

# The role of allergens in allergic airway disease

Thomas A. E. Platts-Mills, MD, PhD *Charlottesville, Va.*

It has been known for more than a century that seasonal upper respiratory symptoms, that is, hay fever, can be provoked by pollen grains, especially the pollens of grasses, trees, and weeds. Pollen grains contain pores through which their associated proteins can be rapidly disseminated to the human nose and upper airways. The allergenic proteins produced in the pollen of each plant are very specific, accounting for the high degree of variability among humans in their sensitivity to different pollens. Thus, both hay fever and seasonal asthma are primarily associated with allergy to a wide variety of outdoor pollens.

The factors contributing to perennial asthma, however, are more difficult to determine. In general, it seems that perennial asthma is associated with sensitivity to indoor allergens, primarily those of dust mite, cockroach, cat, and dog. This article will describe findings relating to the development of hay fever, seasonal asthma, and perennial asthma.

## EFFECTS OF OUTDOOR ALLERGENS

Toward the end of the nineteenth century, Charles Blackley introduced the basic science of allergy. Performing skin tests, pollen counts, and bronchial and nasal provocation, he showed that pollen grains are the cause of hay fever. The degree to which asthma is related to outdoor pollens is more difficult to define. However, a study performed by Reid at Travis Air Force Base provides some useful information in this regard.<sup>1</sup> Travis Air Force Base is located in the Great Central Valley of California, which is seeded with rye grass. In this environment, they were able to demonstrate that both the seasonal rhinitis patients and the seasonal asthma patients at the base hospital were skin-test-positive and immunoglobulin E (IgE)-antibody-positive for rye grass. He further demonstrated that immunotherapy for both the rhinitis patients and the asthma patients was statistically beneficial, strongly suggesting that outdoor allergen exposure is closely linked to seasonal asthma.

## PERENNIAL ASTHMA: EFFECTS OF INDOOR ALLERGENS

### Indoor versus outdoor living

A large body of evidence is accruing to the effect that exposure to indoor allergens lies at the root of perennial asthma. For example, populations of villagers who live largely outdoors in Kenya, New Guinea, or other undeveloped areas of the world do not have symptomatic asthma. Likewise, people living in rural Africa are rarely asthmatic, but may develop asthma on moving to a large city. Thus, it appears that many people with a genetic propensity to become asthmatic do not develop asthma because of differences in environment (i.e., less furniture and bedding, no carpets, no indoor pets).

In the United States and other developed countries, people are spending less and less time outdoors. As people move indoors, their activity decreases and they demand increasing levels of comfort. Houses and apartments, in addition to providing fabric reservoirs for allergens (e.g., wall-to-wall carpets, curtains, bedding), have air circulation that is typically poor. For example, there are many houses in England and the United States that have only about 0.2 air changes per hour. This is in comparison with federally mandated regulations for the care of laboratory rats, which require that they be provided with 10 air changes per hour, or 50 times more than occurs in many houses.

Investigating how these factors affect the development of asthma, we studied the living conditions of patients admitted to Grady Memorial Hospital, an inner-city hospital in Atlanta, Georgia. Asthma is the most common diagnosis for admission of children to this hospital. The houses in the hospital's inner-city district have an average of four television sets, and 82% of the children with asthma have a television set in their own room. They are living in houses infested with dust mites, cockroaches, and other allergens. Thus, the combination of living indoors with little activity and being exposed to a variety of allergens clearly contributes to the development of perennial asthma.

### Impact of indoor allergens

*Dust-mite allergen.* The fecal particle of the dust mite is the indoor equivalent of the pollen grain. It is about 20  $\mu\text{m}$  in diameter, about the same size as some pollen grains. It is important to realize that indoor allergen proteins do not become airborne as molecules or in droplets; rather, they become airborne on particles. With the exception of cat allergens, most particles (e.g., mite roach allergens) do not remain airborne in undisturbed rooms. Therefore, although people entering a house may detect cat allergen immediately, they may not

From the Department of Medicine, Division of Asthma and Allergic Disease, University of Virginia Medical Center, Charlottesville.

Reprint requests: Thomas A. E. Platts-Mills, MD, PhD, Professor of Medicine, University of Virginia Medical Center, MR4 Building, Room 5086, Lane Road, Charlottesville, VA 22908.

J Allergy Clin Immunol 1998;101:S364-6.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/0/86493

identify other allergens. Accordingly, the clinician should not depend on history to define a patient's allergen sensitivities.

There is international recognition that children living in houses or apartments with a high degree of dust-mite allergen are likely to become sensitized to dust mites. It is further recognized that if people become allergic to dust mites, they may develop asthma. In other words, dust-mite sensitization is a risk factor for asthma.<sup>2</sup>

*Cat, dog, roach, and other allergens.* The same process by which sensitization to mite allergen leads to an increased risk of asthma appears to apply to cat, dog, roach, and other indoor allergens as well. For example, there are virtually no dust mites in the northern Swedish town of Kiruna, yet 6% of the town's children are taking inhaled steroids for asthma. Rather than being allergic to mite allergen, the children of Kiruna are sensitized to cat and dog allergens. Interestingly, 42% of the schools sampled in this small town had high levels of dog allergens, probably carried in on the children's clothing.<sup>3,4</sup>

It seems very likely that, as with mite, cat, and dog allergens, sensitization to roach and fungal allergens is a risk factor for developing asthma. With regard to fungal allergens, it should be noted that *Aspergillus* and *Penicillium* spores are about 2  $\mu$  in diameter, making their volume 1000 times smaller than that of grass pollen or the mite fecal particle. Therefore, pollen counts and fungal spore counts should not be equated.

## OTHER FACTORS CONTRIBUTING TO THE DEVELOPMENT OF ASTHMA

Although increased exposure to indoor allergens is clearly related to the rising prevalence of asthma, it should not be assumed that increased exposure to indoor allergens is necessarily the primary cause of the current asthma epidemic. For example, Seaton et al.<sup>5</sup> showed that the level of dust-mite allergen in Aberdeen, United Kingdom, has remained largely constant since 1970, yet the incidence of asthma has climbed dramatically since that time. Thus, living indoors is a risk factor for developing asthma, but many other things determine its severity and exacerbations.

### Respiratory syncytial virus and rhinovirus

Many different factors can act on the airways and lungs to upregulate their response to allergen exposure. Children under the age of 2 years who present to emergency rooms with their first episode of acute wheezing are commonly infected with respiratory syncytial virus, which is a very potent immunogen. In atopic children over the age of 2 years, rhinovirus appears to be a risk factor for acute wheezing because rhinovirus may potentiate the response to allergens.<sup>6</sup>

Recent findings by Canonica et al. provide some insight into how rhinovirus upregulates the allergic response.<sup>7</sup> These investigators analyzed the quantity of intercellular adhesion molecule-1 (ICAM-1), the rhino-

**TABLE I.** Avoidance measures for indoor allergens

|                                                 |
|-------------------------------------------------|
| Cat and dog                                     |
| Keep animal outside whenever possible           |
| Remove reservoirs for allergen or clean weekly* |
| Air filtration                                  |
| Wash animals weekly                             |
| Mite                                            |
| Barriers for mattresses, pillows, comforters    |
| Hot wash bedding weekly                         |
| Carpets: remove, keep dry, clean weekly*        |
| Use acaricides or tannic acid on carpets        |
| Cockroach                                       |
| Obsessional cleaning to remove food             |
| Bait stations and/or boric acid                 |
| Reduce reservoirs                               |

\*Vacuum with double-thickness bag or filter.

virus receptor in the airways. They found that ICAM-1 was increased in conjunctival and nasal epithelial cells following allergen challenge, and that epithelial ICAM-1 was also increased during pollen season or during chronic exposure to mites. Findings such as these show that although prolonged exposure to indoor allergens is a risk factor for developing asthma, many other factors contribute to the severity and intensity of flare-ups associated with asthma.

## AVOIDANCE THERAPY

It is clear that allergen avoidance should be a primary means of treating all allergic patients, including those with asthma. The evidence for dust-mite avoidance as an effective management technique for asthmatic individuals allergic to dust mite is particularly strong. Table I provides a summary of the optimal means of controlling cat, dog, mite, and roach allergen indoors.

## SUMMARY AND CONCLUSIONS

The immune response to inhaled foreign proteins (i.e., allergens) includes both T cells and IgE antibodies. Repeated exposure to these substances can give rise to both rapid and prolonged allergic reactions. Many different sources give rise to allergens in the air that we breathe. Some are encountered predominantly outdoors (e.g., pollens and some fungal spores) and are most strongly associated with seasonal hay fever or seasonal asthma. Other allergens (e.g., those derived from mites, domestic animals, and cockroaches) are produced inside houses, and exposure is almost exclusively indoors. Sensitization to these indoor allergens is associated very strongly with asthma and with perennial rhinitis and atopic dermatitis.<sup>8</sup> The difference in disease association is most likely because exposure indoors is more prolonged. We spend more time indoors (approximately 23 hours/day), and most indoor allergens are present the whole year.

Symptoms caused by chronic (i.e., daily), often low-dose exposure to allergens may be so continuous that the

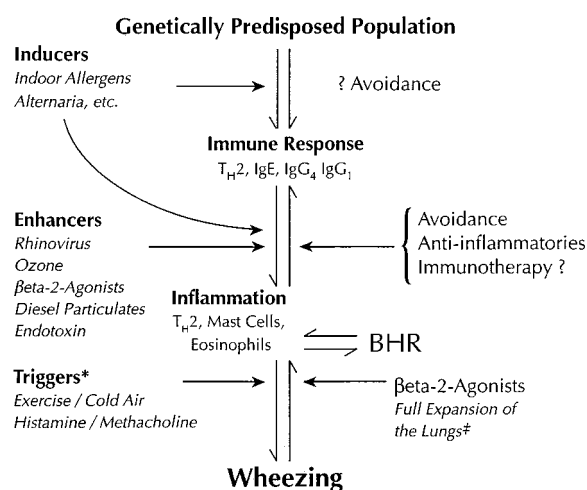


**FIG. 1.** Role of allergens in allergic disease of nose and lungs.  
\*Both inducers and enhancers can act as triggers. ‡exercise.

patients do not recognize any association between exposure and the disease. This is particularly true for mite and cockroach allergic patients with mild to moderate asthma. In addition, many of the short-term increases in symptoms that the patients do recognize are caused by triggers such as cold air, exercise, viral infections, passive smoke, etc. (Fig. 1). Thus, history is not a reliable method of identifying the allergens causing inflammation. Conversely, the best way to reduce the severity of acute symptoms may be to reduce the underlying inflammation that makes the patient sensitive to triggers.

The objective of management is to decrease symptoms (i.e., antihistamines for rhinitis or bronchodilators for asthma) and to reduce or control the underlying inflammation. Controlling inflammation can be achieved by allergen avoidance, pharmacotherapy (local steroids, cromolyn, nedocromil, leukotriene antagonists), and/or allergen immunotherapy. The correct combination of these measures for each case depends on the severity of the case, socioeconomic and, to an increasing degree, on the patients' preferences. Many patients want to address the causes of their symptoms and prefer to use allergen-specific approaches rather than to simply rely

on drugs. In addition, many patients report that nasal sprays make their nose uncomfortable or that antihistamines have unacceptable effects on their mood, etc.

Allergen avoidance has become increasingly specific (Table I) and is now based on detailed understanding of the ways in which allergens are produced and become airborne in a house. For this reason it is essential to define the sensitivity of each patient. Sensitivity or allergy can be identified in part by history, e.g., cat or seasonal hay fever. However, for the major perennial allergens, it is necessary to carry out skin tests or in vitro assays (RAST or CAP). The major allergens in the United States are dust mite, cat, dog, *Alternaria*, *Aspergillus*, German cockroach, grass pollen, ragweed, and tree pollens. When patients do not respond, a wider range of allergens should be tested. Allergen-specific avoidance advice and education is now first-line treatment for extrinsic asthma in children and adults, for perennial atopic rhinitis, and for atopic dermatitis.

## REFERENCES

- Pollart SM, Reid MJ, Fling JA, Chapman MD, Platts-Mills TA. Epidemiology of emergency room asthma in northern California: association with IgE antibody to ryegrass pollen. *J Allergy Clin Immunol* 1988;82:224-30.
- Platts-Mills TAE, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma. Third workshop, Cuenca, Spain. *J Allergy Clin Immunol* 1997;100:S1-S24.
- Wickman M, Nordvall SL, Pershagen G, Korsgaard J, Johansen N. Sensitization to domestic mites in a cold temperate region. *Am Rev Respir Dis* 1993;148:58-62.
- Ronmark E, Perzanowski MS, Lundback B, Platts-Mills TAE. Asthma among children in a dry climate (abstract). *J Allergy Clin Immunol* Vol. 101, January 1998, Part 2.
- Seaton A, Godden DJ, Brown K. Increase in asthma: a more toxic environment or a more susceptible population? *Thorax* 1994;49:171-4.
- Duff AL, Pomeranz ES, Gelber LE, Price GW, Farris H, Hayden FG, et al. Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. *Pediatrics* 1993;92:535-40.
- Canonica GW, Ciprandi G, Pesce GP, Buscaglia S, Paolieri F, Bagnasco M. ICAM-1 on epithelial cells in allergic subjects: a hallmark of allergic inflammation. *Int Arch Allergy Immunol* 1995;107:99-102.
- Squillace SP, Sporik RB, Rakes G, Couture N, Lawrence A, Merriam S, et al. Sensitization to dust mites as a dominant risk factor for adolescent asthma: multiple regression analysis of a population-based study. *Am J Crit Care Med* 1997;156:1760-4.