact the initiation or progression of another disease. Similarly, while data is emerging on the health effects of polyparasitism in defined populations of humans (typically in developing regions of the globe), the full importance of this to suppression of other allergic or inflammatory diseases is not known.

The beneficial effect of parasitic helminths in alleviating colitis in some murine model systems was dependent on the spontaneous rejection of the helminth, but human helminth infections are typically of a chronic nature. In this context, there is evidence that chronic helminth infections do ameliorate disease. For instance, results of a randomized controlled clinical trial on the effect of eradiation of intestinal helminths (*Ascaris* and *Trichuris*) in Gabonese school children showed that the anthelminthic therapy lead to increased development of skin sensitivity to house dust mites (van der Biggelaar *et al*. 2004). In a related study, it was found that schistosome-infected children had reduced responsiveness to Toll-like receptor ligands (TLR) such as LPS, indicating altered signaling in the innate immune response (van der Kleij *et al*. 2004). This suggests that de-worming strategies could leave the individuals susceptible to not only atopic disorders but also to infection with microbes such as *Plasmodium* and *Mycobacterium* that are endemic in geographical regions of high helminth prevalence. However, de-worming could lead to reducing incidence of acquired immune deficiency syndrome (AIDS), since Bentwich and colleagues have suggested that helminth infections increase T cell numbers and their expression of the chemokine receptors that the AIDS virus uses to attach to and invade T cells (Kalinkovich *et al*. 1999; Borkow *et al*. 2000).

One must also question differences between a single 'bolus' of infection used in the laboratory model systems, with that of low-dose, trickle infections with the same species, or constant exposure to a variety of parasitic helminths – conditions representative of areas of endemic helminth infections. Indeed, trickle infection of rats with *N. brasiliensis* may result in a chronic infection and not the rapid rejection response typical of a high-dose infection (Jenkins and Phillipson, 1972). One would expect that this difference in infectivity would be reflected in either quantitatively or qualitatively different immune responses.

Such parasitiological issues are likely to be key to fully understanding how helminth infections modulate the induction and/or course of concomitant disorders in their hosts, and must be incorporated into models of helminth-alleviation of disease based on epidemiological observations. Similarly, these parasitiological issues should be borne in mind when considering the development of therapies based on data from helminth-infected rodents.

In making the case for the 'beneficial helminth', one would be remiss in not drawing attention to a number of caveats. As noted above, animal models are not entirely reflective of human-helminth interactions and so caution must be exercised in extrapolating data from the former to the latter. Also, the choice of helminth is important and obviously as innocuous a species as possible would be desired. It would make little sense to treat the debilitating IBDs with potentially fatal schistosomasis, although infection with non-permissive nematode or cestode species could be effective therapies. If actual helminth infection is considered as a therapy then the issue of palatability for the patient becomes pertinent. Additionally, one would advocate precise evaluation of the patient and their responsiveness to conventional therapies before considering the use of helminth infections. Importantly, one must be aware of the potential problems of introducing a parasite into an abnormal host as underscored by West's comments on the use of *T. suis* to treat patients with IBD (2005). In the abnormal host, the enteric parasite may be faced with a subtly or dramatically altered physio-chemical environment that might permit localization of adults, larvae or eggs to non-intestinal sites (e.g. the nervous system) and the development of pathology. It could take months or years for such adverse effects to appear and their incidence might be low, and so long-term follow-up of patients 'treated' with helminth parasites should be practiced.

So while actual prescription of helminth therapy may be feasible in the future, one can assume that it will come with some degree of concern and skepticism by the medical community; a viewpoint that can be swayed if helminth therapy is highly effective. However, the concerns outlined above relating to treating patients with 'therapeutic helminths' are less relevant in laboratory model systems where the goal is to understand the mechanism(s) by which helminth infections ameliorate diseases, and is so doing allow for the development of pharmacological agents that imitate the beneficial effect(s) of infection with parasitic helminths.

CONCLUSIONS

Undoubtedly helminth infections affect the course of other diseases. Epidemiology studies illustrate

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

an inverse relationship between endemic helminth infestation and a variety of diseases that can be Th1- or Th2-dominated conditions, such as Crohn's disease and asthma, respectively. Corroborating these observations, animal models of disease associated with Th1 or Th2-skewed immune responses can be inhibited by infection with a variety of parasitic helminths. A comprehensive understanding of host-parasitic helminth relationships can yield at least three very significant dividends. First, specific helminths may prove useful as a therapeutic option (a novel probiotic), as testified by the very promising preliminary data relating to the ingestion of *T. suis* eggs and the improvement of disease symptoms experienced by individuals suffering from IBD (Summers *et al*. 2005*a*). Second, analyses of the impact of helminth infections on murine models of human diseases can uncover novel anti-inflammatory and/or reparatory mechanisms that may translate to the human disorders. Precise definition of the cells/mediators responsible for helminth-induced amelioration of another disease may ultimately allow for treatment strategies in the absence of helminth infections. The previous discussion identified a number of candidate regulatory cells/mediators and how these players combine to mediate the beneficial effect of helminth infections needs to be determined. Third, helminths are a source of immuno-modulatory molecules that could be purified and tested as novel drugs, as recently shown for the ES-62 glycoprotein from the filarial nematode, *A. viteae*, which blocked LPS-induced murine arthritis (McInnes *et al*. 2003). A particularly exciting challenge will be the identification of human diseases and groups of patients that will benefit from helminth therapy (or application of treatments derived from the beneficial parasitic helminth paradigm), either alone or in combination with current therapeutics.

Finally, parasitism is by definition detrimental to the host; yet, the data accumulated to date suggests that analyses of the effects of helminth infections in humans and rodent model systems will yield significant insights to inflammatory and auto-immune diseases that are pandemic in economically advanced regions of the world. By juxtaposing appropriate laboratory models with analyses of helminth-infected individuals, and controlled clinical trails, we can comprehensively understand the long-standing relationship between humans and their 'wormy burden'. The knowledge gleaned from such studies can facilitate the development of novel therapies to treat allergic, autoimmune and inflammatory diseases, the incidences of which are increasing at an alarming rate.

Research from the author's laboratory was supported by funding from the Crohn's and Colitis Foundation of Canada.

REFERENCES

Allen, J. E. and Maizels, R. M. (1996). Immunology of human helminth infection. *International Archives of Allergy and Immunology* **109**, 3–10.

Allen, J. E. and Maizels, R. M. (1997). Th1-Th2: reliable paradigm or dangerous dogma. *Immunology Today* **18**, 387–392.

Araujo, M. I., Hoppe, B., Medeiros, M. J. R., Alcantara, L., Almeida, M. C., Schriefer, A., Oliveira, R. R., Kruschewsky, R., Figueiredo, J. P., Cruz, A. A. and Carvalho, E. M. (2004*a*). Impaired T helper 2 response to aeroallergen in helminth-infected patients with asthma. *Journal of Infectious Diseases* **190**, 1797–1803.

Araujo, M. I., Hoppe, B. S., Medeiros, M. J. R. and Carvalho, E. M. (2004*b*). *Schistosoma mansoni* infection modulates the immune response against allergic and auto-immune diseases. *Memorias do Instituto Oswaldo Cruz* **99**, 27–32.

Arechavaleta, F., Molinari, J. L. and Tato, P. (1998). A *Taenia solium* metacestode factor non-specifically inhibits cytokine production. *Parasitology Research* **84**, 117–122.

Bain, K., Zhong, M., Harari, Y., Lai, M., Weisbrodt, N. and Murad, F. (2005). Helminth regualtion of host IL-4α/STAT6 signaling: mechnaism underlying NOS-2 inhibiton by *Trichinella spiralis*. *Proceedings of the National Academy of Sciences, USA* **102**, 3936–3941.

Bashir, M. E. H., Andersen, P., Fuss, I. J., Shi, H. N. and Nagler-anderson, C. (2002). An enteric helminth infection protects against an allergic response to dietary antigen. *Journal of Immunology* **169**, 3284–3292.

Behnke, J. M., Barnard, C. J. and Wakelin, D. (1992). Understanding chronic nematode infections: evolutionary considerations, current hypotheses and the way forward. *International Journal for Parasitology* **22**, 861–907.

Bonini, S., Rasi, G., Bracci-Laudiero, M. L., Procoli, A. and Aloe, L. (2003). Nerve growth factor: neurotrophin or cytokine? *International Archives of Allergy and Immunology* **131**, 80–84.

Borkow, G., Leng, Q., Weisman, Z., Stein, M., Galai, N., Kalinkovich, A. and Bentwich, Z. (2000). Chronic immune activation associated with intestinal helminth infections results in impaired signal transduction and anergy. *Journal of Clinical Investigation* **106**, 1053–1060.

Bradley, J. E. and Jackson, J. A. (2004). Immunity, immunoregulation and the ecology of trichuriasis and ascariasis. *Parasite Immunology* **26**, 429–441.

Castro, G. A. (1989). Immunophysiology of enteric parasitism. *Parasitology Today* **5**, 11–19.

Castrodeza, C. (1979). Non-progressive evolution, the Red Queen hypothesis, and the balance of nature. *Acta Biotheories* **28**, 11–18.

Cooper, P. J. (2004). The potential impact of early exposures to geohelminth infections on the development of atopy. *Clinical Reviews of Allergy and Immunology* **26**, 5–14.

Crompton, D. W. (1999). How much human helminthiasis is there in the world? *Journal of Parasitology* **85**, 397–403.

Delgado, M. and Ganea, D. (2001). Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit expression of Fas ligand in activated T lymphocytes by regulating c-Myc, NF-$\kappa\beta$, NF-AT and early growth factors 2/3. *Journal of Immunology* **166**, 1028–1040.

Desowitz, M. (1981). Harmonious parasites. In *New Guinea Tapeworms and Jewish Grandmothers. Tales of People and Parasites* pp. 179–205. N. W. Norton & Co., London.

Donnelly, S., O'neill, S. M., Sekiya, M., Mulcahy, G. and Dalton, J. P. (2005). Thioredoxin peroxidase secreted by *Fasciola hepatica* induces the alternative activation of macrophages. *Infection and Immunity* **73**, 166–173.

Dzik, J. M., Golos, B., Jagielska, E., Zielinski, Z. and Walajtys-rode, E. (2004). A non-classical type of alveolar macrophage response to *Trichinella spiralis* infection. *Parasite Immunology* **26**, 197–205.

Elliott, D. E., Setiawan, T., Metwali, A., Blum, A., Urban, J. F. Jr. and Weinstock, J. V. (2004). *Heligmosomoides polygyrus* inhibits established colitis in IL-10-deficient mice. *European Journal of Immunology* **34**, 2690–2698.

Elliott, D. E., Li, J., Blum, A., Metwali, A., Qadir, K., Urban, J. F. Jr. and Weinstock, J. V. (2003). Exposure to schistosome eggs protects mice from TNBS-induced colitis. *American Journal of Physiology* (*Gastrointestinal Liver Physiology*) **284**, G385–G391.

Elliott, D. E., Urban, J. F. Jr., Argo, C. K. and Weinstock, J. V. (2000). Does failure to acquire helminthic parasites predispose to Crohn's disease? *FASEB Journal* **14**, 1848–1855.

Farrokhyar, F., Swarbrick, E. T. and Irvine, E. J. (2001). A critical review of epidemiological studies in inflammatory bowel disease. *Scandinavian Journal of Gastroenterology* **36**, 2–15.

Finkelman, F. D., Shea-donohue, T., Morris, S. C., Gildea, L., Strait, R., Madden, K. B., Schopf, L. and Urban, J. F. Jr. (2004). Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. *Immunological Reviews* **201**, 139–155.

Foster, N. and Lee, D. (1995). A vasoactive intestinal polypeptide like protein excreted/secreted by *Nippostrongylus brasiliensis* and its effect on contraction of uninfected rat intestine. *Parasitology* **110**, 97–104.

Fox, J. G., Beck, P., Dangler, C. A., Whary, M. T., Wang, T. C., Ning shi, H. and Nagler-anderson, C. (2000). Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. *Nature Medicine* **6**, 536–542.

Gause, W. C., Urban, J. F. Jr. and Stadecker, J. M. (2003). The immune response to parasitic helminths: insights from murine models. *Trends in Immunology* **24**, 269–277.

Gomez-Escobar, N., Lewis, E. and Maizels, R. M. (1998). A novel member of the transforming growth factor-beta (TGF-β) superfamily from the filarial nematodes *Brugia malayi* and *B. phangi*. *Experimental Parasitology* **88**, 200–209.

Gordon, S. (2003). Alternative activation of macrophages. *Nature Reviews in Immunology* **3**, 23–35.

Grencis, R. K. (2003). Cytokine regulation of resistance and susceptibility to intestinal nematode infection – from host to parasite. *Veterinary Parasitology* **100**, 45–50.

Grencis, R. K. and Entwistle, G. M. (1997). Production of an interferon-γ homologue by an intestinal nematode: functionally significant or interesting artifact? *Parasitology* **115**, S101–S105.

Groux, H., O'Garra, A., Bigler, M., Rouleau, M., Antonenko, S., De Vries, J. E. and Roncarolo, M. G. (1997). A $CD4^+$ T cell subset inhibits antigen-specific T cell responses and prevents colitis. *Nature, London* **389**, 737–742.

Hartmann, S. and Lucius, R. (2003). Modulation of host immune responses by nematode cystatins. *International Journal for Parasitology* **33**, 1291–1302.

Hayes, K. S., Bancroft, A. J. and Grencis, R. K. (2004). Immune-mediated regulation of chronic nematode infection. *Immunological Reviews* **201**, 75–88.

Hesse, M., Piccirillo, C. A., Belkaid, Y., Prufer, J., Mentink-kane, M., Leusink, M., Cheever, A. W., Shevach, E. M. and Wynn, T. A. (2004). The pathogenesis of schistosomiasis is controlled by cooperating IL-10-producing innate effector and regulatory T cells. *Journal of Immunology* **172**, 3157–3166.

Hogaboam, C. M., Valalnce, B. A., Kumar, A., Addison, C. L., Grahmam, F. L., Gauldie, J. and Collins, S. M. (1997). Therapeutic effects of interleukin-4 gene transfer in experimental inflammatory bowel disease. *Journal of Clinical Investigation* **100**, 2766–2776.

Holcomb, I. N., Kabakoff, R. C., Chan, B., Baker, T. W., Gurney, A., Henzel, W., Nelson, C., Lowman, H. B., Wright, B. D., Skelton, N. J., Frantz, G. D., Tumas, D. B., Peale, F. V. Jr., Shelton, D. L. and Hebert, C. C. (2000). FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. *EMBO J* **19**, 4046–4055.

Hunter, M. M. and McKay, D. M. (2004). Review article: Helminths as therapeutic agents for inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* **19**, 167–177.

Hunter, M. M., Wang, A., Hirota, C. L. and McKay, D. M. (2005). Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically-induced colitis. *Journal of Immunology* **174**, 7368–7375.

Ito, A., Nakao, M. and Wandra, T. (2003). Human taeniasis and cysticercosis in Asia. *Lancet* **362**, 1918–1920.

Jackson, J. A., Turner, J. D., Rentoul, L., Faulkner, H., Behnke, J. M., Hoyle, M., Grencis, R. K., Else, K. J., Kamgno, J., Boussinesq, M. and Bradley, J. E. (2004). T helper cell type 2 responsiveness predicts future susceptibility to gastrointestinal nematodes in humans. *Journal of Infectious Diseases* **190**, 1804–1811.

Jenkins, D. C. and Phillipson, R. F. (1972). Increased establishment and longevity of *Nippostrongylus brasiliensis* in immune rats given repeated small infections. *International Journal for Parasitology* **2**, 105–111.

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

Kalinkovich, A., Weisman, Z., Leng, Q., Borkow, G., Stein, M., Greenberg, Z., Zlotnikov, S., Eitan, S. and Bentwich, Z. (1999). Increased CCR5 expression with decreased beta-chemokine secretion in Ethiopians: relevance to AIDS in Africa. *Journal of Human Virology* **2**, 283–289.

Kane, C. M., Cervi, L., Sun, J., Mckee, A. S., Masek, K. S., Shapira, S., Hunter, C. A. and Pearce, E. J. (2004). Helminth antigens modulate TLR-initiated dendritic cell activation. *Journal of Immunology* **173**, 7454–7461.

Khan, W. I., Blennerhassett, P. A., Varghese, A. K., Chowdhury, S. K., Omsted, P., Deng, Y. and Collins, S. M. (2002). Intestinal nematode infection ameliorates experimental colitis in mice. *Infection and Immunity* **71**, 5931–5937.

La Flamme, A. C., Ruddenklau, K. and Backstrom, B. T. (2003). Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis. *Infection and Immunity* **71**, 4996–5004.

Lawrence, R. A., Allen, J. E. and Gray, C. A. (2000). Requirements for *in vivo* IFN-γ induction by live microfilariae of the parasitic nematode, *Brugia malayi*. *Parasitology* **120**, 631–640.

Li, M. C. and He, S. H. (2004). IL-10 and its related cytokines for treatment of inflammatory bowel disease. *World Journal of Gastroenterology* **10**, 620–625.

Liu, T., Jin, H., Ullenbruch, M., Hu, B., Hashimoto, N., Moore, B., McKenzie, A., Lukacs, N. W. and Phan, S. H. (2004). Regulation of found in inflammatory zone 1 expression in bleomycin-induced lung fibrosis: role of IL-4/IL-13 and mediation via STAT-6. *Journal of Immunology* **173**, 3425–3431.

Loke, P., MacDonald, A. S., Robb, A., Maizels, R. M. and Allen, J. E. (2000). Alternatively activated macrophages induced by nematode infection inhibit proliferation via cell-to-cell contact. *European Journal of Immunology* **30**, 2669–2678.

Maizels, R. M., Balic, A., Gomez-Escobar, N., Nair, M., Taylor, M. D. and Allen, J. E. (2004). Helminth parasites – masters of regulation. *Immunological Reviews* **201**, 89–116.

Maizels, R. M. and Yazdanbakhsh, M. (2003). Immune regulation by helminth parasites: cellular and molecular mechanisms. *Nature Reviews Immunology* **3**, 733–744.

Maldonado-Lopez, R. and Moser, M. (2001). Dendritic cell subsets and the regulation of Th1/Th2 responses. *Seminar in Immunology* **13**, 275–282.

Mangan, N. E., Fallon, R. E., Smith, P., Van Rooijen, N., McKenzie, A. N. and Fallon, P. G. (2004). Helminth infection protects mice from anaphylaxis via IL-10-producing B cells. *Journal of Immunology* **173**, 6346–6356.

Masson, S. D., McKay, D. M., Stead, R. H., Agro, A., Stanisz, A. and Perdue, M. H. (1996). *Nippostrongylus brasiliensis* infection causes neuronal abnormalities and altered neurally regulated ion secretion in rat jejunum. *Parasitology* **113**, 173–182.

Mayer, L. (2005). A novel approach to the treatment of ulcerative colitis: is it kosher? (editorial). *Gastroenterology* **128**, 1117–1119.

McGuirk, P. and Mills, K. H. (2002). Pathogen-specific regulatory T cells provoke a shift in the Th1/Th2 paradigm in immunity to infectious diseases. *Trends in Immunology* **23**, 450–455.

McInnes, I. B., Leung, B. P., Harnett, M., Gracie, J. A., Liew, F. Y. and Harnett, W. (2003). A novel therapeutic approach targeting articular inflammation using the filarial nematode-derived phosphorylcholine-containing glycoprotein ES-62. *Journal of Immunology* **171**, 2127–2133.

McKay, D. M. and Khan, W. I. (2003). STAT-6 is an absolute requirement for murine rejection of *Hymenolepis diminuta*. *Journal of Parasitology* **89**, 188–189.

McKay, D. M. and Fairweather, I. (1997). A role for the enteric nervous system in the response to helminth infections. *Parasitology Today* **13**, 63–69.

McKay, D. M., Halton, D. W., Johnston, C. F., Fairweather, I. and Shaw, C. (1990*a*). *Hymenolepis diminuta*: changes in intestinal morphology and the enterochromaffin cell population associated with infection in male C57 mice. *Parasitology* **101**, 107–113.

McKay, D. M., Halton, D. W., McCaigue, M. D., Johnston, C. F., Fairweather, I. and Shaw, C. (1990*b*). *Hymenolepis diminuta*: intestinal goblet cell response in male C57 mice. *Experimental Parasitology* **71**, 9–20.

McKee, A. S. and Pearce, E. J. (2004). $CD25^+CD4^+$ cells contribute to Th2 polarization during helminth infection by suppressing Th1 response development. *Journal of Immunology* **173**, 1224–1231.

Mills, C. D., Kincaid, K., Alt, J. M., Heilman, M. J. and Hill, A. M. (2000). M-1/M-2 macrophages and the Th1-Th2 paradigm. *Journal of Immunology* **164**, 6166–6173.

Moreels, T. G., Nieuwendijk, R. J., De Man, J. G., De Winter, B. Y., Herman, A. G., Van Marck, E. A. and Pelckmans, P. A. (2004). Concurrent infection with *Schistosoma mansoni* attenuates inflammation induced changes in colonic morphology, cytokine levels, and smooth muscle contractility of trinitrobenzene sulphonic acid induced colitis in rats. *Gut* **53**, 99–107.

Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A. and Coffman, R. L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *Journal of Immunology* **136**, 2348–2357.

Mosmann, T. R., Li, L. and Sad, S. (1997). Functions of CD8 T-cell subsets secreting different cytokine patterns. *Seminars in Immunology* **9**, 87–92.

Nair, M. G., Gallagher, I. J., Taylor, M. D., Loke, P., Coulson, P. S., Wilson, R. A., Maizels, R. M. and Allen, J. E. (2005). Chitinase and Fizz family members are a generalized feature of nematode infection with selective upregulation of Ym1 and Fizz1 by antigen-presenting cells. *Infection and Immunity* **73**, 385–394.

Oberhelman, R. A., Guerrero, E. S., Fernandez, M. L., Silio, M., Mercado, D., Comiskey, N., Ihenacho, G. and Mera, R. (1998). Correlations between intestinal parasitosis, physical growth, and psychomotor development among infants and children from rural Nicaragua. *American Journal of Tropical Medicine* **58**, 470–475.

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

O'Garra, A. and Vieira, P. (2004). Regulatory T cells and mechanisms of immune system control. *Nature Medicine* **10**, 801–805.

Omer, F. M., De Souza, J. B., Corran, P. H., Sultan, A. A. and Riley, E. M. (2003). Activation of transforming growth factor-β by malaria parasite-derived metalloproteinases and a thrombospondin-like molecule. *Journal of Experimental medicine* **198**, 1817–1827.

Omer, F. M., Kurtzhals, J. A. and Riley, E. M. (2000). Maintaining the immunological balance in parasitic infections: a role for TGF-β? *Parasitology Today* **16**, 18–23.

Oyewole, F., Ariyo, F., Sanyaolu, A., Oyibo, W. A., Faweya, T., Monye, P., Ukpong, M. and Okoro, C. (2002). Intestinal helminthiases and their control with albendazole among primary school children in riverine communities of Ondo state, Nigeria. *Southeast Asian Journal of Tropical Medicine and Public Health* **33**, 214–217.

Paalangara, R., McClure, S. and McCullagh, P. (2003). Intestinal exposure to a parasite antigen in utero depresses cellular and cytokine responses of the mucosal immune system. *Veterinary Immunology and Immunopathology* **93**, 91–105.

Perdue, M. H. and McKay, D. M. (1994). Integrative immunophysiology in the intestinal mucosa. *American Journal of Physiology* (*Gastrointestinal Liver Physiology*) **267**, G151–G165.

Ramaswamy, K., Kumar, P. and He, Y. X. (2000). A role for parasite-induced PGE2 in IL-10-mediated host immunoregulation by skin stage schistosomula of *Schistosoma mansoni*. *Journal of Immunology* **165**, 4567–4574.

Reardon, C., Sanchez, A., Hogaboam, C. M. and McKay, D. M. (2001). Tapeworm infection reduces the ion transport abnormalities induced by dextran sulphate sodium (DSS) colitis. *Infection and Immunity* **69**, 4417–4423.

Reiner, S. L. (2001). Helper T cell differentiation, inside and out. *Current Opinion in Immunology* **13**, 351–355.

Rigano, R., Profumo, E., Bruschi, F., Carulli, G., Azzara, A., Ioppolo, S., Buttari, B., Ortona, E., Margutti, P., Teggi, A. and Siracusano, A. (2001). Modulation of human immune response by *Echinococcus granulosus* antigen B and its possible role in evading host defenses. *Infection and Immunity* **69**, 288–296.

Rodriguez-Sosa, M., Satoskar, A. R., Calderon, R., Gomez-Garcia, L., Saavedra, R., Bojalil, R. and Terrazas, L. I. (2002). Chronic helminth infection induces alternatively activated macrophages expressing high levels of CCR5 with low interleukin-12 production and Th2-biasing ability. *Infection and Immunity* **70**, 3656–3664.

Romagnani, S. (2004). Immunologic influences on allergy and the TH1/TH2 balance. *Journal of Allergy and Clinical Immunology* **113**, 395–400.

Saldiva, S. R., Silveira, A. S., Philippi, S. T., Torres, D. M., Mangini, A. C., Dias, R. M., Da Silva, R. M., Buratini, M. N. and Massad, E. (1999). Ascaris-Trichuris association and malnutrition in Brazilian children. *Paediatric Perinatal Epidemiology* **13**, 89–98.

Sasaki, A. (2000). Host-parasite co-evolution in a multi-locus gene-for-gene system. *Proceedings in Biological Sciences* **267**, 2183–2188.

Satoguina, J., Mempel, M., Larbi, J., Badusche, M., Loliger, C., Adjei, O., Gachelin, G., Fleischer, B. and Hoerauf, A. (2002). Antigen-specific T regulatory-1 cells are associated with immunosuppression in a chronic helminth infection (onchocerciasis). *Microbes and Infection* **4**, 1291–1300.

Sawa, Y., Oshitani, N., Adachi, K., Higuchi, K., Matsumoto, T. and Arakawa, T. (2003). Comprehensive analysis of intestinal cytokine messenger RNA profile by real-time quantitative polymerase chain reaction in patients with inflammatory bowel disease. *International Journal for Molecular Medicine* **11**, 175–179.

Schopf, L. R., Hoffman, K. F., Cheever, A. W., Urban, J. F. Jr. and Wynn, T. (2002). IL-10 is critical for host resistance and survival during gastrointestinal helminth infection. *Journal of Immunology* **168**, 2383–2392.

Shea-Donohue, T., Sullivan, C., Finkelman, F. D., Madden, K. B., Morris, S. C., Goldhill, J., Pineiro-Carrero, V. and Urban, J. F. Jr. (2001). The role of IL-4 in *Heligosomoides polygyrus*-induced alterations in murine intestinal epithelial cell function. *Journal of Immunology* **167**, 2234–2239.

Smith, P., Walsh, C. M., Mangan, N. E., Fallon, R. E., Sayers, J. R., McKenzie, A. N. and Fallon, P. G. (2004). *Schistosoma mansoni* worms induce anergy of T cells via selective up-regulation of programmed death ligand 1 on macrophages. *Journal of Immunology* **173**, 1240–1248.

Summers, R. W., Elliott, D. E., Urban, J. F. Jr., Thompson, R. and Weinstock, J. V. (2005*a*). *Trichuris suis* therapy in Crohn's disease. *Gut* **54**, 87–90.

Summers, R. W., Elliott, D. E., Urban, J. F. Jr., Thompson, R. and Weinstock, J. V. (2005*b*). *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* **128**, 825–832.

Suzuki, R., Furuno, T., McKay, D. M., Wolvers, D., Teshima, R., Nakanishi, M. and Bienenstock, J. (1999). Direct neurite-mast cell (RBL) communication *in vitro* occurs via the neuropetide substance P. *Journal of Immunology* **163**, 2410–2415.

Tchuem-Tchuente, L.-A., Behnke, J. M., Gilbert, F. S., Southgate, V. R. and Vercruysse, J. (2003). Polyparasitism with *Schistosoma haematobium* and soil-transmitted helminth infections among school children in Loum, Cameroon. *Tropical Medicine and International Health* **8**, 975–986.

Thomas, P. G., Carter, M. R., Atochina, O., Da'Dara, A. A., Piskorska, D., McGuire, E. and Harn, D. A. (2003). Maturation of dendritic cell 2 phenotype by a helminth glycan uses a Toll-like receptor 4-dependent mechanism. *Journal of Immunology* **171**, 5837–5841.

Toenjes, S. A. and Kuhn, R. E. (2003). The initial immune response during experimental cysticercosis is of the mixed Th1/Th2 type. *Parasitology Research* **89**, 407–413.

Turner, J. D., Faulkner, H., Kamgno, J., Cormont, F., Van Snick, J., Else, K. J., Grencis, R. K., Behnke, J. M., Boussinesq, M. and Bradley, J. E. (2003).

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press

Th2 cytokines are associated with reduced worm burdens in a human intestinal helminth infection. *Journal of Infectious Diseases* **188**, 1768–1775.

Udani, V. (2005). Pediatric epilepsy – an Indian perspective. *Indian Journal of Pediatrics* **72**, 309–313.

Vallance, B. A., Blennerhassett, P. A. and Collins, S. M. (1997). Increased intestinal muscle contractility and worm expulsion in nematode-infected mice. *American Journal of Physiology* (*Gastrointestinal Liver Physiology*) **272**, G321–G327.

Van Der Biggelaar, A. H., Rodrigues, L. C., Van Ree, R., Van Der Zee, J. S., Hoeksma-Kruize, Y. C., Souverijn, J. H., Missinou, M. A., Borrmann, S., Kremsner, P. G. and Yazdanbakhsh, M. (2004). Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese school children. *Journal of Infectious Diseases* **189**, 892–900.

Van Den Biggelaar, A. H., Van Ree, R., Rodrigues, L. C., Lell, B., Deelder, A. M., Kremsner, P. G. and Yazdanbakhsh, M. (2000). Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* **356**, 1723–1727.

Van Der Kleij, D., Latz, E., Brouwers, J. F. H. M., Kruize, Y. C. M., Schmitz, M., Kurt-Jones, E. A., Espevik, T., De Jong, E. C., Kapsenberg, M. L., Golenbock, D. T., Tielens, A. G. M. and Yazdanbakhsh, M. (2002). A novel host-parasite lipid cross-talk. Schistosomal lyso-phosphatidylserine activates toll-like receptor 2 and affects immune polarization. *Journal of Biological Chemistry* **277**, 48122–48129.

Van Der Kleij, D., Van Den Biggelaar, A. H., Kruize, Y. C., Reta, R., Fillie, Y., Schmitz, M., Kremsner, P. G., Tielns, A. G. and Yazdanbakhsh, M. (2004). Responses to Toll-like receptor ligands in children living in areas where schistosome infections are endemic. *Journal of Infectious Diseases* **189**, 1044–1051.

Velazquez, P., Wei, B. and Braun, J. (2005). Surveillance B lymphocytes and mucosal immunoregulation. *Springer Seminars in Immunopathology* **26**, 453–462.

Wang, A. and McKay, D. M. (2005). Immune modulation by a high molecular weight protein from the rat tapeworm *Hymenolepis diminuta*. *Parasitology* **130**, 575–585.

Wei, B., Velazquez, P., Turovskaya, O., Spricher, K., Aranda, R., Kronenberg, M., Birnbaumer, L. and Braun, J. (2005). Mesenteric B cells centrally inhibit $CD4^+$ T cell colitis through interaction with regulatory T cell subsets. *Proceedings of the National Academy of Sciences, USA* **102**, 2010–2015.

Weinstock, J. V., Summers, R. W., Elliott, D. E., Qadir, K., Urban, J. F. Jr. and Thompson, R. (2002). The possible link between de-worming and the emergence of immunological disease. *Journal of Laboratory and Clinical Medicine* **139**, 334–338.

Welch, J. S., Escoubet-Lozach, L., Sykes, D. B., Liddiard, K., Greaves, D. R. and Glass, C. K. (2002). TH2 cytokines and allergic challenge induce Ym1 expression in macrophages by a STAT6-dependent mechanism. *Journal of Biological Chemistry* **277**, 42821–42829.

Wescott, R. B. and Colwell, D. A. (1980). Influence of numbers of *Nematospiroides dubius* upon delayed rejection of *Nippostrongylus brasiliensis* in mice. *Journal of Parasitology* **66**, 858–859.

West, A. B. (2005). Letter to the Editor. Potential danger in the medical use of *Trichuis suis* for the treatment of inflammatory bowel disease. *Inflammatory Bowel Disease* **11**, 515.

Whelan, M., Harnett, M. M., Houston, K. M., Patel, V., Harnett, W. and Rigley, K. P. (2000). A filarial nematode-secreted product signals dendritic cells to acquire a phenotype that drives development of Th2 cells. *Journal of Immunology* **164**, 6453–6460.

Wilson, M. S. and Maizels, R. M. (2004). Regulation of allergy and autoimmunity in helminth infection. *Clinical Reviews in Allergy and Immunology* **26**, 35–50.

Wohlleben, G., Trujillo, C., Muller, J., Ritze, Y., Grunewald, S., Tatsch, U. and Erb, K. J. (2004). Helminth infection modulates the development of allergen-induced airway inflammation. *International Immunology* **16**, 585–596.

Yazdanbakhsh, M., Van Den Biggelaar, A. and Maizels, R. (2001). Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. *Trends in Immunology* **22**, 372–377.

Yazdanbakhsh, M., Kremsner, P. G. and Van Ree, R. (2002). Allergy, parasites and the hygiene hypothesis. *Science* **296**, 490–494.

Zang, X., Taylor, P., Wang, J. M., Meyer, D. J., Scott, A. L., Walkinshaw, M. D. and Maizels, R. M. (2002). Homologues of human macrophage migration inhibitory factor from a parasitic nematode. Gene cloning, protein activity, and crystal structure. *Journal of Biological Chemistry* **277**, 44261–44267.

Zhao, A., McDermitt, J., Urban, J. F. Jr., Gause, W. C., Madden, K. B., Yeung, K. A., Morris, S. C., Finkelman, F. D. and Shea-Donohue, T. (2003). Dependence of IL-4, IL-13 and nematode-induced alterations in murine small intestinal smooth muscle contractility on stat6 and enteric nerves. *Journal of Immunology* **171**, 948–954.

https://doi.org/10.1017/S003118200500884X Published online by Cambridge University Press