

REVIEW

House dust mite exposure as a cause of asthma

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Introduction

It is well known that inhalation of an allergen is capable of inducing wheeze in a sensitized individual. But the idea that allergen exposure is a primary cause of asthma has encountered opposition. Recent advances have made it possible to study the relationship between house dust mite allergen exposure and asthma [reviewed in 1]. These include the purification of the major allergens [2], the development of ELISA techniques which have facilitated allergen measurement [3] and a series of epidemiological studies from many parts of the world. In this article, we review the information from diverse studies which when combined strongly suggests that exposure to allergens is an important cause of asthma. We focus on the evidence related to house dust mite allergens because it is the most complete. However there are a number of other inhaled allergens which are of importance in individual cases, in certain geographic areas or at specific times of the year. The implication from these studies is that the primary cause of asthma, especially the asthma occurring in children and young adults, is inhalation of allergens.

For an allergen to have a clinical effect, prior sensitization must have occurred. Sensitization requires the combination of an innate ability to respond and exposure. Immediate sensitivity, characterized by IgE antibody production, is part of the immune response to these proteins, which also involves antigen presenting cells, T cells, B cells and other effector cells. Exposure of a non-sensitized individual to even large quantities of an allergen will not provoke symptoms, whereas a sensitized individual is capable of reacting to extraordinarily small concentrations of allergens, i.e. in the picogram range. Immediate sensitivity can be measured by either the level of allergen specific IgE antibody or by skin testing [4,5,6]. The development of asthma can be considered to consist of two distinct processes: (i) a period resulting in sensitization followed by (ii) exposure of the sensitized person resulting in inflammation and clinical wheeze. This latter process was elegantly referred to as 'excitement' in the early literature. The presence of inflammation may make the lung more sensitive not only to the specific allergen

which produced the sensitization but also to other irritants such as cold air, viral infections and smoke, i.e. it demonstrates non-specific bronchial hyperreactivity. For historical reasons, and also out of simple prejudice, sensitization of asthmatics to common allergens has often been considered as an epiphenomena, an association with no causal significance and of no consequence. Indeed to support this argument a number of studies have shown that infants who wheeze and adults with 'late onset' asthma show no evidence of allergen sensitization to the normal panel of allergens. By contrast when one considers the largest group of asthmatics, children and young adults, the majority are sensitized. The crucial question—if potentially asthmatic infants were never exposed to allergens would they develop asthma—has not yet been answered. However, indirect evidence suggests that this is indeed the case, and that allergen exposure plays a major role in both the development of asthma and ongoing symptoms.

When Dekker proposed that mites were important in provoking attacks of asthma in adults he speculated that many more diseases would be found to be due to their presence [7]. It was subsequently suggested that mite allergen may be of importance in cot deaths and the development of Kawasaki's disease although there is no convincing evidence to substantiate these claims [8,9]. In contrast there is good evidence to support their importance in the development of rhinitis and atopic dermatitis [10,11]. However, dust mite allergen has only been proposed to *cause* one specific disease of the lung, namely asthma.

House dust mites and their allergens

House dust mites belong to the subclass Acari of the class Arachnida. They are widely distributed but 'their size and dislike for light makes them easily overlooked' [12]. The species of known importance are *Dermatophagoides pteronyssinus* (literally—skin eating, feather loving), *D. farinae* (farina is latin for flour, in which they were first identified), *D. microceras*, *Euroglyphus maynei* and *Blomia tropicalis*. The main determinants for survival are high humidity, moderate temperatures and an adequate food source (amply provided by human skin scales and other detritus of domestic life). *D. pteronyssinus* and *E. maynei* are the commonest European species, while *D.*

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farinae, which is more resistant to desiccation, is equally common in North America [reviewed in 13–15].

Two main groups of allergens appear of importance. Group I allergens (*Der p* I [previously named antigen P1], *Der f* I, and *Der m* I) are proteolytic enzymes (MW 25 000) secreted from the digestive tract and found in high concentrations in faecal pellets. Mites are coprophagic, i.e. they re-ingest faecal pellets, and it is possible that the presence of these enzymes allows a more extensive digestion to occur after defaecation [16]. Group II allergens (*Der p* II, *Der f* II) are found both in faecal pellets and mite bodies. They are pH and acid resistant and have a MW of 14 000. Each of the Group I allergens have species specific and common epitopes whereas the only serologically defined epitopes on Group II allergens are genus specific, i.e. are common to *Der p* II and *Der f* II [reviewed in 17].

House dust mite allergen as a cause of sensitization

Factors which have been proposed as being important determinants of allergen specific immune response are: an individual's degree of susceptibility to allergens, the immunogenic properties of the allergen, and the degree of exposure [18]. In any population there is a gradient in the ability to respond to allergens: ranging from individuals who do not become sensitized regardless of exposure to others who show extensive sensitization to many different allergens. The ability to respond is genetically determined although the exact pattern of inheritance is disputed [19,20]. Even among individuals with a tendency to respond the development of sensitization to an allergen is dependent on exposure. This is best illustrated by patterns of sensitization: in N. Europe where ragweed pollen is rare, sensitization to it is equally rare; similarly the pollen of the olive tree is not recognized as an allergen in N. America; additionally among groups where it is rare to find a domestic cat, sensitization to cat is uncommon. Between the extremes of no allergen exposure and excess allergen exposure there is a gradation of exposure to a particular allergen. Threshold values have been proposed as markers above which sensitization becomes increasingly likely [21]. If sufficient exposure occurs the probability of sensitization for susceptible individuals becomes so high that it becomes inevitable. Indeed the house dust mite allergens appear to be especially immunogenic. In areas with high mite exposure such as in the U.K., N. Europe, Australia, New Zealand, the Gulf coast and the Pacific Northwest of America, Brazil, and Japan, the level of mite exposure appears sufficient to sensitize 'all' potentially atopic children [15,22,23].

Evidence to support the idea that the degree of sensitization to an allergen is dependent on the level of exposure

to that allergen in a dose-dependent manner comes from a number of studies. A retrospective and prospective study have shown a significant difference and a trend respectively towards an increasing degree of sensitization with increasing exposure during infancy [24,25]. Studies of children have shown a significant difference between the level of sensitization and current exposure, whether this is measured in house dust or as an airborne concentration of mite allergen [26,27]. In contrast, a study in an area with high levels of mite exposure showed no difference in the level of current exposure and sensitization in older children [25]. Similarly, in adults the cumulative exposure experienced under different living conditions is likely to confuse any clear distinctions between exposed and unexposed individuals. Thus it is not surprising that the clearest examples have been in younger children who are more likely to have lived in one house or one neighbourhood. By contrast, in populations living with low year round levels of exposure (e.g. communities living at high altitudes) differences in sensitization persist into the adult age range. In a random population study comparing the sensitization of those living in Briançon (altitude 1362 m) and those living at sea level in Marseilles the prevalence of sensitization was significantly different (10.2% compared with 27.5%) [28].

Sensitization to an allergen can occur at any age. There are studies of immigrants developing sensitization to ragweed and rye grass in middle age, population studies of sensitization when novel aero-allergens are introduced, and anecdotes of retired sea captains developing pollen sensitization [29,30]. The predisposed infant does however appear to be more susceptible to allergen sensitization. Evidence for this comes from a number of studies; including several that relate the month of birth and subsequent sensitization to pollens [31,32]; long-term follow-up studies relating allergen exposure in infancy with sensitization in later childhood [25,33]; and also from animal work [reviewed in 34]. Raised levels of mite specific IgE and skin weal reactions to mite appear during infancy in areas of high mite exposure [35,36]. Once sensitization has developed it appears that this often lasts into adult life although serological evidence of it diminishes with increasing age. Repeated challenge with an allergen (as with any antigen) can cause a secondary response with an increase in allergen specific IgE levels [37,38]. It is apparent that wheeze can occur in early infancy, i.e. prior to any evidence of sensitization and it could be argued that the temporal requirement that a cause (i.e. sensitization) precedes its effect has not been met. However, on long-term follow-up it appears that many factors can cause wheezing in early childhood and it is only those children capable of developing immediate hypersensitivity who continue to wheeze and who develop

persistent wheeze [39,40]. In addition it appears that the minority of infants who develop severe asthma are those who are highly sensitized [41]. This is in keeping with population studies which have shown that episodes of wheezing in infancy generally have a good prognosis [42,43]. In contrast, the prognosis of asthma in older children with asthma on very long-term follow-up does not appear as favourable as previously thought, with a tendency for it to recur in early adult life [44].

Numerous cross-sectional studies [45–49] and a prospective study [25] have shown an increased prevalence of immediate hypersensitivity in children and young adults with asthma. Elevated total serum IgE levels have been shown to be predictive of asthma in young children [50] and, when age and sex adjusted, total IgE is also a discriminatory marker for adult asthmatics [51]. In studies from the U.K. approximately 80% of asthmatic children have been reported to be sensitized to the house dust mite, with the prevalence increasing with age [45,46]. Indeed, so common is this finding that it is sometimes argued that there is no need to look for house dust mite allergen sensitization in children as it will invariably be found. The increased risk of sensitization to house dust mite was found to be seven times higher in German children if their current exposure to *Der p 1* was greater than 2 µg/g and 11 times higher for exposure above 10 µg/g [26]. A Danish study showed a sevenfold increase in the exposure of newly diagnosed house dust mite sensitized asthmatics to house dust mites when compared to a control population with a clear dose-response relationship between the prevalence of sensitization and the degree of exposure. In addition, the population attributable risk was 60%, indicating that the majority of disease could be attributed to house dust mite exposure [52]. In a cohort of children at risk of developing immediate hypersensitivity the increased risk of suffering from asthma among children who became sensitized to the house dust mite was found to be 14.7 [25]. To put these risks in perspective the increased risk of developing lung cancer from cigarette smoking has been estimated at 8–20 higher in smokers [53] and the risk of men with a blood cholesterol greater than 6 mmol/l (240 mg/dl) developing ischaemic heart disease is three times higher than those with levels less than 5 mmol/l (200 mg/dl) [54]. For these often fatal conditions, the odds ratios have been considered sufficient to launch major public health programmes.

House dust mite allergen as a cause of inflammation and symptomatic asthma

Sensitization is considered to be an asymptomatic process. However, subsequent exposure to the same allergen may result in the release of mediators, the development of local inflammatory reactions and clinical symptoms.

Indeed inflammation is now thought to play an important role in the development of symptomatic asthma. Studies have shown that mite allergen is capable of causing mediator release, inducing proliferative responses in T cells and can cause recruitment of basophils and eosinophils in sensitized individuals. These involve a completely different set of effector mechanisms than those required to produce sensitization. In most studies the prevalence of sensitization is higher than the prevalence of asthma, suggesting that a higher level of exposure is required for the development of symptoms. Indeed, a threshold level of dust mite exposure of 10 µg *Der p 1* has been proposed for exacerbation of wheeze [21]. The situation is analogous to the exacerbations of asthma in pollen sensitized asthmatics which occur when the pollen count is greater than 500 grains/cm² [55].

The *in vitro* effects of house dust mite extracts and purified house dust mite allergens have been studied by a number of groups. Mediator release was first demonstrated in mite sensitized adults with atopic dermatitis. Histamine release could be obtained from peripheral blood basophils at a *Der p 1* concentration as low as 10⁻⁶ µg/ml, but only in those who had developed immediate hypersensitivity [56]. A study of asthmatic children showed a similar pattern, although maximal histamine release occurred at a higher concentration of 10⁻² µg *Der p 1*/ml. The level of histamine release was related to the current level of exposure with an odds ratio of 19 if exposure was greater than 2 µg *Der p 1*/g, increasing to 32 if current exposure was greater than 10 µg/g (for the comparison with those children exposed to less than 0.4 µg/g [26]). While most of the work on mediator release in humans has used ragweed [reviewed in 57], and ovalbumin is the preferred allergen in animal models, there is no reason to believe that house dust mite allergens are not capable of activating the release of other mediators. Indeed release of a chemotactic mediator, probably PAF, has been described from basophils obtained from asthmatic patients sensitized to house dust mite when stimulated with dust mite extract [58]. Migration of basophils and eosinophils to the site of house dust mite allergen challenge has also been described in the skin [56]. In addition, bronchial challenge with allergens, including those derived from the house dust mite, has recently been shown to upregulate the expression of the intercellular adhesion molecule (ICAM-1) in bronchial epithelium [59], to increase the numbers of circulating eosinophils, basophils and their progenitor cells [60] as well as increase the number of eosinophils in broncho-alveolar lavage (BAL) fluid [61]. These challenge results provide a plausible mechanism for the observed accumulation of these cells in the bronchi of asthmatics under conditions of natural exposure.

Several studies have shown that mite allergens are capable of inducing proliferative T cell responses *in vitro* [62,63]. Human mite specific T cell clones have also been isolated, with responses to purified mite allergen primarily seen in allergic individuals [63–70]. Recent evidence suggests that mite allergen specific T cell clones particularly those derived from atopic individuals, support IgE synthesis *in vitro*. These clones appear to be of the 'TH₂' phenotype and produce IL-2, IL-4 and IL-5, but not IFN gamma on stimulation with mite allergens. This may explain the origins of the preferential IgE antibody response in those individuals genetically determined to recognize allergenic epitopes [66,71].

Application of the fibre-optic bronchoscope to the study of asthma has enabled the effects of localized allergen challenge to be studied *in vivo*. Instillation of house dust mite allergen causes erythema, mucosal oedema and bronchoconstriction in sensitized individuals. An early report noted that installation of 10 µg of house dust mite extract into a lobe gave auscultatory evidence of wheeze over that lobe in subjects sensitized to house dust mite [72]. In addition BAL fluid recovered after local challenge contained increased concentrations of prostaglandin D₂ suggesting local mast cell degranulation. These results have been confirmed with the added observation that histamine and peptide leukotrienes show an immediate increase following segmental challenge with house dust mite allergen. No increase in mediator release occurred in the non-sensitized controls [73]. Allergen instillation has not only been shown to cause an increase in the number of eosinophils but also a rapid stimulation of alveolar macrophages [74], and an immediate fall in the ratio of CD4/CD8 T cells in BAL fluid in sensitized individuals [75].

Inhalation of house dust mite allergen is well known to cause bronchoconstriction and wheeze in sensitized adults and children in a dose dependent manner [76–81]. It can induce both immediate and late responses [82]. These late responses were observed in 75% of children who were house dust mite sensitized [78]. In addition if the early response is blocked with a beta agonist it is possible to challenge with larger doses of allergen and almost all sensitized adults will then show a late response [83]. It is also well established that following bronchial provocation with allergen the sensitivity of the lung to subsequent challenge with either histamine or allergen is increased [84,85].

While it is clear from these experimental studies that inhalation of house dust mite allergen is capable of producing airway obstruction and that the prolonged responsiveness and cellular infiltration closely mimics the findings of clinical asthma, the relevance of these experimental studies to natural allergen exposure is often

questioned. Indeed the inhalation of 10 µg of allergen over a few minutes hardly matches natural allergen exposure. For allergens such as ragweed it has been calculated that the cumulative yearly dose is of the order of 1 µg [86]. Two explanations have been proposed to explain these discrepancies. Faecal particles contain approximately 0.1 ng *Der p* I/particle [87]. The allergen elutes rapidly from these particles on mucous surfaces, resulting in an extremely high local concentration of *Der p* I in the order 10 mg/ml (this is 100 000 times greater than the concentration of *Der p* I which stimulated histamine release from human basophils). *Der p* I in these 'physiological' concentrations has also been recently shown to be capable of enhancing the bronchial epithelial permeability to proteins [88]. Although these areas of intense inflammation would be small, if enough faecal particles were inhaled the cumulative effect could be sufficient to cause airway obstruction. Indeed such a high local concentration may be important in the development of an inflammatory response and subsequent increased bronchial reactivity. An alternative explanation is that chronic low level exposure provides a sufficiently large cumulative exposure to match the quantities of allergen inhaled in provocation studies. Faecal particles only become airborne during disturbance. The level of airborne mite allergen measured has been surprisingly consistent between different groups. In an undisturbed room it is usually below the level of detection of an ELISA assay (i.e. <0.2 ng/m³). In one study the undisturbed level was reported as 29 picograms/m³ and with disturbance the level rose a thousand-fold to 30.9 ng/m³ [89]. In U.K. studies the mean levels were 24 ng/m³ and ~30 ng/m³ [27,90]. The highest measured allergen level following disturbance was 90 nanograms/m³ and levels as high as 750 ng/m³ have been recorded in a basement room in the U.S.A. following vigorous disturbance [91]. Assuming a mean level of 10 ng/m³ and a tidal minute volume of 15 litres, an adult would inhale 1 µg of allergen in approximately four and a half days while at the highest level it would take only one and a half hours. The level of mite allergen in the 'reservoir dust' of a mattress or carpet can be as high as 200 µg *Der p* I/g with a usual range of 1–50 µg/g in the U.K. Intimate contact with these surfaces would occur during sleep or as an infant crawls and this might considerably increase the quantity of allergen inhaled. It is therefore not inconceivable that sufficient allergen could be inhaled over a period of a week or month to match that inhaled during an acute inhalation challenge.

Influence of exposure on the prevalence of asthma

If house dust mite exposure is the dominant cause of asthma, one would expect a lower prevalence of the

disease in areas of low mite exposure. These areas however tend to be climatically inhospitable, sparsely inhabited and often populated by people with a unique genetic background. There is evidence that the prevalence of asthma is indeed low in Native Eskimos [92], rare in Highland Natives in Papua New Guinea [93], lower in native born children in Briançon than in children living at sea level [94] and significantly different in adults in these two locations (2.4% compared to 4.1%) [28]. The report from Papua New Guinea described how contact with western civilization was followed by an increase in the prevalence of asthma. An explanation for this has been that the provision of blankets, which became mite infested, resulted in the exposure of this naive population to sufficient allergen to result in their sensitization and the subsequent development of asthma. Further support for this temporal argument that allergen exposure precedes symptoms comes from areas with a large seasonal fluctuation in mite numbers, notably N.E. America [95]. In a study from Virginia an increase in symptoms was found to follow an increase in *Der p* I levels in sensitized subjects (96). It has also been proposed that increases in mite allergen levels in the late summer in temperate countries may contribute to the autumnal increases in hospital admission of asthmatics, and asthmatic deaths in young adults [97] observed during this period.

Recent studies have investigated the houses of children with exacerbations of asthma severe enough to warrant hospital treatment. In the U.K. it was found that 80% of children admitted to hospital were mite sensitized (this was almost invariable in children over the age of 4 years) and 60% were both sensitized and exposed to high levels of mite allergen (10 μ g *Der p* I/g) [98]. Furthermore the results suggested that continued high levels of exposure increased the risk of readmission with asthma. A similar study of children attending an emergency room for treatment of asthma in Florida found that 90% of children were sensitized to the house dust mite compared to 36% in a control group of children attending hospital because of injuries. The level of mite exposure in both groups were similarly high [99]. It would be tempting to speculate that the high mortality reported in New Zealand among asthmatics is not only related to medication usage [reviewed in 100] but also due to very high mite allergen exposure: the damp climate supports luxuriant mite growth.

Conversely, if mite exposure is causally related to asthma, removal of a symptomatic individual from an environment of high mite exposure should result in an improvement of their symptoms. Removal to high altitudes, where mite numbers are very low, has been a traditional treatment of severe asthma. Indeed a study of mite sensitized children from an alpine sanatorium

showed progressive improvement in their bronchial responsiveness to histamine over a prolonged stay [101]. Attempts to create these conditions at lower altitude have provided similar results in adults staying in the 'allergen free' environment of a hospital although it took 2 to 3 months for improvements to occur [102]. There are conflicting reports about whether such an allergen free environment can be produced in a patient's home. The measures necessary to reduce dust mite numbers were not clearly understood until recently, so that many of the early studies used measures which were not aggressive enough and in addition follow-up was not long enough. Encasing of mattresses, box springs and pillows has been shown to contain allergen such that the level measured on their surface fell one hundred-fold [103]. In addition hot washing of bedding and the removal of bedroom carpets can eliminate other major sources of mite allergen. Using these measures it has been shown that bronchial hyperresponsiveness to histamine decreased, symptoms improved and medication use fell in a controlled study of children [104]. Vacuum cleaning is ineffective in removing mites and their allergen, in fact most vacuum cleaners increase airborne mite allergen [105]. An influential study, which dampened enthusiasm for mite avoidance measures in the U.K. because it showed no greater improvement in the treated group than in a control group, restricted cleaning methods to vacuuming and damp dusting [106]. Children appear to improve more rapidly than adults following avoidance measures, suggesting that the histological changes which occur in asthmatics may be increasingly difficult to reverse if allergen exposure has been prolonged.

Conclusion

Asthma is increasingly being described as an inflammatory condition [107,108]. This would suggest that there is a primary causative stimulus. However, most of the papers on lung inflammation do not define what this stimulus is. Allergens, especially those derived from the house dust mite, appear to fill the role of a primary stimulus in the development of asthma, and as a trigger for the exacerbation of symptoms. A biologically plausible mechanism would involve sensitization of susceptible individuals, with the development of allergen specific B and T cells, as well as IgE coated mast cells. Subsequent allergen exposure would cause mediator release, bronchoconstriction and cellular infiltration resulting in histological changes: allergen stimulation being the driving force behind the inflammatory changes. Various other trigger factors for asthma have been suggested, such as viral infections, cigarette smoke, atmospheric pollution, and stress. While they can certainly precipitate attacks of

Table 1. Hill's criteria for causality and the evidence supporting a causal link between mite allergen exposure of a sensitive person and the development of asthma

- 1 The strength of association is large.
 - (i) Population studies [7,22,46,94]
 - (ii) Control studies [26,45,52,99,115]
 - (iii) Prospective study [25]
- 2 Repeated observations in different populations have consistent findings.
 - (i) U.K. [25,27,45,46]
 - (ii) Europe [26,28,52,116]
 - (iii) U.S.A. [96,115]
 - (iv) Other [93,104].
- 3 A cause leads to a specific effect [8,9].
- 4 A cause precedes an effect [93,96].
- 5 There is a dose response gradient [25,28,52,81]
- 6 There is experimental evidence
 - (i) Avoidance studies [101,102,104]
 - (ii) Challenge studies [72–82,84,85]
- 7 There are analogous explanations [55].
- 8 The mechanism is biologically plausible.

wheeze the evidence that they are related, in anything more than an adjuvant role, to the development of asthma in the majority of patients is meagre. In contrast a consistent primary role for allergens has been demonstrated in a number of studies. Indeed, all of Hill's requirements [109] for demonstrating that an 'association' represents a causal relationship have been fulfilled for the two processes of mite allergen exposure leading to: (i) sensitization (in genetically predisposed individuals) and (ii) the development of asthma (in a previously sensitized individual) (Table 1). While there is most evidence for house dust mite allergen exposure, sensitization and the later development of asthma there are an increasing number of studies suggesting that allergens derived from cats, cockroaches and the fungus *Alternaria alternata* are capable of producing similar results [110–113]. It has been suggested that 'asthma' may be due to heterogenous causes all having the same final pathway resulting in wheeze. While inhalation of allergens does not explain all cases of asthma, it would appear to be of primary importance in the development of asthma in the majority of children and young adults. Furthermore, while it is clear that some adults with asthma are neither

sensitized to inhalant allergens or exposed to them, some of these late onset of 'intrinsic' cases may be related to antigenic exposure from intrinsic sources such as *Dermatophyte* fungi [114].

The therapeutic implications of these studies are that allergen avoidance regimes could prevent the onset of asthma in some susceptible infants. Furthermore, if asthma has already developed, and objective evidence of sensitization is present, allergen avoidance regimes could have an important role in the treatment of asthma. The wider implication is that the application of principles designed to reduce dust mite growth in homes could reduce both the prevalence and the severity of asthma.

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