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EXPOSURE TO HOUSE-DUST MITE ALLERGEN (*Der p 1*) AND THE DEVELOPMENT OF ASTHMA IN CHILDHOOD

A Prospective Study

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Abstract Background and Methods. Children with asthma commonly have positive skin tests for inhaled allergens, and in the United Kingdom the majority of older children with asthma are sensitized to the house-dust mite. In a cohort of British children at risk for allergic disease because of family history, we investigated prospectively from 1978 to 1989 the relation between exposure to the house-dust mite allergen (*Der p 1*) and the development of sensitization and asthma.

Results. Of the 67 children studied in 1989, 35 were atopic (positive skin tests), and 32 were nonatopic. Of the 17 with active asthma, 16 were atopic ($P < 0.005$), all of whom were sensitized to the house-dust mite, as judged by positive skin tests and levels of specific IgE antibodies ($P < 0.001$). For house-dust samples collected from the homes of 59 of the children in 1979 and from 65 homes in

1989, the geometric means for the highest *Der p 1* exposure were, respectively, 16.1 and 16.8 μg per gram of sieved dust. There was a trend toward an increasing degree of sensitization at the age of 11 with greater exposure at the age of 1 ($P = 0.062$). All but one of the children with asthma at the age of 11 had been exposed at 1 year of age to more than 10 μg of *Der p 1* per gram of dust; for this exposure, the relative risk of asthma was 4.8 ($P = 0.05$). The age at which the first episode of wheezing occurred was inversely related to the level of exposure at the age of 1 for all children ($P = 0.015$), but especially for the atopic children ($r = -0.66$, $P = 0.001$).

Conclusions. In addition to genetic factors, exposure in early childhood to house-dust mite allergens is an important determinant of the subsequent development of asthma. (*N Engl J Med* 1990; 323:502-7.)

MOST asthma in children and young adults is found in association with immediate hypersensitivity to inhaled allergens and is associated with a familial tendency toward various forms of hypersensitivity, a condition known as atopy.^{1,2} The clear evidence that atopy is inherited, its correlation with HLA types,^{3,4} and its tentative localization⁵ to the long arm of chromosome 11 emphasize the importance of genet-

ic factors in predisposing people to allergic disease. However, the expression of atopy and allergic disease are dependent on exposure. Aeroallergens derived from the house-dust mite are powerful inducers of allergic responses in children.⁶ *Dermatophagoides pteronyssinus* is the predominant house-dust mite in the United Kingdom and many other parts of the world. The most important allergen of this mite is a protein with a molecular weight of 24,000, *Der p 1*, derived from its gastrointestinal tract.^{7,8} This protein has recently been cloned⁹ and identified as a cysteine proteinase. *Der p 1* can be measured in house dust to give an index of the concentration of mite antigen, and levels of exposure that represent a risk for the development of asthma have recently been proposed.^{10,11}

The majority of schoolchildren with asthma in the United Kingdom are sensitized to the house-dust

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mite; 80 percent of children with asthma show skin hypersensitivity to the house-dust mite, as compared with 30 percent in control populations.¹² The view that the house-dust mite is an important determinant of the development of asthma is only partly accepted, despite studies showing the development of asthma in communities newly exposed to this and related mites,¹³ and clinical improvement when patients with asthma are removed from such exposure.¹⁴⁻¹⁶ The presence of dust mites in most houses means that first exposure to these allergens will usually occur very early in life. A number of studies in both humans and laboratory animals have suggested that a newborn's first exposure to aeroallergens may be an important determinant of later respiratory symptoms^{17,18} and sensitization.¹⁹⁻²¹

To obtain reliable information on the outcome of early exposure to allergens in infants at risk because of their family history requires a longitudinal study. In 1978 we began a cohort study in 93 infants to investigate the factors involved in the later development of eczema and wheezing.²² When the children were only one year old, dust was collected from various sites in their homes and assayed for *Der p* I allergen. We report here on 67 of the children, now 11 years old, with respect to the relations between exposure to *Der p* I allergen at ages 1 and 11, sensitization to dust mite allergens, and active asthma.

METHODS

In 1978 a cohort of 93 couples with children born in 1977 or 1978 was recruited from the Poole General Hospital Antenatal Clinic on the basis of one partner's having asthma or hay fever. They gave informed consent to enter their infants into this study, which was approved by the Poole General Hospital Ethical Committee. Seventy-three of the children were still available for study at the age of 5, and 67 at the age of 11. In 1989 the homes of 65 of these children were visited, and house dust collected. Of the 67 children seen at the age of 11, 59 had had their homes visited during infancy. The cohort was followed prospectively each year for the first 5 years and studied again at the age of 11. During the first 5 years all respiratory symptoms were reported to the hospital, and wheezing episodes were confirmed by clinical examination. At the age of 11 the children, with the help of their parents, answered a questionnaire about the occurrence of wheezing episodes since the age of 5 and current use of medication. The atopic status of the children was determined by skin-prick testing with a panel of six allergens (*D. pteronyssinus* extract, mixed-grass pollen, cat fur, dog dander, hen's egg, and cow's milk; Bencard UK). The responses were compared with a positive histamine test (10 mg per milliliter) and a negative control. Throughout the study period the company used the same manufacturing techniques for the allergens, and the mite extract was standardized for *Der p* I content.⁷ Skin testing was performed according to a standard technique²³ at the ages of 1, 2, 3, 4, 5, and 11 years. The same investigator performed these tests from the second year onward. A positive reaction was recorded if the mean diameter of the skin wheal was ≥ 4 mm larger than that of the negative control, and the children were considered to be atopic if they responded to one or more allergens at any age.

Blood was obtained from the children at the age of 11, and IgE antibodies specific to the house-dust mite, cat dander, and rye-grass pollen were measured. The results were expressed in radioallergen sorbent-test (RAST) units²⁴; each unit is equivalent to approximately 0.1 ng of IgE antibody. Sensitivity to these allergens was graded as positive if the skin wheal was ≥ 4 but < 8 mm in diameter or the RAST value was > 40 but < 200 units; strongly positive if the

skin wheal was ≥ 8 mm or the RAST value was ≥ 200 but < 800 units; and very strongly positive if the RAST value was ≥ 800 units.

A deVilbiss nebulizer was used to assess bronchial responsiveness to inhaled histamine in the children at the age of 11 according to the technique of Yan et al.²⁵ After a saline challenge, increasing doses of histamine were administered and followed one minute later by measurements of forced expiratory volume in one second with a Vitalograph spirometer. The histamine dose was progressively doubled until the forced expiratory volume in one second decreased to 80 percent of the value after saline challenge. Children were considered hyperresponsive if this occurred at or before the maximal cumulative dose of 7.8 μ mol of histamine. The majority of the children were challenged four times during the course of the year and were considered hyperresponsive if they had a positive reaction during any season. Testing was deferred if they had had a cough or cold in the preceding month. In this age group the test has been shown to be repeatable within one doubling dilution of histamine. The children were considered to have asthma if they had wheezed in the previous year (1988-1989) and showed bronchial hyperresponsiveness.

Dust was collected by a standard procedure¹¹ from the mattress, bedroom floor, and living-room carpet between October 1979 and March 1980, when the children were one to two years old. Additional samples were collected in the same manner from corresponding sites in the homes between February and April 1989. The dust samples were sieved and weighed, and after aqueous extraction the content of *Der p* I allergen was measured.⁷ In 1979 a double-antibody inhibition radioimmunoassay was used to measure *Der p* I, with radiolabeled antigen P1 (now named *Der p* I) and rabbit anti-dust mite antibody.⁷ In 1989 a two-site monoclonal-antibody enzyme-linked immunoassay was used with a *D. pteronyssinus* standard.²⁶ Both the standards — that used in 1979 and that used in 1989 — were adjusted to match the World Health Organization international standard (NIBSC 82/518), which contains 12.5 μ g of *Der p* I per ampule.²⁷ In keeping with the recommendations of an international workshop, the results were expressed as micrograms of *Der p* I per gram of sieved dust.¹⁰ The limit of detection of *Der p* I was 0.1 μ g per gram, and the coefficient of variation for repeated assays was 8 percent.

Comparisons between the clinical groups were made by nonparametric methods. Contingency tables were analyzed by the chi-square method and a two-tailed Fisher's exact test. Data sets were analyzed by Spearman's rank-correlation test. Relative risk was calculated as the ratio of prevalence of disease among exposed children to the prevalence of disease among unexposed children, as described by Schlesselman.²⁸ The significance of the relative risk was calculated by the chi-square test. The relation between exposure and sensitization to mites was analyzed for linear trend in the proportion of sensitive children.²⁹

RESULTS

Sensitization and Asthma

The total cohort of 67 consisted of 35 atopic and 32 nonatopic children (Table 1), as determined by skin testing. Of the 67, 42 had a history of wheezing, including 26 of the 35 atopic children. Bronchial hyperresponsiveness to histamine was demonstrated in 23 of the children examined in 1989. Of these, 17 had wheezed in the previous year and were classified as having asthma. Eight of these children were receiving medication for asthma regularly during 1989 (inhaled β_2 -agonists in six children, inhaled corticosteroids in four, and inhaled cromolyn sodium in three).

So that the relation among atopy, dust mite sensitivity, and asthma could be analyzed, the children were divided into four groups: those who had never wheezed, those who had wheezed at least once in their lives, those with active asthma, and those with asthma

Table 1. Atopic Status, Sensitivity to the House-Dust Mite, and Asthma in 67 Children in 1989.

CHARACTERISTIC	NO HISTORY OF WHEEZING	HISTORY OF WHEEZING		
		TOTAL	ACTIVE ASTHMA	RECEIVING MEDICATION
No. of children	25	42	17	8
Atopy	9	26	16*	7†‡
Mite sensitivity§				
Very strongly positive	0	7	5	3
Strongly positive	6	5	2	0
Positive	2	10	9	4
Total positive (%)	8 (32)	22 (52)	16 (94)	7 (88)
Negative	17	20	1*	1¶

* $P < 0.001$ for the comparison with children with no history of wheezing, by the chi-square test.

† $P < 0.02$ for the comparison with children with no history of wheezing, by Fisher's exact test.

‡One nonatopic child was receiving medication but had not wheezed or showed bronchial hyperresponsiveness to histamine in the previous year.

§The numbers of positive responses are based on the results of skin tests and analyses of serum IgE antibodies.

¶ $P < 0.01$ for the comparison with children with no history of wheezing, by Fisher's exact test.

who were receiving medication. The third group was a subgroup of the second, and the fourth group was a subgroup of the third (Table 1). It is clear that active asthma was very strongly associated with both atopy and sensitivity to the house-dust mite, as demonstrated by skin testing. Of the 17 children with active asthma, 16 were atopic and all 16 were sensitized to the house-dust mite. The relative risk of active asthma in an atopic child was 14.6, as compared with that in a nonatopic child ($P < 0.005$), and 19.7 if the child was sensitized to the house-dust mite ($P < 0.001$). According to the same criteria, 12 of the 17 children with active asthma were sensitive to cat dander, and 11 of the 17 were sensitive to rye-grass pollen. Fifteen of the 17 children with active asthma had bronchial hyperresponsiveness to histamine on two or more occasions.

An examination of the time course of skin reactivity to mites showed that 40 percent of the children who were positive at the age of 11 had had positive responses by the age of 5. It was unusual for children to lose reactivity; indeed, eight of the nine children with positive responses at the age of 5 were still judged to be positive at the age of 11. Sixty percent of the children became sensitive between the ages of 5 and 11. However, five of the seven children receiving treatment for asthma in 1989 formed a wheal ≥ 2 mm in diameter in response to mite antigens at the age of five, and four of them had a skin response at the age of two. There were clear examples of children who had skin reactivity for two or more years before their first episode of wheezing and of other children who wheezed for several years before skin reactivity developed.

Exposure and Sensitization

House-dust samples were collected from the homes of 59 children in 1979 and of 65 in 1989. The geometric mean values in 1979 were 2.4 μg of *Der p* I per

gram of sieved dust for the living-room floor, 4.3 μg per gram for the bedroom floor, and 18.4 μg per gram for the mattress (Fig. 1). Comparable mean values were obtained in 1989: 4.5, 4.4, and 10.6 μg of *Der p* I per gram, respectively. In subsequent analyses, the highest recorded level of *Der p* I in the house was used as an index of exposure; the mean value for this was 16.1 μg per gram in 1979, and 16.8 μg per gram in 1989. The highest levels were found in the mattress in 73 percent of the homes in 1979 and 60 percent of the homes in 1989.

There was only a weak relation between the degree of sensitization of the children in 1989 and exposure to *Der p* I in 1979 (Table 2). However, none of the children who had been exposed to less than 2 μg of *Der p* I per gram had evidence of sensitization, and exposure to increasing concentrations of *Der p* I was associated with a trend toward increasing degrees of sensitization ($P = 0.062$).

Exposure and Asthma

Among the 59 children from whose homes dust was collected in 1979 and in 1989, 36 had a history of wheezing and 21 of these 36 were atopic. Twenty-three of these children had wheezed in the previous

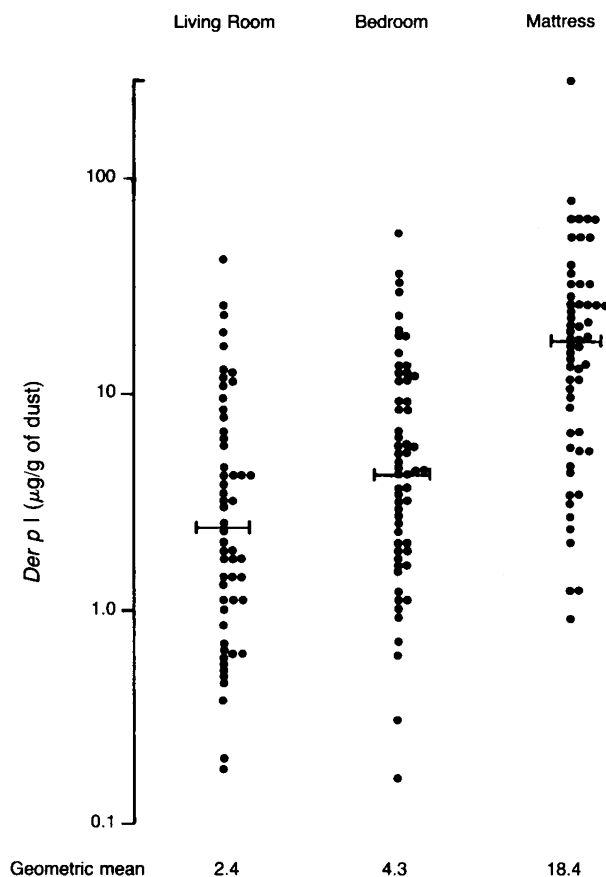


Figure 1. Levels of the House-Dust Mite Antigen, *Der p* I, in Dust Collected from Various Sites in the Homes of 59 Children in 1979.

The horizontal bars indicate the geometric means.

Table 2. Exposure in 1979 to the House-Dust Mite and Sensitivity in 1989 in 59 Children.

EXPOSURE TO MITE ALLERGEN*	NO. OF CHILDREN	ATOPY	SENSITIVITY†			
			—	+	++	+++
$\mu\text{g/g}$		no. (%)				
<2	3	0	3	0	0	0
2–10	13	5 (38)	8	3	1	1
11–50	34	17 (50)	20	5	7	2
>50	9	7 (78)	3	1	2	3

*Expressed as the highest level of *Der p 1* measured in the house.

†Sensitivity to dust mite was assessed by skin tests, measurements of IgE antibodies, or both (see Methods). Analysis for linear trend in the data on mite sensitivity showed a P value of 0.062.²⁹ The minus sign denotes a negative response, + a positive response, ++ a strongly positive response, and +++ a very strongly positive response.

year (1988–1989), and 16 of these also had bronchial hyperresponsiveness.

There was considerable overlap in the degree of exposure of the four groups, with no significant differences between mean exposures (Fig. 2). However, all but one of the children with active asthma and all those receiving treatment in 1989 had been exposed to more than 10 μg of *Der p 1* per gram in infancy. Furthermore, there was a significant correlation between early exposure and current wheezing. This correlation was not apparent with current exposure. The relative risk of active asthma in any child was 4.8 times greater if he or she had been exposed to more than 10 μg of *Der p 1* per gram in infancy ($P = 0.05$). A weak inverse relation was observed ($P = 0.015$) between exposure at the age of one and the age at which the first episode of wheezing occurred for all children who wheezed. However, when the atopic children were considered separately, there was a significant relation between high levels of exposure and early onset of wheezing ($P = 0.001$) (Fig. 3).

DISCUSSION

In this prospective study of children at risk for asthma, there was a strong correlation between wheezing at the age of 11 and sensitization to the house-dust mite. This relation was weak at the age of five and not apparent before that time. The criteria used for analysis of sensitivity were stringent, since for the skin testing only wheals ≥ 4 mm in diameter — the standard used for adults — were regarded as indicating a positive response. The children who wheezed also had an increased prevalence of skin sensitivity to extracts of cat dander and to rye-grass pollen. The present study involved children with only one allergic parent. The objective was to focus on a population at risk for atopy both to improve compliance and to increase the chances of observing the onset of sensitivity. However, this level of risk probably affects more than half the children in the United Kingdom, since about one third of the population has some evidence of allergy. We assume that atopy is a genetically inherited trait whose expression is dependent on exposure. Many of the children in whom sensitivity developed by the age

of 11 would have been judged to be nonatopic at age 5. As has been made clear by previous studies, a substantial number of children have clear evidence of sensitivity and are continually exposed but do not have symptoms of asthma or bronchial hyperresponsiveness.¹⁰ Some of these children have rhinitis or atopic dermatitis, but the majority, as in this study, have no symptoms.

Analysis of the time of the onset of sensitization did not reveal whether sensitization preceded or followed wheezing. For example, some children had clear sensitivity two years before they started wheezing, whereas others wheezed before they had evidence of sensitivity. There are many possible explanations for these discrepancies. Wheezing in children under the age of five may well be related to viral infections, which in some cases lead to persistent bronchial reactivity. If this is the case, however, it appears that bronchial reactivity persists in the children with immediate hypersensitivity. Thus, immediate hypersensitivity and ongoing exposure may be seen as the main factors that allow lung inflammation to persist beyond the age of five. Additional evidence to support this concept comes from observations about the natural history of wheezing in this group of children. Atopy, defined at the age of 11, was the chief determinant of

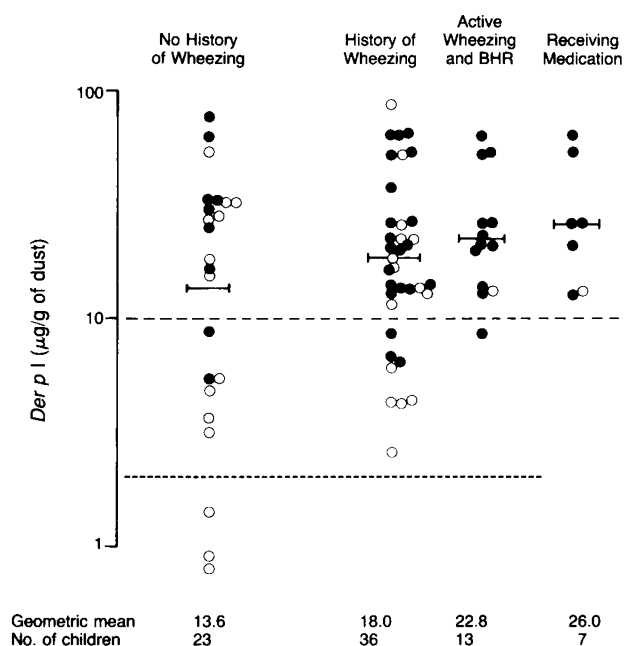


Figure 2. Relation between the Highest Concentration of *Der p 1* Measured in House Dust in 1979 and the Four Clinical Groups. The children with active wheezing and bronchial hyperreactivity (BHR) in 1989 and those receiving active treatment in 1989 are subgroups of the group with a history of wheezing. Solid circles denote atopic children, and open circles nonatopic children. The horizontal bars indicate the geometric means. The shorter dashed line denotes the minimal level of allergen exposure associated with sensitization of the airways, and the longer dashed line denotes the level of allergen exposure predicted to produce symptoms of asthma.

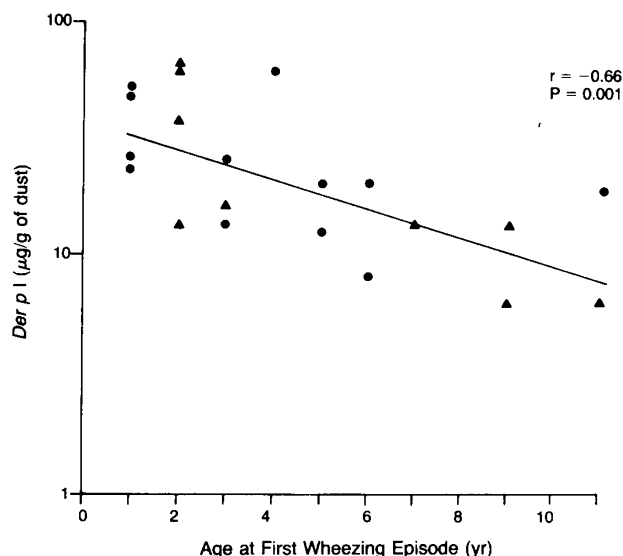


Figure 3. Relation between the Age at the Onset of the First Wheezing Episode in 21 Atopic Children and the Highest Level of *Der p I* in House Dust in 1979.

Circles denote children with active asthma in 1989, and triangles those in whom asthma developed between the ages of 1 and 11.

the persistence of wheezing. In contrast, among the children who wheezed in the first 5 years but were not wheezing at the age of 11, there was no significant correlation with atopy or sensitivity to mite allergen. It is possible that some of the children had local sensitization of the lungs to mite antigens before the development of skin sensitivity or serum IgE antibodies. At present, there is no good evidence to establish or refute a role for local sensitization. The view that viral infections trigger or allow the development of IgE antibody responses was not supported by the present study. Despite careful monitoring of the children during the first five years of life,^{22,30} no consistent relation was demonstrated between viral infections and the onset of immediate hypersensitivity.

The children's homes were assayed twice during the study. Although the assay used in 1979 was not the same as that used in 1989, the standard used — the World Health Organization international standard for *D. pteronyssinus*²⁷ — did not change. The levels of mite allergen in these houses were generally high. For example, 56 of the 59 houses sampled in 1979 had one sample with 2 µg of *Der p I* per gram of sieved dust. The presence of this level of *Der p I* has been proposed as a risk factor for the development of sensitivity to mite allergen and asthma.¹⁰ In keeping with such a high degree of exposure, evidence of sensitivity to mite allergen was found in a large proportion of the children over the next few years. In 1989, 61 of the 65 houses studied contained one dust sample with more than 2 µg of *Der p I* per gram. Thus, nearly all the children and 15 of the 16 with asthma were exposed to high levels of the allergen. It is therefore not surprising that no significant correlation was found between exposure in 1989 and current symptoms.

The present study was carried out on the southern coast of England, which has a mild, damp climate in which mites flourish year-round. In many areas of the world, such as inland northern California, inland Australia, and high-altitude areas of Europe, levels of mite allergen as high as 2 µg per gram, equivalent to 100 mites per gram of dust, are unusual. In such areas, sensitivity to mite allergen is less common and does not appear to be strongly associated with asthma.^{31,32} Other perennial sources of inhaled foreign proteins, such as domestic animals, fungal spores, rodents, and cockroaches, may also be important.³³ Indeed, a recent study of 114 patients with acute asthma in Delaware suggests that sensitivity to dust-mite, cat, and cockroach allergens is each of major importance in North America.³⁴ Exposure levels for these allergens have not been established, although preliminary evidence suggests that a level of 8 µg of the cat allergen, *Fel d I*, per gram of dust may be relevant.

In view of the very high prevalence of asthma in the community (8 to 12 percent) and evidence that morbidity due to asthma is increasing,³⁵ it is important to consider the therapeutic implications of our results. They suggest that high levels of exposure to inhaled allergens at an early age are important in the development of asthma. When the present results are combined with those of previous studies showing an association of asthma with sensitization to house-dust mite allergen, of the onset of asthma with exposure, and of improvement of the disease with avoidance, there seems to be sufficient evidence to suggest a causal relation between exposure to house-dust mites and asthma. This implies that exposing young children to high levels of foreign proteins in their homes should be regarded as an important health risk. Over the past 30 years, many of the changes we have made in our houses, such as increased temperatures and the use of fitted carpets, tighter insulation, and detergents effective in cool water, have improved the conditions needed for dust mites to grow. In view of these changes, we believe that increased exposure to dust mites and other indoor allergens may be a factor contributing to the recent increases in the morbidity and mortality associated with asthma.

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