

EDITORIAL

Pre- and post-natal events leading to allergen sensitization

For many years, the association which exists between allergen sensitization and the manifestations of clinical asthma in an individual was thought to be coincidental and not causal. It is now becoming clear however that, in the majority of asthmatic individuals, the most important aetiological factor in the development of their asthma is that of allergen sensitization, with over 90% of childhood asthmatics and 50% of adult asthmatics demonstrating hypersensitivity to one or more allergen [1]. Sporik *et al.* [2] have elegantly described how, for house dust mite sensitization and the development of asthma, Hill's requirements [3] for demonstrating that an association represents a causal relationship are fulfilled.

The economic cost of asthma in the U.K. (Health Services, sickness benefit, and loss of productivity and earnings) is almost £950 000 per year, and related diseases such as allergic rhinitis, allergic eye disease and eczema add to this morbidity. It is essential therefore to ascertain which factors determine whether or not an individual will undergo allergen sensitization, as some of them may be amenable to intervention, and manoeuvres such as allergen avoidance might be a valid approach to the prevention of certain allergies and of the related atopic diseases.

Although genetic factors associated with T-lymphocyte function are the most important determinants of susceptibility to allergic disease, the ultimate expression of the allergic phenotype depends on a variety of additional factors, many of them environmental, which affect the integrity of the mucosal barrier against antigenic material and the function of the T-cell and antigen-presenting cell systems. It is the initial encounter with an individual allergen which is crucial in determining sensitivity to that allergen in later life, and therefore it is early infancy which is the critical time for primary sensitization to occur [4]. Later in life, age has an inverse relationship to the degree of susceptibility. Although sensitization can occur at any stage of life, the likelihood of this occurring is dependent upon the following factors: the level of genetic susceptibility, the potency of the relevant allergen, the concentration and duration of exposure, and the degree of exposure to adjuvant factors. The factors known to influence the development of allergen sensitization are summarized in Fig. 1, and will be discussed in turn.

Genetic factors

There exists within a population a spectrum of ability to respond to allergen exposure, and this ability to respond

is largely genetically determined, 35% of children with single parental allergy and 60% of those with bi-parental allergy themselves developing an allergic disorder. The exact mode of inheritance is not yet clear [5], and the nature of the genetic factors controlling atopy are difficult to define due both to the lack of information regarding IgE dysregulation, and the multifactorial aetiology of atopic disease [6], but we do know that the major histocompatibility locus controls a number of specific IgE responses in man [7]. IgE production is thought to be coordinately regulated by negative signals from gamma-interferon producing CD4⁺ T-Helper-1 (TH-1) cells and positive signals from IL-4 producing TH-2 cells. That the T-helper cell may be the major target for genetic regulatory factors controlling expression of the IgE responder phenotype is supported by work demonstrating that young children with a positive family history and therefore at high risk for the development of atopy have a slower rate of T-cell post-natal maturation with decreased production of gamma-interferon and IL-4 compared to children with no family history [8].

Given a significant level of genetic predisposition, what factors increase the likelihood of that individual becoming sensitized to one or more allergen? In agreement with previous studies [9,10], Arshad *et al.* [11] found that when the family history includes maternal disease, this was a higher risk factor than paternal disease, although as questionnaires are more usually completed by the mother, this may only reflect reporting bias. Male gender is known to be a risk factor for the development of asthma and eczema [12] but recently has also been shown to be associated with a significantly increased risk of specific allergen sensitization [11,13,14]. This gender difference may reflect a difference in the biological ability to react to allergens, especially in the crucial stage of early infancy when sensitization as opposed to tolerization is more likely to be the result of allergen exposure [4], and indeed, serum IgE levels are higher in males when compared to females [15].

Birth weight

The association of low birth weight and allergen sensitization has been confirmed by Arshad *et al.* [11], whether low birth weight resulted from prematurity or from a full-term infant being small-for-dates. Premature babies will be exposed to environmental allergens when their T-cell system is even more susceptible to allergen sensitization than normal due to immaturity. Small-for-dates infants

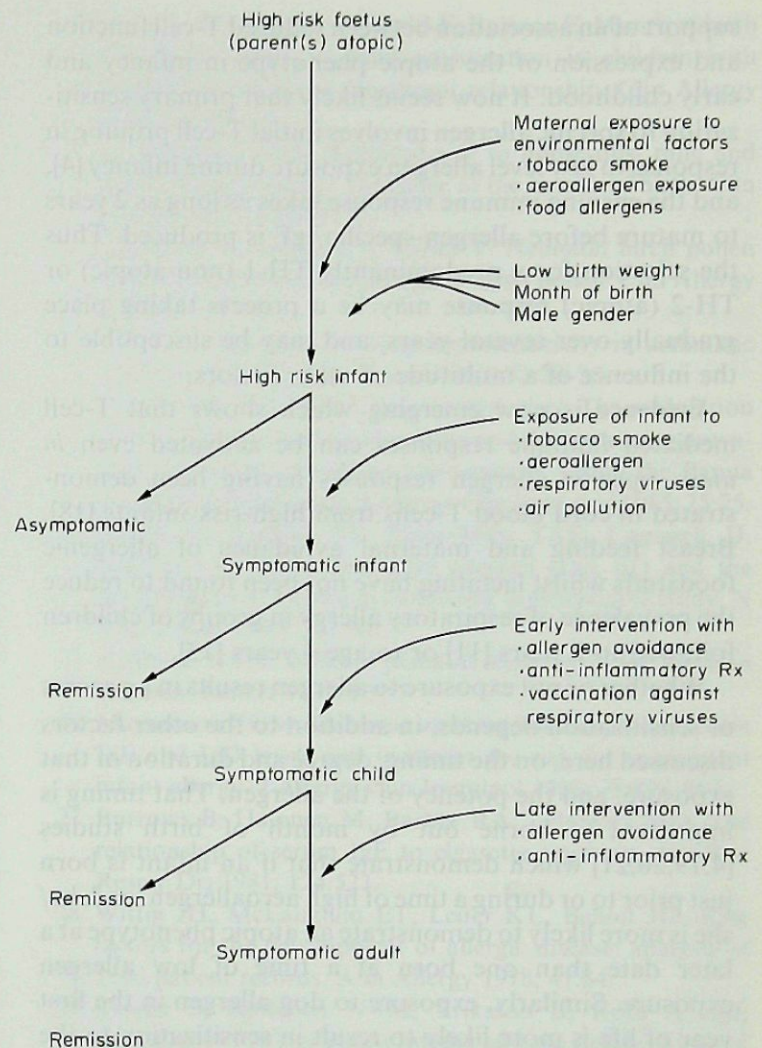


Fig. 1. Factors influencing the development of atopic disease.

might be compromised secondary to pre-natal nutritional deficiencies and their effects on the immune system.

Allergen exposure

That environmental factors make an important contribution to the ultimate expression of genetic potential for the high IgE responder phenotype is evident from the finding of discordance in serum IgE levels in identical twins of high-risk families [16]. For an allergen to produce a clinical effect, prior sensitization must have occurred, and that requires both an innate ability to respond and exposure. The respiratory tract is well designed to afford protection against exposure to inhaled allergens, with a number of mechanisms acting in synergy; filtration of inhaled air in the nasopharynx, deposition of the bulk of inhaled particles in the large airways due to aerodynamic factors, tight junctions between epithelial cells which limit

permeability, and the combination of mucociliary clearance mechanisms and phagocytic cells which clear particles from the small airways. However, these barriers are not absolute, and small amounts of inhaled allergen are able to pass into peripheral blood [17]. Thus the immune system needs to have a back-up mechanism which, in normal individuals, ensures that a process of tolerization rather than sensitization to these small amounts of allergen occurs. In the neonatal period, however, there is a deficiency in the ability to generate cellular and humoral immune responses which appears to be more marked in infants with a positive family history for atopy. Holt *et al.* [8] have demonstrated that there is both a decreased number of T-cells in cord blood, and that these cells are less mature and hence less active in 'high-risk' infants. This delayed maturation results in a decreased capacity to secrete bioactive cytokines following stimulation. These workers have provided the first quantitative evidence in

support of an association between reduced T-cell function and expression of the atopic phenotype in infancy and early childhood. It now seems likely that primary sensitization to specific allergen involves initial T-cell priming in response to low level allergen exposure during infancy [4], and the ensuing immune response takes as long as 2 years to mature before allergen-specific IgE is produced. Thus the selection for a predominantly TH-1 (non-atopic) or TH-2 (atopic) response may be a process taking place gradually over several years, and may be susceptible to the influence of a multitude of other factors.

Evidence is now emerging which shows that T-cell mediated immune responses can be activated even *in utero*, specific allergen responses having been demonstrated in cord blood T-cells from high-risk infants [18]. Breast feeding and maternal avoidance of allergenic foodstuffs whilst lactating have not been found to reduce the prevalence of respiratory allergy in groups of children followed to 2 years [11] or to age 4 years [13].

Whether or not exposure to allergen results in a process of sensitization depends, in addition to the other factors discussed here, on the timing, degree and duration of that exposure, and the potency of the allergen. That timing is important is borne out by month of birth studies [4,19,20,21] which demonstrate that if an infant is born just prior to or during a time of high aeroallergen load, he/she is more likely to demonstrate an atopic phenotype at a later date than one born at a time of low allergen exposure. Similarly, exposure to dog allergen in the first year of life is more likely to result in sensitization to the major dog allergens than if a dog is introduced to the home after the first year of life [22]. However, although infancy constitutes a particularly vulnerable period, sensitization can occur at any age in susceptible individuals if the stimulus is strong enough, as shown by the experience of the inhabitants of the highlands of Papua New Guinea when exposed to the house dust mite in adulthood [23]. The effect of dose has been highlighted by a prospective study of the correlation between levels of exposure to *Der p* I in the home and the development of asthma, which demonstrated a dose-dependent relationship between levels of exposure and degrees of allergen sensitization [24].

Adjuvant factors

Environmental tobacco smoke exposure and virus infections are the two most powerful adjuvant factors which promote sensitization to an allergen in an individual already at risk. Passive smoking has been shown to trigger the IgE response in infants [25]. Exposure to the harmful ingredients of tobacco smoke can commence *in utero* and maternal smoking can exert an effect on the IgE system in

foetal life, predisposing even 'low-risk' infants to subsequent sensitization [26]. Pre-natal maternal smoking increases cord IgE in a dose dependent fashion [26], and this is more marked in children with no parental history of atopy, perhaps because in 'high-risk' children, atopic heredity overshadows the weaker effect of tobacco smoke. This immune response could result from the effect of tobacco allergens, but in view of its dose dependent nature and its potential reversibility [27], it is more likely that tobacco smoke affects the regulation of immunoglobulin synthesis via an action on T-cells. Post-natal exposure to tobacco smoke results in a higher incidence and an earlier age of onset of allergic disease [28], possibly by rendering the mucosa less able to exclude allergenic material, in conjunction with a deleterious effect on the T-cell system. The consequent rise in cord blood IgE does seem to be of clinical significance, as 70% of newborns having raised cord-blood IgE will develop allergic symptoms before the age of 18 months [29].

There are certain similarities between the effects of passive exposure to tobacco smoke and respiratory tract viral infections, in that transient mucosal damage and an increase in serum IgE precede allergen sensitization in both, and both of these adjuvant factors exert their maximal effect during early childhood. Animal models have demonstrated that viral infection preceding allergen exposure can markedly augment sensitization to that allergen [30], and viruses seem to promote allergen sensitization in a similar manner in humans [31]. Environmental air pollution is another important adjuvant factor [32].

To date, studies which have investigated the effect of food allergen avoidance and environmental manipulation on the development of atopy have yielded negative results [13]. However, as our understanding of the mechanisms which determine whether or not the allergic phenotype is expressed increases, it is likely that measures more effective in preventing allergen sensitization in the 'at-risk' individual will unfold. However, in view of the apparent strength of the heritable risk factors, and the diversity and ubiquitous nature of some of the environmental risk factors, perhaps we also need to investigate the possibilities for intervention and prevention at an immunological and genetic level.

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