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News and commentaries

Does atopy protect against enteric infections?

Allergic sensitization to inhaled allergens and foods is common and is linked to the development of asthma, allergic rhinitis and eczema. In view of the morbidity associated with these diseases it is not clear why the genetic predisposition to atopy is so common. Children who are atopic are less likely to develop oral tolerance to ingested foods and as a result are more likely to have manifestations of food allergy including wheezing, skin rashes and gastrointestinal symptoms. Oral tolerance also develops to micro-organisms in the gastrointestinal tract. Children who are atopic may be protected against enteric infections in early childhood because they are less likely to be tolerant of these organisms. This may explain why individuals who are atopic are less likely to have evidence of previous infection with hepatitis A and other enteric organisms although they are just as likely to have been infected with respiratory pathogens.

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Atopy is characterized by increased production of IgE antibodies to specific environmental allergens and is associated with asthma, allergic rhinitis and eczema. In affluent countries 30–40% of the population is atopic as judged by positive skin tests to one or more inhalant allergens (1–3). Although the mechanisms underlying the development of atopy have not been fully elucidated, twin studies have confirmed that there is an important genetic contribution to atopy (4). However, there is substantial variation in the prevalence of asthma, allergic rhinitis and eczema in different populations. In the ISAAC study the prevalence of wheezing in 13–14 year olds in the last 12 months was 1.6% in Indonesia and 36.8% in the UK (5). There is a similar variation in the prevalence of allergic rhinitis and eczema. Atopic diseases are not only common but are associated with significant morbidity. This begs the question as to why the genetic tendency to develop atopic disease is so common if it leads to adverse effects. IgE antibodies are involved in the response of the immune system to parasitic infection. This led to the suggestion that atopy may have evolved to provide increased responses to parasitic infection but individuals who are not atopic do not appear to be any less able to mount an immune response to parasites. A study of 2865 children in Ecuador found that the children with the presence of IgG_4 antibodies to *Ascaris lumbricoides* and the highest levels of total IgE had fewer positive skin tests to inhalant allergens (6). Other studies have also demonstrated an inverse relationship between antibodies to parasites and evidence of allergic sensitization (7). This suggests that there may be another reason why so many individuals have a predisposition to atopy. An alternative explanation is that atopy protects against the development of gastroenteritis in the first few years of life. This would be potentially very important because gastroenteritis remains the most important cause of death in infancy worldwide. The normal response of the gut immune system is to develop tolerance to foreign antigens in food and to the commensal bacterial flora in the gut. Atopic children are less likely to successfully develop tolerance to food antigens. Although this would appear to be a disadvantage it may also be associated with increased protection against viral and bacterial infections where the site of infection or portal of entry to the body is the gastrointestinal tract. The evidence for this is outlined below.

Oral tolerance

Oral tolerance occurs when oral feeding of a protein leads to systemic immunological unresponsiveness to that protein. The development of oral tolerance is not just limited to Th2 responses to allergens but can also involve Th1 responses to micro-organisms such as bacteria. The need to develop oral tolerance to antigens in food and to the microbial flora in the gut is easy to understand. It would be a problem if we experienced hypersensitivity reactions every time we ate a meal and if we mounted an inflammatory response to the commensal micro-organisms in the gut. The development of tolerance is an active process that requires the presence of the gut-associated lymphoid tissue and it is not simply the failure to mount an immune response. TNF-α knockout mice, which do not develop Peyer's patches and mesenteric lymph nodes, are not able to develop oral tolerance (8). On the

contrary, administration of flt3L, a growth factor for dendritic cells, to mice not only leads to a marked increase in the number of dendritic cells in the gut mucosa but also promotes the development of oral tolerance (9). A number of cytokines have been identified as being important for the development of oral tolerance including interferon-γ and interleukin-10 (10). Because the development of oral tolerance is an active process it would not be surprising if it was more difficult for it to develop if the immune system was immature. There is the evidence that children who become atopic have slower maturation of the immune system (11). At birth, the production of cytokines by lymphocytes in response to allergens is polarized to a Th2 response in all children regardless of whether they go onto become atopic or nonatopic. Over the first year of life nonatopic children develop a Th1 pattern similar to adults and by 1 year of age there is an increase in the production of interferon-γ and a decrease in the production by peripheral blood mononuclear cells of interleukin-10 and other Th2 cytokines (11). In contrast atopic children produce lower concentrations of both interferon-γ and Th2 cytokines at birth and over the next 2 years the increase in the production in interferon-γ is less than in nonatopic children while the production of Th2 cytokines does not decrease to the same extent (11).

Children who are atopic may develop food allergy because of a failure to develop oral tolerance to food antigens. In children with food allergy, immediate responses to the foods such as milk and egg can include skin rashes, wheezing and gastrointestinal symptoms. The prevalence of food allergy peaks at 6–8% at 1 year of age and then falls progressively to 1–2% in late childhood (12). Reactions to food are also implicated in eczema which is the most important manifestation of atopy in the first few years of life (13). As children become older positive skin prick tests to foods become less common and aeroallergens become the most important allergens on skin testing (14). This parallels the reduction in clinical manifestation of food allergy in older children. The failure of some atopic children to develop oral tolerance to food antigens in the first few years of life may be because of the delays in the maturation of the immune system.

Atopy and enteric infections

There are a number of studies that provide evidence of fewer enteric infections in atopic children. Matricardi et al. studied Italian airforce recruits and found that those who had positive skin tests to inhaled allergens were less likely to have antibodies against the Hepatitis A (30% *vs* 16%, $P = 0.004$) and *Toxoplasma gondii* (26% *vs* 18%, $P = 0.027$) (15). Both these pathogens are transmitted by the orofaecal route. However, there was no association between antibodies to a variety of pathogens transmitted through airborne infection. The same workers have also demonstrated an inverse relationship between atopic sensitization and hepatitis A seropositivity in the US population using data from NHANES III (16). Similar findings were reported in a Danish population (17) (Table 1). Umetsu and his colleagues studied the relationship between atopy, seropositivity to hepatitis A, and a mutation in the gene for TIM-1 (18). TIM-1 acts as a receptor for the entry of the hepatitis A virus into cells. They identified a mutation for TIM-1 (157insMTTTVP) and speculated that it may interfere with entry of the virus into cells. They only found an inverse relationship between seropositivity for hepatitis A and atopy in individuals if they had the 157insMTTTVP mutation. In other words individuals who acquired hepatitis A infection, despite having a mutation that potentially protects against infection, were those who were least likely to be atopic. Cullinan et al. performed skin tests in a cohort of adults in Ashford in the UK and then studied general practice records to determine the number of presentations with respiratory and gastrointestinal infec-

Table 1. Relationship between atopy and hay fever and seropositivity to hepatitis A virus and *Toxoplasma gondii*

	Controls (% seropositive)	Atopy (% seropositive)	Odds ratio (95% CI)	Hay fever (% seropositive)	Odds ratio (95% CI)
Matricardi et al. (15)*					
Hepatitis A	73	39	0.44 (0.29–0.69)		
T. gondii	63	42	0.60 (0.38–0.93)		
Matricardi et al. (16)†					
Hepatitis A	43.3			17.2	0.36 (0.28–0.46)
Linneberg et al. (17)‡					
Hepatitis A	40.2	20.5	0.57 (0.38–0.86)	12.3	0.58 (0.36–0.95)
T. gondii	40.6	28.9	0.76 (0.57–1.00)	19.5	0.75 (0.55–1.04)

*Study of Italian air force cadets (17–24 years). Control group of 240 individuals who were nonatopic were compared with 240 individuals who had positive skin tests to one or more inhalant allergens.

†Analysis of data from Third National Health and Nutrition Examination Survey conducted in USA (1988–1994). The values shown are from 6396 individuals between 20 and 39 years. The comparison was between individuals who had ever had a diagnosis of hay fever and those who had not.

‡Cross-sectional study of 1112 individuals between 16 and 69 years of age who were studied in Copenhagen, Denmark in 1990–1991. Control group consisted of individuals who were skin test negative for a panel of inhalant allergens.

tions in the first 5 years of life (1). They found a significant inverse relationship between the number of gastrointestinal infections (presumably most of these episodes represented viral gastroenteritis) and the odds of atopy. In contrast there was a positive association between atopy and the number of respiratory infections (Table 2). The studies cited above have been interpreted as showing that enteric infections in early life protect against the development of atopic disease but it is as plausible that the converse is true. Being atopic may protect against enteric infection because individuals who are atopic may be more likely to mount an immune response to enteric pathogens in the same way that they are less likely to develop tolerance to food antigens. In the case of enteric pathogens, however, it is Th1 rather than Th2 responses that are likely to be important. Ruuska reported another study that is relevant to the relationship between atopy and infectious diarrhoea (19). A total of 371 children were followed over the first 2 years of life and the number of episodes of acute diarrhoea was recorded as was the development of eczema. The children were not skin tested but total serum IgE was measured. After exclusion of the children with diarrhoea due to food allergy there was no difference in the number of episodes of diarrhoea between those with eczema and those without, but in both groups the serum IgE was higher in those who did not have any diarrhoea compared with those with one or more episodes (Table 3). This finding is also consistent with the idea that allergic sensitization may be associated with protection against infectious diarrhoea.

Table 2. Relationship between atopy and infection in the Ashford cohort

	No infections (% atopic)	≥1 infections (% atopic)	Adjusted odds ratio (95% CI)	*P*-value
All infections	39	36	1.01 (0.98–1.04)	0.41
Upper respiratory infections	35	37	1.00 (0.94–1.07)	0.93
Lower respiratory infections	36	37	1.08 (1.01–1.16)	0.02
Gastrointestinal infections	39	29	0.75 (0.59–0.97)	0.02

Records on childhood infections in first 5 years of life were obtained for 738 adults in a cohort study in Ashford, UK. Atopy was defined as one or more positive skin tests (≥3 mm) to *Dermatophagoides pteronyssinus*, cat fur or grass pollen. Odds ratios were adjusted for age, sex, socioeconomic status, parental allergic disease and number of brothers. Adapted from Cullinan et al. (1).

The inverse relationship between infection with helminths and the presence of atopy has already been noted (6, 7). A variety of explanations have been proposed for this observation including the suggestion that helminths lead to formation of counter-regulatory cytokines such as interleukin-10 (20). An alternative explanation is that atopy protects against the acquisition of infection with helminths in the first place in the same way that it may protect against the development of other enteric infections such as hepatitis A.

The hygiene hypothesis

The hygiene hypothesis argues the rise in allergic disease in recent decades is attributable to a decrease in childhood infections and a consequent skewing of the immune system towards a TH_2 bias with a consequent increase in allergic sensitization. If the predisposition to atopy had evolved to reduce the risk of dying from diarrhoeal illnesses in early life one would not expect to see much a marked increase in allergic sensitization in recent years. It is not clear, however, if the increase in asthma, allergic rhinitis and eczema is attributable to an increase in allergic sensitization. Few of the studies looking at changes in disease prevalence have performed skin tests to common allergens. Although there has been increase in asthma, hay fever and eczema in the developed world this has not been paralleled by equally high rates of these diseases in the developing world. Interestingly several studies have confirmed the differences in the prevalence of asthma between developed and developing countries while demonstrating much smaller differences in the frequency of positive skin tests. A study comparing Chinese children living in Hong Kong and in San Bu, in Southern China, found the prevalence of asthma was 6.6% in Hong Kong and 1.6% in San Bu while the proportion of children with positive skin tests was similar at 57.7% in Hong Kong and 49.0% in San Bu (21). In another study the prevalence of wheeze in 8–11-year-old children was 21.9% in Australia and 10.2% in Nigeria

Table 3. Serum IgE levels in relationship to acute diarrhoea

	Birth	6 months	12 months	24 months	*P*-value
Atopic eczema					
Diarrhoea ($n = 28$)	0.29 ± 0.45	7.0 ± 13.4	14.3 ± 22.8	16.3 ± 21.6	0.025
No diarrhoea ($n = 30$)	0.46 ± 0.82	23.7 ± 92.8	22.7 ± 50.7	30.3 ± 36.6	
No eczema					
Diarrhoea ($n = 82$)	0.24 ± 0.56	5.9 ± 11.3	13.6 ± 25.8	15.4 ± 16.2	0.265
No diarrhoea ($n = 104$)	0.35 ± 0.72	12.4 ± 27.6	31.2 ± 81.5	38.8 ± 91.6	

Values represent IgE (kU, mean ± SD). A group of children in Tampere, Finland were followed from birth to 2 years. Serum IgE levels are shown according to whether or not the children had eczema and whether they had any acute episodes of diarrhoea. Children who had diarrhoea during follow-up were compared with those who did not using analysis of variance. Adapted from Ruuska (19).

but rates of atopy measured with skin prick tests were 32.5 and 28.2%, respectively (3). Similar findings have been reported from other studies (22). Peat et al. compared 8–10-year-old children in two Australian towns in 1982 and 1992. Although the prevalence of recent wheeze increased from 10.4 to 27.7% in one town and from 15.5 to 23.1% in the other town there was no change in the prevalence of atopy on skin prick testing (23). An exception to these observations comes from comparisons between Western European countries and some of the former communist countries in Eastern Europe. Braback et al. studied children in Sweden, Estonia and Poland in 1991–1992 and found rates of sensitization of 30.3% in Sweden compared with 13.6% in Poland and 10.9% in Estonia (24). von Mutius et al. compared 9–11-year-old children in East and West Germany between 1989 and 1992 and found that the rates of allergic sensitization were 7.2 and 18.4%, respectively (25). Compared with studies from elsewhere in the world, the rates of allergic sensitization to inhalant allergens in Eastern Europe, soon after the collapse of communism, were surprisingly low and this raises the possibility that environmental factors in these countries protected against allergic sensitization. However, despite the findings from Eastern Europe, rates of allergic sensitization are high in both developed and developing countries in many parts of the world. It is not unreasonable to suggest that the rates of allergic sensitization were also high in the past in many countries and that what has changed to a greater extent in these countries are the clinical manifestations of asthma, eczema and rhinitis.

Implications for future research

It should be possible to test the hypothesis that atopy has evolved to protect against gastrointestinal infections. If the hypothesis is correct, a decrease in gastroenteritis and enteric infections should be evident in early childhood in individuals who have been demonstrated to have allergic sensitization. There are a number of cohort studies underway where children have been skin tested early in life and it will be interesting to see if children who are skin test positive at 1 or 2 years of age have fewer enteric infections over the subsequent years than other children.

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