

Editorial

Environmental exposures, genetic predisposition and allergic diseases: one size never fits all

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A remarkable increase in the prevalence of allergic disease appears to parallel the postindustrial lifestyle changes in westernized societies. Insufficient microbial exposure during infancy and early childhood is one of the proposed explanations for the increase in prevalence of atopic sensitization and associated clinical phenotypes (asthma, allergic rhinitis, eczema). Within this context, childhood vaccination may be associated with an increased risk of allergies [e.g. children whose parents refuse the vaccination have less atopic diseases (1)]. However, it has to be emphasized that major benefits of childhood vaccination programmes and successes in the prevention and treatment of infectious diseases (with global reduction in mortality and morbidity) clearly outweigh the risk of the possible promoting effect on allergic disease.

There is growing evidence that one of the inadvertent consequences of the fight against infectious diseases and our obsession with cleanliness might have been the interference with the immune system development. The changing pattern of microbial exposure, with the decline in some infectious diseases, may lead to a slower maturation of the immune system, with a delayed development of the optimally balanced immune responses. This notion forms the immunological basis of the hygiene hypothesis. However, the hygiene hypothesis originated from epidemiological studies.

Searching for the cause of allergy: the link between epidemiology and immunology

Family size. The pioneering proposal by David Strachan that a decrease in family size reduced the possibility of

cross-infections, facilitating the clinical expression of allergic rhinitis had led to intense interest in this area (2). His findings were confirmed in a number of studies (3), and within the same context, exposure to other children in day-care centres was found to be protective against asthma and atopy (4). Yet, the effects of family size, position in sibship or day-care arrangements may not be mediated by the exposure to infectious agents, but some other underlying aspect of immune response (5).

Helminths. Children in developing countries who are infested with helminths are less likely to develop atopy and allergic disease. Furthermore, long-term treatment of intestinal helminths in infested children increases specific sensitization to house dust mite (6). In addition, there appears to be an inverse dose-response relationship between the burden of infestation by helminths and expression of allergic disease (7). However, helminths may only be a marker of environmental exposure to other microbial agents and/or endotoxin.

Helminthic infections enhance the secretion of T_H2 type cytokines, mimicking response observed in patients with atopic background. In this issue of *Allergy*, an extensive review by Mingomataj et al. has focused on the down-regulating properties of parasite derived anti-inflammatory molecules (8). In addition to priming T_H2 response, helminths secrete potent immuno-modulatory molecules which may induce T-cell hypo-responsiveness. The fascinating question which needs addressing is whether allergic disease can be treated, or even prevented by exposure to helminths or their products.

Intestinal microbiota. Recently, a number of studies have suggested that nonpathogenic intestinal microbiota may have potent immuno-modulatory effect on the development of immune system. Indeed, gastrointestinal system is quantitatively the most colonized area of human body. Composition of gut microbiota may influence the development of allergic disease, but the effect may differ depending on the geographical region, diet and hygiene practices. A comparison between Estonian and Swedish children suggested differences between predominant intestinal species present before sensitisation and the clinical expression of allergic disease (9). Overall, these findings and those from animal models suggest that the colonization of the GI tract with bacteria is crucial to immune development, and that the presence or absence of certain bacteria is linked to allergic disease. However, an alternative hypothesis would be that the observed differences in gut microbiota are not the cause of the subsequent sensitization and clinical expression of allergic disease, but rather a consequence of the primary abnormality of the mucosal surfaces (i.e. that different mucosal surfaces with different inherent properties become colonised by different micro-organisms). As such, different microbiotas would be markers of a primary abnormality in structure of the mucosal membranes.

There has been a special interest in probiotic supplementation as a potential therapeutical or preventative modality for allergic diseases. Although *Lactobacillus GG* strain has been shown to improve symptoms of eczema, the effect appeared time transient (10). A recent double blind prospective randomized study by Passeron et al. has aimed to prolong the effect of probiotics by combining it with prebiotics (11). However, no significant differences in eczema severity were detected between children who were supplemented with only probiotics and those who received the combination. Furthermore, as there was no placebo group, no conclusions can be drawn on the potential effect of either of the two treatments.

Farming and anthroposophic lifestyle. Evidence suggesting that farming lifestyle is protective against allergic disease is consistent, and has been reproduced in a number of studies from different countries. Children who have regular contact with stable and farm animals have lower incidence of atopic sensitisation, hay fever and asthma (12). The recently conducted large multi-centre cross-sectional study (PARSIFAL) has demonstrated that not only living on farms, but also leading anthroposophic lifestyle during early childhood is protective against atopy and allergic disease (13). In another cross-sectional study of adults living in rural region, Radon et al. reported that those individuals who had contact with farm animals in their childhood were less likely to be sensitized to common allergens compared with those who have never had regular contact (14). However, there was no difference between adults who reported farm animal contact only in adulthood when

compared with control subjects, suggesting that the timing of exposure is critical.

Growing up on farms is associated with exposure to endotoxin, helminths, lactobacilli and saprophytic mycobacteria, whilst anthroposophic lifestyle is related to less interference with common childhood infections because of reduced antibiotic use and vaccination, and consumption of naturally fermented vegetables and biodynamic food. Therefore, rather than considering a single exposure that may prevent allergic disease, all these indicate that a number of different exposures which differ between modern and traditional lifestyles may act together in impacting on the development of allergic disease.

There is an ongoing debate as to whether there is a specific infection which could exert protection from allergic diseases. A number of studies have concentrated on specific infectious agents (15, 16), whereas others proposed an overall 'microbial burden' as being protective (17). Although infectious agents like *Mycobacterium tuberculosis* (18) and Hepatitis A (16) exert a sustained effect on the host immunity by stimulating T_H1 cytokine secretion and are inversely related to allergic disease in cross-sectional studies, the conclusive evidence for causality from prospective studies is lacking. Furthermore, although unlikely, reverse causation cannot be completely excluded.

Environmental exposures, genetic predisposition and development of allergic disease – from whole population to individuals at risk

It is important to emphasize that the potential protective effect of any of the above mentioned exposures is not going to be applicable to every individual in the population, but only to those with a particular genetic susceptibility. Consequently, broadly speaking exposure to 'dirt' may be beneficial for some, have no effect on the others, and there may be individuals within population in whom these exposures may be detrimental. Our problem is that we cannot as yet clearly identify those individuals who may benefit from any intervention and/or exposure.

The ongoing PASTURE birth cohort conducted in rural areas of five European countries, apart from assessing relevant protective exposures such as lifestyle factors, level of endotoxin and microbial components in dust samples, includes genotyping for polymorphisms and measurement of expression levels for TLR2, TLR4 and TLR9 (19). By this approach, the study group aims to elucidate protective exposures and determine environmental and genetic basis for subsequent allergic immune responses.

In order to understand risk factors for asthma and allergies one needs to study the interaction between the inherited risk and the environment. We really need to move away from the concept of 'one size fits all' assessment of risk and the consequent blanket advice on what may be beneficial aimed at everybody, to the tailor-made assessments of individual susceptibilities coupled with therapeutic or preventive measures which are specific

to individuals at risk. Long-term, it will be necessary to deduce the common protective factors from all the published studies and distil them to interventions that

would be acceptable to the western lifestyle, but at the same time making sure that such intervention will not exacerbate other disease processes.

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