

REVIEW: presented at the British Society for Allergy and Clinical Immunology Annual Meeting, September 1989

Parasites and allergy: evidence for a 'cause and effect' relationship

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Introduction

There are a number of similarities between protective immune responses against helminth parasites and IgE-mediated allergic diseases. Both are associated with elevated concentrations of IgE, increases in the number of tissue and blood eosinophils and signs and symptoms of mast cell activation. It has previously been suggested that these inflammatory cells and their immunoglobulin-dependent secretory processes may have been retained in phylogeny because, on balance, they appear to confer biological advantages in adoptive immunity against certain helminthic parasites [1]. Thus, the IgE/mast cell system almost certainly evolved to enhance protection rather than simply to mediate clinical allergic reactions against normally harmless substances to which man is constantly exposed. For example, acute inflammatory reactions known to be associated with the so-called 'type I' hypersensitivity may play an important role in mucosal defence against parasitic helminths [2,3]. In immunity to tissue-dwelling worms, the release of vasoactive and spasmogenic mediators (following the interaction between reinventing larvae with already sensitized mast cells) may contribute to increases in local concentrations of complement and specific antibodies. In addition, the recruitment and activation by chemotactic factors of secondary inflammatory cells such as eosinophils and neutrophils, may further enhance the effector function of these cells [5,6]. Conversely, similar vasoactive mediators are believed to contribute to deleterious changes, such as mucosal oedema, mucus hypersecretion and smooth muscle contraction which accompany most clinical allergic conditions, especially bronchial asthma. The array of biologically active mediators and cytokines released by newly recruited cells may also result in the amplification of the inflammatory reaction in the affected tissue.

The association between atopy and metazoan parasitic

infections (in which circulating eosinophils [7] and IgE [8] levels are elevated) has led to the development of a number of conflicting hypotheses. These are: (1) that infection with helminthic parasites predisposes towards atopy; (2) that parasite infection prevents or modulates atopy; and (3) that an atopic state can be protective against parasite infection(s). The potential inter-relationship between these theories is shown in Fig. 1.

In this article, we review the evidence to support these hypotheses, we discuss the various immune and inflammatory mechanisms operative in 'protective' reactions against worms, which appear to be shared with allergic inflammation, we discuss the reasons why definitive conclusions about the phylogenetic relationship between atopy and helminthiases cannot be made based on the currently available data, and suggest some future directions in research.

Does parasite infection pre-dispose the host towards sensitization to other environmental stimuli, leading to the development of atopy and asthma?

The evidence for this hypothesis is based on anecdotes and a few facts. For instance, bronchial asthma tends to be more widespread in areas where parasite infection is endemic [reviewed in reference 9]. It is also claimed that anthelmintic treatment causes a resolution of asthma [10–12]. These observations are supported by the occupational sensitization of laboratory workers to aerosolized *Ascaris*, and by the generation of an 'asthmatic state' in initially parasite-free primates by *Ascaris* infection [13–17]. As pointed out, however, these parasite allergens are not usually delivered by the aerosol route [18].

The epidemiological observation of Tullis [19], that individuals in a group of Canadian asthmatics were invariably parasitized with gastrointestinal nematodes was, at the time, considered to be strong evidence for believing that parasites 'caused' the asthma. This work was later criticized on the basis of mistaken identification of parasite ova in faeces [20]. Furthermore, others failed to confirm these findings [21].

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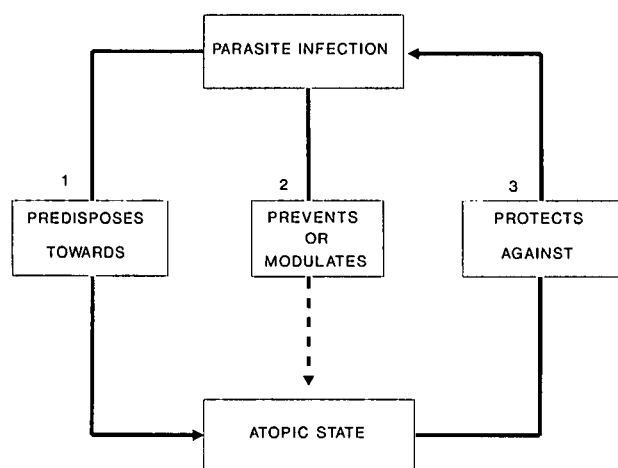


Fig. 1. An illustration of the possible relationships between parasite (helminth) infection and atopy.

Similarly, Joubert's contention [22,23] that subjects with an immediate skin reactivity to *Ascaris* extracts had a higher prevalence of asthma was counter-interpreted by Grove [20] to be equally indicative of an increased ability of asthmatics to mount a reaginic response to parasite antigens.

Lynch [18] concluded that 'under conditions of sporadic or mild intestinal helminthiasis, allergic reactivity is potentiated'. However, he later qualified this statement by describing a situation in which intense helminth infection can have a suppressive effect on the development of allergic disease caused by environmental allergens. In this context, it is worthy of note that host age and the timing of infection in relation to allergen exposure, as well as the intensity of infection, are important considerations for the subsequent development of allergic disease [24–26]. It must, however, be pointed out that studies of pulmonary function in subjects with severe chronic iron deficiency anaemia secondary to hookworm infection [27], showed a diminution in oxygen consumption/litre of ventilation as well as a reduction in carbon dioxide production. It would appear that lung function can be directly affected by the physiological effects of parasite infection, without the involvement of allergic mechanisms.

Thus, the evidence for the development of this hypothesis is conflicting. The undeniable ability of most helminths to induce a specific IgE response [15], to potentiate anti-allergen IgG responses [24], and to cause a mastocytosis in the infected host [28], could undoubtedly enhance the allergic state. In addition, the proven crossreactivity between *Sarcoptes scabiei* (which is a human ectoparasite) and *Dermatophagoides pteronyssinus* indicates that in some circumstances, parasites are able to enhance allergic reactivity to environmental allergens directly [29].

Can parasites prevent or modulate the development of allergic disease and asthma?

Turton [30] described how a self-infection with *Necator americanus* 'cured' his seasonal hay fever. This was attributed to the ability of hookworms to increase specific and total IgE levels [31], thus preventing mast cell sensitization by allergen-specific IgE. This 'blocking' theory is supported by the observation that parasite infection appears to raise total IgE levels disproportionately to parasite-specific IgE [32,33]. For example, approximately 10% of the increase in circulating IgE following *S. mansoni* infection is parasite-specific [34]. If we assume that IgE of all specificities have equal affinities for the FcεR1 on mast cells [35], the presence of excess IgE of an unknown and irrelevant specificity could in fact 'block' mast cells to the extent that the necessary bridging of adjacent IgE molecules of identical specificity to cause mediator release [36] would not occur. As this argument is one of the cornerstones of the hypothesis that parasites can modulate allergic disease, its experimental basis will now be discussed briefly.

Firstly, Prausnitz-Kustner (PK) reactions are difficult to perform in patients with high, helminth-induced serum IgE levels [37]. PK reactions can also be inhibited by IgE myeloma paraprotein, and the Fc fragment of IgE [38]. Controlled proteolysis experiments indicated that a site between the CE2 and CE3 domains of the IgE Fc region was involved [39]. This is consistent with the observations of Baird and Holowka [40] and Holowka *et al.* [41], who mapped the binding site in the CE3 domain. Blocking has also been achieved with synthetic peptides derived from the CE3 sequence [42]. However, an early study, in which an IgE-derived synthetic peptide exhibited anti-allergic activity in humans, [43] was later shown to be unrelated to any interference of IgE binding [44]. Since the advent of recombinant DNA techniques, both the CE2 and CE3 domains in tandem have been shown to be involved in 'conformation' binding to the IgE receptor [45].

Convincing as this evidence appears to be, it should be noted that blocking is not particularly effective in some cases of active sensitization [46,47]. Once again, the degree and timing of infection in relation to allergen exposure could be important variables worthy of consideration when interpreting this data. Further evidence of the potential of parasites to prevent or modulate the development of atopy comes from the observation that some helminths can 'stabilize' mast cells through the secretion of inhibitory factors [48] and prevent the development of mastocytosis in some instances [49]. It has also been suggested that worm parasites can suppress sensitivity to pharmacologically active agonists, e.g. methacholine [50].

Further evidence that parasites prevent or modulate asthma comes from prevalence and case studies [9,18,20]. Grove [20] stated that the relevance of the arguments described above 'can only be indicated by epidemiological investigations of the prevalence of asthma in areas similar in all aspects except for the presence or absence of endemic helminth infections'. Furthermore, he stated that 'this ideal is almost impossible to achieve'. Lynch [18] endorsed this view and was critical of the methodology involved in the evaluation of tropical populations. Indeed others [51,52], using a bronchial provocation test, identified asthmatics in the so-called asthma-free rural areas of the tropics. Therefore, the data compiled by Masters and Barrett-Connor [9] give the impression that asthma is less common in areas where intestinal parasites are common. Nevertheless, they drew attention to the fact that 'where asthma was rare, surveys used very broad definitions, while survey criteria were stricter where it was more prevalent'.

Case-control studies are even less definitive in endorsing the view that parasites prevent asthma. Masters and Barrett-Connor [9] showed that in only 1/7 studies reviewed was the frequency of intestinal parasites in asthmatics significantly different from controls. On balance, therefore, the epidemiological evidence that parasites prevent asthma is weak. Indeed, if elevated IgE levels are important to the parasite-induced protective effect then it is surprising that there were little differences in IgE levels between asthmatics and non-asthmatics in the tropics [52]. One study [53], which reported lower IgE levels in asthmatics compared to normal African non-asthmatics, suggested that this latter group were protected from atopic disease by developing high 'blocking' levels of non-specific IgE, most probably against gastrointestinal helminths. In addition, there is little evidence that immediate skin reactivity to environmental allergens was reduced in parasitized populations [54]. As a result, it is impossible at this juncture to favour either of the hypotheses proposed. The relationship between the parasite and the host's immune system is probably so dynamic that the variables which have to be considered in evaluating these hypotheses are numerous (see later). However, a number of studies have taken into account the relationship between the degree of parasitaemia and the presence of asthma [55,56].

Are asthmatics and atopics protected against parasites?

This hypothesis is, at first glance, difficult to reconcile with the theory that parasites protect against allergic asthma by blocking the effector arm of the immune response. By inference, the parasite will be simultaneously capable of blocking the immune response against itself,

through the production of excess (total) IgE. Despite this apparent paradox, there is some evidence that asthmatics in tropical areas harbour fewer parasites than their non-asthmatic counterparts. Grove and Forbes [55] found that the hookworm egg output of asthmatics in Papua New Guinea was significantly less than that seen in non-atopics, with non-asthmatic atopics occupying the middle ground. Shield *et al.* [56] also found that asthmatics in Papua New Guinea tended to produce fewer hookworm eggs than non-asthmatics, but neglected to mention the criteria used to assess asthma. More recently, Venge and Shaw [57], in a study in Zambia, demonstrated that 70% of their non-asthmatic subjects were parasitized, in contrast to 15% among the non-asthmatic subjects. Despite this evidence, future studies to determine whether an inverse relationship exists between parasites and asthma will have to be controlled more carefully. Masters and Barrett-Connor [9] correctly suggest that they should take into account genetic predisposition, nutritional status, psychosocial variables, and the time and degree of allergen exposure. Obviously, it would also be advantageous to determine the duration of infection in relation to allergen exposure, but this might be an impossible goal to achieve under field conditions. It should also be borne in mind, in relation to any of these hypotheses, that not all parasites act in the same way. For example, *Heligmosomoides polygyrus* suppresses both immunity in general [58] and the mastocytosis induced by *Trichinella spiralis*, and could be described as counter-allergenic. It is, on the other hand, possible that some parasites may be more allergenic than others, either because of their ability to induce IgE production, or their ability to induce mast cell degranulation (either directly, e.g. *Ascaris*, or via IgE). The site of residence of the parasite could also be important. Furthermore, circulating IgE levels may not be indicative of the allergic state (mediated by sequestered IgE). Individuals may also vary in their ability to express Fcε receptors (types 1 and 2), in their sensitivity to mediators and in their capacity to generate appropriate amine-containing cells. Recent work would suggest that the ability to produce and respond to IL4 should be considered, as should the relative abundance of the human T-helper cell type 2 equivalent [59], and the presence of IgE binding factors [60]. The diligent field investigator of the future faces a very difficult task!

Experimental evidence

The interaction between multicellular helminth organisms and the host's tissues elicits a complex cascade of immunological responses, whose relevance to the protection of the host is as yet not fully clear. These multifactorial immunological events culminate in inflammation,

which in many cases appears to be mainly IgE-dependent. Helminth-induced inflammatory responses involve an interplay between parasite antigens and the various types of immune and inflammatory cells which infiltrate and proliferate within the relevant tissue. This process also involves the elaboration of an array of potent cell-derived and humoral mediators. A major part of our current knowledge of the immunological and inflammatory mechanisms controlling immunity to helminthic infection is based upon work on experimental animal host/parasite models. Most of these studies have concentrated on intestinal mucosal responses to a number of helminths. In these infections, the worms, both as larvae and adults, provide potent and complex immunogens, which in rats and mice stimulate protective responses which lead to the elimination of most of the worm burden from the host. Worm expulsion during the course of a primary infection is known as 'spontaneous cure'; in which worm elimination is achieved within 12–14 days post-infection. It is believed that T-cell dependent mechanisms control and regulate both the specific (immunological) and non-specific (inflammatory) elements of the response. It is generally accepted that expulsion is mediated by the gross inflammatory changes in the tissue rather than the immune responses that lead to it. When immune animals are challenged soon after expelling an initial infection, they develop an anamnestic response against the new inoculum and expel this new worm load within 4–24 hr. This accelerated loss of worms, known as 'rapid expulsion', is typical of an immediate type hypersensitivity reaction and prevents the establishment, and curtails the survival of these worms in these presensitized hosts. Whether similar mechanisms are operative in human subjects who are exposed, in many cases repeatedly, to worm infections is not known. Since there are marked differences in immune responses between mammalian species, it is necessary to be cautious in making a direct extrapolation from rodent to human infections. The roles played by the various components of the immune and inflammatory (allergic-type) reactions in these host/parasite systems are outlined below. This enables a comparison of the characteristics of responses to helminthic infections, at least in animal models, with similar features of the allergic reaction.

Role of T lymphocytes

The central role of the T lymphocyte in initiating and regulating the inflammatory responses against helminthic parasites (especially intestinal nematodes) has now been well established in several host/parasite systems [reviewed in 61]. In the mouse, CD4⁺ T cells from parasite-sensitive animals can adoptively transfer immunity to *T. spiralis*

[62]. T cells also appear to be essential for worm rejection, the development of intestinal mast cell hyperplasia and the IgE response during primary infection with *Nippostrongylus brasiliensis* [63]. Accelerated expulsion of *T. spiralis* from normal rats can be transferred by immune CD4⁺ T cells. Similarly, eosinophilia and resistance to *Mesocostoides corti*, a peritoneal-dwelling cestode, can be transferred by parasite-specific CD4⁺ cells [64]. There is no evidence, however, that T cells themselves mediate worm expulsion directly. Lymphokines produced by these cells, following specific interaction with worm antigens, may promote the growth and activation of other cells (e.g. mast cells, eosinophils and goblet cells), which in turn mediate a non-specific inflammatory response detrimental to worm establishment and survival. For example, repeated administration of IL-3 to nude (i.e. T-cell deficient) mice restored their ability to expel *Strongyloides ratti* and to mount an intestinal mucosal mastocytosis [65]. Both IL-3 and IL-5 have been shown to enhance antibody-dependent *in-vitro* cytotoxicity by human eosinophils [66]. Activated T cells have also been shown to be involved in epithelial cell hyperplasia and villous atrophy [67], both of which are important features of the intestinal pathology of worm infection [68].

In allergic inflammation, the T lymphocyte was recognized for its involvement in the induction and regulation of IgE synthesis by B cells. Recent studies, using monoclonal antibodies and recombinant DNA methods, have demonstrated that T cells can also exert a direct pro-inflammatory action and possibly orchestrate the events associated with allergic tissue reactions, possibly in a fashion similar to that observed in anti-parasite responses. T lymphocytes have been shown to have a clear role in the recruitment and activation of effector cells [69], which are present in allergic reactions as well as their coordination by lymphokines secreted in response to specific antigen stimulation.

Role of mast cells and IgE

The participation of both IgE and mast cells in allergic-type reactions is well documented and does not require further review here. In helminth immunity, mast cells and IgE appear to have a strong association with the pathophysiological changes known to occur, at least in the infected intestine. Very high levels of IgE are produced following infection with intestinal nematodes [70] and there is strong evidence of mast cell activation during the process of worm expulsion [71]. Rats treated with anti-epsilon antiserum showed diminished resistance to *T. spiralis* infection [72]. Although IgE-dependent effector mechanisms have been reported, *in vitro*, there is no evidence that such mechanisms may also operate *in vivo*

against worms. Whether helminths, which invade tissues and mucosal surfaces, can become susceptible to IgE-dependent, inflammatory cell-mediated cytotoxicity is not yet clear, although parasite killing in the skin of hyperimmune animals has been described [73].

The role of eosinophils

An increase in the number of peripheral and tissue eosinophils is a major hallmark of helminthic infections, especially those with tissue-invading stages [74] as well as allergic inflammation [75]. Accumulation of eosinophils in mucosal surfaces during worm infections may arise as a result of chemotactic factors (e.g. PAF, LTB₄ and histamine) released following mediator cell/IgE-worm antigen interaction, T-cell mediated eosinophilopoiesis, either in the bone marrow and/or locally, and chemo-attractants released from the worms themselves. While there is abundant evidence of the helminthiocidal activities of eosinophils *in vitro*, there are, as yet, only limited data to support a protective role for these cells *in vivo* against worm infections. However, there is evidence of eosinophil activation during helminthic infection and the immune expulsion of some nematodes can be partially delayed by treatment with anti-eosinophil serum [76]. In humans, the evidence to date shows that peripheral blood eosinophilia reflects, but does not determine, the worm burden or its fate.

Role of allergic mediators

Allergic and inflammatory mediators, elaborated by various effector cells during allergic reactions, are thought to be involved in the pathophysiology of a number of hypersensitivity reactions. The exact role of these mediators, both preformed and *de novo* synthesized, in enhancing worm-associated inflammatory processes, and the extent of their contribution to worm damage, is as yet unclear. However, experimental evidence suggests that a number of allergic mediators have the potential to participate in events leading to worm elimination, at least in the rodent model. It is unlikely that a single mediator is responsible for the final trigger which causes worm expulsion. It is more probable that a combination of mediators is involved in creating unfavourable conditions in the relevant tissue sites which ultimately leads to parasite elimination.

Leukotrienes (both SRS-A sulphidopeptides and LTB₄) were shown to be released *in vivo* in previously sensitized rats undergoing systemic anaphylaxis induced by *N. brasiliensis* antigen [77] and also during rapid expulsion of *T. spiralis* from immune rats [78]. Leukotrienes were present in intestinal luminal washings, intestinal homogenates and blood plasma and their

generation was temporally associated with mucosal mast cell activation. PAF has also recently been shown to be released into the intestinal lumen of *N. brasiliensis*-immune rats undergoing systemic anaphylaxis as a result of intravenous challenge with worm antigen [79].

The release of these allergic mediators in association with helminthic parasites suggests that, like allergic cells and IgE, they are important elements in mucosal protection against helminths. It is likely that their retention within the allergic inflammatory response is a phylogenetic extension of their anti-parasite function.

Reconciliation and conjecture!

On the basis of the above, it seems possible to reconcile between hypotheses 1 and 3 (Fig. 1), as it could be argued that genetically predisposed atopsics are more prone to develop atopy/asthma following the additional allergenic stimulation provided by parasite infection. The immune response generated, and the heightened immunological reactivity provoked, could in turn be deleterious to the parasite. Furthermore, the genetically predisposed atopsics could conceivably be sub-divided on the basis of some of the observations described above. Experimental data from early experiments [24] indicate that the relative timing of exposure to allergen and infection is of particular importance. Pre-exposure to allergen, followed by infection, leads to a potentiated IgE response to the allergen and a seemingly significant 'non-specific' IgE component. This is potentially the blocking antibody that modulates allergic reactivity. However, it has already been stated that blocking is difficult to achieve following active sensitization, and it is possible that predisposed atopsics that experience early allergen exposure will develop asthma but control or expel their parasite burden (possibly as in the asthmatic non-parasitized group of Grove and Forbes [55]). No potentiation of the IgE response to allergen is seen if parasite infection occurs first [24], and suppression occurs if the stimuli are simultaneous; we would suggest that the former is most likely to occur. It could be argued that this pre-infected group of potential atopsics, because of their reduced immunological reactivity, would be more prone to retain their parasite infections (possibly as in the atopic, non-asthmatic intermediately parasitized group of Grove and Forbes [55]). Finally, the non-atopic proportion of the population would form the most heavily parasitized group.

Future direction

It is clear that future studies to answer the questions posed will have to take into account at least some of the

variables described above. The recently demonstrated linkage between IgE responses underlying asthma and rhinitis and chromosome 11q [80], will enable the typing of atopically predisposed individuals in human populations. Longitudinal studies of the kind recently conducted in Papua New Guinea by Pritchard *et al.* [7], in which expulsion chemotherapy was conducted to evaluate worm burdens together with nutritional, haematological and immunological data should, in combination with the genetic analysis described above, enable firmer conclusions to be made about the relationship between atopy and parasitism. It will be of particular interest to determine whether the apparent predisposition to reinfection following chemotherapy, already found in the above study population, has an atopic or immunological basis.

Acknowledgments

The authors would like to thank Professors A. B. Kay and D. Wakelin for their helpful comments on the manuscript, Mr A. J. MacDonald for his valuable assistance and Mrs Christine Bensted and Avena Guppy for their help in the preparation of this manuscript.

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