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Epidemiology of dust-mite-related disease

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ABSTRACT

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For many years it has been suggested that allergens derived from the house dust mite played a major role in the pathogenesis of asthma, eczema and some cases of allergic rhinitis. Recently, house dust mite allergens have been purified and specific immunoassays developed with which exposure to house dust mites and their allergens can be more easily determined. Using these tools, epidemiological studies have provided confirmatory evidence that not only is house dust mite exposure associated with the majority of cases of asthma in children and young adults, but that it is causally related to the development of asthma.

INTRODUCTION

House dust has been known to be a trigger of asthma for many years, yet it was not until 1964 that the Dutch researchers Voorhorst and Spieksma (1967) identified a pyroglyphid mite, *Dermatophagoides pteronyssinus*, as the major source of allergens in house dust. For susceptible individuals these proteins are a potent cause of sensitisation. This form of sensitisation can be detected by measurement of serum IgE antibodies or allergen skin testing and has been associated with each of the three main allergic diseases: asthma, rhinitis and atopic dermatitis (eczema). Extracts of house dust had been shown to produce an immediate skin test in many patients with asthma as early as 1921 (Kern, 1921), and van Leeuwen (1927) showed that avoidance measures could reduce the severity of asthma. Despite this, there has been a tendency for the treatment of asthma to focus on pharmacology rather than allergen-specific treatment. Sufficient evidence has accumulated not only to support the idea that there is a close association between sensitivity to mite allergens

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and asthma, but indeed strongly suggests that there is in fact a causal relationship between mite allergen sensitisation and asthma. Similarly Tuft (1949) stressed the role of inhalant allergens in atopic dermatitis, especially in older children. His work has largely been ignored, however there is now increasing evidence to suggest that there is a close relationship between mite allergen exposure and atopic dermatitis. In 1873 Blackley's pioneering work established beyond doubt that rhinitis was caused by sensitisation and exposure to pollen (hayfever). There is also a subgroup of individuals with perennial rhinitis who are solely sensitised to house dust mite, suggesting that this disease can also be caused by house dust mites. In parallel with the accumulation of evidence that allergens derived from house dust mites are responsible for these diseases has come the emergence of avoidance protocols. Treatment regimes are progressively changing from drug protocols which provide symptomatic relief to those which control the actual cause of these illnesses.

Mite allergens

Over the past ten years there has been great progress in the immunology of mite allergens. The WHO nomenclature for allergens uses the first three letters of the genus, the first letter of the species, followed by a Roman numeral to indicate the chronological order of their purification, *Der p* I (previously antigen PI) representing the first allergen purified from *Dermatophagoides pteronyssinus*. There are probably over twenty allergens derived from mite, although two main groups, Group I and Group II, account for most of its allergenicity. There is very high cross-reactivity between allergens of the same group derived from different species. Recently *Der f* I and II, and *Der p* I and II have been sequenced and cloned (Dilworth et al., 1991; Trudinger et al., 1991).

The Group I allergens (molecular weight (mw) 24 000) are heat- and pH-sensitive proteins which occur in very high concentration in mite feces ($\sim$0.2 ng per particle, i.e. $\sim$10 mg/ml) and elute rapidly, within 2 min (Tovey et al., 1981). Both common and species-specific epitopes have been identified on *Der p* I, *Der f* I, and *Der m* I. They are proteolytic enzymes secreted in the mite digestive tract and show protein sequence homology to thiol proteases e.g. papain. Mites are coprophagic i.e. they re-ingest fecal pellets, and it is possible that the presence of these enzymes allows a more extensive digestion to occur ex-vivo (T.G. Merrett, pers. commun.).

The Group II (mw 14 000) allergens are derived from both mite bodies and feces. They are heat and pH resistant, they have not been shown to have enzymatic activity and surprisingly show no sequence homology with other known proteins. The Group III allergens (mw 29 000) have been partially sequenced and show sequence homology with serine proteases such as trypsin and chymotrypsin.

Measurement of mite levels

Measurement of the level of exposure to mites has followed advances in the characterisation of mite allergens. The original methodology was to count the number of mites in house dust, which can be done either by a flotation or a filter method. It is still of use to identify mite species and their viability, however it is an extremely time-consuming procedure, which does not lend itself to large epidemiological studies.

With the advent of monoclonal antibodies to mite allergens, it became possible to develop ELISA techniques to assay the absolute quantity of allergens in dust (Chapman et al., 1987), which occur in nanogram to microgram concentrations. These levels reflect more accurately the allergen exposure, for example during the summer there is a time lag of several weeks between highest mite counts and the highest allergen levels. An even simpler method of measuring the levels of guanine, which is present in mite feces, has been described and appears to correlate well with *Der p* I levels (van der Brempt et al., 1991). Ideally, the airborne concentration of mite allergen should be measured (Price et al., 1990) although the heavy fecal particles do not readily become airborne and are in such low concentrations that an international workshop decided that the reservoir levels of mite allergens, from which the airborne allergens are derived, is a more accurate and consistent measurement of mite exposure (Platts-Mills and De Weck, 1989). The best way of expressing the reservoir levels of allergen, whether as a concentration, amount per unit surface area or total amount was also addressed and it was proposed that the standard way of expressing exposure should be as a concentration (i.e. μg *Der p* I/g sieved dust). This would allow comparison between studies and still allow researchers to express exposure using their own indices, if they felt them to be appropriate. The potency of allergens in producing symptoms can be illustrated by estimates that the total seasonal pollen allergen exposure of an adult is not more than 1 μg, and much less is required to produce individual episodes (Marsh, 1975). The quantity of dust mite allergen inhaled in a house can approach 20 ng h^{-1}, and bronchial responses have been observed in sensitised individuals with as little as 20 ng (Tovey et al., 1981).

MITE EXPOSURE AND ILLNESS

Asthma

Sufficient evidence has accumulated to state that sensitisation to house dust mite allergen and the development of asthma are causally linked. In areas where dust mites are not found in large numbers, other allergens may similarly be of importance; but as measurements of these allergens were not possible until recently, the evidence to date is not as complete. Causal inference from epidemiological studies is based on the sum of evidence from many

studies: it can never be derived from a single study. It has been suggested that the following conditions need to be fulfilled for causality to be invoked: (1) the *strength* of association is large, (2) repeated observations in different populations, under different conditions have *consistent* findings, (3) a cause leads to a *specific* effect, (4) the cause *precedes* the effect in time, (5) there is a *dose response* gradient, (6) there is *experimental* evidence, (7) there are *analogous* explanations, and (8) the mechanism is biologically *plausible* (Hill, 1965; Rothman, 1986). Most of these requirements have been fulfilled for the relationship between mite allergens, immediate hypersensitivity and asthma.

The strength and consistency of findings

There are studies from areas of perennial high mite exposure e.g. the UK and Florida, from areas of seasonal mite exposure (Virginia) and from areas of very low mite exposure (high altitudes and hospitals). In areas of high mite exposure it has been repeatably demonstrated that patients with asthma have positive skin tests and serum IgE antibodies to dust mites (Miyamoto et al., 1968; Smith et al., 1969; Sarsfield, 1974). In these areas the association of positive skin tests and asthma is strongest in children, with up to 80% showing evidence of sensitisation. In a prospective study of children at risk of developing immediate hypersensitivity those who had been exposed to high levels of mite allergen in infancy had a 5-fold increased risk of developing asthma, and 94% of these were mite sensitised compared to 32% of these who had not wheezed (Sporik et al., 1990). Sensitisation to mites increased the risk of asthma by 20 fold over that of children who were not sensitised to any allergen. In a study of children admitted to hospital for asthmatic exacerbations it was found that over 80% were mite sensitised and 60% were both sensitised and exposed to high levels of house dust mite. Furthermore the results suggested that continued levels of high exposure to dust allergens increased the risk of readmission with asthma (Sporik et al., 1991). A similar study of children attending hospital for exacerbations of asthma in Florida showed that 90% were mite sensitised compared to 36% of a control group of children attending hospital because of injuries. The levels of mite exposure were similarly high in both groups (Di Nicolo et al., 1991). In areas of low mite exposure the level of sensitisation is correspondingly lower and other allergens appear to be of more importance (Pollart et al., 1988; O'Hallaran et al., 1991). Data on the prevalence of asthma in areas of very low mite exposure is lacking, as these tend to be climatically inhospitable, sparsely inhabited and populated by people often with a unique genetic background. In one such area, the subarctic, the prevalence of asthma was very low in the native Eskimos (Herxheimer and Schaefer, 1975), however, this may reflect low levels of exposure or the lack of a genetic predisposition towards either sensitisation or asthma. When populations have migrated to areas of high mite exposure,

usually the affluent first world, this has frequently been followed by an increase in the reported prevalence of asthma (Pearson, 1973). From all these studies it appears that "asthma" does not develop on exposure to allergen except in individuals who are first sensitised to the relevant antigen, and that this ability to become sensitised is genetically determined. It should be noted that in all these studies there is a minority of subjects with evidence of sensitivity to mites who are nevertheless symptomless. Some of these individuals may develop asthma in later life (Ohman et al., 1991).

Specific effect

The causal relationship between exposure and disease is more convincing if the response is specific, i.e. exposure consistently produces the same response. Systemically the effect of mite allergen exposure is the development of an IgE immune response. In each of the target organs exposure is associated with a specific effect: in the lungs – asthma; the nose – rhinitis; and the skin – atopic dermatitis. Furthermore in each case the symptoms can be reproduced by challenge studies. What is unclear is why under conditions of natural exposure some sensitive individuals develop one form of disease while others another, although overlap of symptoms is frequently seen. It may be worth pointing out that no evidence connecting mite allergen exposure or sensitivity with such diseases as diabetes, cancer or coronary artery disease has been reported.

Temporal relationships

Temporal evidence that acute exposure to mites precedes symptoms in sensitised individuals comes from areas with seasonal fluctuations in mite populations. In a study from Virginia an increase in symptoms was found to follow an increase in *Der p* I levels in sensitised subjects (Platts-Mills et al., 1987). Studies from Papua New Guinea, where good conditions for mite growth were inadvertently introduced with the provision of woollen blankets, found that there was a subsequent increase in the prevalence of asthma, a previously rare condition (Dowse et al., 1985). It also seems likely that increases in mite allergens in the late summer contribute to seasonal increases in emergency room attendences and hospital admissions of asthmatics, but this has not yet been proven.

Dose response

There are a number of prevalence studies and a single prospective study which have shown a trend towards increasing level of sensitisation with increasing levels of exposure (Lau et al., 1989; Charpin et al., 1990; Sporik et al., 1990). It has been proposed that exposure to >2 μg *Der p* I/g of sieved house dust (corresponding to approximately to 100 mites/g sieved dust) is a risk factor for the development of mite sensitisation and asthma, and >10 μg

Der p I/g (500 mites/g) increases the risk of acute exacerbations of wheeze (Platts-Mills and De Weck, 1989). These values were based on prevalence studies and the exposure and sensitisation of adults and children presenting with exacerbations of asthma (Platts-Mills et al., 1987). When areas within countries with different mite exposures are compared e.g. inland to coastal Australia (Peat et al., 1987), high altitude to coastal France (Charpin et al., 1990), N. California and Virginia (Platts-Mills et al., 1990), there was a difference in the level of skin test reactivity or IgE levels to mites. Additional evidence to support the view that sensitisation depends on exposure, and occurs in infancy or early childhood, comes from studies which looked at the month of birth and the subsequent development of higher rates of sensitisation to seasonal allergens found during the first 6 months of life (Smith and Springett, 1979; Zeiger, 1988).

Experimental evidence from challenge and avoidance studies

Further evidence of the induction of symptoms by increased mite exposure comes from bronchial provocation studies where both early and late increases in airway resistance can be induced on inhalation of mite allergens, albeit in large quantities. Bronchial reactivity to histamine or methacholine is widely used as a method for assessing the nonspecific reactivity of the lungs and is used as an indirect marker of the severity of asthma. Challenge of the lungs of sensitive individuals with mite allergen can produce both short-term increases in airway resistance and prolonged increases in bronchial reactivity (Warner, 1976). In keeping with the ability of the pollen season to induce prolonged increases of bronchial reactivity in sensitised individuals, analogous increases can be shown following bronchial provocation with mite allergen.

Evidence that mite avoidance results in an improvement in the symptoms of asthma comes from a number of studies. Reported studies on the use of avoidance measures in the home have produced conflicting results, although in some studies it was felt that the measures recommended were not "aggressive" enough and in fact did not cause a measurable fall in allergen exposure. A traditional treatment for asthma has been the removal of individuals to high altitudes, where mite levels are very low. Studies of children in these environments show that bronchial reactivity of the mite-allergic patients is, at least, a partially reversible phenomenon and that reductions in bronchial reactivity take six weeks or more. However, these reductions in bronchial reactivity only occur under conditions that include very extensive avoidance regimes. Similar findings have been duplicated in young adults in the "allergen"-free environment of a hospital, where mite allergen levels were below 0.4 μg/g (Platts-Mills et al., 1982), and it has been suggested that admission to this environment is one of the main benefits of hospital admission for asthma. These findings have recently been duplicated in the homes of a small number of asthmatic children, who were solely mite sensitised, using the sim-

ple procedure of encasing mattresses and by using an allergen-denaturing agent. It was shown that over a period of a year there was a 5-fold reduction in the bronchial reactivity which was significantly different from that of an untreated control group (Ehnert et al., 1992).

Analogous explanations

There is good evidence to suggest that seasonal pollen exposure is capable of causing exacerbations of asthma in sensitised individuals (Pollart et al., 1988). Sensitisation to an aeroallergen derived from the fungus *Alternaria alternata*, in an area of low mite exposure, the North American mid west, has also been shown to be associated with asthma severe enough to cause respiratory arrests (O'Hallaran et al., 1991). Where mite allergens differ from pollen and fungal allergens is in their greater ability to cause sensitisation in susceptible individuals, and that frequently they are present on a perennial, rather than a seasonal basis, which makes it difficult to correlate exposure and symptoms. The lack of an obvious mite season and associated symptoms make patients, and some physicians, unwilling to attribute asthma to dust mite exposure, whereas with pollen it is often strikingly obvious.

Plausible biological mechanism

It is relatively easy to propose a credible mechanism by which allergen inhalation could cause an increase in bronchial reactivity leading to wheezing in a sensitised individual. This would invoke surface IgE on mast cells, mediator release, cellular infiltration and subsequent bronchoconstriction, allergen stimulation being the driving force behind the "inflammatory" changes of asthma (Bousquet et al., 1990; Djukanovic et al., 1990). There also is some evidence to suggest that following sufficient inflammation of this kind, structural changes occur which can result in non-reversible airway reactivity so that asthma becomes independent of further allergen exposure.

It must be remembered that the definition of asthma is difficult, some investigators despairing of the task and instead describe it. It may well cover heterogenous conditions with wheeze being the final common pathway. It is becoming common to talk of the asthmas and there may be many causes for the disease, exposure to house dust mite being one of these. However, among children exposed to high levels of mite allergen it seems to be able to explain the majority. To focus on house dust mites highlights a potentially avoidable cause and suggests that in areas where mites are less common other allergens could play a similar role.

Rhinitis

No epidemiological studies have been undertaken linking rhinitis and house dust mite exposure. There is, however, no shortage of patients with nonsea-

sonal (or semiseasonal) nasal symptoms whose dominant or sole skin sensitivity is to dust mites. Nasal provocation tests, using mite extract, have been reported as being a useful way to determine aetiology (Clark, 1987; Hosen, 1988) and the results agreed well with skin prick tests. The diagnosis is suggested by a history of (1) repeated sneezing first thing in the morning, (2) exacerbations on bed making, and (3) feeling better outside the house. Conjunctivitis is unusual. Once the diagnosis of specific sensitivity has been made, avoidance measures would appear to be the treatment of choice.

Atopic dermatitis

In recent years there has been renewed interest in the role of allergens in the aetiology of atopic dermatitis. The evidence that house dust mites play a role is based on cross-sectional and interventional studies. Atopic dermatitis is difficult to diagnose accurately in epidemiological studies, frequently being confused with seborrhoeic dermatitis in studies on infants, and there are no studies relating mite exposure and atopic dermatitis. Until recently objective markers of this condition have been lacking. It has been shown that patients with atopic dermatitis have high levels of IgE, frequently amongst the highest recorded, and specific IgE antibodies to the house dust mite (Ohman and Johansson, 1974; Chapman et al., 1983; Bametson et al., 1987). It has also been shown that these patients have circulating mite-specific T cells (Rawle et al., 1984).

Using the dermatological equivalent of allergen bronchial challenge, the patch test, it has been shown that when purified mite allergen is applied to a small area of skin, in a susceptible individual, a delayed eczematous reaction occurs (Mitchell et al., 1982). A novel objective method of quantitating the severity of atopic dermatitis has been proposed by Deuell et al. (1991). The amount of exfoliated skin scales in a patient's bed sheets are estimated by vacuuming these on a daily basis and measuring the total IgG content of the dust collected. Using this as a marker they found a gradual reduction in the level of exfoliation when a small number of young adults were placed in an allergen-free environment, which paralleled clinical improvement.

There are several anecdotes (Tuft, 1949; Lobitz and Jillson, 1958) and a case study (Roberts, 1984) of improvements in atopic dermatitis following removal to high altitudes, hospitalization or cleaning patients' bedrooms. Recently a study of hospitalization of children with severe atopic dermatitis was undertaken (Delvin et al., 1991) in association with strict dietary restrictions, where improvements occurred although the mean period until improvement was 70 days, which may reflect the severity of their disease, similar to the time period found for the reduction of bronchial hyperreactivity. A Germany study (Zimmerman, 1987) has also shown an improvement in symptoms where an acaracide was used to reduce mite exposure.

CONCLUSION

The accumulation of evidence for a causal relationship between mite allergen exposure and asthma is now very strong. The association has been seen repeatedly, there is an apparent dose relationship, and experimental studies with provocation or avoidance have shown significant effects. Finally there is a highly plausible hypothesis that mite exposure of sensitised individuals is a major cause of the inflammation that is now recognised as a central feature of asthma. In his discussion on causality, Hill (1965) concludes: "All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be modified by advancing knowledge. That does not confer on us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time." We suggest that sufficient evidence has accumulated to suggest that mite allergens are capable of causing asthma, rhinitis and exacerbating atopic dermatitis. The implication is that positive action should be taken to reduce exposure of vulnerable individuals to these allergens. There is increasing evidence that reducing exposure is a practical proposition in many houses, and that this can reduce symptoms. It remains to be determined whether measures taken to control exposure prophylactically can reduce the prevalence of sensitisation or disease.

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