

Aero-allergen avoidance in the prevention and treatment of asthma

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Introduction

There is a common perception from around the world that there has been a real increase in the prevalence of allergic disorders, including asthma. Clear-cut epidemiological evidence to support this has been slow to accumulate. However, the most recent studies have suggested that there has been an increase in the prevalence of all allergic conditions in childhood. One excellent study from South Wales amongst 12-year-olds showed a change in point prevalence between 1973 and 1988 from 4 to 9% for asthma, 5 to 16% for eczema and 9 to 15% for hayfever [1]. Studies have also identified a dramatic increase in hospital admissions for childhood asthma over the last 8–10 years with no reduction in severity on admission, no increase in re-admission ratio and no evidence of diagnostic transfer [2]. As there has been no appreciable alteration in the genetic make-up of the community over this time, it is likely that environmental factors are involved. A relatively small shift in population susceptibility due to changes in the environment could account for both the increase in the frequency of disease and the even greater increase in the numbers having severe disease.

If this population shift in susceptibility is to be reversed then detailed study of the environment is essential. Only large longitudinal studies will have the power to establish which of the many possible factors are critical to the development of allergy and one of its most important manifestations, asthma. The ultimate aim must be to identify avoidable factors which might lead to the prevention of disease.

Inheritance

Recent research has identified that there is likely to be a single gene which determines predisposition to allergy, located on the long arm of chromosome 11 [3]. Work is now proceeding to identify the gene itself and the gene product. It is likely that the gene product will have an influence on some aspect of immune responsiveness. Current studies of the chromosome have been restricted to retrospective analysis in large families where allergy is already established in many family members. The ultimate test of this putative atopy gene will require a prospective study identifying the carriers of the gene at birth to establish how many actually develop allergy and allergic disease.

Host defects

A large number of primary immunological defects have been associated with an increased risk of allergy. Indeed, allergy may be seen as the commonest manifestation of immuno-deficiency and these defects have been reviewed in detail in many publications [4]. The abnormalities include deficiencies of IgA, opsonization, the second component of complement (C₂) [5], or IgG2 sub-class [6], and a range of defects of T-lymphocyte function [7,8]. It has been proposed that there is a genetically determined defect in T lymphocytes of allergic subjects which leads to an upset in the control of IgE antibody production [8]. Animal, and now human studies, have shown that there are differences in T-cell generation of the peptide regulators interleukins 4 and 5 between allergic and non-allergic individuals [9,10]. As interleukin 4 is an essential factor for the induction of IgE synthesis and interleukin 5 stimulates eosinophil proliferation and activation, these

may be looked upon as pivotal in the generation of allergy and asthma. However, it has yet to be identified whether differences in T-cell generation of these peptide regulators are primary defects or secondary phenomena.

Environment

Whilst primary defects of immune response may be inherent and have a considerable influence on the development of allergy, there appears to be much less influence on the manifestation of allergic disease. Even in identical twins, concordance for the development of asthma can be as little as 20% [11]. Thus, whilst genetic factors influence the development of atopy, other factors may be more important in relation to manifestations of allergy, which may be an independently inherited characteristic such as bronchial hyperactivity in asthma [12], or more likely an influence of the environment. Asthma is more common in second generation West-Indian immigrants than their parents born overseas, which also suggests a strong environmental influence in individuals of similar genetic stock [13]. Furthermore, studies in the Papua New Guinea highlands have identified a group who have had a dramatic increase in the prevalence of asthma associated with the development of house dust mite allergy and the detection of house dust mites in bedding in their homes [14].

Most prospective studies to date have focused on diets in the evolution of food intolerance, with particular reference to atopic dermatitis. This has occurred because it is relatively easy to monitor diet and to document the presence or absence of a skin problem. Furthermore, atopic dermatitis evolves within the first year or two of life, which means that prospective studies can be of relatively short duration.

The prospective controlled studies have shown that breast-feeding has a protective effect, which may [15] or may not [16] have an effect which extends beyond the period of dietary control. However, the study suggesting protection extended beyond the period of diet also employed aero-allergen avoidance measures, including a reduction in house mite levels in babies' bedding and the banishing of family pets [15].

The prospective dietary studies and immunological abnormalities associated with atopy, which are mostly only operative in early infancy, suggest that environmental control for a limited period at the outset of life may truly prevent the development of allergic disease [17]. Indirect evidence that this is indeed the case comes from studies of month-of-birth in relation to particular seasonal allergies. In Finland and Sweden, allergy to birch pollen occurs most frequently in individuals born just before the birch pollen season. This exposure influences

the frequency of allergy into adult life [18,19]. Indeed, the authors of the study have suggested that if month-of-birth could be manipulated, the frequency of birch pollen allergy could be reduced by 28%. Our own studies have identified similarly that there is a variation in month-of-birth related to the house dust mite season [20]. Businco *et al.* in a recent paper have reviewed these data in great detail, revealing that there are significant associations between month-of-birth and specific allergies in many countries around the world, involving a range of allergens [21].

There is also evidence that exposure to dog allergen in the first year of life is more likely to lead to a positive provocation test to dog, than if the dog is introduced after the first year of life [22]. All of these studies indicate that early aero-allergen exposure may be critical to the development of allergy and subsequently both asthma and rhinitis.

House dust mite

House dust mite has long been recognized to be the most important allergic trigger of asthma [23]. Many assays have been developed to measure major allergen (*Der p 1*) of this species in dust samples and there are reports of a link between these levels and the risk of development of asthma in exposed subjects [14]. A recently published report has set thresholds for levels of mite allergen exposure in susceptible individuals [24]. It proposed that a level of 2 µg of *Der p 1*/g of dust, equivalent to 100 mites/g, should be regarded as a risk factor for sensitization and the development of asthma. A higher level of 10 µg of *Der p 1*/g of dust was proposed as a major risk factor for the development of acute asthma in mite-allergic individuals. The same report suggested that airborne levels of *Der p 1* were difficult to detect and unpredictable in quantity. These conclusions were based on sampling air in undisturbed rooms or rooms in which violent disturbance was taking place. Thus the authors came to the conclusion that only dust, not air sampling, was valid.

However, asthma is triggered by inhaled allergens and the measurement of airborne levels during normal domestic activity is necessary to ascertain its role in disease. We have shown that the airborne content of the major house dust mite allergen *Der p 1* in the homes of 68 allergic asthmatic children was strongly associated with allergy to the mite. This was in contrast to the non-significant relationship found when assessing allergy in relation to the previously published threshold levels in carpet dust. There was a significant association with lower threshold levels of *Der p 1* in carpet dust (0.5 µg/g) but at no level was the association as strong as with air measurements. There was an interesting variation in the level of airborne

house dust mite allergen in different domestic environments. Levels were increased in those with wool carpeting in comparison with synthetic carpeting or hard flooring. Most importantly, these studies identified that it was possible to detect allergen in the air utilising a low-volume sampler running at 2 l/min, which is the approximate minute tidal volume of a small baby. Indeed, this form of sampling provided a more satisfactory measure of true aero-allergen levels than higher volume sampling, which appeared to clean the air faster than the allergen was produced [25].

Cat dander

In our study of the homes of 68 atopic asthmatic children we were also able to detect significant quantities of the principle cat dander allergen (*Fel d 1*) in the air collected by a low-volume sampler. The presence of *Fel d 1* was strongly related to the presence of allergy to cat fur and its absence was usually associated with no allergy. Furthermore, there was a strong association between the presence of a cat at the birth of the child and the highest risk of having an allergy to cat dander. However, sometimes high levels of *Fel d 1* were found in homes where apparently no cat had ever been present, indicating that sometimes exposure can occur by indirect means, perhaps by allergen being brought into the home on clothing [26].

Early exposure to aero-allergen and subsequent allergy

The homes of the 68 atopic asthmatic children were sampled in the month after those children's birthdays and only those families who had not moved home or substantially altered their house since the child's birth were selected. Thus our measurement of allergen concentration was taken as an estimate of the likely exposure of the asthmatic child when he or she was a newborn baby. The strong link between allergy and levels in the air for cat dander and house dust mite held true for all children under 7 years of age. However, for those older than 7 years of age the relationship was not significant. This suggests that early aero-allergen exposure may well be relevant to the development of allergy in early childhood but may not be so critical in older children. It remains to be seen whether early onset of allergy and allergic asthma has more sinister connotations than a later onset. However, epidemiological data would suggest that this may well be the case [27].

We also took air samples to measure the grass pollen, tree pollen and mould spore counts in the homes of the 68 atopic asthmatic children. We detected very high levels of fungal spores in the air both indoors and outdoors. Indeed the exposures in terms of number of particles/m³

of air sampled were infinitely greater than for any other potential allergen.

However, the frequency of sensitivity to moulds was relatively low. We believe that this may be due to the lack of release of any significant antigenic material from mould spores when they land on the respiratory mucosa. Indeed, in studies we have been conducting on *Aspergillus fumigatus* cultures, antigen is not detected in culture medium until at least 48 hours, even when cultured at body temperature [28]. It is to be expected that spores would have been swept out of the respiratory tract long before any antigen could be released. Thus sensitization is relatively unlikely to occur and a relationship with month-of-birth is unlikely to be apparent. Despite this, we found a weak association with exposure to high concentrations of *Alternaria* mould, which is similar to studies from Strasbourg [29]. *Alternaria* does appear to be a somewhat more potent allergen, releasing antigenic materials more rapidly than other moulds. We failed to find any relationship between mould-spore concentration and allergy for *Cladosporium* or *Aspergillus* species.

We found a strong relationship between tree pollen grain levels, both indoors and outdoors, and sensitivity to tree pollen. Indeed there was a correlation between the degree of sensitivity by IgE antibody level and the degree of exposure. This relationship did not hold true for grass pollen. We suspect that grass pollen is so highly potent as a sensitizer that it can produce allergy during exposure in subsequent years even in a relatively immunologically intact individual. However, tree pollen with its moderate antigenic potency will usually only sensitize an individual with a pre-existing susceptibility as might occur in infancy [30].

On the basis of these observations we would like to suggest a hypothesis of the relationship between the various influences on the development of sensitivity to aeroallergens. This can be summarized in the form of the equation:

$$\begin{aligned} \text{probability of developing sensitivity to aero-allergens} = \\ \text{degree of atopic susceptibility} \times \\ \text{concentration of exposure} \times \\ \text{potency of the allergen.} \end{aligned}$$

Clearly the degree of atopic susceptibility is to a considerable extent under genetic influence. However, age has an inverse relationship to the degree of susceptibility. There are other factors which may transiently increase susceptibility such as viral infection [31], exposure to cigarette smoke [32] and other environmental pollutants [33]. Concentration of exposure is influenced by particle size, which dictates whether it will reach the respiratory tract, and potency of the allergen will be dictated by its molecular structure and also by the rapidity with which it

is released from particles. Utilizing this formula, it should be possible to construct prospective studies both to identify susceptibility and to consider preventive regimens.

Secondary allergen avoidance

Whilst house dust mite sensitivity is the commonest allergy in asthmatics, in many parts of the world attempts to reduce exposure to this agent have met with considerable difficulties [23]. The warm and humid conditions which exist in bedclothes are ideal for mite replication. Most simple hygiene measures are ineffective, whilst the use of sprays which kill the mite do not eliminate enough of the allergen to be effective clinically, and even new bedding will be recolonized by mites within 1–2 months [34]. It has been shown that with fairly draconian measures it is possible both to reduce house dust mite levels and symptoms in house dust mite sensitive asthmatic children [35]. However, most families would consider these manoeuvres unacceptable and, therefore, the pursuit of alternative simpler, effective measures remains an important enterprise.

Our own studies of natamycin spray which reduces house mite numbers by killing mould spores on which the mites depend for optimal growth have been very disappointing. The spray neither reduced the levels of mites nor asthmatic symptoms nor bronchial hyper-reactivity [36].

We are currently investigating the value of a new anti-mite spray (Allersearch DMS) which not only kills the mites but also alters the antigenicity of allergens in dust as it contains a tanate derivative. We have been able to demonstrate that this will reduce the levels of both *Der p 1* and *Fel d 1* in dust and furthermore reduce the skin test responsiveness of asthmatic patients to their own house dust. However, it remains to be seen whether this will be of value clinically. Our finding of reduced *Der p 1* in the air of homes with synthetic rather than wool carpeting raises the intriguing possibility that static charge may be trapping allergens. We are currently re-investigating the value of ionizers in reducing aero-allergen load.

It is clear that allergen avoidance at its best can achieve dramatic results. Admission of house dust mite sensitive asthmatics to hospital where there are few, if any, house dust mites has been shown to produce a decrease in bronchial hyper-reactivity over three months [37]. We have also shown that in children resident in a special institution at high altitude for nine months there is a decrease in bronchial hyper-reactivity, coincident with a dramatic improvement in asthma and reduced requirement for asthma prophylactics [38]. High altitude with low humidity avoids exposure to house dust mites. However, in the institution other factors including avoid-

ance of animal danders, pollens, cigarette smoke, industrial pollution and emotional stress may also have contributed to the improvement. Nevertheless, in the ideal environment it is clear that improvements in asthma control may be considerable and may avoid the requirement for many other anti-asthma therapies. Thus we feel that further research in this area is of the highest priority.

Conclusion

It is clear from many studies that aero-allergen exposure is important both in the genesis and potentiation of asthma. Whilst avoidance measures are currently difficult, if not often impossible, this should not deter further research in this area. Effective aero-allergen avoidance may not only reduce the severity of established asthma but also have the potential to prevent the development of the disease in the first place.

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