

EDITORIAL

Clinical & Experimental Allergy

The allergy epidemic: can helminths supply the antidote?

This editorial discusses the findings of the paper in this issue by P. Endara et al. [3] pp. 1669–1677.

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Allergic diseases are common, and the incidence is rising in industrialized countries and urbanized areas of the developing world [1]. While having a family member with allergic disease is a strong risk factor, the rapid rise in prevalence cannot be explained by genetic factors alone. There is strong epidemiological evidence for the existence of protective environmental factors associated with a rural lifestyle. The hygiene hypothesis suggests that the change that has occurred with urbanization has affected exposure to microorganisms, primarily due to better sanitation, but possibly also due to vaccination and the use of antibiotics [1]. The proposal is that the lack of such infections at an early age, when the immune system is developing, has resulted in dysregulated immune responses to allergens and an increase in allergic disease. Although there is great support for the hygiene hypothesis and animal models have convincingly shown protective effects of infection with or exposure to a variety of microbial factors, the data from human studies have been somewhat inconsistent and disappointing, most likely because of influences from a large number of confounding factors. In the last few years several studies have aimed to determine whether worm infection protects individuals from developing allergies. In developing countries, most children are exposed to helminth infections. It has long been known that helminths are immunosuppressive, can impair vaccine responsiveness, and modify the response to other infections. It, therefore, seems reasonable to propose that the absence of these large, long-lived organisms, and the lack of the immunomodulatory activity that they generate, could be a major contributor to the current allergy epidemic in developed

countries. Human studies on helminth infections have been encouraging [2], but more data are needed (as provided by Endara et al. [3], this issue) to clearly gauge and understand their protective role.

Mechanistically, it has been suggested that infectious agents control inflammatory diseases such as allergies and autoimmunity by active regulatory processes [4]. Helminth infection is associated with the induction of a regulated immune phenotype, sometimes referred to as 'modified Th2 [4]', with the induction of regulatory cells and the expression of the suppressive cytokines, IL-10 and TGF- β . Regulatory T cells (Tregs) can act on many different levels to suppress immune and inflammatory responses involved in the induction and severity of allergic diseases. They can influence the development of tolerogenic dendritic cells, inhibit the activation of Th2 cells, thereby reducing the production of cytokines such as IL-4, IL-5, IL-13, and IL-9, exert suppressive effects on mast cells, basophils and eosinophils, as well as suppress IgE production [5]. Such effects are achieved via a number of mechanisms, including the secretion of cytokines and contact-mediated effects. IL-10 and TGF- β are thought to play a mechanistic role in clinical allergen-specific immunotherapy; therefore, the increased levels induced by helminth infections are also likely to be important. Although Tregs have been studied most intensively, other suppressive cell types, including regulatory B cells [6] and myeloid suppressor cells [7], are thought to mediate protection from allergy.

Most epidemiological studies on helminth infections and the development of allergies have been cross-sectional, where individuals with or without helminth infections have been compared. An inverse relationship between skin prick test (SPT) responsiveness and helminth infections has been consistently found, but the evidence is less clear for protection against the development of clinical allergic disease, asthma, eczema, and allergic rhinitis [2]. Cross-sectional studies have shown that infection by at least some helminths is associated with a

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reduced prevalence of clinical asthma but there is little evidence available for effects on eczema or allergic rhinitis [8]. While cross-sectional studies are relatively quick, uncomplicated ethically, and can determine the prevalence of allergic parameters, they cannot, however, determine causality and are limited by confounding factors, not all of which can be predicted or accounted for.

Interventional studies can establish cause and effect. The majority of studies where the prevalence of allergies was measured following helminth eradication therapy have also shown that SPT responsiveness increases after treatment [2]. In one study, however, short-term treatment of gastrointestinal (GI) helminth infection had no effect [9]. This may have been due to the short time scale of the intervention (only 12 months). Such studies are hampered by the fact that we do not yet understand the protective mechanisms and how they are influenced by helminth eradication. The numbers of circulating helminth-specific memory cells are unlikely to drop sharply, and individuals will remain exposed to helminths and may re-acquire infections before effects on allergy can be assessed. There is also evidence that some anthelmintic drugs, such as ivermectin, have immunomodulatory effects on the immune system [10]. It is therefore very difficult to establish cleanly distinct infected and uninfected groups. Also because the strongest effects have been observed in young children, we have no way of knowing whether exposure to helminths early in life has some permanent influence on the immune system. Prospective birth cohort studies are an ideal way to address these possibilities and several are currently underway. However, retrospective studies on the long-term effects of the removal of environmental factors suspected of being involved are an alternative. The study by Endara et al. [3] took advantage of an ongoing control programme for onchocerciasis using ivermectin treatment, which is also effective against all GI helminths. The results showed that the prevalence of a positive SPT in school-aged children in an area that has received more than 15 years of anti-helminthic treatment was double that of a comparative area that had not been treated. The effects on clinical allergic disease were again, however, equivocal. Although treatment resulted in an increased prevalence of eczema, this was neither associated with reductions in GI helminths nor were symptoms of asthma and allergic rhinitis affected. While this study has made an important contribution to our understanding in this field, it was not designed specifically to address the question. As a result, it is less powerful than it might be as there are no pre-treatment values for helminth prevalence or abundance in the community. Also there were a number of confounding issues between the study area and the comparative control area where there had been no ivermectin treatment, the major being socioeconomic status. While attempts have been made to account for these confounding factors statistically, there may be others that

cannot be predicted. For example, colonization with intestinal commensal or pathogenic bacteria, and exposure to viral and fungal infections may be different between the communities, and these factors are reported to positively and negatively influence the risk of allergic diseases such as asthma (reviewed in [11]).

The heterogeneity in results between human epidemiological studies can be explained by differences in the study populations and the endemicity of the helminths being studied. There may also be differences in the composition of multiple infecting worm species. Helminths have a diverse range of physical characteristics and life histories. They have different life spans: some being tissue dwelling, some having a tissue migratory phase, while others live entirely in the gut. Some helminths also penetrate the lungs, and this property has even been used in models of pulmonary disease. It is therefore unlikely that all are equally good at preventing inflammatory and allergic diseases. It is difficult to establish species-specific effects on allergy in human studies because most individuals simultaneously harbour more than one helminth species and treatment is not specific. Meta-analyses have shown that schistosomes and hookworms have the strongest associations with protection against atopy and asthma [2, 11]. Our own studies have shown that both *Ascaris* and *Trichuris* infection were associated with an increased production of the regulatory cytokines TGF- β and IL-10. Only *Ascaris* infection, however, yielded statistically significant differences in measures of immune responsiveness [12]. A further complicating and confusing issue is that a few studies have shown that some helminth infections, again most notably *Ascaris lumbricoides*, are actually associated with a significantly increased risk of asthma and allergy (reviewed in [11]). This has been proposed to occur via several mechanisms including up-regulation of the α -chain of the IL-4 receptor on naïve CD4⁺ T cells, and stimulation of IL-4-secreting basophils, which act as Th2-promoting antigen-presenting cells. Transient infections are thought to be more likely to lead to allergic sensitization than chronic infections, and thus again this may impact on the data of Endara et al. [3].

One way to demonstrate if helminths actually do exert protective effects against allergy in humans is to administer experimental infections. The results of two randomized double-blind controlled trials have recently been published, and these ambitiously aimed to examine effects on pre-existing clinical allergy and asthma in adults. Bager et al. [13] administered *Trichuris suis* infections with the aim of inhibiting grass pollen-induced allergic rhinitis, but no therapeutic effects were observed. Feary and colleagues [14] found trends of improved bronchial responsiveness in individuals with asthma who had been given hookworm infections. Unfortunately, however, the differences between infection and placebo groups were not statistically significant. Neither of these studies were,

therefore, able to prove or refute the possibility that helminth infections provide protection against allergy. Possible reasons include that effects on the pre-existing clinical conditions would have required potent immunomodulation, and the infections were administered at doses too low to be effective in inducing such immune responses. In the case of the Bager study, the infections may have been administered at a time too close to the onset of the hayfever season, providing insufficient time to build up a protective-level immune response (as raised in [15]). As mentioned previously, it is possible that helminth infections do not have the same effect on the adult immune system, because the most profound protective associations have been observed in studies of childhood atopy.

It may also be difficult to alter the progression of asthma once established. This is a complex disease, and while helminth infections induce a high-level Treg response, the airways of patients with moderate to severe asthma are also known to contain large numbers of these cells. This implies that the lack of protection against clinical asthma observed in human helminth studies may not simply be because of insufficient numbers of regulatory cells. It may be that something prevents them functioning effectively. For example, the IL-7-like cytokine thymic stromal lymphopoeitin has been reported recently to reduce IL-10 secretion and the functional activity of pulmonary Tregs [16]. High levels of this factor are present in the asthmatic lung. The suppressive action of helminth-induced Treg cells may therefore be impaired during asthma. Despite evidence that the protective effects may be more complex than first thought, several groups have been studying parasite-derived immunomodulatory molecules, such as ES62 from *Acanthocheilonema vitae*, and are now considering their therapeutic potential [17].

While effects on clinical allergies have not as yet been conclusively demonstrated, either after the removal of worms or by actively administering them, there is an expanding body of evidence to show that helminths do have effects on atopy and allergic skin sensitization. This is encouraging when one considers the plethora of other factors that differ between life in a rural developing country and an urbanized western lifestyle. It seems unlikely that any one of these factors single-handedly protects against allergies, but a combination of many interacting factors is probably involved. The human immune system has coevolved to combat pathogens and coexist with commensal organisms, but modern living has disrupted this delicate ecosystem. Data indicate that early-life exposures are critical for protection against the subsequent development of allergies [18, 19]. There is a vast difference between looking for an improvement in an existing condition and preventing its development in the first place. Thus, more long-term prospective or retrospective cohort studies such as that described by Endara and colleagues are urgently required. These should inves-

tigate infections in early life, and be specifically designed to examine multiple environmental factors known to have effects on allergy and asthma, including chronic infections such as helminths, the bacterium *Helicobacter pylori*, intestinal microflora, viral respiratory infections, and exposure to fungi such as *Aspergillus fumigatus* and *Trichophyton*.

An important concern is that a sharply increased incidence of atopy could arise from the progressive urbanization of developing countries. In order to improve experimental design and truly provide definitive evidence, it is clear that we need to increase our understanding of the potential protective mechanisms. An obvious goal for such research is to ultimately derive therapeutic agents that are more effective against pre-existing clinical atopic conditions. It is also important to investigate prophylactic strategies to turn the tide against the increasingly common development of these diseases in developed countries. The immunological mechanisms behind this may be different, but more research is in urgent need because allergic diseases cause significant morbidity and mortality, and represent a substantial financial burden on health services. Studies such as that of Endara and colleagues are therefore of priority, and have the potential to make a huge difference to the health of the world's population.

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