

## **Development of allergic sensitivity to house dust mites and worsening of morbidity due to asthma, eczema and allergic rhinitis**

Mites are arthropods of the Order Acari, related to ticks, chiggers and spiders. These eight-legged animals are too small to be easily seen with the naked eye. The term 'house-dust mites' (HDM) is used to designate about 10 species of the family *Pyroglyphidae* that have been reported to occur with relative frequency in house dust, four of which are dominant: *Dermatophagoies pteronyssins* (DP), *D. farine* (DF), *D. microceras* (DM) and *Euroglyphus maynei* (EM). The optimal growth of HDMs requires a high humidity, moderate temperature (70-80°F, 21-27°C) and adequate food sources such as human scales. The largest numbers of mites are usually found in dust samples taken from uncovered mattress surfaces, bedding, upholstered furniture and floor carpeting. However, stuffed toys, clothing and drapes can also be important mite habitats. Seasonal variations in mite levels occur mainly in carpets and other places where drying occurs relatively rapidly.

Three groups of mite allergens have been successfully defined and are designated group 1, 2 and 3 allergens. The group 1 allergens (Der p 1, Der f 1 and Eur m 1) are proteases of approximate molecular weight of 25,000, which are secreted from the digestive tract and found in high concentration in mite feces. Group 2 allergens (Der p 2 and Der f 2) are found in both fecal pellets and mite bodies. Their function is unknown. Over 80% of mite-allergic patients have immunoglobulin E (IgE) antibodies to group 1 and 2 allergens, and these are considered major mite allergens. Group 3 allergens are considered to be a minor allergen. Group 1 mite allergens have approximately 75% amino acid homology within the group, and there is moderate cross-reactivity. Group 2 allergens demonstrate a greater degree of cross-reactivity as judged either by IgE antibodies or monoclonal antibodies, and have approximately 85% amino acid sequence homology within the group. There is no cross-reactivity or sequence homology between group 1 and group 2 allergens. There are many other components of dust mite extracts which have been shown to bind IgE antibodies but their relative importance in sensitization, exposure and symptom causation is less well defined.

### **Sensitization and exposure to house-dust mites**

Upon exposure to allergens, a certain proportion of the population (10-20%) will become 'sensitized' and develop a specific immune response that included the production of IgE antibody. Whether or not a given individual develops sensitization to a specific allergen depends on several factors, including the individual's genetic make-up, the immunogenic properties of the allergen and the timing and degree of exposure. The importance of genetics in determining the ability of an individual to respond to allergens is well supported by family and population studies. In keeping with this there is a high degree of heritability of serum IgE levels. Certain human leukocyte antigen (HLA) haplotypes (B8 and possibly DW3) have been shown to be associated with IgE hyperresponsiveness as manifested by multiple positive skin tests to a variety of allergens.

HDM allergens seem to be particularly immunogenic. Indeed, in areas of high exposure, it appears that almost all the potentially atopic children become sensitized

to mite antigens over the first 14 years of life. Sensitization seems to be dependent both on the quantity of exposure and to some degree on the timing. Although this can occur at any age, predisposed individuals are more susceptible to sensitization during infancy. Evidence from a number of studies has shown that there is a dose-response relationship between exposure and sensitization to indoor allergens. In areas where because of low humidity mites do not flourish sensitization to mite allergens is unusual. These observations have led to the proposal of threshold levels of exposure above which sensitization becomes increasingly more likely. For HDMs, the proposed level is 2 microgram of group 1 allergen per gram of dust. The same studies have also suggested that exposure of sensitized individuals to levels greater than 10 microgram of group 1 allergen per gram of dust increased the risk of acute asthma attacks. However, the evidence for a dose-response relationship to symptoms is less complete than for sensitization. Once sensitization to inhaled allergens develops, it usually persists in adult life, and repeated challenges with allergen can cause a secondary or anamnestic response with an increase in allergen-specific IgE levels.

### **House-dust mites as a cause of asthma**

It has been over 60 years since Dekker proposed that exposure to dust mites was a cause of asthma in Germany. Inhalation of dust mite allergen in sensitized subjects can cause immediate and late bronchoconstriction and wheezing. Following such bronchial provocation, there is an eosinophil infiltrate and increase in responsiveness of the lung to histamine or allergen challenge, which persists for some days or weeks. Many studies have shown the association between sensitization to dust mite allergens and asthma. In a prospective study of a cohort of children in New Zealand, there was a highly significant association between dust mite sensitization and the development of asthma. Case-control studies from around the world have confirmed this association in mite-allergic subjects. A prospective study reported from the UK indicated that exposure to greater than 10 microgram of mite allergen per gram of dust in early childhood was an important predictor of the development of asthma by age 11. Additional controlled studies of patients presenting to emergency rooms with asthma have demonstrated significant associations with dust mite sensitization and exposure. It has been shown that dust mite sensitization is the strongest independent risk factor for asthma among school children in Virginia. Overall it is clear that the association between mite exposure and the development of asthma in sensitized individuals is very strong and that this association is consistent among different populations.

It is generally accepted that inflammation is a central element in asthmatic lung. HDMs and other allergens have been shown to be capable of causing many of the elements of inflammation including:

1. Mediator release from peripheral blood basophils.
2. Release of a chemotactic factor from basophils of sensitized asthmatics when stimulated with dust mite extract.
3. Migration of eosinophils and basophils to the site of allergen challenge in the skin.
4. Up-regulation of expression of the intercellular adhesion molecule ICAM-1 in bronchial epithelium after allergen challenge.
5. Increased numbers of circulation eosinophils and basophils as well as bronchoalveolar lavage (BAL) fluid eosinophils after bronchial challenge.
6. Proliferative in vitro T-cell responses.
7. Erythema, mucosal edema and bronchoconstriction following allergen challenge.

Thus, the ability of dust mite allergen to elicit inflammatory responses is clear. A causal role of mite exposure in asthma is further supported by evidence that the prevalence of the disease is lower in areas of low mite exposure. Interestingly, following contact with western civilization, an increase in prevalence of asthma from 0.7% to 7% was noted in some villages of Papua New Guinea. However this increase was the consequence of the introduction of blankets with subsequent mite infestation, resulting in sensitization and development of asthma in a previously non-exposed population. In other studies, decreased exposure to mite allergens have been shown to result in an improvement of symptoms and decreased bronchial hyperresponsiveness (BHR). Thus, HDM allergens appear to be both a primary stimulus in the development of the inflammation of asthma, as well as an ongoing stimulus maintaining the bronchial reactivity that underlies symptoms. While inhalation of allergen cannot explain all cases of asthma, it is of primary importance in the development of the disease in most children and many young adults. The obvious therapeutic implication is that allergen avoidance should be a primary treatment for asthma in allergic patients.

### **House-dust mites as a cause of allergic rhinitis**

Chronic symptoms of a blocked runny nose and sneezing can be very troublesome and the causes are sometimes difficult to diagnose accurately and treat. Allergy to HDM is the most important cause of chronic perennial allergic rhinitis (AR). Although chronic rhinitis is sometimes thought to be a trivial illness, the morbidity and economic burdens associated with it are immense. Rhinitis is the most common of the allergic diseases, even more common than asthma. Traditionally allergic rhinitis has been managed with the use of topical nasal steroids or the use of systemic antihistamines. Allergen avoidance has always occupied a central role in the management of allergic rhinitis. Attempts at HDM reduction in individuals with perennial AR are logical and when implemented correctly and systemically usually result in good clinical results.

### **House-dust mites as a cause of atopic dermatitis**

Atopic dermatitis (AD) affects 10% of children and its prevalence is increasing steadily. Onset is usually in the first weeks and months of life and the dermatitis may persist into adult life. There are many factors including allergies, infections, emotional climatic and other environmental influences that contribute to the causation of AD in genetically predisposed individuals. Environmental allergen levels are probably the major determinant of whether sensitization of genetically predisposed individuals occurs. Induction of sensitization occurs postnatally and during childhood and reduced exposure to allergens may be associated with diminished expression of atopic clinical syndromes. Avoidance of exposure to HDM and food allergens for the first year of life was associated with significant diminution in the proportions of clinically detectable eczema and asthma. It has been proposed that the risk of becoming sensitized to HDM is greatly increased by exposure to 10 mcg/g of Der p 1 while even 2 mcg/g confers a significant risk. There is uncertainty as to the route of exposure by which sensitization occurs - via mucosa or the skin. Eczema is usually the earliest clinical manifestation of atopy, and the antigens to which initial sensitization develops in infants are thought to be food derived. Once the eczematous skin reaction begins the permeability barrier is broken

and the penetration of the large protein allergens from dust mites for example can occur resulting in sensitization.

The role of aero-allergens such as HDM in provoking or maintaining AD has been the subject of controversy and uncertainty. Epicutaneous patch test challenge elicits a delayed-type response that clinically resembles the naturally occurring eczema.

These reactions are induced by various aero-allergens and most authors have found that they seem to be restricted to individuals with atopic eczema rather than those with respiratory or mucosal forms of atopy. The patch test responses which are characterized by infiltration of T lymphocytes and eosinophils have been investigated as a 'model' of the naturally occurring dermatitis. The generation of these delayed-type responses via T-cell mediated mechanisms have been shown in a number of ways. There is evidence to indicate that IgE plays a part in the presentation of atopic allergens to T cells. IgE is found on the surface of Langerhans cells, the epidermal antigen-presenting cells, in individuals with AD. In the naturally occurring eczema, dust mite antigen-bearing Langerhans' cells are found in both the epidermis and dermis.

There is clear evidence that HDM and their allergens are of pathogenetic significance in the provocation or maintenance of AD. A double-blind, placebo controlled trial was performed of a regimen of house dust mite eradication measures, including encasing of mattress and bedding, vacuum cleaning and use of a spray with acaricidal and allergen-denaturing properties. The active treatment resulted in major reductions in the quantities of Der p 1 in the bed and carpets and this was associated with a highly significant clinical benefit in both children and adults with moderate to severe AD.