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Con: House Dust Mites in Atopic Diseases Accused for 45 Years but Not Guilty?

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OLD DOGMA—THE QUESTION

A common dogma that dust mites are closely associated with allergic disease has existed for decades. Irrespective of numerous studies since the discovery of the organism as a dust allergen in the early 1960s (1) and the advances in mite biology the role of dust mites in the development of allergic disease remains unclear.

Background

Several studies have suggested that house dust mites (HDM) are causally associated with asthma (2, 3), and that a simple dose-dependent relationship between the level of exposure and sensitization to HDM exists (4, 5). This view has, however, been challenged in recent studies (reviewed in References 6, 7). In addition, measures aimed at reducing exposure to HDMs in homes of individuals with asthma who are mite-sensitive, or those with allergic rhinitis, have been clinically ineffective (8, 9) or the data are of poor quality for objective evaluation (9). The links between exposure, sensitization, and occurrence and/or severity of atopic disease have proved to be more complex and multifaceted than initially thought, and a nonlinear relationship between exposure and response appears to exist (7, 10).

Pearce and colleagues published in 2000 a review article in which the role of HDM in asthma was questioned (6). Fundamental novel data from prospective population studies and experimental studies of tolerance have been published thereafter. Here, we reappraise the significance of mites in asthma and related symptoms based on data of population studies from the year 2000 onwards.

House Dust and Storage Mites

Mites (phylum *Arthropoda*, subphylum *Chelicerata*, class *Arachnida*, order *Acarina*) are ubiquitous free-living or parasitic organisms that abound in soil, humus, stored food, fresh and salt waters, on plants and animals. Approximately 50,000 species of these microscopic or barely visible organisms have been identified, some of which have exploited unusual micro-environments, e.g., nasal passages of birds and mammals, the hair follicles of humans and other mammals, the skin of mammals, and the feathers of birds (11). Mites are abundant in the environment and occur, for example, in normal soil at the level of 1,000 to 10,000 mites per cubic decimeter of soil (12).

In 1964, Voorhorst and colleagues discovered that dust mites are the major source of allergen in house dust (1) and proposed an association between these mites and allergic respiratory diseases (13). HDMs, which include species such as *Dermatophagoides pteronyssinus*, *D. farinae*, and *Euroglyphus maynei*, feed mainly on human desquamated skin scales; on the contrary, storage mites (most commonly *Acarus siro*, *Lepidoglyphus destructor*, *Glycyphagus domesticus*, and *Blomia tropicalis* in the tropics) feed on plant material, fungi, and organic degradation products but are also frequently found in house dust.

Interestingly, mites have also been shown to carry a number of bacteria, which may have implications for their immunobiological properties. Detailed descriptions of the biology and the allergens of dust mites have been published elsewhere (11, 14).

Earlier Data

Earlier data are discussed in the following three major areas of study: (i) type of studies, (ii) type and size of populations recruited, and (iii) type of HDM sensitization (mono- versus polysensitization) measured, all issues that must be taken into consideration when interpreting the results and objectively appraising the studies.

Most studies cross-sectional. The bulk of the literature on the association between HDM and atopic diseases is published in the 1980s and early 1990s. Although significant associations between levels of exposure or sensitization rates to HDM and occurrence of asthma have been reported (3), nearly all studies are cross-sectional. The possibility of reverse causation, i.e., an increased susceptibility to become sensitized and affected by mite (and other) allergens in individuals prone to allergy and asthma, cannot in such studies be excluded. Childhood asthma

is assumed to begin very early in life, and risk/protective factors may affect in the first years of life or even in utero (15).

Prospective data on the association between mite exposure in early life and occurrence of atopic disease in later life have, until the last few years, been almost lacking. One small study with 59 high-risk children from 1990 showed that dust mite levels in infancy predicted early sensitization, later childhood asthma, and bronchial hyperresponsiveness (BHR) (2). Another prospective study 3 years later among 453 high-risk children could not replicate the results of that study (16).

High-risk children versus general population. Earlier studies have largely included individuals with a high risk for atopic diseases. Few data have been available on the association between exposure to mites and occurrence of atopic disease in general populations. The effects of mite exposure among general populations are expected to be different from those among genetically predisposed (6, 17) and is an important issue to be taken into consideration insofar as the majority of children with asthma appears to come from low-risk families (18).

Monosensitization versus polysensitization. Finally, studies that have analyzed separately the association between HDM mono-sensitization (sensitization solely to HDM), in contrast to polysensitization (sensitization to HDM plus one or more other allergens), and occurrence of atopic diseases are surprisingly rare. This information is, however, important to adequately evaluate the significance of HDM sensitization in atopic disease. Most patients with asthma for example, are sensitized to more than one allergen, and the relative contribution of each in the manifestation of the disease and symptoms is thus far unknown. A large population study in the United States with more than 10,000 participants aged 6 to 59 years (the Third National Health and Nutrition Examination Survey [19]) revealed that those individuals who are sensitized to HDM, are, on average, sensitized additionally to four other allergens. Similarly, we have found that of more than 38,000 symptomatic patients referred to the Allergy Clinic of the Helsinki University Central Hospital and skin prick tested in 2003 to 2007, only 1.3% were monosensitized to HDM, and this figure has been similar over the years (Tari Haahela, unpublished data). As HDM sensitization in Western countries frequently occurs with sensitizations to other allergens that may be more closely associated with atopic disease, adjustment by other allergens abolished, not unexpectedly, the significant relationship between HDM exposure and asthma initially found in unadjusted analysis (19).

Some authors have suggested that monosensitized patients belong to an intermediate group between nonatopic and fully atopic individuals, and that monosensitized children may develop polysensitization in later life (reviewed in Reference 20). This is, however, unlikely to be a universal pattern, as the burden of atopy and atopic disease (e.g., in Russian Karelia) has remained low in repeated surveys (21, 22) and in generational analyses (22), irrespective of relatively high HDM monosensitization rates among Russian children (22). The role of atopy in different phenotypes of asthma is a further interesting issue but is beyond the scope of this paper. To summarize, earlier data suggested a causal association between HDM and asthma, but due to the several major limitations and flaws discussed above, such an association has been strongly questioned. Novel data have neither been able to confirm those earlier results.

THE CON POSITION

Recent Evidence—Dust Mites Innocent Bystanders?

As mites, including HDM and storage mites, are an integral part of the environmental microbiota that have coexisted with man since ancient times, similarly to environmental saprophytic

bacteria and parasites, sensitization to HDMs or storage mites may largely be only a marker of exposure rather than a harbinger of an increased risk for atopic diseases in general populations in temperate areas. Dust mites share many features common to ectoparasites, which readily induce IgE responses (e.g., *Sarcoptes scabiei* in scabies). Several lines of recent evidence from different settings now support the concept of mites as innocent bystanders. This evidence includes (i) studies among the children of farmers versus nonfarmers, (ii) studies performed in affluent versus nonaffluent countries/areas, (iii) prospective studies of exposure in general populations and in high-risk children, and (iv) prospective intervention (avoidance) studies among high-risk children and people with asthma.

Farms and eastern nonaffluent areas represent microbe-rich environments in which exposure even to dust mites is frequently high but the occurrence of atopic diseases is low. These studies have provided valuable data for appraising the role of mites in atopic diseases. In addition, prospective studies, examining both the effect of mite exposure in general populations and that of mite avoidance among people with asthma, are mandatory to get any clues to causality.

Farming Studies and Studies in Nonaffluent Countries

The farm environment appears to be associated with increased exposure to mites in house dust (25). A comparison of dust mite concentrations in different locales (offices, restaurants, day care centers, schools, markets, paper plants, textile factories, and farm houses) revealed by far the highest mite concentrations (both HDMs and storage mites) in samples obtained from farms (barns, farmers' homes, and clothing), even during winter time (Sirpa Pennanen, unpublished data). Irrespective of this, more than 30 studies have provided evidence that children raised on a farm have a reduced risk of asthma and atopic conditions (reviewed in Reference 23). Thus, higher exposure to dust mites among the children of farmers seems to be associated with similar or higher sensitization rates but lower allergy and asthma rates compared with children of nonfarmers (24, 25).

We found substantial differences in the prevalence of atopy (determined by skin prick tests) and atopic disease among school children and their mothers between Finnish and Russian Karelia, irrespective of the proximity of the areas and similarity of the geoclimatic and vegetative conditions (22). The risk of atopy among Finnish children was 4-fold and among mothers 2.4-fold compared with their Russian counterparts; however, consideration of each allergen separately showed that, contrary to most other allergens, no significant differences were found in sensitization rates to HDM among children (9% in both areas) or their mothers between the two countries. Irrespective of this, substantially higher prevalences of asthma, rhinitis, and eczema were found in Finland among children and their mothers, in line with our earlier study among adults only (21). The results were similar even if specific IgE was considered to define atopy (26). Furthermore, when the effects of HDM monosensitization on atopic diseases among children were analyzed separately we found no association between HDM monosensitization and allergic rhinitis or atopic eczema, using a logistic regression model adjusted for possible confounders. Asthma could not be included in the model because no asthma cases were associated with HDM monosensitization in Finland or in Russia (27). Of the 34 (9%) HDM sensitized children in Finland, only 5 (15%) were monosensitized, whereas in Russia, of the 40 (9%) HDM-sensitized children, 23 (58%) were monosensitized, suggesting an innocent bystander role for HDM in this general population (Figure 1).

Microscopic analysis of dust samples revealed substantial differences in house dust between the countries. Both HDMs

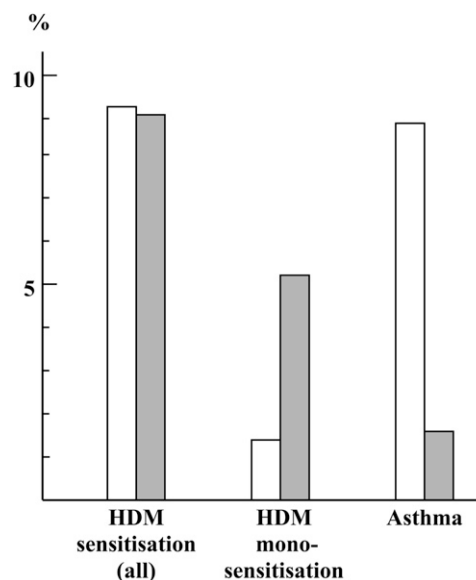


Figure 1. Prevalence of house-dust mite (HDM) sensitization (all), HDM monosensitization and asthma among children in Finnish and Russian Karelia. (HDM sensitization defined as skin prick test positivity to HDM without considering positivity to other allergens, monosensitization defined as skin prick test positivity solely to HDM; asthma defined as parental-reported "physician-diagnosed asthma" and/or "asthma ever.") $P < 0.0001$ for the difference in asthma prevalence between the Finnish and Russian children. Open bars = Finland; gray bars = Russia.

and storage mites were found in Russian dusts and, particularly in the homes of sensitized (primarily to HDM) children, the number of mites and their diversity were striking. In contrast, none of the Finnish dust samples contained mites (see Table E1 in the online supplement). This study setting is of interest because Russian Karelians still adhere to the traditional lifestyle. Living conditions on the Russian side of the border resemble those seen in Finland approximately 50 years ago (27).

Data from other former socialist countries, in line with the Karelia Allergy Study, have shown that simple living conditions and more traditional lifestyle are associated with higher mite concentrations in house dust (28, 29). Climatic conditions cannot explain such differences between adjacent areas (27), whereas housing factors, such as floor level, building material, heating system, dampness, and crowding appear to play a role here (30, 31).

To summarize, an accumulating body of evidence, mainly from temperate regions, suggests that farming and simple living conditions are associated with higher exposure to dust mites (as well as to other environmental microorganisms) but with reduced risk of asthma and atopic conditions.

Prospective Studies of Exposure in General Populations and in High-risk Children

Prospective studies are the prerequisite to properly evaluate the nature of the association between HDM exposure and atopic diseases. In addition to the two earlier studies referred to above (2, 16), seven reports of prospective studies (10, 32–37), four of which are in general populations (10, 33, 36, 37), have been published.

A German birth cohort study (MAS) of 939 low- and high-risk children showed that, irrespective of the positive relationship between HDM exposure and sensitization, no consistent relationship between early exposure and physician-diagnosed asthma, current wheezing, wheezing ever or bronchial responsiveness at the age of 7 years could be found (32).

Cullinan and colleagues (10) examined the relationship between early HDM exposure and occurrence of atopic diseases at the age of 5.5 years in a British cohort of 625 unselected children. No significant association between HDM exposure and either sensitization or wheezing was found, although in a further analysis, a bell-shaped curve between exposure and the clinical outcomes emerged, similarly to cat allergen. At low levels of HDM exposure, a steep increase in risk occurred, particularly in high-risk and first-born children, whereas at increasing doses of exposure, the risk for sensitization and atopic wheeze decreased (10).

Data from the Childhood Allergy Study (CAS) among 428 unselected children in the U.S. (33) found no overall association between physician-diagnosed asthma, current asthma, or sensitization to any of the seven allergens tested at the age of 6 to 7 years and the levels of HDM (Der p1 + Der f1) exposure at 2 years. Unexpectedly, a *reduced* risk for BHR emerged, both at higher and lower exposure, although statistical significance was achieved only for the latter. As part of this CAS study, a small cohort of children with high cord blood IgE were followed from birth until the age of 6 to 7 years (34). Dust samples were collected repeatedly from the children's bedroom floors during the first 2 years of life. There were no differences in mean or maximum levels of exposure to HDM allergen measured at 6 months or at 2 years between the children with or without BHR, or between children with and without physician-diagnosed asthma. An *inverse* association of borderline significance was found between HDM exposure and BHR and asthma (34).

A recent Dutch study examined the impact of mite allergen exposure at 3 months of age on the development of sensitization, wheeze, and physician-diagnosed asthma in the first 4 years of life (35). Although mite (as well as cat) allergen exposure in infancy was associated with increased risk of specific sensitization, no significant association could be found between mite allergen exposure and physician-diagnosed asthma.

Another large birth cohort study among 1,289 unselected British and Spanish children did not reveal any association between the level of exposure to Der p1 in infancy and the development of any type of wheezing by the age of 4 years (36). These children were followed for a further 2 years, and the final results were published last year (37). The authors showed that exposure to Der p1 in early life was not related to specific prick test positivity or to asthma or persistent wheeze at 6 years of age, whereas the cat allergen, Fel d1, was found to be associated with all of these outcomes, underscoring the importance of considering different indoor allergens separately.

Contrary to data referred above, a recent report (38) of the MAS (32), which followed high- and low-risk children from birth to the age of 13 years, suggested that persistent exposure to indoor allergens in the first 3 years of life is associated with early sensitization and reduced lung function at school age (38). However, exposure to indoor allergens in this report was pooled, whereas in their earlier report, allergens were assessed separately.

Prospective studies of mite exposure and asthma and related symptoms among children published from the year 2000 onwards are summarized in Table 1.

To conclude, the bulk of the available data does not support the concept that increased exposure to HDM in early life is associated with an increased risk of asthma and related symptoms in later life. The causal association between HDM and atopic disease has been questioned previously (6), and the recent large well-conducted prospective studies including more than 4,000 children have further corroborated the earlier conclusion.

Prospective Intervention (Avoidance) Studies in High-risk Children and in Asthmatic People

If any given allergen is closely related to atopic disease, as has been suggested to be the case of HDM, it is logical to assume

TABLE 1. PROSPECTIVE STUDIES ON EXPOSURE TO DUST MITES AND SUBSEQUENT DEVELOPMENT OF ASTHMA AND RELATED SYMPTOMS AMONG CHILDREN PUBLISHED IN 2000–2007

Reference (no.)	Population, n	Follow-up, years	Time Points of Mite Measurements	Outcome
Lau <i>et al.</i> , 2000 (32)	High-risk and low-risk children, 939	0–7	6, 18 mo, and 3 yrs (carpets), 5 yrs (children's mattresses) Der p1 (Fel d1)	Childhood asthma not related to mite or cat allergen exposure in early life although sensitization to mite and cat allergen was associated with exposure. Association between sensitization to mite and cat and prevalence of wheezing and BHR found.
Cullinan <i>et al.</i> , 2004 (10)	Unselected children, 625	0–5.5	8 wk (living room floors) Der p1 (Fel d1)	Risk of specific IgE sensitization to Der p1 and Fel d1 and atopic wheeze increased at low levels of Der p1 (and Fel d1) primarily in first born and high-risk children. With high levels of Der p1 (and Fel d1) exposure, occurrence of sensitization and wheeze decreased.
Johnson <i>et al.</i> , 2004 (33)	Unselected children, 428	0–6 to 7	2 yrs (bedroom floors) Der p1 + Der f1	No overall association between exposure to dust mite allergen levels and any of the outcome measures found a weak inverse association between BHR and exposure to mites emerged.
Carter <i>et al.</i> , 2003 (34)	High-risk children, 64	0–6 to 7	Monthly from birth to 2 yrs (bedroom floors) Der p1 + Der f1	No difference in mite allergen levels in homes of children with or without BHR or asthma. Sensitization to HDM associated with asthma.
Polk <i>et al.</i> , 2004 (36)	Unselected children, 1,289	0–4	<1 yr (home dust) Der p1 (Fel d1)	Exposure to mite allergen did not show any association with the development of wheezing.
Brussee <i>et al.</i> , 2005 (35)	High-risk and low-risk children, 663	0–4	3 mo (mattresses) Der p1 (Fel d1)	Increased mite (and cat) allergen exposure associated with increased risk of sensitization to HDM (and cat). No significant association between the level of exposure to HDM and persistent wheeze or phys-dg asthma found.
Torrent <i>et al.</i> , 2007 (37)	Unselected children, 1,611	0–6	3 mo (living room) Der p1 (Fel d1)	Exposure to Der p1 in early life not associated with sensitization, asthma or persistent wheeze at 6 years. (Fel d1 was related to all of these outcomes.)

Definition of abbreviations: BHR = bronchial hyperresponsiveness; Der p1 = the major HDM allergen; Fel d1 = the major cat allergen; HDM = house dust mite; phys-dg = physician diagnosed.

that a reduction in the allergen level would improve the condition or even prevent its development in those with high-risk but without established disease. Different chemical (acarosides) and physical (impermeable bedding covers, vacuum-cleaning, heating, freezing, ventilation, washing, air filtration, and ionizers) methods or their combinations to reduce mite concentrations have been used.

High-risk children. Data from the six intervention studies that focused on high-risk children have been reviewed previously (39). Some of these studies have shown a reduction in HDM sensitization rates (40, 41), improvements in clinical outcome (42, 43), or both of these (44). One study has even found increased HDM sensitization rates but *improved* lung function in the active group (45). The results are discordant and no definite conclusions can be drawn at this stage.

People with asthma. An updated Cochrane meta-analysis on the effect of reducing exposure to HDM antigens in the homes of persons with mite-sensitive asthma, which was based on 54 trials with 3,002 patients, came to the conclusion that chemical and/or physical methods aimed at reducing exposure to HDM allergens have virtually no clinical effect and cannot be recommended (8).

One recent intervention study among inner-city children with asthma (46) showed that, in homes of inner-city residents with asthma, significant reduction in levels of cockroach and Der f1 (but not in Der p1) can be achieved using individually tailored, multifaceted, 12 months of intervention. This reduction was associated with reduced occurrence of asthma-related symptoms. The effect lasted until the end of the follow-up of an additional 12-month period. However, no improvements in lung function measured by spirometry or PEF were found. Moreover, as the study was not blinded and the intervention group was visited more frequently than the control group, the possibility that this contributed to an improvement in the occurrence of parental-reported symptoms cannot, as noted also by the authors, be excluded.

It is now widely assumed that mono-allergen avoidance has generally no effect in primary or secondary prevention, whereas multifaceted interventions can provide some benefit (as reviewed in References 47 and 48). Such multifaceted interventions have included the reduction of environmental tobacco smoke, encouragement for breast-feeding, and dietary interventions, in addition to indoor allergen avoidance. In such study settings, the significance of one factor separately is, again, impossible to evaluate. In addition, the reporting bias by parents noted above cannot be excluded because interventions cannot be blinded entirely. Due to their complexity, multifaceted interventions are not the solution for community problems such as asthma and allergies. To conclude, like prospective studies in general populations, avoidance studies among people with asthma have not been able to provide support for a causal role of HDM in asthma.

Overall, the avoidance of inhalant allergens is difficult, if not impossible. For example, although reduction of mite allergens in homes is achieved, they may still commonly occur in other locales, such as markets, day care centers, and schools, as well as in pets. Therefore, instead of allergen avoidance, tolerance in populations should be strengthened. To change the course and halt the allergy epidemic, a new nationwide action program has been started in Finland (49).

Tolerance

Compared with bacteria and protozoans, dust mites are complex multicellular organisms that are composed of, and produce, thousands of different proteins and macromolecules (14).

Exposure to mites in a natural environment means exposure to adult mites and their fragments, nymphs, fecal matter, and eggs. Immune responses elicited by such a variety of different macromolecules are multifaceted and very difficult to examine. Hardly anything is known about the Toll-like receptors (TLR) involved, and data concerning the role of regulatory T (T reg) cells in induction of tolerance to HDMs in healthy subjects are scanty.

It has been widely assumed that there is a simple, linear dose-response relationship between HDM exposure and sensitization that differs from the relationship between cat allergen exposure and sensitization. This view has now been challenged (7, 56), and the most recent data suggest that there is a bell-shaped curve between HDM exposure and sensitization; at low doses exposure increases sensitization rates, whereas at high doses, sensitization rates decrease, a finding similar to that found for cat, mouse, and rat allergen and endotoxin (reviewed in Reference 49).

Successful application of specific immunotherapy (SIT) in children and adults with asthma who are sensitized to HDM has provided compelling evidence that repeated exposure to mites at high maintenance doses is able to induce tolerance and ameliorate respiratory symptoms. Success has been achieved during the last few years in unraveling the underlying mechanisms in the development of tolerance, and evidence is accumulating that specific cells of the regulatory network, primarily T reg cells, are the major players (49). It is now becoming increasingly clear that the delicate balance in frequency or function between T reg and T effector cells is the key issue in a normal versus atopic immune response to environmental allergens (50–52).

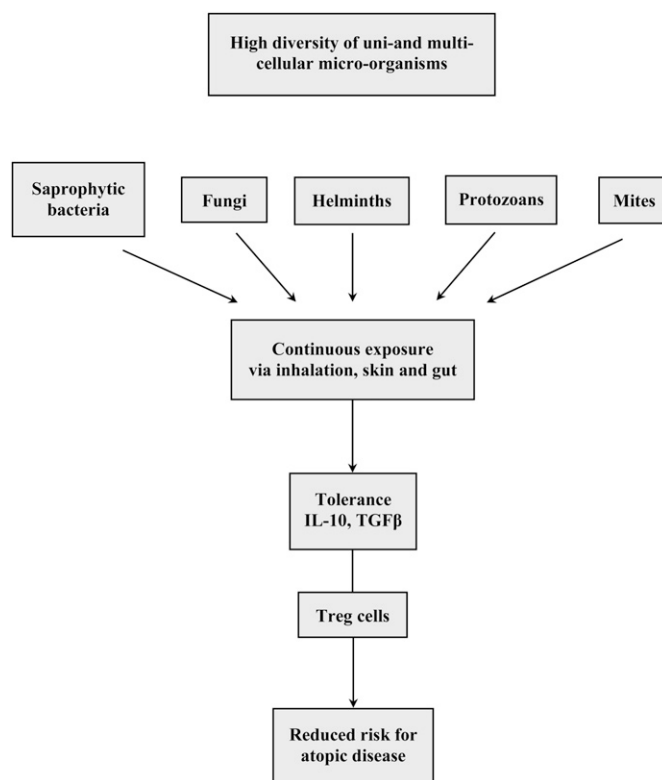


Figure 2. A hypothetical model of the factors involved in the inverse relationship between occurrence of atopic disease and continuous exposure to a high diversity of micro-organisms in the environment.

Conclusion

A rapid increase in the prevalence of atopic diseases started in many countries, along with the increasing affluence, in the early 1960s. In 1964, Dutch investigators first presented their mite theory (1), which appeared to offer a plausible explanation for rising asthma and atopy prevalence in the Western world where people increasingly began to spend their time indoors.

Novel prospective data, data from avoidance studies, as well as studies from farming and other microbe-rich environments, do not lend support to the dogma that dust mites are causally associated with asthma and related symptoms. As with many allergens and bioparticles, high exposure to dust mites is likely to be involved in the development of peripheral tolerance and induction of regulatory network. It seems also likely that the whole environmental microbiota is involved in maintenance of mucosal tolerance, as interaction between TLRs with their ligands (conserved microbial structures) has been found to be crucial for the normal function of mucosal epithelia (53) and for preventing allergen-specific Th2 cytokine production (54) (Figure 2). Although some people with asthma may benefit from staying in hypoallergenic environments, e.g., at high altitudes (57), it is equally possible that the reduction of allergen level in some cases may increase morbidity as the relationship between dose and response for may allergens, including HDM, appears to be nonlinear (10, 56).

The Dutch investigators wrote in their hallmark paper, "Now it seems that we have found Mr. X, and everything indicates that he may be the criminal. Nevertheless, a court of lawyers must declare the mite to be guilty and to be the only guilty one, but this can only be done after a long process of examination has taken place" (1). After 45 years of intensive examination, the court may reach the verdict: Have attended the place of crime but not guilty of assault.

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Rebuttal from Dr. Platts-Mills and Colleagues

The arguments proposed by von Hertzen and Haahtela in their Con editorial (*see pp. 113–119*), in keeping with earlier reports from our group as well as those of Pearce and colleagues, are based on the assumption that measurements of allergen in a child's home are a useful surrogate for real measurements of exposure of the child's nose and lungs (1, 2). There are obvious and not-so-obvious situations where this is not true. The first assumption is that differences in real allergen exposure between houses are sufficiently large that single (or repeated) samples of dust from a house will provide a guide to *differences* in exposure. The reliability of measurements depends on sampling techniques, assay techniques, and variations both within the home and over time (3). The seven studies reported in their Table 1 only reflect

results from four groups. For two of them the study age is too young, i.e., age 5 and age 4; in addition, the range of mite results is insufficient to reach firm conclusions (4, 5). For the two studies quoted from Detroit, mite levels are generally low, and the primary impact of the study was on the effects of cat and dog exposure (6). The second assumption is that relevant exposure to the allergen occurs either exclusively or predominantly in the child's home. A major change has occurred in our understanding of the role of exposure outside the home. It is now clear that living in a house with a cat (or dog) does not increase the risk of asthma or of sensitization to that animal (6, 7). Indeed in some studies the majority of children with cat allergy had never lived in a house with a cat (8). Until recently, it was tacitly assumed that exposure

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