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Editorial

**Is there a dose-response relationship
between exposure to indoor allergens and
symptoms of asthma?**

Over the last 40 years most populations in the western world have retreated indoors, and we now spend 95% or more of our time in tightly sealed, overheated buildings. During this same period, the morbidity and prevalence of asthma have progressively increased, and multiple reports on the association between asthma and sensitization to the common indoor allergens have been published. Indeed, there are many reasons for considering that there must be a causal relationship between exposure to indoor allergens and asthma.¹ On the other hand, several groups have failed to find a clear dose-response relationship between symptoms of asthma and current exposure to indoor allergens.²⁻⁵ In this issue of the JOURNAL, Marks et al. (pages 441-8) of Sydney, Australia report that the concentration of mite allergens was no higher in the houses of asthmatic patients with mite allergy than in other houses in the town. Ingram et al. have also recently reported that among school-children who are allergic to cat or dog allergens, there is very little relationship between current exposure and whether the children report symptoms of asthma (see pages 449-56). These findings are important both because the results confirm those of previous studies and because they appear

Abbreviation used

BHR: Bronchial hyperreactivity

to question whether there is a causal relationship between indoor allergen exposure and asthma.

In 1873 Charles Blackley published his studies on *catarrhus aestivus*, which included a detailed description of the technique for counting pollen grains and an estimate of the weight of pollen necessary to produce symptoms.⁶ The fact that patients only experienced symptoms at that time of year when pollen was in the air was a major argument for a causal relationship between pollen exposure and hay fever. More recently, studies on the daily symptom scores of groups of patients with hay fever, followed up through the season, have shown a good dose-response relationship with the pollen count.⁷ In a few areas where the pollen counts are very high it is also possible to observe a seasonal peak in asthma attacks.⁸⁻¹⁰ Similarly, an increased severity of asthma among *Alternaria*-sensitive individuals has been reported during the "*Alternaria* season."¹¹ The essence of these reports is that there is a simple technique for identifying and counting the specific airborne particle (e.g., pollen grain or *Alternaria* spore), which provides a reliable "index of exposure." It is also central to these observations that outdoor particles change with the season from near zero to greater than 200 particles per cubic meter.

The most obvious difference between indoor and

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outdoor allergens is that the airborne particles indoors cannot be identified or counted microscopically. Thus there is no indoor equivalent of the pollen count. Although counting mites, cockroaches, or cats may be a reasonable guide to the quantity of allergen in a house, the best measurement of exposure established to date is the immunochemical assay of major allergens in extracts of dust obtained from bedding, carpets, or sofas.^{2, 12, 13} The concentration of allergens in houses can vary widely either in different parts of a house or within a town.¹⁴ Because of this, it was assumed that measurements of allergen would have to be made in each patient's house. For many indoor allergens (e.g., cat, dog, cockroach), there is little or no seasonal variation, and even in areas where there are large seasonal fluctuations in humidity (e.g., Cincinnati, Ohio and Charlottesville, Virginia), the seasonal variations in mite allergen levels are not as great as those for outdoor allergens.^{14, 15} The case for a causal relationship would best be supported by evidence for a dose-response relationship between allergen exposure and symptoms. Most of the data have been published in relation to specific threshold values for sensitization or symptoms. In 1969 Voorhorst et al.¹⁶ suggested that the presence of 100 or more mites per gram of dust created a risk of allergic symptoms and asthma. Subsequently, when assays for the Group I allergens (Der p I and Der f I) became available, a threshold level of 2 $\mu\text{g/gm}$ dust was proposed.^{2, 14, 17} (This level is broadly equivalent to 100 mites per gram.) Initially, it was not clear whether this was a threshold for production of IgE antibodies or for symptoms; however, over the last 10 years this distinction has become clear. Studies from England, Australia, France, Denmark, the United States, and Germany have all demonstrated that children growing up in houses with greater than 2 μg of Group I mite allergen per gram of dust are at risk for developing positive skin test responses and serum IgE antibodies.¹⁸⁻²⁰ Much of the data applies to genetically atopic individuals. In the July 1994 issue of the *JOURNAL*, Kuehr et al.²¹ of Frieberg, Germany published an elegant prospective study of 1802 children showing a dose-response relationship between the concentration of mite allergen on bedding and sensitization of "atopic" school-age children. In that study, increased sensitization became significant at $\sim 2 \mu\text{g}$ of Group I allergen per gram. In contrast, their data showed that sensitization of children who did not have a preexisting positive skin test response to an inhalant allergen other than mite (i.e., were not

atopic) required exposure to concentrations of mite allergen as high as 80 $\mu\text{g/gm}$.²¹

Many studies on the relationship between indoor allergen exposure and symptoms of asthma assume that patients with the highest concentrations of allergen in their houses should have the worst symptoms. Indeed, it is often implied that this would be expected from a comparison with hay fever. This view is based on an oversimplification of pollen allergy. In a cross-sectional population study during the ragweed pollen season, only sensitization to ragweed would be useful in predicting which individuals would have symptoms. However, in a population in which all individuals were exposed to pollen, even accurate measurements of IgE antibody to ragweed or quantitative skin tests would not accurately predict severity of symptoms. Among a group selected only by the presence of positive skin test responses to ragweed (or grass) pollen, there will be individuals who do not experience symptoms of hay fever during the relevant pollen season. Similarly, there are individuals with positive skin test results for mite or cat who can nonetheless live in a house with high levels of mite or cat allergen with minimal or no symptoms of asthma, atopic dermatitis, or rhinitis.^{2, 3, 5, 22} We have attempted to illustrate our concept of this relationship in Fig. 1. The conclusion is that even if there were a simple dose-response relationship between quantitative exposure to indoor allergens and the symptoms of asthma for each individual, the variability within a group of patients would obscure it.

Three different kinds of studies have been used to examine the relationship between exposure to indoor allergens and symptoms of asthma among allergic individuals: (1) comparison between different geographic areas, (2) comparison of houses within a community, and (3) "avoidance experiments." Studies comparing different geographic areas are often confounded by the low prevalence of sensitization in areas with low exposure. Thus in Alice Springs, Australia or Los Alamos, New Mexico there are very few "natives" who are allergic to mites. Thus it is difficult to study the symptoms of allergic but unexposed individuals.^{4, 7, 23} In cross-sectional studies within communities, such as those by Tovey et al. and Ingram et al. in this issue, the results have not been consistent. Most studies that compare the houses of asthmatic patients with those of nonasthmatic, nonallergic control subjects in the same town do not demonstrate significant differences in the concentrations of allergen. In Atlanta, the concentrations of mite and cockroach

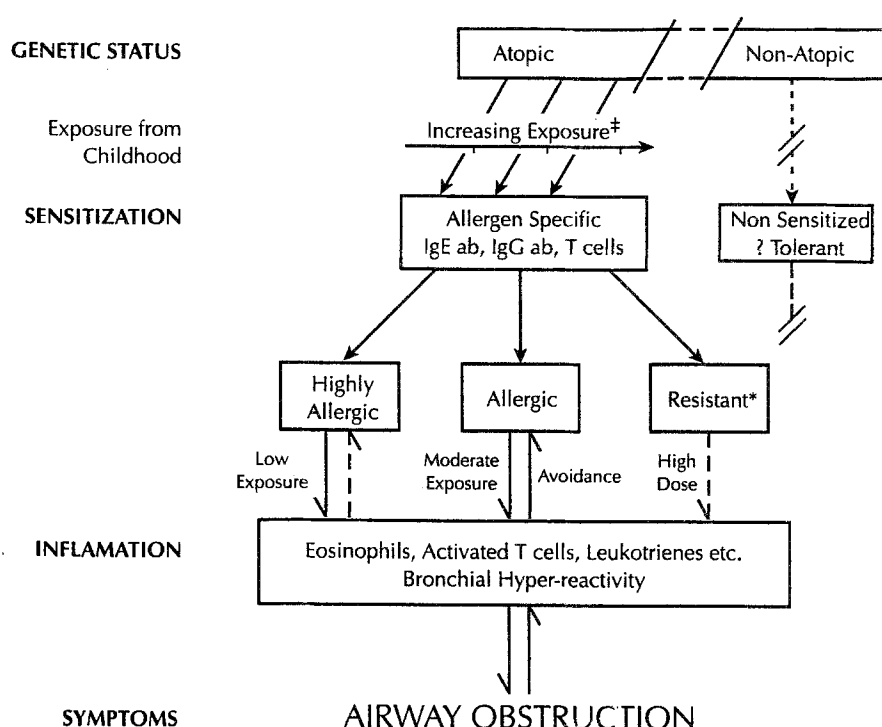


FIG. 1. Dose response of the relationship between allergen exposure and asthma. †The genetic status of individuals before becoming allergic cannot be accurately determined, although recent studies suggest that this may be possible. With increasing exposure, a larger percent of the population will become sensitized. It is also assumed that high levels of exposure will accelerate the process. Nonatopic individuals may have some form of immune response as judged by T-cell proliferative responses, but they do not demonstrate IgE antibodies or symptoms and they do not have symptoms or inflammation when they are challenged with allergen. *Under normal circumstances, the "resistant" patients will have mild or no symptoms. In contrast, allergic patients will respond to moderate exposure and can be helped by simple avoidance measures. However, it is not clear what percent of the total is in this category. *ab*, Antibody.

allergens were very similar in dust from the apartments of asthmatic children and control subjects.³ Among adult patients who came to an emergency department in Wilmington, Delaware, the strong correlation between sensitization and asthma was only slightly strengthened by factoring in current exposure to relevant allergens.²² On the other hand, in Aarhus, Denmark, Korsgaard¹⁹ reported that asthmatic patients with mite allergy lived in houses with higher levels of allergen than random control subjects. In Marseilles, Vervloet et al.²⁴ observed a dose-response relationship between mite allergen concentration in dust and the severity of asthma symptoms among individuals with mite allergy. Avoidance studies strongly suggest that continuing exposure plays a role in most cases of chronic asthma. Major reductions (i.e., $\geq 95\%$) in allergen exposure can reduce symptoms, bronchial reactivity, and signs of inflammation.²⁵⁻²⁸ This is strong evidence that continuing exposure plays an important role in symptoms. However, reduc-

tions in bronchial hyperreactivity (BHR) during allergen avoidance commonly take weeks or months and are not observed in all the patients (Fig. 1).

Several assumptions are inherent in the expectation of a simple relationship between allergen concentrations and symptoms of asthma. The first assumption is that the measurement of allergens in dust samples is an accurate index of exposure. The second assumption is that the size of skin test reaction or concentration of IgE antibody is a good guide to the inflammatory response that occurs in the lungs when allergen particles land on the epithelium. The third assumption is that the severity of symptoms is closely related to the degree of inflammation in the lungs. The truth is that there are significant problems in each case. It is obvious that measuring the concentration of cat, dog, mite, or cockroach allergen in dust obtained from a carpet is not a direct measurement of the allergen entering the lungs. However, there is no method of

measuring allergen entering the lungs, and despite one enthusiastic report, most groups have not been able to obtain measurements of airborne allergens, which could be used to evaluate exposure in epidemiologic studies.²⁹⁻³² Furthermore, because allergen is airborne on particles, which range in size from 2 to 20 μm in diameter, knowing the quantity airborne may not be an adequate measurement of lung exposure without knowledge of the particle size.^{31, 33} Certainly, the results of natural exposure cannot be compared with a challenge in which the same quantity of allergen is delivered through a nebulizer. Although measurements of reservoir dust may be rather distant from an actual measurement of allergen entering the lungs, nonetheless, for mite and cockroach allergens are the best *index of exposure* that is available. For cat allergen it is clear that airborne allergen is carried on a wide range of particle sizes and that the relationship between airborne levels and floor samples is extremely variable.³⁴ Swanson et al.³⁵ reported a poor correlation between airborne Fel d 1 and floor dust allergen. More recently, Bollinger et al.³⁶ have shown that significant amounts of Fel d 1 could be found airborne in houses without a cat, even though the levels in the floor dust were generally less than 1 μg of Fel d 1 per gram of dust. This is important because several recent studies have confirmed that measurable cat allergen is common in houses without a cat.^{4, 22}

Calculations of the concentration of allergen in a pollen grain or a mite fecal particle suggest that the local concentration of allergen where they land in the lungs may be very high (i.e., >1 mg/ml).³³ This concentration would be expected to produce a local patch of "inflammation," including local eosinophil recruitment and a T-cell response. There is overwhelming evidence from bronchial provocation experiments that this response occurs selectively in allergic individuals; however, there is very little evidence to show that it is quantitatively related to the size of skin test reaction or titer of IgE antibody. Presumably, multiple foci or repeated stimulation may have cumulative effects on the lungs, and the speed with which these foci heal may represent another major variable. There are good reasons for believing that the consequences of an inflammatory response can last for weeks or months, which would further obscure a simple dose-response relationship.^{26-28, 37, 38} If the timing of first exposure to allergens is critical to the development of the immune response and/or bronchial inflammation, this would also make it more difficult to demonstrate a relationship between

current exposure and symptoms of asthma. In our prospective study in England we reported that asthma symptoms at age 11 correlated better with the allergen concentration that had been found in the subjects' houses at age 2 than with the current concentration (i.e., at age 11).⁵ We still do not understand the difference between the response to allergen in an asthmatic patient and that in a patient with rhinitis. When segmental provocation of the lungs is performed, the response, as judged by the number of inflammatory cells in bronchoalveolar lavage, is similar. Thus the relationship of "inflammation," BHR, and symptoms is not well understood. However, Cockcroft et al.³⁷ have demonstrated a highly significant relationship between late reactions after bronchial provocation and prolonged increases in BHR. Recently, Boner et al.³⁹ have shown that reductions in number of eosinophils in lung secretions from asthmatic children correlated with decreases in BHR during allergen avoidance at Misurina in the Italian Alps.^{40, 41} Those experiments provide more evidence suggesting that the inflammation is a cause of the BHR and that continued allergen exposure is necessary to maintain inflammation.

The traditional textbook view of allergens as triggers of acute attacks of asthma leads to the assumption that acute episodes would be related to short-term increases in allergen exposure. As is clear from the preceding discussion, we now see allergens as an important long-term cause of inflammation. Short-term increases in symptoms can be triggered by many different irritants including cold air, exercise, passive smoke, ozone, and changes in the weather. All of these will confound any relationship between current allergen exposure and the severity of symptoms.³⁷ However, none of these factors has been convincingly shown to be a cause of respiratory tract "inflammation." In contrast, recent studies in several different laboratories have provided clear evidence that intercurrent viral infection can exacerbate symptoms and increase eosinophil or eosinophil products (major basic protein and eosinophil cationic protein) in the respiratory tract.⁴¹⁻⁴³ This is important because it appears that there is a positive interaction between rhinovirus (or picornavirus) infection and the response to allergen exposure.⁴¹ If correct, this means that many, or even most, exacerbations of symptoms in allergic children are not triggered by a short-term change in allergen exposure.

It is generally assumed that the dose-response relationship between allergen exposure and asthma symptoms is linear. However, it is likely that the

relationship is complex and for each individual it could be linear, log linear, or sigmoidal. If the response curves were sigmoidal, this could have important consequences. In many areas, all houses would have allergen concentrations above the level that is sufficient to maintain bronchial reactivity. Thus a difference between 5 $\mu\text{g/gm}$ and 20 $\mu\text{g/gm}$ might not be significant in causing symptoms. Certainly, in the suburbs of Sydney, Australia, where mite levels are generally high, all the houses could have sufficient allergen to maintain bronchial reactivity in a large proportion of patients with asthma (see Marks et al., pages 441-8). A sigmoidal relationship could also have great relevance to studies of avoidance treatment. A reduction in allergen exposure from 20 $\mu\text{g/gm}$ to 5 $\mu\text{g/gm}$ might not be sufficient to produce a measurable clinical effect in a group of patients.⁴⁴ An equally important concept is that the dose response for symptoms may not be comparable to the dose response for sensitization. In addition, patients who require very little exposure for sensitization to develop are not necessarily those who only require low levels of exposure to cause symptoms, or vice versa.

In conclusion, the role of inhalant allergens in asthma depends on two interrelated events: first, sensitization, and second, the production of chronic bronchial inflammation. In the 1990s the allergens primarily responsible for this process are indoor allergens, the seasonal variation of which is modest or nonexistent. For the first phase (i.e., sensitization) there is clear evidence for a dose-response relationship such that the higher the levels of allergen in the homes of a community, the larger the percent of children who will become sensitized. In contrast, the evidence for a dose-response relationship between exposure and symptoms of asthma among sensitized individuals is indirect and unlikely to be demonstrated by cross-sectional studies of a population, such as those reported in this issue of the JOURNAL (Marks et al. pages, 441-8 and Ingram et al., pages 449-56).

The factors that obscure the relationship between measurements of allergen in houses and symptoms of asthma can be considered in three groups: (1) the relative inaccuracy of measurements of allergen in a reservoir as a method of determining the quantity of allergen entering the lungs, (2) individual differences in the local inflammatory response in the lungs, which may be only weakly correlated with quantitative skin test results or the titer of IgE antibodies (Studying this relationship is also confounded by the lack of a simple method of quantitating inflammation in the

lungs.), and (3) the multiple factors, in addition to allergens, which can trigger an attack of asthma in a patient with "inflamed" lungs including ozone, passive smoke, cold air, and SO_2 , and most importantly, rhinovirus in young patients.

In many areas the majority of children and young adults with asthma are sensitized to common indoor allergens. However, in a town where high concentrations of one or more of these allergens are present in most houses, the content of allergen in each house will not provide a good guide to the current severity of symptoms, even if only the sensitized individuals are considered.

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