

EDITORIAL

Immunoglobulin E and allergic disease in Africa

Although the prevalence of allergic disease appears to be increasing in most parts of the world [1–3], there are still important differences in the prevalence and pattern of disease both between and within developed and developing countries [4]. Studies in Africa, for example, have found a generally lower prevalence of self-reported asthma symptoms [4–6] exercise-induced bronchospasm [7], and allergic rhinoconjunctivitis [6] relative to the developed world, especially in rural compared with urban areas [5,8–10]. In addition to this generally lower prevalence of allergic disease, immunoglobulin (Ig) E levels in African populations tend to be high [11–15], and levels in nonasthmatics tend to be higher than in asthmatics. Since asthma, bronchial hyperreactivity and allergic disease tend to be associated with high IgE levels in the developed world [16–18], this apparent paradox calls for a reappraisal of the role of IgE in allergy in these populations. One hypothesis is that the high levels of IgE in African populations are caused by parasitic infestation, and that this in turn somehow reduces the risk of allergic disease. In this issue of *Clinical and Experimental Allergy*, Selassie *et al.* provide some new evidence relating to this hypothesis [19].

Intestinal parasites are potent stimulators of both parasite-specific IgE, which is important in the host immune response to parasite [20,21], and polyclonal or non-specific IgE. Parasite specific IgE attaches to high-affinity Fc receptors on mast cells, and neighbouring specific immunoglobulins cross-link and trigger mast cell degranulation. This process mediates an antiparasite response via the release of pro-inflammatory cytokines. The same mechanism is involved in the pathogenesis of asthma and other allergic disease in which immune responses are triggered by allergen-specific IgE [17]. Since the immune responses involved in dealing with both parasites and allergy appear to be similar, it is plausible that parasitosis and allergy are somehow interrelated. The nature of this relationship has been extensively reviewed [22–24] but is still not understood. From experimental data [23,25] it has been postulated that saturation of IgE receptors by the Fc fragment of parasite-induced non-specific IgE will block the cross-linking of allergen-specific IgE on the surface of mast cells and therefore prevent their degranulation and the subsequent allergic response. Thus parasite infestation may protect against allergy whilst, by the same token, the parasite-killing response is likely to be similarly inhibited. It has been postulated that the ability to generate this polyclonal response has evolved in the parasite because it helps to evade host immunity [24]. This latter theory is supported by

work in *Ascaris*-endemic areas of Venezuela where Hagel *et al.* found that high total IgE was a marker of increased risk of re-infection after anthelmintic treatment [21]. Other studies have reached similar conclusions [20,26].

This hypothesis, that current parasitic infection can protect against development and exacerbation of allergic disease, has been proposed to explain much of the available epidemiological evidence, but has not yet been definitively explored. Some studies provide evidence in support of this hypothesis, including a descriptive study of asthma in Kenya [27] which found that only 9% of stools from asthmatic patients showed parasite infestation compared with 26% of a control group. Unusual evidence was also reported by Turton [28], who found that his hay fever improved markedly after three separate self-infections with hookworm (*Necator americanus*). He also demonstrated that his specific antiparasite IgE level increased threefold during the 13-month period in which the infections occurred, but his total IgE did not increase in relation to pre-infection levels. These findings, though based on the experience of a single individual, suggest that parasite-specific IgE was blocking the allergic response. Further evidence comes from surveys in The Gambia [12] and Rhodesia [11], which both found higher levels of IgE in rural areas, in association with lower rates of asthma. They attributed the differences in IgE levels to differences in parasitosis in the rural areas, but did not determine whether these subjects were carrying intestinal parasites. The importance of this omission is demonstrated by a study in Nigeria where lower levels of IgE were observed in asthmatics, but with no difference in stool parasite counts between cases and controls [13]. Similar findings in Tanzanian school-children [14] also do not support the parasite-protective hypothesis.

There is rather more evidence that parasitic infestation, as opposed to protecting against allergic disease, actually increases the risk. Lynch and colleagues [29] studied asthmatic children in Venezuelan slums and found that their asthma control improved significantly after anthelmintic treatment. Dold *et al.* studied school children from the former East and West Germany [30], looking at clinical evidence of allergic disease and immunological markers of parasitic infection. In a longitudinal study, in which a cohort of children was surveyed twice 3 years apart, they observed an increase in the prevalence of allergic rhinitis in children who became seropositive to *Ascaris* IgE. They also found a higher frequency of allergen-specific IgE in those who were *Ascaris*-seropositive at either survey, and that a positive *Ascaris* IgE result was a stronger risk factor for allergic

sensitization to inhalant allergens than a family history of allergic disease.

Another possibility in the 'allergy-parasite' story is that the atopic state may confer protection from parasitic infestation, a selective advantage that may account for the evolutionary persistence of an otherwise apparently negative trait. Further studies from *Ascaris*-endemic areas of Venezuela compared the parasite burden of children from an area known to have a high prevalence of atopic disease, with those from an area of similar socioeconomic status where there was a lower prevalence of atopy [26]. They found the intensity of parasitic infection was considerably lower in the atopic children, who had higher levels of specific anti-*Ascaris* IgE, emphasizing the importance of the specific antiparasite IgE in the protective immune response. A French paediatric outpatient population study [31] found the prevalence of intestinal parasitosis to be similar in atopic subjects and nonatopic controls, but observed that the atopic children experienced far less gastrointestinal symptoms than nonatopics. This study therefore suggests that the atopic phenotype may somehow downregulate the host systemic response to parasites, or simply result in lower parasite loads.

In the study published in this issue [19], Selassie *et al.* compare two groups of urban adult outpatients attending a teaching hospital in Gondar, Ethiopia. The cases were patients with recurrent episodes of wheezy breathlessness, in whose case notes was recorded either a diagnosis, or treatment for, asthma. The controls were selected from other outpatients who had no recorded history of asthma or wheezy breathlessness and were attending the same hospital for non-respiratory conditions. The diagnosis of asthma was supported in this study by objective measurement of airway hyperresponsiveness, which was found in 81% of cases and 4% of controls, and although not formally matched, the groups appear similar in terms of age and sex. The authors found the total IgE levels to be high but not significantly different in cases and controls. There were, however, higher levels of *Ascaris*- and *Necator*-specific IgE antibodies in the controls than among the asthmatics, suggesting a protective effect of parasites against asthma. Like so many others, however, this study did not measure intestinal parasite burden, so we cannot determine whether the current parasitic load was responsible for this effect.

The other significant finding in this study was the positive correlation between sensitivity to house dust mite antigen and a diagnosis of asthma. Raised levels of specific IgE antibodies to Der p 1 were found in 93% of asthmatics compared with 48% of controls, supporting previous findings in urban African environments [5,32,33]. The authors conclude that since there was no relationship between specific antiparasite IgE and the Der p 1 IgE levels, the 'protective effect' of parasite infection on asthma must be

mediated by an effect independent of sensitization to common aeroallergens. This is inconsistent with previous theories that the parasite IgE mast cell saturation effect acts by blocking sensitization to subsequent environmental allergens [24]. The relationship between allergen sensitization and asthma is not straightforward, however, [4,5], and appears to be dependent upon environmental factors. The Ethiopian study by Yemaneberhan *et al.* [5] found that skin prick test reactivity to *Dermatophagoides pteronyssinus* was positively correlated with wheeze in the urban environment, but appeared to be protective in the rural areas. A study comparing asthma and atopy in Australia and Nigeria [4] found that the prevalence of atopy was similar in the two countries, but there was significantly less reported wheeze and persistent cough in Nigeria, implying a much weaker relationship between asthma and atopy in the developing country. Interestingly, in Kenyan school children [15] the association of high IgE and exercise-induced bronchospasm (EIB) differed between the urban and rural children. In the urban area, raised IgE levels were correlated with EIB, whereas in the rural area, there was a non-significant trend towards an inverse association between IgE and EIB. This all suggests that other factors, probably related to the level of 'urbanization', account for the expression of allergic disease in those who are allergen-sensitized.

By studying a group of outpatients, Selassie *et al.* will inevitably be susceptible to selection bias and possible confounding. Given the terrain and poor communications in Ethiopia, it may be expected that those who attend the hospital will be predominantly from urban areas, or will be the more affluent, or those who place a greater sense of priority on their health. As the data are not adjusted for urban-rural residence, they have to assume the relationship between atopy and asthma within their study population is constant. This may reduce the sensitivity of their study for detecting an association between allergen reactivity and *Ascaris* infection. Those who seek medical help may also have a greater sense of hygiene, and hence any estimate of prevalence of parasitosis in the group may underestimate that of the general population. Alternatively the more hygiene-conscious individual may stay well away from the government hospital environment, preferring to attend private clinics, and thereby distort the findings in the opposite direction! This may be important, as it has been suggested that the level of parasitic burden may determine its effect on the allergic phenotype [29]. In areas where parasite levels are only moderate, parasite infestation has been found to exacerbate the allergic response [30], whereas in populations where parasite burden is heavy, parasitic infestation appears to downregulate the same response [34]. Another constitutional factor, which may be important in determining the immune response, is the nutritional status of the host. It seems very likely that malnutrition causes

immunosuppression, and hence may affect both the anti-parasite and the allergic response. In Venezuelan *Ascaris*-infected children the specific anti-*Ascaris* antibody response was significantly lower in the malnourished group, whereas the total IgE and IL-4 levels were significantly higher. This pattern of antibody response fits with malnourishment being associated with an increased susceptibility to parasites in this tropical environment. The nutritional status of the subjects in the current study [19] was not assessed.

Thus this new study adds further evidence that exposure and/or immunity to parasitic infestation appears to be associated with a reduced risk of asthma, and also provides more weight to the growing evidence that sensitization to dust mite is an important risk factor for asthma in urbanized African communities. However, the study does not help us to understand why atopy appears to be less strongly related to asthma in more rural areas, and it also does not define the nature of the cause and effect relationship in the parasite–allergy association. To resolve these issues we need studies that measure exposure and sensitivity to environmental allergens, intestinal parasite burden and the immunological response to both the allergens and parasites. Ideally, such studies should also be able to investigate the importance of the timing of these various exposures in a longitudinal cohort, and will need to collect information on confounders such as nutritional status and other socioeconomic factors. In conclusion, the role of IgE in allergic disease, and the influence of parasites on this relationship, is clearly very important, and this fascinating subject is in great need of further investigation.

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